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ENHANCED PROTECTIVE EFFICACY OF A *PLASMODIUM FALCIPARUM* MALARIA VACCINE USING A HETEROLOGOUS PRIME-BOOST IMMUNIZATION WITH A BACULOVIRAL VACCINE AND CHAD63 EXPRESSING PFCSP AGAINST CHALLENGE WITH TRANSGENIC *P. BERGHEI* SPOROZOITES

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We have recently developed a new vaccine platform system based on the baculovirus *Autographa californica* nucleopolyhedrosis virus (AcNPV) called the baculovirus dual-expression system (BDES). BDES is capable of displaying an antigen on the viral envelope by the use of a baculovirus-derived polyhedrin promoter and expressing it upon transduction of mammalian cells by cytomegalovirus (CMV) promoter and so can function as both a vaccine component and a DNA vaccine, respectively. In our study, a heterologous prime-boost immunization regime using the newly-developed BDES vaccine and the clinically relevant recombinant chimpanzee adenovirus 63 (ChAd63) expressing the *Plasmodium falciparum* CSP (PfCSP) transgene was assessed for its protective efficacy and immunogenicity in a mouse model, using a rodent malaria *P. berghei* chimeric parasite expressing PfCSP as *in vivo* challenge model. We performed a series of animal experiments to evaluate protective efficacy of the heterologous immunization regime. BALB/c mice were primed with ChAd63 and boosted with BDES, and then challenged by intravenous injection of 1,000 *P. berghei* chimeric sporozoites. ChAd63-BDES immunization elicited higher protection than BDES alone with statistical difference. Assessment of immunological analysis is ongoing to find the relationship between immunogenicity and protective efficacy. These findings serve to inform us new insight to develop a new malaria vaccine using the ChAd63-BDES platform.

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CRYOPRESERVATION RELATED LOSS OF ANTIGEN SPECIFIC IFNγ PRODUCING CD4+ T-CELLS: LESSONS FROM A MALARIA VACCINE TRIAL SUBSTUDY

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Ex vivo functional immunoassays such as ELISpot and intracellular cytokine staining (ICS) by flow cytometry are crucial tools in vaccine development both in the identification of novel immunogenic targets and in the immunological assessment of samples from clinical trials. Cryopreservation and consequent thawing of PBMCs via validated processes has become a mainstay of clinical trials due to processing restrictions inherent in the disparate location and capacity of trial centres and also in the logistical and financial requirement to batch process samples from multiple study timepoints. Using ELISpot and ICS assays to assess antigen specific immunogenicity in blood samples taken from subjects enrolled in a phase II malaria heterologous prime-boost vaccine trial, this study has shown that the freeze thaw process can result in a 3-5 fold reduction of malaria antigen specific IFNγ producing CD3+CD4+ effector populations from PBMC samples taken post vaccination. We have also demonstrated that it is likely that peptide responsive CD3+CD8+ T-cells are relatively unaffected as well as more persistent CD3+CD4+ populations that do not produce IFNγ. These findings contribute to a growing body of data that could be consolidated and synthesised as guidelines for clinical trials with the aim of improving the analysis of vaccine candidates.

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RTS,S MALARIA VACCINE EFFICACY DOES NOT VARY WITH SEASONAL PRECIPITATION: RESULTS FROM LILONGWE, MALAWI

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Phase 3 trials of the efficacy and safety of the candidate malaria vaccine RTS,S are complete, but site-specific data are limited. This study assesses the interaction of precipitation and vaccine efficacy and corresponding estimates of clinical malaria episodes averted in a seasonal-transmission region of sub-Saharan Africa. We followed children (5-17 months of age) and infants (6-12 weeks of age) who were randomly assigned to a vaccine group, vaccine with booster group, or control group. Primary efficacy was defined as development of clinical malaria (fever ≥37.5°C and *P. falciparum* parasitemia >5,000 per microliter). Precipitation data were obtained from the Chitedze Agricultural Center in Lilongwe. Cox proportional hazards models were used to assess time until first malaria case. Effect modification was assessed by including interaction terms for vaccination status and precipitation. Vaccine efficacy against multiple malaria cases was estimated using negative binomial regression. Over the duration of follow-up, 744 of 1513 (49.1%) children and infants had at least 1 case of clinical malaria. Among children, vaccine efficacies were 42.7% (95% CI 25.7%, 55.8%, p<0.001) for the vaccine with booster group and 33.1% (95% CI 14.5%, 47.7%, p=0.001) for the vaccine group for first malaria case. Precipitation was significantly associated with increased malaria incidence, with each 1-inch increase in rainfall per month elevating the hazard of malaria by 12.6% (95% CI 9.6%, 15.6%, p<0.001) among children. There was no evidence of modification of vaccine efficacy by precipitation (p=0.85). The estimated numbers of cases averted were 9.4 (95% CI 2.5, 11.3) per 100 children per year in the vaccine group and 17.7 (95% CI 4.6, 32.0) in the vaccine with booster group, compared to the control group. In Malawi, an area of malaria mesoendemic, seasonal transmission, RTS,S vaccine efficacy was not modified by seasonal variation in precipitation. The WHO has selected Malawi as one of the sites to pilot roll-out of RTS,S to children. Our findings could be used by program implementers to help determine the most effective roll-out strategies.

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ANALYSIS OF THE CELLULAR IMMUNE RESPONSE IN C57BL/6 MICE TO FMP014 - A SELF-ASSEMBLING PROTEIN NANOPARTICLE BASED MALARIA VACCINE - DELIVERED IN ALF ADJUVANTS

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In the past decade, new developments in particle based vaccines and adjuvant systems have improved antigen presentation and immune system stimulation. These particle based vaccine platforms show great potential due to their ability to present high-density repetitive epitopes on the surface of the particle, which facilitates the presentation and processing of antigens by the innate and adaptive immune system. We have previously

reported promising results with the use of a self-assembling protein nanoparticle (SAPN) malaria vaccine that displays epitopes from the *Plasmodium falciparum* circumspozorzoite protein (PfCSP). These studies have shown that this vaccine platform induced long-lived and protective immune responses against infection in a mouse model incorporating an otherwise lethal challenge with a transgenic *P. berghei* parasite containing the full-length PfCSP gene (Tg-Pb/PfCSP). We have made additional modification of the PfCSP based SAPN particle and produced under cGMP conditions the falciparum malaria protein 14 (FMP014). FMP014 contains improved antigenic display of the αTSR and NANP repeat regions in addition to several CD4+, CD8+ and universal TH epitopes. We have combined the FMP014 antigen with several new liposome based adjuvant formulations referred to as ALF or Army Liposome Formulation. We have examined various FMP014/ALF vaccines with and without the addition of the aluminum hydroxide Alhydrogel® and the saponin QS21. These formulations produce strong humoral, cellular and protective immune responses in C57Bl/6 mice. Here we report on the cellular analysis of the FMP014/ALF vaccine formulations as determined by flow cytometry, ELISpot and multiplex cytokine arrays (Mesoscale Discovery). The FMP014/ALF vaccine formulations are currently undergoing safety and immunogenicity evaluation in non-human primates and are expected to enter a phase 1/2a study followed by a controlled human malaria infection (CHMI) challenge in 2017.

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ANTIBODY RESPONSES TO VACCINATION WITH *PLASMODIUM FALCIPARUM* APICAL MEMBRANE ANTIGEN 1 ARE BIASED TOWARD THREE CONSERVED IMMUNODOMINANT EPITOPES AND DO NOT MIMIC THOSE TO NATURAL INFECTION

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Plasmodium falciparum apical membrane antigen 1 (AMA1) is a highly polymorphic blood stage malaria vaccine antigen. The AMA1 subunit vaccine FMP2.1/AS02$_A$, tested in a Phase 2 clinical trial in Bandiagara Mali, elicited strong antibody responses, but limited and strain-specific protective efficacy against clinical malaria. When sera from FMP2.1-vaccinated children was probed on a whole-protein microarray containing 263 variants of the AMA1 ectodomain, anti-AMA1 antibody titers increased several-fold, regardless of AMA1 sequence. We hypothesized that the vaccine was biased towards cross-reactive, highly immunogenic epitopes that saturated the signal, obfuscating the smaller, strain-specific, response. To test this, we used sera from 20 of the same Malian children before and 90 days after AMA1 or control vaccination to probe a diversity-reflecting, ultra-dense, small linear peptide array, created using the same AMA1 sequences as the whole protein array, and an additional 68 AMA1 sequences derived from publically-available databases. The array was constructed using unique 16 amino acid long peptides covering the entire length of AMA1 and overlapping by 15 amino acids. Sera from AMA1-vaccinated children showed an increase in antibody titers at three conserved epitopes several-fold higher than control sera over the same time period. Sera from controls who experienced symptomatic malaria illness during the 90 days of follow-up had elevated titers of antibodies targeting different AMA1 epitopes; including epitopes that fell outside the AMA1 vaccine sequence. The high and broad vaccine-induced seroreactivity seen on the whole-ectodomain protein microarray can be attributed to three conserved and cross-reactive immune-dominant epitopes identified by the peptide array. While seroreactivity to tiled, linear peptides may not pinpoint the location of functional conformational epitopes, it may be useful to test whether the patterns acquired after malaria parasite exposure match antibody signatures generated by vaccines.

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LESSONS LEARNED FROM THE MANAGEMENT OF THE INVESTIGATIONAL PRODUCT DURING PHASES 1B &2B MALARIA VACCINES TRIAL IN BURKINA FASO

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An effective malaria vaccine will be a powerful tool that will contribute to reduce malaria burden. We report here experiences gathered in managing investigational product during many vaccines trial in CNRFP. All the trials were double-blind randomized controlled and have involved in total 925 children and 75 adults who have received three doses of either the malaria vaccine candidate or the control. The main storage of study vaccines was in CNRFP headquarters with frequent shipments to the two field sites, namely Balonghin and Banfora located respectively at around 45 minutes and 6 hours drive where participants were immunized. More than 2000 doses of malaria vaccine and 4000 doses of control were received from the various sponsors. Logistical constraints were increased since in some trials, the two vaccines required different condition of storage: Between +2°C and 8°C for control and - 65°C or -20°C for the malaria vaccine. In addition, the two vaccines were different in colours. Strategies for masking were used to keep the blinding for the subject and the vaccinator. We have experienced three temperature deviations of a cumulative duration of 13 hours. Main causes of deviation were material failure and power failure. Vaccines quality was not affected. More than 3500 doses were given with less than 3% of doses lost. In conclusion, despite many challenges, it was possible to ensure that vaccines were managed in accordance with international standards that protect the safety and well-being of trial participant in an African setting with resources limitation constraints.

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BIVALENT CONJUGATE VACCINE TO BLOCK MALARIA TRANSMISSION AND TYPHOID FEVER

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Conjugation of bacterial polysaccharide to a carrier protein is an effective tool to overcome poor immunogenicity of polysaccharide vaccines and to transform the T-cell independent immune response to T cell dependent one. Recent studies evaluating conjugates of Vi polysaccharide from Salmonella Typhi (Vi) to carrier proteins revealed the remarkable finding that conjugation to Vi may enhance immunogenicity of proteins in certain instances. Based on this observation, we have explored the possibility of generating a bivalent vaccine against malaria and typhoid fever, two diseases co-endemic in many parts of the world with high levels of morbidity and mortality, by conjugating malaria antigens to Vi, an approved vaccine for typhoid fever. A malaria Transmission Blocking Vaccine (TBV) that targets the mosquito stages of the parasite is being pursued as a product to interrupt transmission and contribute to elimination. Our laboratory has been evaluating a number of TBV antigens as chemical conjugates with protein carriers to enhance immunogenicity.

Here we describe our efforts to develop a bivalent vaccine consisting of TBV antigen conjugated to Vi to block malaria transmission and typhoid fever. We synthesized a number of conjugates of Vi polysaccharide with Pfs25, a TBV antigen, and evaluated their immunogenicity in mice. Our results showed that chemical conjugation results in enhancement of antibody responses against both Vi polysaccharide and Pfs25 compared to un-conjugated Vi and Pfs25. This increase in antibody titer was also found to be dependent on the conjugation method used for the synthesis. Functional studies using Standard Membrane Feed Assay showed enhancement of functional activity consistent with the increase in antibody titer. This Vi-malaria antigen conjugate concept will be further developed and tested for efficacy in other animal models as well as in human clinical trials if warranted.

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IMPACT OF THE ADDITION OF A SIGNAL SEQUENCE ON THE IMMUNOGENICITY OF A MULTI-STAGE VACCINE AGAINST *PLASMODIUM VIVAX* DELIVERED BY A NOVEL RECOMBINANT SIMIAN ADENOVIRUS VECTOR

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Plasmodium infections still pose a serious threat to public health worldwide. Several vaccine candidates have been tested but none of the formulations has been able to induce both robust cellular and humoral responses. Here, we describe a proof-of-concept study testing the effect of the inclusion of the signal peptide leader sequence, derived from the murine immunoglobulin kappa light chain, on the immunogenicity of a multistage malaria vaccine delivered as a transgene using the simian adenoviral vector serotype 36 (SAd36). The adenoviral transgene included the signal sequence in frame with the coding sequences of two *P. vivax* chimeric recombinant proteins previously developed by our group: PvRMC-CSP and PvRMC-MSP1, which targets the pre-erythrocytic antigen circumsporozoite protein (CSP) and the erythrocytic stage antigen merozoite surface protein 1 (MSP-1) respectively. Comparative experiments were conducted in mice using the recombinant vectors with, or without the signal sequence and heterologous adenoviral prime-protein boost regimens. Mice immunized with the adenoviral vector that included the signal sequence exhibited significantly higher antibody titers after the priming and significantly higher levels of IgG2a when compared to mice receiving the adenoviral vector without the signal sequence. The cellular response was also improved by the addition of the signal sequence as T cells produced higher levels of IFN-γ, TNF-α, and IL-2 upon *ex vivo* stimulation with the *P. vivax* chimeric proteins. Overall, our results demonstrate that the addition of a signal sequence is able to increase the immunogenicity of malaria vaccines delivered through adenoviral vectors.

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ANTIBODY RESPONSES TO HEPATITIS B SURFACE ANTIGEN FOLLOWING ADMINISTRATION OF RTS,S/ASO1E TO HIV-INFECTED AFRICAN INFANTS AND CHILDREN

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The RTS, S/AS01E malaria vaccine has been evaluated for efficacy, safety and immunogenicity in infants and children in sub-Saharan Africa. It consists of sequences of the circumsporozoite (CS) protein and hepatitis B surface antigen (HBsAg), making it also a hepatitis B vaccine. During a Phase III trial(NCT01148459) conducted at two centers in Kenya from July 2010 to May 2013, the vaccine was evaluated for safety and immunogenicity against the CS protein and HBsAg. Two hundred infants and children aged 6 weeks to 17 months who had HIV stage 1 or 2 disease, were randomized in a ratio of 1:1 to receive either the RTS,S/AS01E or rabies control vaccine each administered in 3 doses 1 month apart. Study participants received Hepatitis B vaccine prior to or during the study according to the Kenya vaccination schedule where it is administered at 6, 10 and 14 weeks of age. Anti-HBs antibody titers were measured prior to vaccination, 1 month post Dose 3 and 12 months post Dose 3 and the percentage of subjects with seroprotective levels of anti-HBs (10 mIU/ml and 100 mIU/ml) determined. Based on a threshold of 10mIU/ml, at baseline 57.1% (95%CI: 45.4-68.4) of individuals on the RTS,S/AS01E arm and 54.8% (95%CI: 42.7-66.5) of individuals on the rabies vaccine arm had seroprotective titers of anti-HBs with anti-HBs Geometric Mean Titers (GMTs) of 24.1 mIU/ml (RTS,S/AS01E arm) and 19.2 mIU/ml(rabies arm). One month post-dose 3, 100% (95%CI: 95.1-100) of subjects in the RTS,S/AS01E arm and 52.3% (95%CI: 39.5-64.9) in the rabies arm were seroprotected for anti-HBs with anti-HBs GMTs of 13,637.6 mIU/ml (RTS,S/AS01E arm) and 19.9 mIU/ml (rabies arm). Twelve months post-dose 3, 100% (95%CI: 94.9-100) of subjects in the RTS,S/AS01E arm and 39.1% (95%CI: 27.1-52.1) in the rabies arm were seroprotected for anti-HBs with anti-HBs GMTs of 2,294.8 mIU/ml(RTS,S/AS01 arm) and 11.8 mIU/ml (rabies arm).The RTS,S/ASO1E malaria vaccine generated a strong immune response to Hepatitis B Surface antigen. Therefore, it could have the additional benefit of providing protection against Hepatitis B to children who have not been fully protected through routine vaccination programmes.

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A CLINICAL TRIAL TO EVALUATE THE SAFETY AND INFECTIVITY OF DIRECT VENOUS INOCULATION OF ASEPTIC, PURIFIED, CRYOPRESERVED *PLASMODIUM FALCIPARUM* (7G8 AND NF54) SPOROZOITES IN MALARIA-NAÏVE ADULTS IN BALTIMORE, USA

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Controlled human malaria infection (CHMI) by the bites of infected *Anopheles* mosquitoes is a safe and reproducible method to assess malaria vaccine and drug efficacy, but requires considerable capital and labor investment. Direct venous injection (DVI) of aseptic, purified, cryopreserved *Plasmodium falciparum* (Pf) NF54 sporozoites (SPZ) (Sanaria® PfSPZ Challenge) closely mimics CHMI by mosquito bite, simplifying malaria vaccine and therapeutics testing. As multiple, genetically diverse *Plasmodium* strains with varying susceptibility to antimalarial drugs circulate in endemic areas, testing malaria vaccines and therapeutics using a single parasite strain is not optimal. Development of additional strains for CHMI by DVI would facilitate vaccine and therapeutics testing against parasites that represent strains circulating in nature and that are heterologous to vaccine strains. Pf7G8 is a Brazilian strain with a divergent genomic sequence from PfNF54. Unlike PfNF54, Pf7G8 parasites are resistant to chloroquine, but both are susceptible to atovaquone-proguanil. This single center, randomized controlled human study aims to identify the dose of Pf7G8 SPZ administered by DVI that achieves 100% infection rates. Thirty-six participants will be randomized to one of five groups. Four groups receive escalating doses of Pf7G8 (800, 1600, 3200 and 4800 SPZ) and one control group receives standard dose PfNF54 that infects 100% of malaria-naïve participants (3200 SPZ). Participants will be monitored clinically and malaria positivity will be determined by qPCR. Study objectives compare increasing doses of 7G8 versus NF54 with respect to safety and reactogenicity, infectivity, and time to patency. The study is planned for summer 2016 and initial results will be presented. This clinical trial will serve to standardize optimization testing of other strains slated for CHMI by DVI.

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EVALUATION OF THE SAFETY AND IMMUNOGENICITY OF NANOPARTICLE FORMULATIONS WITH RECOMBINANT *PLASMODIUM FALCIPARUM* TRANSMISSION-BLOCKING ANTIGEN PFS25

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An important consideration for vaccine development is the identification of an appropriate adjuvant, which is capable of eliciting an optimal protective immune response without raising any safety concerns. The objective of this work was to screen various nanoadjuvants and to evaluate the toxicity and immunopotentiating ability *in vitro* and *in vivo*. We compared Alum, nanoemulsions (NE), poly (lactic-co-glycolic acid) (PLGA), gold nanospheres (GNP) and gold nanoprism (GNPR) formulated with a malaria vaccine candidate, CHrPfs25, which has been extensively investigated in our lab. We assessed *in vitro* cytotoxicity using human monocytic cell line (THP-1, bone marrow derived dendritic cells (BMDC) and hepatic carcinoma cell line (HepG2). Cells were exposed to the nanoadjuvanted vaccine for 24h, and an MTT assay was used to assess the viability of cells. THP-1 and BMDC did not demonstrate any cytotoxicity. HepG2 cells showed varying levels of mild cytotoxicity. GNP was most the biocompatible and PLGA exhibited more cytotoxicity. CHrPfs25 formulated with different nanoadjuvants were also evaluated in mice for *in vivo* cytotoxicity and immune-potentiating effects. The results revealed that CHrPfs25 delivered with GNP elicited stronger humoral responses than other groups. There was no apparent toxicity associated with the administration of these formulations. PLGA elicited the lowest response. In an attempt to understand the action of these adjuvants *in vivo*, mice were immunized intramuscularly with different CHrPfs25-nanoadjuvanted formulations followed by assessment of DC and Macrophageϕ ((antigen presenting cells) infiltration at site of injection, sera cytokine and blood profiles after 3, 7 and 14 days of immunization. The results from these studies will be presented.

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EVALUATING THE POTENTIAL TO TRANSMIT MALARIA FROM HUMANS TO MOSQUITOES DURING CONTROLLED HUMAN MALARIA INFECTION WITH *PLASMODIUM FALCIPARUM* AND *P. VIVAX*

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The controlled human malaria infection (CHMI) model has been used successfully to assess efficacy of drugs and vaccines targeting the pre-erythrocytic and blood stages of malaria infection. However, existing models are yet to be used to assess the ability of interventions to interrupt transmission of malaria from humans to mosquitoes. Such a model would be an invaluable tool for selecting the most promising transmission blocking interventions (TBIs) for further evaluation. Our ongoing work uses the induced blood stage malaria (IBSM) model with either *Plasmodium falciparum*- or *P. vivax*- infected red blood cells to initiate blood stage infection in malaria naïve volunteers. Volunteers are subsequently treated with licensed or experimental antimalarials to assess drug activity. As a secondary aim, we are investigating if the gametocytes that appear in peripheral circulation during these CHMI studies, either before drug treatment in the case of P.v infection or after drug treatment in the case of P.f infection, can be transmitted to *Anopheles* mosquitoes. During these studies the development of parasitemia and gametocytemia are monitored in the volunteers by qPCR and qRT-PCR, respectively. Following detection of gametocytes, transmission studies are performed using both direct feeds on volunteers and membrane feeding assays on venepuncture blood. Mosquito infection is then determined 7-10 days post feeding assay by detecting oocysts in the mosquito midgut. In recent clinical trials we have achieved successful transmission of both P.f and P.v at low levels. Current work now aims to optimise this system to enable assessment of its potential for evaluating TBIs. Analysis of specific quantitative biomarkers is being undertaken to improve our understanding of factors that may contribute to transmission efficiency, including male:female gametocyte sex ratios and gametocyte commitment, and in addition we are aiming to optimise the susceptibility of vector mosquitoes to infection. This work will contribute to the development of a reproducible model for rapid selection of effective transmission-blocking drugs and vaccines.

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CLINICAL DEVELOPMENT OF A VAR2CSA-BASED PLACENTAL MALARIA VACCINE PLACMALVAC: DECRYPTION OF THE ANTIBODY ACQUISITION AGAINST THE VACCINE CANDIDATE ID1-ID2

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Placental malaria (PM) is an important cause of maternal anemia, stillbirth and delivery of low birth weight babies, the latter representing a major risk factor for infant mortality in Africa. Many studies have underlined the key role of the parasite protein VAR2CSA in placental malaria (PM), the leading PM vaccine candidate. A specific immune response against VAR2CSA is acquired during the first pregnancies and reduces the harmful effects of placental malaria during subsequent pregnancies. This has led to the development of a candidate vaccine by an EU-funded consortium (PlacMalVac project) which is currently under Phase I trial in Germany and Benin.As part of the PlacMalVac project, we quantified anti-Id1-Id2 IgG and subtype responses to the VAR2CSA subunit vaccine candidate using ELISA in a cohort of Beninese pregnant primigravidae enrolled before the beginning of pregnancy. Clinical and parasitological data were collected monthly from 37 nulligravid women who became pregnant and followed through to delivery. Similar antibody measurements were performed in samples from a sub-cohort of 470 pregnant women of different parities who were followed up throughout pregnancy in the stoppam study. Preliminary analysis shows that antibody levels are dependent on pregnancy, parity status, and are associated with the occurrence of infection during pregnancy. These analyzes highlight the key role of anti-Id1-Id2 IgG3 in protection against placental malaria.

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ANTIBODIES TO PLANT-PRODUCED *PLASMODIUM FALCIPARUM* SEXUAL STAGE PROTEINS EXHIBIT TRANSMISSION BLOCKING ACTIVITY

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Transmission blocking vaccines are considered a critical component in the overall strategy for control and eventually elimination of malaria world-wide. Sexual-stage proteins expressed by *Plasmodium falciparum*, Pfs230 and Pfs25, are the main transmission blocking antigens moving through clinical trial development. Antibodies generated upon vaccination with either of these results in interruption of sporogonic development in the mosquito, and transmission to the next host. Using a plant based transient expression system, we have produced Pfs25 and Pfs230 fused to various carrier proteins in *Nicotiana benthamiana*, purified and characterized the proteins, and evaluated the vaccine candidates in animal models for generation of transmission reducing antibodies (TRA)/ transmission blocking antibodies (TBA). The Pfs25 and Pfs230 vaccine candidates are expressed at high levels, and induced TBA that persist up to 6 months post immunization. These data demonstrate the potential of the new malaria vaccine candidate and also support feasibility of expressing *Plasmodium* antigens in a plant-based system.

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QUANTIFICATION OF BED-NET LOSS AND LEAKAGE FOLLOWING A MASS-DISTRIBUTION CAMPAIGN ON BIOKO ISLAND USING THE CAMPAIGN INFORMATION MANAGEMENT SYSTEM (CIMS)

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Between December 2014 and June 2015, the Bioko Island Malaria Control Project (BIMCP) distributed 149,287 long lasting insecticidal nets (LLIN) to 61,000 households on Bioko Island, achieving an Island-wide coverage of at least 1 LLIN per household of 87%. Of the 87% of households contacted who received a net, universal coverage (at least one net per two people) was achieved in 89% of them, for an Island-wise universal coverage of at least 77%. The BIMCP planned and implemented the distribution campaign through a tablet-based Campaign Information Management System (CIMS) that contains a georeferenced listing of all households on the Island, linked to a unique household identifier. Using the CIMS, data were collected on household size, number of pre-existing nets, and number of nets distributed. Between August and October of 2015, approximately 7 months after the mass distribution, the BIMCP carried out a Malaria Indicator Survey (MIS), taking a representative sample of all communities in the Island. The MIS included questions about bed-net ownership and usage. The MIS showed that net ownership had dropped by 22% between the time of distribution and the 2015 MIS, with 69% of households reporting owning at least one LLIN in the MIS. Universal coverage dropped by 45%, with only 42% of households reporting having at least one net per every two people. Using the geo-referenced unique household identifier, we were able to compare net ownership in 4,992 households. Fifty seven percent of these households reported having at least one less net at the time of the MIS than were distributed during the distribution campaign, and 34% reported at least two fewer nets. While many households reported a loss of nets, others reported a gain of nets. An in-depth analysis of the net code inscribed during the distribution and reported in the MIS, which reveal the original community LLINs were distributed to, will be conducted to investigate possible redistribution of nets. Additionally, results from the 2016 MIS will be analyzed to quantify net loss one year following the mass-distribution and better evaluate the characteristics of households with net gain and loss.

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DYNAMICS OF ENTOMOLOGICAL INOCULATION RATES FOLLOWING INDOOR RESIDUAL SPRAYING IN MALI

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Entomological monitoring is used to assess the impact of indoor residual spraying (IRS) on entomological indicators such as the entomological

inoculation rate (EIR). We assessed the impact of IRS on EIR in sprayed and un-sprayed areas over four years in one district in Mali. *Anopheles gambiae* s.l. were sampled using human landing catches. Baseline data (pre-IRS) were collected at the beginning of the high malaria transmission season one week before spraying. Post-spray campaign follow-up data were collected during the high malaria transmission season for two months in 2012, three months in 2013 and 2014, and five months in 2015. Intervention areas were sprayed with bendiocarb in 2012, 2013 and 2014 and pirimiphos-methyl (300CS) in 2015. An enzyme-linked immunosorbent assay estimated the proportion of mosquitoes positive for *Plasmodium falciparum* sporozoites. In 2012, the pre-spray EIR/night was 0 and 2.64 in the intervention and control areas, respectively. Post-spray EIR was 0.35 in the intervention area and 8.88 in the control area. In 2013, pre-spray EIR/night was 0.60 in the intervention area and 0.97 in control area. Post-spray EIR was 0.49 in the intervention area and 1.47 in control area. In 2014, pre-spray EIR/night was 0.58 in the intervention area and 3.32 in control area. Post-spray EIR was 0.27 in the intervention area and 2.31 in the control area. In 2015, pre-spray EIR/night was 0.75 in the intervention area and 0.84 in the control area. Post-spray EIR was 0.89 in the intervention area and 3.53 in the control area. IRS was effective in maintaining or reducing *An. gambiae* s.l. EIR, which is a measure of malaria transmission. Further malaria case reporting is needed to monitor the impact of IRS.

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USE AND USER CHARACTERISTICS OF INTACT OR "TOO TORN" INSECTICIDE-TREATED MOSQUITO NETS IN TANZANIA

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Sleeping under insecticide-treated mosquito nets (ITNs) is one of the most effective ways for people in malaria-endemic countries to protect themselves against malaria. As most of Sub-Saharan Africa is moving towards universal coverage of the population with mass ITN distribution campaigns, net use rates have been increasing. However, there is still a lack of data on user characteristics, especially of nets with different degrees of physical damage. Two cross-sectional household surveys were carried out in eight districts in Tanzania in 2014 and 2015 to collect data on net ownership, use and physical condition (hole surface area and proportionate Hole Index) combined with household member characteristics. The surveys were conducted in 2,944 households with 15,627 household members and 4,793 used mosquito nets. This data will be analysed to assess who uses mosquito nets of what quality under different ITN ownership scenarios. Results will be presented on characteristics of ITN users (e.g. age, gender, pregnancy status, role in household), whether certain user groups are more likely to sleep underneath "good" or "too torn" nets and whether household ownership of ITNs has any effect on who uses nets of different qualities. This study provides important information, to our knowledge for the first time, on who uses mosquito nets of varying physical integrity, and whether this depends on the access of household members to ITNs. These factors will help malaria policy makers target the right audiences when developing behavioural communication strategies and net replacement campaigns.

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ENTOMOLOGICAL INDICATORS OF MALARIA TRANSMISSION AFTER IRS WAS DISCONTINUED: FINDINGS FROM SAVELUGU NANTON DISTRICT AND ITS IMPLICATIONS FOR MALARIA CONTROL IN GHANA

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Savelugu Nanton District (SND), in the northern region of Ghana, was a beneficiary of the President's Malaria Initiative (PMI) supported indoor residual spraying (IRS) program between 2008 and 2014. Entomological monitoring data showed that parity rates of *An. gambiae* s.l. had been reduced from 44.8% in 2011 to 28.1% by 2014. Sporozoite infection rates ranged between 0.23% and 1.89% between 2011 and 2012, and remained significantly low at a level that could not be detected for two consecutive years (2013 and 2014). IRS was withdrawn from the district after the 2014 IRS campaign due to low coverage and indications of emerging insecticide resistance.Monthly entomological data from three sentinel communities in the district revealed a significant increase in parity, sporozoite rate and entomological inoculation rates (EIR) of the local vector species just one year after the withdrawal of IRS. Parity rate of *An. gambiae* s.l. increased from 28.1% in 2014 to 51.2% in 2015 ($p<0.0001$) after IRS withdrawal. The sporozoite infection rate increased from a level that could not be detected for two consecutive years (2013 and 2014) to 1.10% (4/361 mosquitoes analyzed). Consequently, the EIR increased from undetectable levels in 2013 and 2014 to 14.7 infective bites/man/year in 2015. In Bunkpurugu Yunyoo District, where spraying continued without interruption, EIR declined from 3.3 ib/m/yr in 2014 to 0.82ib/m/yr in 2015. The results from the surveys show that the IRS program maintained low levels of the two most important indicators of malaria transmission: parity and infectivity rates of the malaria vectors. However, there was a significant resurgence following withdrawal of IRS from the area. Epidemiological data is needed to understand the impact of IRS on malaria transmission.

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A COMPARISON OF THE EFFECTIVENESS OF BEHAVIOR CHANGE COMMUNICATION (BCC) PLUS REPAIR KITS AND BCC ALONE IN PROMOTING REPAIR OF LONG-LASTING INSECTICIDAL NETS IN BENIN

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We compared strategies to increase net durability in 2014. Three groups of 300 households (HH) were randomly assigned to two intervention and one control arm. Arm 1 received behavior change communication (BCC) messages; Arm 2 received BCC plus a net repair kit; Arm 3 was the control. Twelve villages in southeastern Benin were enrolled. Community health workers delivered BCC messages about preventing damage to long-lasting insecticidal nets (LLIN) caused by fire or sharp objects, and

promoting repair as soon as holes appeared. Data were collected from all HH at 4-5 month intervals for 20 months. Net damage was measured using the WHO Proportional Hole Index (pHI). At 20 months the overall HH dropout rate was 21% (17% for Arm 1, 23% for Arm 2 and 24% for Arm 3). Only one of five control HH (Arm 3) reported hearing messages about net care or repair. Net attrition (LLIN not available to sleep under) was significantly lower in Arms 1 and 2 (9%), than in Arm 3 (16%) ($p<0.0001$). LLIN use among children under five years was higher among those receiving BCC and repair kits (83%) than those receiving only BCC (73%) ($p=0.02$). Intervention Arms 1 and 2 reported more net use (73% and 83%, respectively) than the control arm (63%) ($p<0.0001$). Frequent LLIN washing (>1 wash/3 months) resulted in reduced net integrity in the control group. Reduced insecticide activity was also more common in the control arm (78%) than Arm 1 (69%) and Arm 2 (56%) ($p<0.0001$). The proportion of nets without holes was significantly higher in Arm 2 (53%) than in Arm 3 (38%) ($p=0.019$), but no difference was observed in the prevalence of holes between Arm 1 (41%) and the control arm (38%). Nets in Arms 1 and 2 showed more signs of repair (57% and 58%, respectively) than controls (22%) ($p<0.0001$). The proportion of nets with large and/or numerous holes (pHI >63) was significantly lower in Arm 1 (13%) and Arm 2 (9%) than in Arm 3 (36%) ($p<0.0001$). All LLIN in all three arms had good insecticide retention measured by x-ray fluorescence and WHO cone test. BCC messaging significantly increased care and repair practices in intervention villages in Benin. Whether these practices can prolong LLIN durability requires further study.

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DRY SEASON MALARIA TRANSMISSION REDUCES THE IMPACT OF SEASONAL INDOOR RESIDUAL SPRAYING IN BENIN

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Indoor residual spraying (IRS) in Benin is based on a single round of spraying to coincide with the annual period of highest transmission (peak vector density). It is assumed that during the dry season, when IRS is not done, vectors should be few and the level of malaria transmission low. In this study, we tested this assumption by measuring the intensity of malaria transmission during the peak transmission and low transmission (dry season periods) using entomologic measures. We assessed *Anopheles* population dynamics over a five year period by measuring human-biting behavior and entomological (*Plasmodium falciparum* sporozoite) inoculation rates during periods when IRS was done and during the dry season when it was not carried out. A total of 3,752 *Anopheles* (*An. gambiae*, *An. coluzzii* and *An. funestus*) were collected. During the period of IRS impact (June-October: rainy season) *An. gambiae* was the most abundant species (87.8% in Atacora and 94.3% in a similar comparison area, not under IRS). In dry season, when IRS insecticidal effect was not operating (November to May), the percentage of *An. gambiae* dropped to approximately 20%, but two other species, *An. coluzzii* and *An. funestus* made up 68.4% and 12%, respectively, of the *Anopheles* caught). More importantly, however, transmission of *P. falciparum*, continued, estimated to be approximately three infective bites per human per month for *An. gambiae* s.s. and one infective bite per human per month for *An.* funestus, which was higher than expected for a period when the most *An. gambiae* s.s. breeding sites were assumed to dry up. The abundance of *An. coluzzii* and *An. funestus* in dry season probably owes its origin to breeding sites maintained by permanent and semi-permanent streams in the Atacora foot hills.

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EFFECT OF IVERMECTIN ON *PLASMODIUM VIVAX* IN ITS INTERACTION WITH *ANOPHELES AQUASALIS*

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The use of insecticide-treated nets and indoor residual insecticides targeting adult mosquito vectors is a key element in malaria control programs. However, mosquito resistance to the insecticides used in these applications threatens malaria control efforts becoming in a major public health issue. Alternative methods like Ivermectin administration to humans has been suggested as a possible vector control to reduce *Plasmodium* transmission. *Anopheles aquasalis* isa competent vector for *P. vivax* and it has been responsible for various malaria outbreaks. This study analyzed the effect of Ivermectin on vector competence of *An. aquasalis* for *P. vivax* using two experimental protocols: (A) One single Ivermectin dose (200 µg/mL) was taken by volunteers and blood samples were drawn at distinct times. *An. aquasalis* was infected by membrane feeding with different concentration of these blood samples mixed with *P. vivax* from malaria patients. Seven days after the infective bloodmeal, the mosquitoes were dissected to check the oocyst presence and the infection rate. (B) Additionally, the *in vitro* effect of the addition of Ivermectin on cultivated *P. vivax* was observed. Ivermectin significantly reduced the proportion of *An. aquasalis* that developed oocysts (40ng/mL concentrationor plasma 4 h, but with the metabolized Ivermectin on 5, 10 and 14 d post-treatment it was not reduced ($p=0.06$; $p=0.91$; $p=0.80$ respectively). *Plasmodium vivax* infection was significantly reduced in the survived *An. aquasalis* that ingested Ivermectinin the 40ng/mL concentration and plasma 4h post-treatment. In the *in vitro* cultures, Ivermectin (plasma 4 h concentration) significantly affected the *P. vivax* asexual development, reducing the number of schizonts (50% of inhibition). In conclusion, Ivermectin reduces the infection rate of *P. vivax* in *An. aquasalis* and increased the mortality of mosquitos. These findings support the idea that Ivermectin is useful to reduce *P. vivax* transmission in endemic areas.

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DETECTION OF *PLASMODIUM FALCIPARUM* INFECTION IN *ANOPHELES SQUAMOSUS* IN AN AREA TARGETED FOR MALARIA ELIMINATION, SOUTHERN ZAMBIA

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Southern Zambia is the focus of strategies to create malaria-free zones. Interventions being rolled out include reactive test and treat strategies ('Step D') and distribution of insecticide-treated bed nets. Step D involves the identification of index cases, i.e. non travelers who test positive for malaria at health facilities, who are subsequently followed up at their homes for malaria screening and treatment of all residents and of neighboring households. In 2015 in Macha, Choma District, mosquitoes were collected monthly by light trap from Step D homesteads, set both indoors next to occupied bed nets and outdoors next to goat enclosures to study vector foraging patterns around clusters of malaria cases. Anopheline mosquitoes were identified to species using molecular methods and *Plasmodium falciparum* infectivity was determined by ELISA and real time qPCR methods. Comparing indoor collections of anophelines from Step D households to those of a random selection of households within the community, species composition was similar with domination of the vector *Anopheles arabiensis*, however household densities were

four fold higher in Step D houses suggesting local and focal transmission. Catches from outdoor traps were nine times greater than indoor collections with more than 60% identified as *An. squamosus*. Analysis of a subset (n=1006) of anophelines were analysed by ELISA for malaria sporozoites. Seven were found positive, of which four were confirmed as harboring parasites by qPCR. All seven specimens were caught outdoors. Six were morphologically identified as *An. squamosus* and one as *An. coustani*. Parasite-positive specimens as well as a subset of *An. squamosus* specimens from either the same study or archive collections underwent sequencing of the mitochondrial COI gene. Maximum parsimony trees indicated presence of at least 2 clades of *An. squamosus* with infectious specimens falling in each clade. The single infectious specimen identified morphologically as *An. coustani* could not be matched to reference sequences. This is the first report from Zambia of infections in *An. squamosus* and from outdoor collections.

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FIELD TESTING OF A PYRETHROID QUANTIFICATION KIT (PQK) IN TANZANIA - AN EASY-TO-USE TOOL FOR MONITORING THE QUALITY OF INDOOR RESIDUAL SPRAY CAMPAIGNS

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Insecticide treated nets (ITN) and indoor residual spraying (IRS) are two of the primary methods of malaria prevention in Africa. In order for these methods to be effective it is essential that adequate concentrations of insecticide are present on nets and wall surfaces to kill mosquitoes. There is no easy assay to quantify insecticide levels without expensive laboratory equipment and procedures. To address this, LSHTM has developed a simple field-applicable kit for monitoring pyrethroid residues on insecticide-treated nets- the Pyrethroid Quanitification Kit (PQK)-which can be adapted to other types of treated surfaces. During the initial trial the PQK kit was calibrated against a variety of sprayed surfaces and with different concentrations of lambdacyhalothrin before being taken into the field. Mosquito cone bioassay was conducted to show whether the surface concentrations of insecticide detected by the PQK were sufficient to kill a susceptible strain of mosquitoes. Houses in six villages were visited 3 months after IRS had been conducted in Muleba, Tanzania. The samples were analysed in the field using a handheld spectrophotometer. In each house, five areas of the wall were examined to give an indication of insecticide distribution and within-wall variation. Results showed that the actual spraying results differed from expectation. Preliminary results showedthat only 28% of houses had all rooms sprayed, leaving 72% of housespartially sprayed, and insecticide concentration varied dramatically across sprayed walls. The PQK is an easy to use quality assurance tool for monitoring of pyrethroid application rates and improving the quality of IRS campaigns.

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A COMPREHENSIVE ACCESS METRIC FOR ESTIMATING THE GAP IN INSECTICIDE TREATED NET USE CONDITIONAL ON ACCESS

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The complement of the proportion of people who use insecticide treated nets (ITNs) out of those who have access is a measure of the behavioural gap (BG) in ITN use. The updated Global Malaria Action Plan's access measure (UGMAPAM) is based on the assumption that two people can sleep under one ITN. However, often ITNs are shared by more than two people, and the number of people using an ITN can be larger than the UGMAPAM (resulting in a use : access ratio larger than one, and consequently a negative BG if not floored at zero), while there may still be people not using ITNs despite having access. The fact that the UGMAPAM-based use : access ratio is not a true proportion makes it unsuitable for standard statistical analyses. For the purpose of estimating the BG, we propose a comprehensive access measure (CAM), counting those who slept under an ITN as having access, as well as those who could have used spare spaces under an ITN, with one spare space for a single-occupied ITN and two spaces for an unoccupied ITN. The use : access ratio with the CAM as denominator is a true proportion, and its complement, the proportion of people who had access to a full person-size space under an ITN but did not use it, is an easy interpretable measure of the BG. We analyzed 85 Demographic and Health Surveys and 20 Multiple Indicator Cluster Surveys with specific information on mosquito nets from 44 countries over 2001-2015. An average of 46.2% (range: 15.1-71.8) of ITN users shared their net among three people or more. Compared to the CAM-based BG, the UGMAPAM-based BG (floored at zero) was on average 8.0 percent-points (range: 0-18.8) smaller, and the difference was largest at intermediate BG. We conclude that the use of the UGMAPAM-based BG has underestimated the potential for ITN use-stimulating interventions such as behavioural change communication and ITN improvements to increase acceptability.

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MALARIA UPSURGE FOLLOWING WITHDRAWAL OF INDOOR RESIDUAL SPRAYING IN NORTHERN UGANDA

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Uganda has registered significant declines in malaria prevalence in the recent past. However, concerns about maintaining the gains made are apparent. Starting 2009, indoor residual spraying (IRS) was implemented in 10 high burden districts in Northern Uganda resulting in suppressed transmission to very low levels. Based on this achievement and the country's deployment of long-lasting insecticidal nets universally in 2013 - 2014, IRS was withdrawn in November 2014. However, in March 2015 routine surveillance showed a marked increase in malaria cases and deaths suggestive of an epidemic in that region. We describe here the investigation and confirmation of the epidemic. Following reported increases in malaria cases, an epidemic preparedness and response team was constituted to investigate the upsurge in affected districts. A review of hospital records and malaria parasite testing of 11,000 blood smears collected between June-August 2015 was done to confirm the malaria case load. Mean indoor resting density of malaria vectors was done for entomological assessment. Reported malaria cases and slide positivity rate (SPR) were compared for the period during and after withdrawal of IRS. Out of 11,000 blood smears examined, 81% were positive for *P. falciparum*. Seventy two percent of hospital admissions were due to confirmed malaria. Based on hospital records, malaria incidence increased from 61 to 142 cases per 1,000 population and SPR from average 11% to 75% [difference 64%, CI:63.7-64.3] $p < 0.001$, before and after IRS withdrawal respectively. Entomological assessment indicated re-bound of vectors with mean indoor resting density of 4 female *Anopheles* mosquitoes per house visited. A dramatic increase in reported malaria cases, an SPR above the established epidemic thresholds confirmed

presence of a malaria epidemic in this region. Indoor Residual Spraying gains are fragile and can potentially be lost in the absence of a clear exit strategy.

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COVERING HOUSE EAVE GAPS AND CEILINGS WITH OLYSET® NET REDUCES RISK OF *PLASMODIUM FALCIPARUM* PARASITE INFECTION AMONG CHILDREN: A CLUSTER RANDOMIZED CONTROLLED TRIAL

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Long-lasting insecticidal bed nets have been widely used for reducing malaria cases. A persisting challenge is how to protect children who do not adhere to net use. This study examined whether covering house eave gaps and ceilings with a fabric made of Olyset®Net (ceiling nets) reduces risk of *Plasmodium falciparum* parasite infection among children under 10 years of age. Bed nets (Olyset®Net) were provided to cover all residents in the study area in western Kenya. Then, the area was divided to eight sub-areas, and four sub-areas were randomly selected for the treatment. Ceiling nets were installed in all houses in the selected sub-areas. The PCR-based pre-intervention infection rate of *P. falciparum* was 68.9%, and reduced to 27.3% (OR: 0.84; p<0.001) in the sub-areas covered with ceiling nets and bed nets. Similarly, the PCR-based infection rate significantly reduced from 60.9% to 44.9% in the sub-areas with bed nets only (OR: 0.94; p<0.001). The post-intervention infection rate in the sub-areas with ceiling nets was significantly lower than that in the sub-areas without them (OR: 0.45; p=0.031). While bed nets reduced risk of *P. falciparum* parasite infection, ceiling nets provided additional protection.

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REPELLENCY OF THREE ESSENTIAL OIL AND MAJOR CONSTITUENTS TO WILD ADULT *ANOPHELES KLEINI*

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Repellency of 20 plant essential oils to malaria main vector in the Republic of Korea (ROK), *Anopheles kleini*, was evaluated using skin direct contact bioassay. *An. kleini* showed the highest repellency to Pelargonium graveolens(Geranium oil)with EC50 value of 0.244 mg/cm2, followed by *Pinus sylvestris* (Pine oil) and *Cinnamomum camphora* (camphora oil) with EC50 values of 0.484 mg/cm2 and 0.862 mg/cm2. The lowest repellency of *An. kleini* was revealed from Clary sage oil with EC50 value of 4.665 mg/cm2. *An. kleini* did not demonstrated any repellency to Lemon, Orange, Neem, Cocount and Olive oil over 20 mg/cm2. Major repellent constituents of Geranium, Pine and Camphora oil were analyzed and identified using Mass-data, GC and GC-Mass. Major constituent of Geranium were β-citronellol (37.0%) and Camphora, 1,8-cineole (35.8%) and Pine, α-terpineol (39.5%). *An. kleini* showed higher repellency to β-citronellol and 1,8-cineole than to DEET and IR3535 and did not showed any repellency to sabinene and γ-eudesmol over 20 mg/cm2. Residual repellent time of 1,8-cineole and β-citronellol were 26 and 41 min, respectively and DEET, 84 min and IR3535, 102 min. In the light of global efforts to reduce the level of highly toxic synthetic repellents, the three essential oils and their major constituents described merit further study as potential biorepellents for the control of *An. kleini* populations .

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PREVALENCE OF SOME ENTEROPATHOGENS AMONG DIARRHOEIC AND APPARENTLY HEALTHY CHILDREN IN EKET AND IBENO, AKWA IBOM STATE, NIGERIA

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In this study, some intestinal bacterial pathogens involved in diarrhoea causation was investigated in Eket and Ibeno between October, 2013 to April, 2014. A total of 150 freshly - voided diarrhoeic samples of children attending Primary Health Care Centre, Eket and General Hospital, Ibeno, and 50 non - diarrhoeic samples were collected which served as controls. Standard bacteriological media and procedures were used in the identification of bacterial isolates. Antibiotic susceptibility test was done by standard procedures.The overall prevalence rates recorded for enteropathogens among children were 74% and 72% in Eket and Ibeno, respectively and the mean prevalence was 73%. Data obtained from the questionnaires given to subjects' mothers for socio - demographic information showed a high prevalence of enteropathogens in the following parameters examined; subjects within the age group of 7 - 12 months, subjects whose source of drinking water was stream, subjects' mothers in the civil service and self - employed groups, exclusively breastfed subjects. A decrease with increase in educational level of subjects' mothers was observed. The bacterial pathogens considered were *Escherichia coli*, Salmonella enteritidis, *Shigella dysenteriae* and Enterobacter species. *Escherichia coli* was the most prevalent with rates of 43.5% and 45% in Eket and Ibeno, respectively. Enteropathogenic *Escherichia coli* (EPEC) O26 and O111 were identified with an overall prevalence of 46.7%. In the antibiotic susceptibility test done, the organisms were mostly susceptibility to Ciprofloxacin and resistant to Cotrimoxazole. The study has revealed that the incidence of enteropathogens in children could be traced primarily to poor personal hygiene and faulty weaning practices. Therefore, a systematic effort to teach nursing mothers and children to practice good personal hygiene are the best approaches to reduction of the scourge of intestinal pathogens.

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DEFINING THE BURDEN AND EPIDEMIOLOGY OF SHIGELLOSIS IN RURAL ASEMBO, WESTERN KENYA, 2007-2014

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Shigella is a leading cause of diarrhea and dysentery in low- and middle-income countries. Population-based data on the Shigella burden in African settings are very limited. We describe the incidence of medically attended shigellosis in a population of ~25,000 who reside ≤5 kilometers from a surveillance clinic in Asembo, rural western Kenya that provides free medical care. From January 1, 2007-December 31, 2014, stools and demographic data were collected from all patients presenting with diarrhea (≥3 loose stools within 24 hours). The specimens were cultured and isolates identified biochemically and confirmed by serotyping. Participants were visited at home biweekly and queried about acute illnesses and care-seeking. We calculated the incidence of Shigella infections per 1000 person-year-observation (pyo); we adjusted for the proportion of diarrhea cases with no stool sample, and for the proportion of diarrhea cases reported during household visits that sought care at a health facility other than the surveillance clinic. A total of 11,775 cases of diarrhea presented to the clinic during the study period. Of these a stool specimen was collected from 1,658 (14%), and Shigella was isolated from 418 (25%). The overall adjusted incidence rate was 11.1/1000 pyo;

among those aged <5 and ≥5 years, it was 9.1 and 11.2 per 1000 pyo respectively. Peaks in incidence were seen in young children (<12months 15.0/1000 pyo, 12-23 months 12.7/1000 pyo) and older adults (35-49 years 19.0/1000 pyo, ≥50 years 23.7/1000 pyo). The annual adjusted incidence was highest in 2011 (13.8/1000 pyo) and lowest in 2013 (7.4/1000 pyo). *Shigella* species isolated included: *S. flexneri* 251 (60%), *S. dysenteriae* 57 (14%), *S. sonnei* 42 (10%), *S. boydii* 39 (9%) and non-typeable 29 (7%). We found an important burden of *Shigella*, particularly *S. flexneri*, among children and adults, with both age extremes most heavily affected. Prevention strategies, such as access to safe water and sanitation and future vaccines, should address disease burden across all age groups.

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RISK FACTORS ASSOCIATED WITH TYPICAL ENTEROPATHOGENIC *ESCHERICHIA COLI* INFECTION AMONG CHILDREN <5 YEARS OLD WITH MODERATE-TO-SEVERE DIARRHEA IN RURAL WESTERN KENYA, 2008-2012

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Typical enteropathogenic *Escherichia coli* (tEPEC) infection is a major cause of diarrhea and contributor to mortality in children <2 years old in developing countries. Limited data are available on risk factors associated with tEPEC infection in young children. Data were analyzed from the Global Enteric Multicenter Study (GEMS) examining children <5 years old seeking care for moderate-to-severe diarrhea (MSD) in Siaya County, Kenya. MSD was defined as ≥3 loose stools in the previous 24 hours, with onset in the previous 7 days, and ≥1 of the following characteristics: loss of skin turgor, sunken eyes, dysentery, required IV rehydration or hospitalization. Stool specimens were tested for enteric pathogens, including by multiplex PCR for the gene targets of tEPEC (i.e. positive for both *eae* and *bfpA*). Demographic, clinical, and anthropometric data were collected at enrollment and at a ~60-day follow-up visit. To examine factors associated with tEPEC among MSD cases, a multivariable logistic regression model was constructed. Linear regression was used to assess linear growth faltering. Of the 1,778 cases enrolled between Jan 31, 2008 and Sep 30, 2012, 135 (7.6%) children tested positive for tEPEC. Among these, 85 (63%) had ≥1 additional enteric pathogen. Overall, 65% of tEPEC cases were infants 0-11 months old. There was a 3-fold greater odds of identifying tEPEC among infant MSD cases than among children in older age groups (adjusted odds ratio [aOR] 3.02, 95% CI: 1.73-5.24). The odds of tEPEC were higher for MSD cases with loss of skin turgor (aOR 2.86, 95% CI: 1.08-4.82) and convulsions (aOR 2.95, 95% CI: 1.17-7.45), compared to those without. Infant cases with tEPEC compared to those without were associated with linear growth faltering (p=0.002) between enrollment and follow-up. Among 36 infant MSD cases who died, 9 (25.0%) had tEPEC compared with 77 (10.8%) of 764 infants who survived (OR 2.98, 95% CI: 1.35-6.56). Typical EPEC was a significant contributor to morbidity and mortality among infants with MSD in rural Kenya. Interventions aimed at reducing the burden of tEPEC and its sequelae should be urgently investigated, prioritized and implemented.

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CAUSES AND CONSEQUENCES OF *GIARDIA* INFECTION IN THE FIRST TWO YEARS OF LIFE IN THE MAL-ED BIRTH COHORT

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Giardia is a common enteropathogen detected in both diarrheal and non-diarrheal stools among children in low-resource settings. We describe the epidemiology of *Giardia* in the first two years of life in MAL-ED, a multisite birth cohort study. From 2,089 children, 34,916 stools collected during monthly surveillance and diarrhea were tested for *Giardia* by enzyme immunoassay. We quantified the risk of *Giardia* acquisition, identified risk factors, and assessed the associations with micronutrients, gut biomarkers, diarrheal risk, and growth using multiple linear regression with general estimating equations. Incidence of at least one *Giardia* detection varied by site, from 37.7% in Brazil to 96.4% in Pakistan, and was more common in the second year of life. Exclusive breastfeeding (hazard ratio (HR) for first *Giardia* detection in monthly surveillance stools: 0.46, 95% CI: 0.28, 0.75), higher socioeconomic status (HR: 0.74, 95% CI: 0.56, 0.97) and recent metronidazole treatment (risk ratio for any surveillance stool detection: 0.69, 95% CI: 0.56, 0.84) were protective. Associations with hygiene and environmental risk factors suggest that the fecal-oral and waterborne routes may both be important modes of transmission. *Giardia* persistence (2+ consecutive detections) in the first 6 months of life was associated with reduced subsequent diarrheal rates in Pakistan, but not in any other site. *Giardia* was also associated with an increase of 0.25 (95% CI: 0.10, 0.40) in lactulose-mannitol ratio. Across sites, *Giardia* persistence in the first 6 months was associated with -0.29 z-score (95% CI: -0.53, -0.05) deficit in weight and -0.29 z-score (-0.64, 0.07) deficit in length. Because detection of *Giardia* in non-diarrheal stools was common, attributing diarrheal etiology to *Giardia* may often be inappropriate. However even in the absence of diarrhea, *Giardia* infection, especially when persistent in the first 6 months, may impact child development through stunted growth. Interventions to interrupt transmission may better reduce the burden and impact of *Giardia* than mass drug administration since metronidazole only transiently reduced detection.

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DETERMINANTS OF HEALTH AND PREVALENCE OF INFECTIOUS GASTROINTESTINAL DISEASE IN CHILDREN LIVING IN THE PERUVIAN AMAZON RIVER BASIN

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Diarrheal disease continues to be a leading cause of childhood morbidity and mortality in resource-poor settings, lacking proper water sanitation infrastructure. The community of Belen in Iquitos, Peru experiences intermittent seasonal flooding from the Ataya river, a tributary of the Amazon River. This project studied the differences in prevalence of various enteric pathogens as well as qualitative differences between "high" and "low" zones. Zone distinctions were based on levels of recent seasonal flooding, with low zones experiencing flooding throughout the majority of the year. Households involved in the study completed a questionnaire in Spanish and water was collected from the home's source and storage for

analysis of fecal coliforms and the presence of chlorine. Additionally, stool samples from a child under the age of five were obtained and screened for presence of bacteria and parasites. Samples were collected from 232 households. 100 households were determined to be in the low zone and the remaining 132 in the high zone. The overall prevalence of enteric pathogens in the high zone was 50% (66/132), compared to the 70% (70/100) prevalence in the low zone (p=0.0022). In both source and stored water, there was a higher rate of coliform contamination in the low zone (both p<0.0001). In addition, there was a difference in education levels between high and low zones (p<0.0001). Distinct educational differences between the high and low zones were observed in Belen that were associated with the presence of fecal coliforms in source and stored water and enteric pathogen prevalence. Overall, households in the low zone had lower education levels and experienced higher coliform contamination of their water and higher prevalence of enteric pathogens in stool samples. Additional studies or analysis will include sources of contamination of household water with respect to previously identified geographical differences.

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THE SHIFTING PATTERN OF *VIBRIO CHOLERAE* O1 SEROTYPES OVER A PERIOD FROM 1996 TO 2016 IN 2016 IN BANGLADESH

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Vibrio cholerae O1, the primary cause of epidemic cholera, has two biotypes, El Tor and Classical, and two major serotypes, Ogawa and Inaba. They have distinct phenotypes and differ with respect to the severity of the disease they can cause, the ability to survive outside the human host, and the seasonal pattern of infection. The changes of these serotypes with time and associated immune response in patients is important to understand the pathogenesis of cholera. We therefore followed the data for cholera for the last 20 years to determine the variability of the serotypes and its impact on demographic characteristics, clinical disease and on immune responses generated in cholera patients attending the diarrheal hospital at the icddr,b in Dhaka, Bangladesh. We analysed data from cholera patients at the icddr,b hospital from 1996 to 2016. Based on this data, we observed that the Ogawa serotype dominated during the period from 1996 to 1999 (80-99%), while the Inaba dominated from 2000 to 2002 (63-85%). From 2003 to 2007 we saw an alternative shift from Ogawa to Inaba (65% Ogawa, 74% Inaba,71% Ogawa, 60% Inaba, 52% Ogawa). However, in 2007 both serotypes were prevalent. However, following this cholera due to the Ogawa serotype started to increase and peaked in 2009-2010 (95-99%) and remained prevalent until December 2015 (89%). Interestingly, after 8 years of prominence of the Ogawa serotype, hospitalization of patients with *V. cholerae* O1 Inaba starts to increase in 2016 (January to March 2016) and reached a predominance of 92%. The cholera vaccine studies that we have been conducting in the urban slum of Dhaka city from the year 2011 to 2016 also enabled us to track this shift in 2016 to the *V. cholerae* O1 Inaba serotype. We found patients infected with Ogawa serotype were younger, presented with shorter duration of diarrhoea and frequent abdominal pain, vomiting and need for intravenous fluids though they had similar status of dehydration. We are also analyzing the immunological responses in the host as well as the genotypic and phenotypic characteristics of *V. cholerae* O1 strains isolated during this shift to the *V. cholerae* O1 Inaba serotype.

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EFFECT OF A BIVALENT, KILLED, WHOLE CELL ORAL CHOLERA VACCINE ON PREGNANCY OUTCOME IN BANGLADESH

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Evidence suggests that cholera during pregnancy has adverse effects on pregnancy outcome. A low cost oral cholera vaccine (OCV; Shanchol) appears to be an effective intervention to prevent cholera incidence. However, the vaccine is not recommended for pregnant women possibly due to lack of evidence of safety. In an efficacy study of a single-dose OCV in an urban slum of Dhaka city, some pregnant women took the vaccine unknowing of their pregnancy status. We therefore carried out this study to determine if the OCV is safe to administer during pregnancy. The objective of the study was to compare the differences in adverse pregnancy outcomes between the vaccine and placebo groups. A pregnancy screening visit among women of reproductive age (15-49 yrs) was conducted two months after the mass vaccination. We interviewed pregnant women whose pregnancy ended before the screening visit and collected necessary information related to their pregnancy outcome retrospectively. For women whose pregnancy was ongoing at the time of the screening visit, were followed up by visits until the pregnancy outcome occurred. The screening visit was conducted on 71,202 women of reproductive age and identified 1323 pregnancies: of these 550 were exposed to OCV during pregnancy and 773 exposed to OCV right before conception. Of 550 women, 405 had pregnancy outcome after the screening visit and were included in the primary analysis. We identified 7 (3.4%) adverse outcome from vaccine arm and 6 (3.0%) from placebo arm. OCV-exposure during pregnancy had no significant effect on adverse pregnancy outcome (Adj. OR: 1.11, 95% CI: 0.36, 3.53). We identified 7 (3.6%) preterm delivery from vaccine arm and 12 (6.1%) from placebo arm. We also found a non-significant protective effect of OCV on low birth weight. This study gave us no evidence of harmful effect on pregnancy outcome due to OCV exposure during pregnancy. The information from this study gives policy makers evidence to create awareness for offering OCV during pregnancy. This will be useful in reducing the number of cholera during pregnancy and also reduce adverse pregnancy outcome.

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ENHANCING DISTRICT-LEVEL CAPACITY TO INVESTIGATE AND RESPOND TO ACUTE DIARRHEAL DISEASE OUTBREAKS - TAMIL NADU, INDIA, 2013-2015

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Acute diarrheal diseases (ADD) account for 46% of reported outbreaks in India. Effective district-level response is constrained by lack of specimen collection, limited laboratory capacity, and incomplete epidemiologic investigation. In October 2013, Tamil Nadu introduced standard investigation tools and initiated focused training to strengthen ADD

outbreak response in two pilot districts, Cuddalore and Kanchipuram (population 2.6 million and 4.0 million, respectively). We reviewed investigation reports to characterize outbreak response over the two-year pilot period. We abstracted standard data for all ADD outbreak investigations conducted in both districts between November 2013-2015 to determine timeliness of response, proficiency in specimen collection and testing, completeness of epidemiologic investigation, and identification of outbreak source. Testing for *Salmonella*, *Shigella*, and *Vibrio* species was conducted at the district microbiology laboratory. In the two-year period, 17 ADD outbreaks were investigated in the two districts. District teams detected and responded to all outbreaks within 24 hours; patient specimens were collected in 13 (76%) outbreaks; bacterial etiology (*Vibrio cholerae* and *Shigella sonnei*) was confirmed in two (12%). Systematic case ascertainment was conducted in 13 (76%); an epidemic curve was developed in 8 (47%), and standard food-history questionnaires were utilized in 4 (29%). A case-control or cohort study was conducted in 5 (29%) investigations. A specific water (n=3) or food (n=7; including shellfish=2, fish=1, rice dishes=4) source was identified in 10 (59%) outbreaks. Over two years, pilot districts demonstrated the ability to lead timely and complete detection and response to ADD outbreaks. Systematic epidemiologic investigation methods supported the identification of food or water sources of illness in the majority of outbreaks. Focused efforts to strengthen district laboratory diagnostic and surveillance capacity will further enhance the ability to detect outbreak etiologies and contribute to global health security in India.

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INCREASING ANTI-ADHESIN IMMUNE RESPONSES BY MODIFYING FIMBRIAL GENE STEM-LOOP STRUCTURE IN LIVE ATTENUATED SHIGELLA/ETEC VACCINES

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Antibodies blocking the function of the adhesin protein of ETEC fimbriae are likely to be effective at preventing ETEC induced diarrheal disease. A way to increase the ratio of tip-adhesins to stem-proteins is desirable for live attenuated vaccines, not only to increase the amount of tip adhesin molecules presented to the vaccinee's immune system, but also to decrease the metabolic strain on the live attenuated vaccine candidate. Using RNA modeling in Geneious software we examined 15 ETEC operons of Chaperone-Usher (CU) type fimbriae and searched for genetic features controlling the production of tip and stem proteins. A stem-loop region was found to follow the stem-encoding genes in all fimbrial operons. We hypothesized that decreasing the stem-loop (SL) region would lead to decreased production of stem proteins, and therefore shorter fimbriae. Operon modification was performed by site-directed-mutagenesis in SL regions in CFA/I and CS5 operons cloned in plasmids and transformed into the live attenuated Shigella strain CVD 1208S. Clones CFA/I SLD1 and CS5 SLD6 with modified SL regions were examined with electron microscopy using negative staining. The lengths of fimbriae were measured in these and in non-modified clones using ImageJ open source software. Guinea pigs were immunized with the CVD 1208S-expressing CS5 SLD6 construct and serum and tears were analysed by ELISA for IgG and IgA responses the CS5 and Shigella LPS respectively. Clone CS5 SLD6 had mean fimbrial lengths of 96.5µm, while the wild type operon mean length was 306.7µm, $p<0.001$. Clone CFA/I SLD1 had a mean fimbrial length of 77.0 µm, while the wild type operon mean fimbrial length was 613.5 µm, $p<0.001$. In three guinea pigs immunised with CVD 1208S(CS5 SLD6) we found strong increases in IgG and IgA antibody towards both Shigella LPS and ETEC CS5. Modifying the stem-loop structure in ETEC fimbrial operons can be used to increase the tip-to stem protein ratio in live attenuated vaccines. The method is also likely to be applicable to other CU fimbriae. Further characterization of the CFA/I and CS5 short fimbriae live vaccine candidates are ongoing, and results will be presented.

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DIARRHEAGENIC *ESCHERICHIA COLI*: PREVALENCE AND PATHOTYPE DISTRIBUTION IN CHILDREN FROM PERUVIAN RURAL COMMUNITIES

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Diarrheagenic *Escherichia coli* (DEC) are common pathogens of childhood gastrointestinal infections worldwide. To date, research tracking DEC has mainly been completed in urban areas. This study aimed to determine the prevalence and pathotype distribution of DEC strains in children from rural Peruvian communities and to establish their association with malnutrition. In this prospective cohort, 93 children aged 6 to 13 months from rural communities of Urubamba (Andes) and Moyobamba (jungle) were followed for 6 months. Diarrheal and control stool samples were analyzed using Multiplex Real-Time Polymerase Chain Reaction (mRT-PCR) to identify the presence and virulence genes of DEC strains. A total of 820 specimens were collected, of which 46 (5.6%) were diarrheal and 774 (94.4%) were non-diarrheal. A median of 10 stool samples per child were collected. The overall isolation rate of DEC was 43.0% (352/820). Enteroaggregative (EAEC, 20.4%), Enteropathogenic (EPEC, 14.2%) and Diffusely aggregative *E. coli* (DAEC, 11.0%) were the most prevalent pathotypes. EAEC was more frequently found in Moyobamba samples ($p < 0.01$). EPEC was the only strain significantly more frequent in diarrheal than asymptomatic control samples ($p < 0.01$). DEC strains were more prevalent among younger children (aged 6-12 months, $p < 0.05$). A decline in Height-for-age Z-score (HAZ) was observed in 75.7% of children who completed follow-up (74/93). EAEC was more frequently isolated among children who had a greater HAZ decline ($p < 0.05$). Compared to periurban coastal areas, DEC strains were more frequently found in stool samples from children in rural communities of the highlands and jungle. Additionally, children with a greater decline in their growth rate had higher EAEC isolation rates, highlighting the importance of this pathogen in child malnutrition.

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BURDEN OF CHOLERA IN THE WHO EASTERN MEDITERRANEAN REGION (EMR): A MAPPING EXERCISE

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Cholera is a persistent public health burden in the WHO Eastern Mediterranean Region, but the geographical distribution of risk in the region is not well characterized. We conducted an assessment of the region's cholera risk in collaboration with the WHO. Cholera incidence data at the lowest available spatial and temporal level between 2005-2015 were obtained from Ministry of Health focal points in 8 countries: Afghanistan, Iran, Iraq, Pakistan, Somalia, Sudan, Syria, and Yemen. A literature review of cholera incidence was done to bolster data quality. For each country, we searched PubMed for "cholera" and the country name, restricted to January 1, 2005-October 31, 2015. A similar search of Index Medicus for the Eastern Mediterranean Region was conducted to retrieve regional publications not indexed internationally. A search of ProMED cholera reports for each country from January 1, 2005 was also conducted. Population data were obtained from the WorldPop project. Hierarchical models incorporating aggregated counts at different spatial scales were used to estimate cumulative incidence. Country-specific maps of 5-year cumulative incidence were created. Based upon the received cholera surveillance data, a total of 850,869 cases of acute watery diarrhea/suspected cholera were reported, including 3,037 confirmations and 2,679 deaths. There was notable variability in the quality, completeness and type of surveillance data received, both in terms of

geographical resolution (district level: Afghanistan, Pakistan, Sudan (2006 only), Iraq (2015 only), and Yemen; province level: Iran, Syria, Yemen; and national level: Somalia) and time period covered. Afghanistan, Pakistan and Somalia experienced seasonal outbreaks associated with the summer months. For countries with district-level data, outbreak severity varied, with the highest case fatalities observed in Sudan and Somalia. The results offer a preliminary characterization of cholera risk in 8 EMR countries. The identification of hotspots can inform targeted prevention and control efforts, including oral cholera vaccine use and water, sanitation and hygiene strategies.

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UNDERSTANDING HOW THE FEEDBACK BETWEEN DIARRHEAL DISEASE AND MALNUTRITION IMPACTS THE DYNAMICS OF ENTERIC PATHOGEN TRANSMISSION: A MATHEMATICAL MODELING APPROACH

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There is growing concern that environmental exposure to enteric pathogens influences long-term malnutrition-related morbidities- such as growth faltering, cognitive development, and chronic inflammation- among children under five in the developed world. Indeed, a dangerous feedback loop exists between infection and nutrition. This feedback-loop is influenced by interacting transmission pathways: nutritional status impacts susceptibility to infection, and diarrheal disease impacts absorption of nutrients to influence overall nutritional status. Thus, use of standard public health tools, such as regression analyses, to study this phenomenon violate assumptions of independence and provide little insight into the system. Rather, in order to appropriately assess the interconnectedness of infection and nutrition pathways a systems-based analysis is required. We use a stratified compartmental model, based on ordinary differential equations (ODE), to understand the mechanisms through which environmental-mediated enteric pathogens transmission is influenced by a child's nutritional status. This model accounts for subclinical and clinical infection states with diarrhea causing enteric pathogens stratified by malnourished and well-nourished children. Where appropriate, bidirectional transmission between nutritional states may occur. Model parameters were identified using enteric pathogen transmission rates as described in the literature. Through use of this model we present a holistic understanding of mechanisms by which environmental enteric dysfunction (EED) may be occurring at the community-level, highlighting potential opportunities for intervention.

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EXPLORING HUMAN GUT MICROBIOTA DIVERSITY ACROSS A RURAL TO URBAN GRADIENT IN ECUADOR AND THEIR RESPONSE TO DIARRHEAL INFECTIONS

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The gut microbiota plays a key role in health and prevention of invasion by pathogens. Environmental factors as well as host genetics and physiology shape the gut microbiota composition. Previous studies have reported that urban lifestyles impact the gut microbiota structure, revealing higher fecal bacterial diversity in less industrialized compared to industrialized settings. In this study, we sought to understand how geographical factors, including access to clean water and sanitation facilities, influence the signature of commensal gut microbiota in healthy individuals sampled as part of a case control study of diarrhea in four sites along a rural to urban gradient in Ecuador. Because diarrheal diseases are an important global health concern mainly in developing countries and little is known about the protective role of microbial diversity during diarrhea infection, we also evaluated the response of the gut microbiota during acute diarrheal disease (ADD). Preliminary taxonomic surveys based on 16S rRNA gene sequences in a group of 13 individuals living across a gradient of remoteness in Northern Ecuador showed that non-ADD (healthy) samples from individuals living in remote villages (rural areas) presented higher OTU richness than those living close to the main city. The estimated number of bacterial species in ADD samples was significantly decreased upon infection (paired t-test, $p = 0.01$). Based on these promising results, we are currently profiling the gut microbiota of 120 fecal samples obtained from 60 individuals living along a more extensive urban-rural gradient and we will report on the results of this analysis. This study combines the effects of enteric infection and geographical factors on the gut microbiome into the same analysis to gain a better understanding on how resilience and geography modulate the gut microbial response during an acute infection.

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THE USE OF ZINC FOR TREATMENT OF CHILDHOOD DIARRHEA IN RURAL WESTERN KENYA, 2010-2014

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Diarrhea is a leading cause of morbidity and mortality among children globally. The World Health Organization Integrated Management of Childhood Illness recommends zinc and oral rehydration solution (ORS) for treatment of all childhood diarrhea irrespective of concurrent symptoms or diagnoses. ORS has been used for decades while the recommendation for zinc in Kenya was implemented in March 2010. Limited data are available on the uptake of zinc for diarrhea management. From June 2010 to May 2014 we examined factors associated with use of zinc among children aged <5 years with medically-attended diarrhea within a population-based infectious disease surveillance platform in rural western Kenya (population <5 years ~4,200). Participants received free care at a study clinic where history of illness, signs/symptoms, diagnosis and management were captured in a structured questionnaire. Diarrhea was defined as ≥3 loose stools in 24 hours. Overall 1,561 cases of diarrhea among 1,123 children were managed at the clinic; 870 (56%) cases were treated with both zinc and ORS, 44 (3%) cases received zinc without ORS, and 657 (41%) cases received no zinc. Factors positively associated with use of zinc included a history of vomiting everything (OR 1.4, 95% CI 1.1-1.8), sunken eyes (OR 2.3, 95% CI 1.4-3.9), unable to feed/ breastfeed (OR 2.6, 95% CI 1.2-5.6) and treatment with ORS (OR 19.7, 95% CI 13.6-28.5). Children aged ≥24 months were less likely to receive zinc compared to children aged <24 months (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.5-0.8). Other factors negatively associated included mucus in diarrhea (OR 0.7, 95%CI 0.6-0.9), malaria diagnosis (OR 0.5, 95%CI 0.3-0.9), treatment with antibiotics (OR 0.3, 95%CI 0.2-0.4) and anti-malarials (OR 0.5, 95%CI 0.3-0.9). Overall the use of zinc for diarrhea management was low. Young children at risk for dehydration are more likely to receive zinc. However clinicians seem to be underutilizing zinc for older children and those with a concurrent clinical diagnosis such as malaria. Further training of health care workers on recommendations for zinc use is needed.

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DECREASED VIRULENCE ASSOCIATED WITH INCREASE EARLY PRO-INFLAMMATORY CYTOKINE INDUCTION BY MYCOBACTERIUM AFRICANUM INFECTED IN MATURE HUMAN MONOCYTE-DERIVED MACROPHAGES

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Mycobacterium africanum (MAF) having been sub-divided into MAF West African 1 (MAF1) (Lineage 5) and MAF West African 2 (MAF2) (Lineage 6), are 2 distinct phylogenetical lineages within Mycobacterium tuberculosis complex (MTBC) and together with Mycobacterium tuberculosis *sensu stricto* (MTBss) (Lineage 4) are the cause of human tuberculosis (TB) in West Africa. However within central West Africa, Ghana represent one of the few countries (Sierra Leone, Ivory Coast and Benin) that are known to have both distinct phylogenetic lineages of MAF. Thus there is little or no knowledge available as to whether their genetic diversity may have a significant variation in terms of virulence in a host-pathogen interaction compared to MTBss.Strains of Lineage 5 and Lineage 6 circulating in South-Western Ghana as well as a comparator Lineage 4 (Cameroon sub-lineage) were identified. We assessed two virulence associated characteristics: mycobacterial growth in mature human monocyte-derived macrophages (MDM) and early pro-inflammatory cytokine induction from 4hrs to 72hrs.In MDM, Lineage 5 strains grew significantly slower than Lineage 4 strains from 24hrs to 72hrs (p&lt0.05). Similarly Lineage 6 strains also grew significantly slower than Lineage 4 strains over the same time period (p&lt0.05). In contrast the mean doubling time of Lineage 5 strains was significantly higher than Lineage 4 strains (p&lt0.05) at 72hrs. Likewise Lineage 6 strains were significantly higher than Lineage 4 strains (p&lt0.05). Lineage 5 strains induced higher levels of early pro-inflammatory cytokines (TNF-α, IL-6 and IL-12p70) than Lineage 4 strains from 24hrs to 72hrs (p&lt0.05). Similarly Lineage 6 strains also induced higher levels of pro-inflammatory cytokines than Lineage 4 strains over the same time period (p&lt0.05).The data shows MAF had a low intracellular growth rate and a higher doubling time in MDM. Likewise MAF induced hyper-inflammatory response thereby inducing a 'slow growth' phenotype highlighting the point that MAF indeed has lower virulence and longer latency leading to slower progression to active disease in the host.

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ANTIBIOTIC RESISTANCE PATTERNS OF COMMON GRAM-NEGATIVE UROPATHOGENS IN ST. PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE, ETHIOPIA

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The resistance of bacteria causing urinary tract infection (UTI) to commonly prescribed antibiotics is increasing both in developing as well as in developed countries. Resistance has emerged even to more potent antimicrobial agents. The study was undertaken to report the last three year antibiotic resistance pattern among common bacterial uropathogens in St.paul's Hospital Millennium Medical College. A total of 2544 urine samples were processed in the last three years starting from September 2012 to 2015. Inoculation was performed onto blood agar and MacConkey agar symoultaniously. Significant bacteriuia was considered with colony counts greater than 105cfu/ml, for a single isolated bacterium. Isolated organisms were identified by conventional biochemical methods. Antibiotic susceptibility was done by Kirby Bauer disk diffusion method. Data entry and analysis was done using SPSSv20. Of the total 2544 samples, 569(22.4%) showed significant growth. Gram negative organisms totaled 508(20.0%), and 61(2.4%) isolates were gram positive. The most frequently isolated gram negative bacterium was *E. coli* followed by *Proteus* and *Klebsiella* spp. 305 (12.5%), 102(4.0%), and 42(1.7%) respectively. Between 2012 and 2013, the resistance rate to Tetracyclin, Ampicilin, Amoxycilin, and Nalidixic Acid was reported as 69%, 64% and 67% respectively. In 2014, the study showed that resistance pattern for all except to tetracycline becomes increased 65%, 78% and 78%. In 2015, however, there was no a single organism which is sensitive to the above listed drugs. The study also showed an emerging resistance to Ciprofloxacilin and Ceftriaxone especially for common gram-negative bacteria. There was relatively low resistance rate to Nitrofurantoin, Gentamycin, and Trimethoprim-Sulfamethoxazole throughout the years. In conclusion, in this study setting resistant rate to Tetracyclin, Ampicilin, Amoxycilin, and Nalidixic Acid were high. Increasing antibiotic resistance trends indicate that it is imperative to rationalize the use of antimicrobials in the community and also use these conservatively.

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FIVE-YEAR SURVEILLANCE OF DIPHTHERIA OUTBREAK IN INDONESIA

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Diphtheria outbreak has become a major problem in Indonesia since 2011. East Java province in Java Island is the most severely affected area. The objective of this study is to analyze the five-year (2011-2015) surveillance report of diphtheria outbreak in East Java Indonesia. This study was based on surveillance data collected at East Java Provincial Health Office from all districts since January 2011 until December 2015. The data came from the district and provincial hospitals, the local health officers, the family of the patients, and the contacts. Microbiology data were collected from one international standard diphtheria laboratory in Surabaya. Here are the results. For five years period since 2011, there were 3004 cases reported from 38 districts (100%), with the peak at 2012 (955 cases). Based on WHO data, this number was the second rank in the world after India. The case fatality rate was 3.4% (103 patients). Male (1607, 53.4%) slightly outnumbered female. Although most patients were below 15 years old (2111, 70.2%), the trend showed the increasing proportion of adults. In 2012, based on the immunization status, the percentage of unimmunized patients, partially immunized, and completely immunized by age were 39%, 49.3%, and 11.7%, respectively. Among those deceased, the youngest and oldest age were 11 month and 70 years, respectively. Only 187 nasal and throat swab specimen were positive for toxigenic *Corynebacterium diphtheriae*. Despite many efforts such as multiple outbreak response immunization (ORI) especially in 2011-2013 this outbreak could not be stopped. As the conclusion, for five years since 2011 there was a diphtheria outbreak in East Java Indonesia. The highest number of patient was in 2012. Most of the patients were not completely immunized. The positivity rate of microbiology culture was low. Many actions in affected area has not been enough to stop the problem.

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TRENDS OF SEVERITY AND OUTCOMES OF PATIENTS WITH PNEUMOCOCCAL PNEUMONIA IN RELATION TO SEASONALITY IN NORTHERN AND SOUTHERN HEMISPHERES

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Despite efficacious antibiotics and vaccines, pneumococcal pneumonia remains a major cause of morbidity and mortality. Incidence of invasive

pneumococcal disease demonstrates a distinct seasonal course in temperate climates, with infection incidence peaking in winter months, the forces which drive this seasonality remain poorly understood. Understanding the trends of invasive pneumococcal pneumonia can aid prevention of pneumococcal pneumonia mortality, which has been reported as upwards to 60% in susceptible populations. We investigated the trends and outcomes of patients with invasive pneumococcal pneumonia in relation to seasonality in the northern and southern hemispheres using data from the Community Acquired Pneumonia Organization (CAPO) databas, an international database of confirmed community-acquired pneumonia cases. Cases of blood cultures positive Streptococcus pneumoniae from multiple sites from both northern and southern hemispheres were included in the anyalsis. Cases from sites with tropical climates were excluded. Prevalence by season was analyzed by chi square testing. Mortality by season was analyzed by multivariable logistic regression, adjusting for pneumonia severity index score, ICU admission, history of chronic obstructive pulmonary disease, and pneumococcal bacteremia. Time to clinical stability and length of hospital stay were analyzed using Kaplan Meier survival curves. Of 4,507 cases of pneumococcal pneumonia, 425 cases met the inclusion criteria. Winter, spring, summer, and fall accounted for 36%, 29%, 9%, and 26% of the cases, respectively. There was a significant decrease in the incidence of invasive pneumococcal pneumonia during the summer ($p<0.001$). Of the 425 cases, 317 (75%) occurred in the northern hemispheres and 108 (25%) in the southern hemisphere. There was no significant difference in mortality, time to clinical stability, or length of hospital stay between these two groups. We found that incidence of pneumococcal pneumonia exhibited a marked seasonality in both hemispheres. However, we found no association between clinical outcome and season of the year.

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MOLECULAR-BASED ASSAYS REVEAL *STREPTOCOCCUS PNEUMONIAE* AS THE LEAD ETIOLOGICAL AGENT IN THE ONGOING MENINGITIS EPIDEMIC IN GHANA

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Like most other countries within the meningitis belt, Ghana experiences sporadic outbreaks of bacterial meningitis frequently; however, the current epidemic in Ghana has received significant impact and media attention. In response to the current bacterial meningitis epidemic in Ghana, rapid diagnostic test kits such as Pastorex, a family of rapid, latex agglutination test and Gram stain are used for detecting meningitis within affected health facilities. However, these tests fail to identify the serotype of the bacteria causing the infection, which is critical to initiating population-level interventions such as vaccination. We therefore aimed to use molecular techniques to aid in the characterization of suspected agents responsible for the current epidemic of meningitis in Ghana. To determine the prevalence and etiology of meningitis, we investigated cerebrospinal fluid (CSF) specimen from 161 individuals suspected of meningitis using standard microbiological methods and a Fast Track Diagnostics (FTD, Luxemburg) real time multiplex polymerase chain reaction (PCR) assay. This multiplex PCR assay consists of primer/probe mix and allows simultaneous detection of N. meningitidis, S. pneumoniae and H. influenzae. In all, 93.3% (148/161) of the cases were from the Brong-Ahafo region, while the remaining were from Greater Accra and Ashanti regions. In total, 53% (85/161) were female with median age of 21 (0.3 - 83 years) for both sexes. A total, 48% (77/161) of the patients were positive for bacterial meningitis; 73% (56/77) were *Streptococcus pneumoniae*, 26% (20/77) were *Neisseria meningitidis,* while 1% (1/77) was positive for *Haemophilus influenzae*. Interestingly, 2.6% (2/77) patients were co-infected with both S. pneumoniae and *N. meningitidis*. PCR-based assay implicates S. pneumoniae as the principal etiologic agent followed by *N. meningitidis* in the ongoing meningitis epidemic in Ghana. In addition to providing necessary logistics and other interventional measures, we highly recommend existing research institutions and referral hospitals within the affected regions should be equipped with molecular based-capacities.

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THE MOLECULAR EPIDEMIOLOGY OF *STAPHYLOCOCCUS AUREUS* SKIN AND SOFT TISSUE INFECTIONS IN THE LAO PEOPLE'S DEMOCRATIC REPUBLIC

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This is the first report of the molecular epidemiology of *Staphylococcus aureus* from skin and soft tissue infections (SSTI) in Laos. Neighbouring countries report high MRSA rates but these are rare in Laos. We selected a randomized sample of 96 *S. aureus* isolates from SSTI samples received at Mahosot Hospital Microbiology Laboratory, Vientiane, between July 2012 - June 2014, including representation from 7 referral sites. All isolates underwent susceptibility testing by CLSI methods, *spa* typing and DNA microarray analysis (Alere Technologies). Whole genome sequencing was performed for rarely described lineages. 43 *spa* types, representing 17 different lineages, were identified. Median age was 19.5 years (IQR 2-48.5 years); 52% were female. The dominant lineage was CC121 (n=39; 41%): all but one encoded Panton-Valentine leukocidin (PVL) and 49% (n=19) were recovered from children aged <5 years. 58% of all isolates (n=56) encoded PVL (representing 6 lineages); half of these (28/56) had abscesses; 3 had positive blood cultures. *S. argenteus* (part of the *S. aureus*-related complex) was identified in 6 (6%) cases; mostly adults >50 years and diabetics. 6 isolates (6%) belonged to a rare lineage, ST2885, with 3 possibly associated with cross-infection in a paediatric intensive care unit. One previously undescribed strain was identified (sequence type pending). Resistance to antibiotics was uncommon, except for penicillin (93; 97%), tetracycline (48; 50%) and fosfomycin (64; 67%) predominantly encoded by *blaZ*, *tet(K)* and *fosb* respectively. 7 (7%) MRSAs were identified, belonging to ST239-MRSA-III, CC59-MRSA-V(T) Taiwan Clone, ST2250-MRSA-IV, ST2885-MRSA-V and CC398-MRSA-V: 3 patients had had recent healthcare contact and 1 had recently travelled. Globally widespread CC5 and CC30 were absent. Our report shows parallels between Laos and neighbouring countries, highlights the prominence of PVL in SSTI and suggests infiltration of MRSA clones of epidemic potential from surrounding countries. Continued vigilance is warranted considering the paucity of antibiotic options in Laos and challenges for robust infection prevention and control.

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DISTINCT ARRANGEMENTS OF VIRULENCE GENE EXPRESSION IN UROPATHOGENIC *ESCHERICHIA COLI* STRAINS

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Most urinary tract infections (UTIs) are caused by uropathogenic *Escherichia coli* (UPEC). The aim of this study was to determine the patterns of expression of genes coding for iron uptake *(iuc, iroN* and *irp2*), adhesins (*fim, afa1, sfa, iha, tsh, papGI, papGII* and *papGIII*), protectins (*KpsMT, ompT* and *iss*) and toxins (*cnf1, hlyA*, *set-1, astA, vat, usp* and *cva/cvi)* in UPEC strains. Using standard biochemical tests, followed by PCR amplification of 16S rRNA gene, we identified 194 strains as *E. coli,*

which were isolated from patients with UTIs at Unidad Médica Familiar No. 64 (Instituto Mexicano del Seguro Social), Estado de México. Virulence gene expression in UPEC strains was determined by real-time PCR after infection of *in vitro* cultured A431 human vaginal cells. Sixty-eight percent (n=132) of UPEC strains expressed *iuc* gene*;* 65% (n=126) *iha*; 61.3% (n=119) *KpsMT;* 59.2% (n= 113) *fim*; 48.4% (n=94) *irp2;* 31.4% (n=61) *set-1;* 31% (n=60) *astA;* 15.5% (n=30) *papGII;* 12.3% (n=24) *afaI*; 11.8% (n=23) *hlyA*; 10.3% (n=20) *iroN;* 9.8% (n=19) *ompT;* 5.7% (n=11) *papGIII* and *vat*, in each case*;* 4.1% (n=8) *papGI* and *iss*, in each case; 3.1% (n=6) *iuc;* 2.6% (n=5) *sfa* and *tsh*, in each case; 1.5% (n= 3) *cva/cvi* and 0% *cnf1.* A total of 106 distinct arrangements of virulence gene expression were identified in the UPEC strains. The most abundant of them (*irp2/ fim/iha/kpsMT/usp*: iron acquisition system/ adhesins/protectin/toxin) was represented by 28 strains (14.1%). Findings of this study revealed that combinations of virulence genes are expressed during infection of A431 cells with UPEC strains, showing that these strains could be highly virulent and cause more severe infections as cystitis or pielonephritis.

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METHICILLIN-SENSITIVE AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) CARRIAGE AT A UGANDAN REGIONAL REFERRAL HOSPITAL

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Despite increasing antimicrobial resistance globally, data are lacking on the prevalence and associated risk factors for *Staphylococcus aureus* (SA) and methicillin-resistant SA (MRSA) carriage in low-resource settings. We enrolled a cross-sectional sample of 500 Ugandan adults from a predominantly rural agricultural area seeking care at a regional referral hospital or clinic, swabbed anterior nares, and tested for SA and MRSA carriage using Cepheid Xpert SA Nasal Complete assay. Mean age was 37 years and 322 (65%) were female. Of 498 participants reporting clinical data, 368 (74%) were currently taking antibiotics, 118 (24%) were recently hospitalized, and 315 (63%) had known risk factors for SA infection including open wounds (188; 38%), rash (99; 20%), recent immunosuppression (66; 13%), or HIV infection (166; 33%). Of 499 samples with a valid Xpert result, 145 (29%) were SA positive and 14 (2.8%) were MRSA positive. SA carriers were more likely than SA non-carriers to be male (44 *vs.* 32%, *P*=0.008) or have a chronic disease (61 *vs.* 47%, *P*=0.005), but less likely to report recent β-lactam antibiotic use (63 *vs.* 73%, *P*=0.02) or open wounds (32 *vs.* 40%, *P*=0.07). SA carriage ranged from 19% on maternity ward to 36% on medical ward (*P*=0.04). Though cases were few, MRSA carriers did not differ from non-carriers by sex (50 *vs.* 35% male, *P*=0.25) or chronic disease status (71 *vs.* 50%, *P*=0.17), but were more likely to be inpatients (86 *vs.* 59%, *P*=0.05), have an open wound (71 *vs.* 37%, *P*=0.01) have contact with pigs (21 *vs.* 5%, *P*=0.04); and less likely to report recent β-lactam use (43 *vs.* 71%, *P*=0.02). MRSA carriage ranged from 0% in HIV clinic to 8% on surgical ward (*P*=0.01). Using multivariable logistic regression, independent predictors of SA carriage were chronic illness (OR 1.73, *P*=0.007) and female sex (OR 1.69, *P*=0.01). β-lactam use was protective (OR 0.6, *P*=0.02). In Uganda, we found low overall prevalence of MRSA carriage, a protective association between β-lactam use and SA and MRSA carriage, and no association between carriage and HIV status. Further research should explore possible increased prevalence of MRSA carriage among hospitalized surgical patients.

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DEFINING THE MECHANISMS OF PROTECTIVE IMMUNITY ELICITED BY TWO VACCINE CANDIDATES AGAINST *ORIENTIA TSUTSUGAMUSHI* INFECTION

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Scrub typhus is an acute, febrile and potentially fatal disease and caused by infection with the obligate intracellular bacterium, *Orientia tsutsugamushi*. It is the most common rickettsial disease seen in the Asia-Pacific region. Since there is no vaccine available, creation of a safe and effective vaccine remains an important goal for public health. Recombinant antigens r56kp and r47kp have been shown to provide up to 100% protection in a mouse challenge model with two different strains. However, the mechanisms of protective immunity against *O. tsutsugamushi* challenge induced by these antigens remain unclear. To determine whether r56kp or r47kp subunit vaccine-induced protection depends on antibody- or T cell-mediated protective immunity in mouse models, we investigated 1) if adoptive transfer of either immune sera or T cells from r56kp- or r47kp-vaccinated mice would provide protection against *O. tsutsugamushi* challenge in naive recipient C3HeB/FeJ mice; 2) whether depletion of CD4+ T cells or CD8+ T cells would affect the ability of r56kp and r47kp vaccine to confer protection against *O. tsutsugamushi* challenge in C3HeB/FeJ mice; and 3) if B cell, T cell, CD4+ T cell or CD8+ T cell deficiency in mice would significantly affect the ability of r56kp and r47kp vaccine to confer protection against *O. tsutsugamushi* challenge. Our results suggest that i) both B cells and T cells contributed to r56kp and r47kp vaccine induced protection; ii) antibody and B cells may play a critical role in r56kp vaccine-induced protection; and iii) T cells may be more crucial for r47kp vaccine-induced protection.

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SCRUB TYPHUS: A LONG NEGLECTED PUBLIC HEALTH THREAT IN THE ASIA-PACIFIC AREA AND WORLDWIDE

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Scrub typhus is a serious public health problem in the Asia-Pacific area. It threatens one billion people globally, and causes illness in one million people each year. It can cause severe multiorgan failure with a case-fatality rate up to 30% without appropriate treatment. The antigenic heterogeneity of *Orientia tsutsugamushi* results in reinfection with scrub typhus. As a neglected disease, there is still a large gap in our knowledge of the disease, as evidenced by the sporadic epidemiologic data and other related public health issues regarding scrub typhus in its endemic areas. Our objective is to provide a systematic analysis of current epidemiology, diagnosis, treatment, prevention and control of scrub typhus in its endemic area and the rest of the world. Preliminary studies have demonstrated the wide and long existence of this endemic disease. We analyzed the epidemiology of scrub typhus through a thorough review of the epidemiology and public health impact of the disease. This study leads us to understand the disease, and provides a foundation for prevention and control. We then described the diagnosis and treatment of scrub typhus, which facilitates the development of the next generation of diagnostics and treatment. Atypical flu-like symptom and repeated failure to respond to antibiotics make the diagnosis and treatment considerably challenging. The last part of the project focuses on the prevention and control of scrub typhus in the Asia-Pacific region and worldwide. The antigenic diversity impedes vaccine development for the prevention of the disease. Our laboratory has been working on the interactions between host immunity and the pathogen. This analysis could largely benefit the control and

prevention of scrub typhus. The research also provides foundations for exploring new measures for other infectious diseases and public health threats.

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PERSISTENCE OF ST217 CLONAL COMPLEX LINEAGE B OF SEROTYPE 1 PNEUMOCOCCAL MENINGITIS IN NORTHERN GHANA - THE PROSPECT OF PNEUMOCOCCAL VACCINES IN AFRICAN MENINGITIS BELT

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Sporadic outbreaks of Serotype 1 pneumococcal meningitis were observed in Northern Ghana between 1998 and 2005 period. To monitor the molecular epidemiology of this strain, a hospital case- based surveillance was maintained from 2006 to 2011 period. Case and Laboratory based surveillances on pneumococcal meningitis were conducted. Specimens collected were analyzed using classical and molecular microbiology. The incidence rate was 18/100,000/population-year. Since the detection of ST217 clonal complex lineage B of serotype 1 pneumococci in this region, this clone persisted for 13 years as the main aetiology. The risk population shifted from the very younger children to adult age group. The host age distribution pattern was more associated with the biology of the strain than the exposure history of the study population. In conclusion, the incidence and case-fatality rates declined by 3 and 7 percentage points, respectively Nevertheless, the changes in age distribution pattern has major policy, programmatic and research implications. The immunization strategy ought to be refined to cover the new at risk population. Strategic platform ought to be developed to coordinate research outcomes of other allied scientist in Ghana to manage pneumococcal infection comprehensibly. Sero-surveillance should be conducted to evaluate the impact of PCV13 introduced in Ghana in 2012. Further research will be needed to consolidate our understanding on the association between strains' biology and host-age trends.

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PREVALENCE OF MATERNAL CARRIAGE OF GROUP B STREPTOCOCCUS AND *ESCHERICHIA COLI IN* SOUTHERN MOZAMBIQUE

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Group B streptococcus (GBS) and *Escherichia coli* are leading causes of neonatal sepsis in many industrialized countries. Reports from low-income countries infrequently identify those pathogens among newborns with sepsis. We assessed the prevalence of GBS and E.coli colonization among pregnant women in a rural Mozambican hospital. A cross sectional study was conducted on pregnant women attending Manhiça District Hospital at two different time-points during their pregnancy (1: during routine antenatal clinics (AC) at gestational age >34 weeks; 2: at delivery, regardless gestational age). Samples from lower genital tract and rectum for GBS and a vaginal sample and urine for E.coli determination were cultured. Thirty-six of the 200 pregnant mothers recruited at the AC (18%) were GBS carriers. Twenty-five of them (12.5%) had positive E.coli culture in their vaginal samples and 4/200 (2.0%) in the urine cultures for E.coli. One hundred and twenty mothers were recruited at delivery. Prevalence of GBS carriers in this group was 26.7% (32/120) and 22.5% (27/120) had positive E.coli culture in vaginal samples and 5% (6/120) in urine. Colonization by *E. coli* vaginal was significantly more common in women recruited at delivery (OR: 2.0, 95% CI 1.1-3-7). HIV-positive status was positive for 117/320 women (36.6%). There was no association between being colonized by GBS and HIV-positive status or others maternal risk factors. Almost 10% of the GBS isolates were resistant to penicillin (5.8% intermediate resistance and 3.8% fully resistant), the usual antibiotic utilized in the developed world to prevent GBS vertical transmission. All GBS isolates except three (2.9%) were sensitive to ampicillin, two of which were highly resistant to both ampicillin and penicillin. We will present results of serotyping and maternal antibodies. The study showed that GBS colonization among near term pregnant mothers is reasonably high in our community. Since screening and intrapartum antibiotic prophylaxis is difficult to implement in low-income countries, effort to prevent GBS vertical transmission should lead to provide effective vaccines.

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QUANTIFYING THE INDIRECT EFFECTS OF *HAEMOPHILUS INFLUENZAE* TYPE B VACCINATION IN CHILDREN UNDER AGE 5 YEARS

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Haemophilus influenzae type b (Hib) was a significant cause of morbidity and mortality among children under 5 years before an effective vaccine became available. Hib vaccine reduced disease beyond that expected from direct protection alone, indicating indirect effects in those not vaccinated provide meaningful protection. We modeled the magnitude of indirect effects as a function of time and population-level vaccine coverage. We regressed the observed disease reduction from pre-post vaccine introduction on the proportion vaccinated among children <5 years. We also compared the observed disease reduction to the expected disease reduction (calculated using the <5 age distribution of invasive Hib disease before vaccine introduction and vaccine rollout schedule) due to direct effects alone to estimate an indirect effect multiplier that can be used to calculate vaccine "effective coverage" to more completely estimate the proportion of the population protected against disease. We validated results by comparing to a study that empirically measured indirect effects on individuals. Using 23 data points identified from 10 studies, the model estimated that 40% vaccine coverage results in 39% (95%CI: 23%, 55%) additional children protected by indirect effects (i.e., 79% effective coverage), the highest indirect effect multiplier (x1.39) estimated; with 60% vaccine coverage over 85% (95%CI: 69%, 100%) disease reduction was predicted. The magnitude of the indirect effect reduces as vaccine coverage increases. Modeled results were similar to those measured empirically. In conclusion, the indirect effects of Hib vaccine in unvaccinated children have substantial impact on disease and in conditions of moderate (e.g., 40%) vaccine coverage can almost equal direct effects. These results can be used to improve estimates of expected disease reduction due to vaccines and should be incorporated into cost-effectiveness analyses. This approach can be applied to other vaccines, such as pneumococcal conjugate vaccine, which may impact vaccination policy decisions regarding introduction.

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BACTERIAL VAGINOSIS IN DAKAR (SENEGAL) IN 2015

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To point-out the importance of bacterial vaginosis (BV) in genital infections and to determine epidemiological, clinical and paraclinical factors linked to BV in Dakar. 1509 females patients enrolled in this study were interviewed

prior to the vaginal fluid collections. Prior to microscopic examination, both genital area and fluids were observed macroscopically. Cultures were performed for bacterial and fungal microorganisms. BV diagnosis was based on the presence of clue cells, pH > 4.5, and absence of Lactobacilli. Statistical analysis was done by Khi2 test and the Odds ratio. Among 1509 females, 33.5% had BV, 21% had Candida, 2.3% Trichomonas vaginalis infection and only 0.4% (N=6) were with gonorrhea. We found more BV from females aged from 25-34 than those aged from 35-44. But Odds ratio shows that BV is not linked to any age. BV is more found in married women than in celibate. In most of cases, genital area was normal. 35.7% cervix were found in association with BV. 39.8% of inflammatory reaction were linked to BV. In 23.1% of BV *Gardnerella vaginalis* was associated with Mobilluncus. Vagina flora was type III or IV in 99.2% of cases. In Dakar, BV belongs to the major genital infections and its management must be effective in Gynecologic and Obstetric services and also in National Campaign against AIDS since it eases the transmission of HIV.

1056

CHANGE IN NASAL COLONIZATION WITH *STAPHYLOCOCCUS AUREUS* IN ACTIVE PERUVIAN MILITARY POPULATION AFTER 1-YEAR FOLLOW-UP

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Antibiotic resistance is one of the greatest threats to the global health. Methicillin-resistant *Staphylococcus aureus* (MRSA) is distributed worldwide and asymptomatic carriers can be a source of transmission. Military personnel are exposed to some characteristics such as being in close quarters, less opportunities for hygiene during training and combat operations, etc., that make them susceptible to being colonized by *S. aureus*, and increasing the risk of infections by *S. aureus* as it occurs in military trainees. We conducted a prospective cohort study at the four largest bases of the Peruvian Air Force, collecting nasal swabs from 756 active duty military personnel (655 at baseline, and 101 at 6 month visit) during 1-year. The goal was to assess the rates of nasal colonization with *S. aureus* at baseline, after 6 months and 1-year follow-up. The samples were cultured to identify the presence of *S. aureus*, and the antimicrobial resistance profile was assessed via disk diffusion. We analyzed the change in the nasal colonization status among those participants who provided at least 2 samples. Only 484 participants met this requirement (390 after 6 months and 94 after 1 year). Nasal colonization with *S. aureus* was lower at baseline (9.7%, n=73/655), but increased over the study period up to 20.4% (n=70/343) among those who supplied a sample at 1-year visit. The incidence rate of nasal colonization (those who changed from negative to positive status) was 11.2%, while the percent clearance was 51%. Two participants were colonized with a MRSA strain (USA 300, SCCmec type IV) after 6 months of follow-up. At 12 months we did not isolate MRSA strains among our participants. The risk of being colonized with *S. aureus* among those participants with a first negative sample, increased in those with a diagnosis of skin and soft tissue infections or who were mobilized to different geographic areas due to military missions but none of them was statistically significant. This was the first study to systematically determine the prevalence and the molecular characteristics of MRSA among Peruvian active duty military population in multiple cities in the country.

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BLOCKADE OF CTLA-4 IMPAIRS ANTIBACTERIAL IMMUNITY BY REDUCING ACTIVATION OF CD8+ T CELLS AND INCREASING PRODUCTION OF IL-10 BY T CELLS IN MURINE *ORIENTIA TSUTSUGAMUSHI* INFECTION

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Post-acute persistence is a hallmark of *Orientia tsutsugamushi* infection in humans and rodents. We hypothesized that negative T cell co-stimulation plays a role in reducing the effector response to *O. tsutsugamushi*, thereby facilitating pathogen persistence. We had shown before that highest bacterial loads are found in the lung in our C57BL/6 mouse model of intradermal *O. tsutsugamushi* infection. Thus, we studied the role of negative costimulation and particularly CTLA-4 in pulmonary T lymphocytes. During the acute phase of infection, a significant reduction in CD4+foxp3+CTLA-4+ regulatory T cells was observed in the lung. However, on CD4+ and CD8+ T cells, expression of CTLA-4, PD-1, TIM-3 and LAG3 increased significantly during acute infection. In order to study the functional significance of CTLA-4 in this model, we blocked CTLA-4 using a monoclonal antibody before and during infection, and analyzed its influence on the pulmonary immune response and bacterial clearance. Other than expected, CTLA-4 blockade had profound effects on composition and phenotype of the pulmonary lymphocyte compartment: (1) more CD4+ and less CD8+ T cells invaded the lung, (2) expression of the activation markers CD44, KLRG1 and CD11a on CD8+ T cells was significantly reduced, and (3) PD-1 expression was increased. Moreover, CTLA-4 blockade caused a significant increase of bacterial loads in the lung. This was not due to decreased production of cytokines, since neither the ability of CD4+ nor CD8+ pulmonary T cells to produce IFN-gamma and IL-2 was impaired. However, re-stimulated splenocytes from mice receiving anti-CTLA-4 treatment revealed an increased production of IL-10. Thus, unlike in other infection models, our data suggest that CTLA-4 blockade is unable to increase effector responses in *O. tsutsugamushi* infection. Instead, its blockade reduces activation of CD8+ T cells and increases production of the regulatory cytokine IL-10, pointing to a novel role of CTLA-4 in *O. tsutsugamushi* infection.

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ANTIBIOTIC RESISTANCE PATTERNS IN BACTEREMIC CHILDREN FROM HOLOENDEMIC *PLASMODIUM FALCIPARUM* MALARIA REGION OF WESTERN KENYA

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Bloodstream bacteria commonly complicate malaria and other illnesses in children residing in *Plasmodium falciparum* holoendemic areas of sub-Saharan Africa. The emergence of antibiotic resistance by blood-borne bacteria increasingly complicates the clinical management of sick children. However, the paucity of data on the prevalence and patterns of antimicrobial resistance of bloodstream isolates continues to hinder rationale management and antibiotic use in pediatric populations. This study investigates antibiotic resistance patterns in bacteremic children (N=158) with malaria [+] (n=90) and without malaria [-] [n=50] upon enrollment at the hospital and during subsequent acute illnesses [n=18]. The study was conducted in a *P. falciparum* malaria holoendemic region, in Siaya County, western Kenya. Antibiotic susceptibility patterns of

the bacterial isolates were determined using disk diffusion according to the Clinical Laboratory Standards Institute guidelines where antibiotic resistance was defined as resistance of a microorganism to an agent to which it was previously sensitive. The results revealed that *Escherichia coli* had high resistance (80%-100%) to ampicillin/ sulbactum, gentamicin, and chloramphenicol, while non-typhodial salmonella (NTS) showed high resistance (71%-100%) to ampicillin/salbactum, amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, chloramphenicol, nalidixic acid and ceftriaxone. Staphylococcus aureas displayed the least resistance (<41%) to ampicillin/sulbactam, gentamicin, amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, and chloramphenicol. Further analysis showed that NTS resistance to chloramphenical was significantly higher in the acute visit group compared to malaria [+] and malaria [-] groups, (p=0.028). Additionally, NTS demonstrated higher resistance to ampicillin/ sulbactam in the acute illness relative to malaria [+] and malaria [-] groups (P=0.010). The current study shows that most bloodstream NTS, *E. coli* and *S. aureus* isolates are resistant to commonly used antibiotics and that NTS characterize acute illness in western Kenya.

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RESISTANCE OF *NEISSERIA GONORRHOEAE* IN REMOTE PERUVIAN JUNGLE SETTINGS

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Gonorrhea is a common sexually transmitted disease that if not treated may lead to chronic reproductive health complications, especially in women. Increasing rates of antibiotic-resistant *Neisseria gonorrhoeae* (NG) has become a public health concern worldwide and continued surveillance for NG is critical, especially in developing countries and underreported areas. We established a NG surveillance network in collaboration with two hospitals and a reference laboratory in the city of Iquitos located in the Peruvian Amazon. NG cultures of urethral and vaginal swabs were plated immediately on GC and Modified Thayer-Martin agar prior to transport to our nearby laboratory. Presumptive identification of colonies was determined by colony morphology, oxidase test, Gram stain, and biochemical identification with the API NH (Biomerieux) kit. Antibiotic susceptibility was determined by E-test (Biomerieux). From February 2013 to March 2016, a total of 189 cases were screened with 70/189 (37%) positive for NG. From 69 isolates with available susceptibilities, 49/69 (71%) and 32/69 (46%) of isolates showed resistance to penicillin and ciprofloxacin, respectively, whereas only 5/69 (7%) were susceptible to both antibiotics. Additionally, 25/69 (36%) showed resistance to tetracycline whereas 15/69 (22%) and 32/69(46%) exhibited intermediate susceptibility to penicillin and ciprofloxacin, respectively. No resistance was found for ceftriaxone, cefixime and azithromycin. Our results shows very high rates of fluoroquinolone resistance among NG in Iquitos, which is still widely used as first line therapy in Peru. The results highlight the need to update Peruvian MoH treatment guidelines to current U.S. Centers for Disease Control and Prevention (CDC) standards.

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PRINCIPLES, PRACTICES, AND KNOWLEDGE OF PROVIDERS EVALUATING CHILDREN PRESENTING WITH FEVER IN KENYA

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Clinicians in low resource settings where malaria is prevalent face many challenges in diagnosing and treating febrile illnesses in children. Given the change in WHO guidelines in 2010 recommending malaria testing prior to treatment in any child presenting with fever, clinicians are now required to expand the differential when malaria testing is negative. Prior studies have indicated that resource availability, need for additional training in differentiating non-malarial illnesses, and lack of understanding within the community of when to seek care play a role in effective diagnosis and treatment. We interviewed 20 clinicians (2 pediatricians, 1 medical officer, 2 nurses, and 15 clinical officers) working at 5 different government-sponsored public clinic sites (2 rural clinics, 1 urban clinic, and 2 larger referral hospitals) in two areas of Kenya where malaria is prevalent. Clinicians were interviewed one-on-one using a structured interview technique. Interviews were then analyzed qualitatively for themes. Themes included the following: 1) Primary reliance of history and physical exam in diagnosis of febrile illness; 2) Strong familiarity with IMCI guidelines and recognition of the "danger signs" but lack of comfort with the diagnosis and treatment of illnesses that deviate from the protocol; 3) Use of antibiotics as a fallback when diagnosis is unknown; 4) Difficulty with community understanding of febrile illness; 5) Lack of resources including diagnostics, medications, and training modalities. These themes persisted across the 5 sites, despite variation in levels of medical care. Within these themes, clinicians consistently expressed a need for reliable basic testing, especially hemograms and bacterial cultures. Providers discussed the use of counseling and education to improve community understanding of febrile illness in order to decrease preventable deaths in children. Our results suggest that since malarial testing has become more widespread, revisions to provider training and diagnostic tools are necessary to improve diagnosis and effective treatment of febrile illness in children in malaria endemic regions.

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HIGH PREVALENCE OF PARASITIC INFECTIONS AMONG RECENT IMMIGRANTS IN CHICAGO

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Extensive testing for infectious diseases is performed on refugees. This testing is not provided to the 42.1 million immigrants living in the US, many of whom share similar risk factors and migrated from countries where parasites are highly prevalent. We recruited 119 asymptomatic recent immigrants into a cross-sectional study to assess the prevalence of parasitic infections in this population. All 119 participants were asked about symptoms and provided stool and blood samples for Ova & Parasite exam, eosinophil count, and Immunoglobulin E (IgE) level; a subset of the samples (73/119) were randomly selected for additional parasite serologic testing. Enrolled subjects had a mean age of 33 years (SD 17.7) and 65 of the 119 subjects were female (55%). Subjects had immigrated primarily from Mexico (30/119, 25%), India (26/119, 22%), other Asian countries (30/119, 25%), and Central and South America (23/119, 19.3%). Twenty of 119 subjects (17%) tested positive for a parasitic infection and

4/20 subjects (20%) with parasites had multiple infections. The most commonly identified infections were: *Blastocystis hominis* (9/119 subjects, 7.6%), followed by *Toxocara* (6/73, 8.2%), schistosomiasis (5/73, 6.8%), strongyloidiasis (3/73, 4.1%), and Chagas disease (1/73, 1.4%). There was no difference in gender (p=.63) or recency of immigration (p=.23) between those with and without parasitic infections. Immigrants from Asian countries had a significantly higher likelihood of infection compared to the other regions (p<.001). IgE was significantly higher in those with a parasitic infection (GM 136.7 IU/mL) compared to those without (GM 65.53 IU/mL, p=.03), but mean AEC did not differ between the groups (p=.69). There was no difference in clinical symptoms between groups (all p values >.05). Based on our preliminary data, parasitic infections likely represent a large and as-yet-unidentified burden of disease in the immigrant population. The lack of symptoms or signs predictive of parasitic infections suggests immigrants might benefit from the same screening provided to refugees, as all of these treatable infections can have significant health impacts.

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THE MHC CLASS I CHAIN-RELATED MOLECULE A (MICA) 129 METHIONINE/VALINE DIMORPHISM ASSOCIATED WITH CHAGASIC MEGACOLON IN BOLIVIA

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Chagas disease, caused by the flagellate parasite *Trypanosoma cruzi* affects 5-6 million people mainly in Latin America and causes over 10,000 deaths per year according to the WHO. The underlying mechanisms that lead to the development of complications from chronic Chagas disease are not fully understood. To identify host genetic factors, we focused on the MHC class I chain-related molecule A (MICA) gene polymorphism, which could change the responsiveness of Natural Killer (NK) cells through its ligand. A single nucleotide polymorphism at residue 129 of the MICA gene change a single amino acid from strong binder (methionine) to a weak binder (valine) of the NKG2D receptor, a C-type lectin receptor expressed on effector cells including NK, αβ- and γδ-T cells. Recently MICA 129 met homozygote was associated to left ventricular systolic dysfunction (LVSD) in patients with Chagas Chronic heart disease. Therefore, we asked whether MICA 129 met/val polymorphism affects the clinical forms of Chagas disease in Bolivia. A total of 303 chronic Chagas patients, 80 cardiac, 99 megacolon, and 72 indeterminate forms, and 87 seronegative controls in Santa Cruz, Bolivia were diagnosed by electrocardiogram and Barium enema colon X-ray. MICA129 polymorphism (A > G, rs1051792) was genotyped by TaqMan Allelic discrimination assay. Here, we report that the MICA 129 A allele (methionine) was significantly decreased in frequency in the megacolon patients compare to indeterminate (OR=0.24, Pcorrected=0.0021) suggesting this allele is resistant against megacolon. Thus, the strong binding between NKG2D and MICA 129 met may be related to the protection against the tissue damage in the colon.

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INCIDENCE AND SPECTRUM OF HEALTH PROBLEMS AMONG TRAVELERS TO MYANMAR

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Nowadays, Myanmar becomes an attractive destination. The number of traveler visiting Myanmar is rapidly increasing every year. However, little is known about their pre-travel preparation and incidence of health problems during their trip. We, therefore, conducted a cross-sectional study at the arrival halls of Bangkok International airports. Travelers who just completed their trip in Myanmar were invited to fill the questionnaire. They were asked about their demographic profile, pre-travel health preparations, and their health problem during their stay in Myanmar. From March to December 2015, 397 questionnaires from Thais and 301from foreigners were collected and analyzed. 48.7% of travelers were male, and the median age was 37 years in both groups. Among foreigner group, most of them were from Europe (73%). Up to 82% of foreigners sought pre-travel health information before their trip, while only 36.5% of Thais did so. The main reason for travel was tourism in 91% of foreigners while only 58.1% of Thais traveled for tourism. Foreigners were more likely to travel as backpackers, and engaging in outdoor activities such as trekking, cycling or swimming than Thais. There was also significant difference in the average length of stay between foreigners and Thais (21.7 days vs 7.08 days, p<0.001). Overall health problems were reported in 29.2% of foreigners, the most common being diarrhea which reported in 22.3% of foreigners followed by upper respiratory tract symptoms, fever, and skin problems. While only 12.6% of Thais reported some health problems. The most common one was upper respiratory tract symptoms followed by diarrhea, fever and skin problem. Most health problems were mild and self limited in both groups. However, six foreign travelers had to visited doctor and two had to be admitted. While only one Thai traveler had to visit a doctor in an out-patient department. In conclusion, health problem was fairly common among travelers to Myanmar. Nearly 30% of foreign travelers reported some health problems. Most health problems were mild and spontaneous recovery; however up to 2% of foreign travelers need to visit a doctor while traveling in Myanmar.

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EVALUATION OF A BOOSTER DOSE OF ROTAVIRUS VACCINE GIVEN CONCOMITANTLY WITH MEASLES AND YELLOW FEVER VACCINES IN MALIAN INFANTS

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Rotavirus vaccines, administered early in the 1st year of life, are modestly effective in low resource countries and immunity may wane. Rotavirus is still a major cause of moderate to severe diarrhea in the 2nd year of life, and a booster dose of rotavirus vaccine might extend protection. We evaluated whether a booster dose of pentavalent rotavirus vaccine given to 9-11 month old Malian infants would interfere with immune responses to routine vaccines. Infants were randomized 1:1 to receive PRV or no PRV co-administered with measles and yellow fever vaccines. Serum was

collected before and 28 days after vaccination. Anti-measles IgG was measured by ELISA; seroconversion was defined as a positive result among baseline seronegatives. Yellow fever neutralizing antibodies were measured by plaque reduction; seroresponse was defined as >4-fold increase in post-vaccination titer. Noninferiority (<10% difference in seroconversion or seroresponse rates) for measles and yellow fever were co-primary objectives. Anti-rotavirus IgA and IgG concentrations were measured by ELISA. From October 15, 2014 to December 18, 2014, 600 infants were enrolled with 300 receiving PRV. 513 were baseline measles seronegative with 255/261 (97.7%) (PRV group) seroconverting compared to 246/252 (97.6%) (no PRV group); difference, 0.1% (95% CI, -4.0 to 4.2). In the yellow fever analysis, 141/293 (48.1%) (PRV group) seroresponded compared to 153/293 (52.2%) (no PRV group); difference -4.1% (95% CI, -12.2 to 4.0). However, with yellow fever seroresponses defined as >2-fold rise, 202/293 (68.9%) (PRV group) seroresponded compared to 206/293 (70.3%) (no PRV group); difference -1.4% (95% CI, -8.8 to 6.1). Post-vaccination anti-rotavirus IgA and IgG geometric mean concentrations rose to 118 (95% CI, 91 to 154) and 364 (95% CI, 294 to 450) in the PRV group compared to 68 (95% CI, 50 to 92) and 153 (95% CI, 114 to 207) in the no PRV group. Concomitant administration of PRV did not appear to interfere meaningfully with immune responses to MV and YFV and substantially increased rotavirus antibody levels. Clinical benefit of a booster dose of PRV in the 2nd year of life should be studied.

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AN OPTIMIZED AGE BASED DOSING REGIMEN FOR SINGLE LOW DOSE PRIMAQUINE FOR TRANSMISSION BLOCKING IN CAMBODIA

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In 2012, the WHO recommended the addition of single low single low (0.25 mg base/kg body weight) dose primaquine (SLDPQ) to artemisinin based combinations to block the transmission of *Plasmodium falciparum* without testing for glucose 6 phosphate dehydrogenase deficiency. The targeted group was non pregnant patients aged ≥ 1 year (later changed to ≥ 6 months) with acute uncomplicated falciparum malaria, primarily in countries with artemisinin resistant *P. falciparum* (ARPf). No dosing regimen was suggested. We, therefore, designed a user friendly, age based, SLDPQ regimen for Cambodia, the country most affected by ARPf. By reviewing PQ's pharmacology, we defined a therapeutic dose range of 0.15-0.38 mg base/kg (9-22.5 mg in 60 kg adult, therapeutic index 2.5). Primaquine doses (1-25 mg) were tested using a modelled, anthropometric database of 28,138 Cambodians (23,338 healthy individuals, 4,199 with malaria, and 1,292 other infections); age distributions were: < 5y [19.35% (n=5,383)], 5 to 17y [20.37% (n=5,469)] and adults [59.65% (n=15,531)]. Optimal age dosing groups were selected according to calculated mg base/kg doses and proportions of individuals receiving a therapeutic dose. Four age dosing bands were defined: (i) 6m-4y, (ii) 5-9y, (iv) 10-14y, (v) ≥ 15y to receive 2.5, 5, 7.5 and 15 mg of PQ base, resulting in therapeutic doses in 97.41% (5,494/5,640), 90.53% (1,511/1,669), 97.68% (1,473/1,508), and 95.69% (18,489/19,321), respectively. Corresponding median (1st, 99th centiles) mg base/kg doses of PQ base are: (i) 0.23 (0.15-0.38), (ii) 0.29 (0.18-0.45), (iii) 0.27 (0.15-0.39), and (iv) 0.29 (0.2-0.42). In conclusion, this SLDPQ regimen could contribute substantially to malaria elimination and requires urgent evaluation in Cambodia and other Greater Mekong Subregion countries with similar anthropometric characteristics. It also guides primaquine manufacturers on suitable tablet strengths and doses for paediatric friendly formulations. Development of similar age based dosing recommendations for Africa is needed.

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COMMUNITY HEALTH WORKER'S SOCIO-DEMOGRAPHIC CHARACTERISTICS AND ICCM PERFORMANCE IN RWANDA

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The health of children under five remains worrying in developing countries. Indeed, nearly ten million children still die annually before reaching the age of five. Since 2008, community health workers (CHWs) in Rwanda have been trained to carry out integrated community case management (iCCM) in children under five. We carried out this study in 2014 to determine the effect of socio-demographic characteristics on CHWs performance. A cross-sectional study was conducted in 25 districts in Rwanda. Data was collected using a structured questionnaire and client satisfaction. We used STATA for data analysis. Descriptive statistics were calculated. Odds ratios (OR) and 95% confidence intervals (CI) for the predictors of the performance were calculated. Relationships were determined using logistic regression. Results A total of 19,402 CHWs were observed delivering iCCM package among sick children. Of these CHWs, 51.2% (10,075) were females. The level of performance was estimated to 87.6% for malaria treatment, 88.7% for pneumonia treatment, 85.4% for diarrhea treatment, 76% for malnutrition assessment, 28.1% for counseling on diseases prevention, and 99% for detection of danger signs. The study showed significant relationships of sex with pneumonia treatment. Females CHWs were 1.08 more likely to treat pneumonia than males (OR=1.089, 95%CI: 1.027-1.156). In addition, CHWs aged 35 and above are 1.09 more likely to give more advices on disease prevention than other age group (OR=1.098, 95%CI: 1.029-1.173). CHWs with at least one year of secondary school were 1.06 and 1.08 more likely to treat malaria correctly (OR=1.062, 95%CI: 1.024-1.101) and pneumonia (OR=1.088, 95%CI: 1.050-1.124) when compared to CHWs with education level of primary school. Conclusion Socio-demographic characteristics of CHWs in Rwanda affect iCCM performance in different ways. We recommend targeted interventions and appropriate intensive refresher training for CHWs on iCCM package.

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PATIENT PERCEPTIONS OF TRACHOMATOUS TRICHIASIS SURGERY IN THE FAR NORTH REGION OF CAMEROON

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In Cameroon, trachoma mapping conducted in 2010-2011 identified 13 health districts (HDs) in the Far North region with a prevalence of trachomatous inflammation-follicular (TF) of over 10% in children aged 1-9 years. Out of these HDs, 8 were identified with trachomatous trichiasis (TT) over 1% in persons aged 15 and over in the population. Surgery is an important component of the SAFE (Surgery, Antibiotic treatment, Facial cleanliness and Environmental improvement) strategy to achieve trachoma elimination. Cameroon conducted the TT surgery campaign in the region with the support of the United States Agency for International Development's MMDP Project, managed by Helen Keller International. Six

months following the TT surgery campaign during which 1,080 patients were operated, a patient follow-up survey was conducted to evaluate patients' perception of the surgery and surgery outcomes. A convenience sampling of 213 patients that received TT surgery in the previous 6 months was realized and a questionnaire was administered to assess patients' perception and satisfaction. Median age of patients at surgery was 60 years. 126 (59.2%) of the surveyed patients were female and 86 (40.4%) were male. The following outcomes were recorded: 10 (4.7%) returned to the hospital because of the sand sensation in the operated eye, 6 (2.3%) returned due to excessive tearing and 16 (7.5%) returned for eye pain. The following patients' perceptions were recorded: 210 (98.6%) reported improved vision, 205 (96.2%) patients with less difficulty in performing daily activities after surgery, 210 (98.6%) patients would recommend surgery to others, 211 (99.1%) patients with less pain after surgery. Patient perception on TT surgery is one way to evaluate the quality of surgery in order to help investigate on surgery refusals and improve the quality of care. The results showed a successful TT surgery campaign in the region.

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MEASURING THE EFFECT OF SOIL-TRANSMITTED HELMINTH (STH) INFECTIONS ON COGNITIVE FUNCTION IN CHILDREN: SYSTEMATIC REVIEW AND CRITICAL APPRAISAL OF EVIDENCE

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Recently the role of STH infections in cognitive developmental impairment of children has been under intense scrutiny. We conducted a systematic review of the evidence for associations between STH infections and cognitive function of children. We aimed to summarise the effect size by domains of cognitive function in three age strata (i.e. children <24 months; children 24-59 months and school-aged children). Using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) protocol we searched relevant databases including PubMed, CINAHL, EMBASE, Medline via Web of Science, Cochrane, ScienceDirect, Psych Articles and PsychINFO via APA PsychNET and Scopus. A total of 42 papers fulfilled the inclusion criteria for the systematic review; these include 10 studies from a recent Cochrane review. We next conducted a critical appraisal of the variability of cognitive function measurement tools used to assess the effect of STH infections on different domains of cognitive function of children of different age groups. Our findings demonstrate remarkable variation in tested domains and lack of consistency in the use and analysis of measurement tools. Cognitive function measures in children under five years of age has been mainly limited to domains of gross motor, fine motor and language skills, whereas in school-aged children most studies tested domains such as memory and processing speed. Even within the same age group the results on the association between STH infections and measures of cognitive development were often conflicting. This study demonstrates the need for the establishment of methodological consensus in the deployment and analysis of adequate measurement tools to detect the effect of STH infections on different domains of cognitive function in children at different ages. This will be an imperative next step to improve study validity and generate conclusive evidence of the role of STH infections in cognitive development in children.

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VARICELLA ON SHIPS: IS THERE A RISK TO TRAVELERS?

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Masters of ships with U.S. ports of call are required to report certain illnesses to CDC Quarantine Stations. We describe varicella case reports recorded in CDC Quarantine Activity Reporting System from January 2010 to February 2016. Denominators vary according to the number of cases for which data were available. There were 1,000 reports of varicella from ships during the study period. Most case-patients were male (79.79%, 525/658) and older than age 15 years (89.66%, 503/561). Cruise ships reported 93.30 (933/1,000) of cases, and 6.30% (63/1,000) of cases were reported by cargo ships. On cruise ships and cargo ships, 83.82% (782/933) and 98.41% (62/63) of cases, respectively, were in crew members. Crew member cases were most often from the Philippines (23.46%, 99/422), Indonesia (18.72%, 79/422), and India (17.06%, 72/422). Passenger cases were most often from the United States (21.95%, 18/82), the United Kingdom (10.98%, 9/82), Canada (8.54%, 7/82), and Sweden (8.54%, 7/82). Case-patients typically presented with a rash (99.80%, 998/1,000) and fever (54.30%, 543/1,000). Cases were reported every month of the year. Cruise ship case-patients were isolated, on average, 0.65 days (n = 292, SD 0.96) after rash onset and reported to CDC, on average, 2.32 days (n = 793, SD 4.66) after rash onset. Cargo ship case-patients were isolated, on average, 1.15 days (n=20, SD 1.39) after rash onset and reported to CDC, on average, 5.17 days (n=59, SD 9.56) after rash onset. Varicella cases resulted in hospitalization in 3.52% (20/568) of reports; one case was fatal (0.10%, 1/1,000). Crew members on cargo and cruise ships frequently are from tropical regions where there usually is a higher susceptibility to varicella among adults, or varicella vaccination is not routinely provided. A majority of cases reported were crew members, who, as adults, are at higher risk of complications due to varicella. Given that exposure to varicella on ships can occur year round, varicella vaccination prior to boarding a ship is advisable for those without evidence of immunity.

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SPLENOMEGALY IN CONGOLESE REFUGEES APPLYING FOR RESETTLEMENT FROM UGANDA TO THE UNITED STATES

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In 2014, the International Organization for Migration (IOM) reported a high number of United States (US)-bound Congolese refugees from Uganda with splenomegaly of unknown etiology. In March and July 2015, refugees with splenomegaly on physical examination were offered evaluation and treatment, including abdominal ultrasonography and laboratory testing. Among 987 persons screened, 145 (14.7%) had splenomegaly and received further testing. Of the 144 who had abdominal ultrasound, 122 (84.7%) had massive splenomegaly (defined as >4 a standard mean for splenic size adjusted for height), 135 (93%) had normal liver architecture, and 8 (5.5%) had hepatic nodules/masses.

Thirty-nine (26.9%) were positive for malaria by RDT® (Bioline HRP2/Pan LDH); all tested negative by thin blood smear (thick films were not performed). Eighty-six percent (135/145) were positive for PFMSP-1 IgG (indicating past exposure to *Plasmodium falciparum*). Three (2.1%) tested positive for *Schistosoma mansoni* ova by stool wet prep. Urine ova and parasite were negative. All tested negative for *Leishmania* by rK39 testing, but 1 (0.7%) was positive by serology. Five (3.5%) had positive HBsAg, and 10 (6.9%) had detectable HCV antibodies. Refugees with palpable splenomegaly were treated with antimalarials at the time of diagnosis, and all refugees are given presumptive treatment with artemether-lumefantrine prior to departure to the US - thus those with splenomegaly received two treatment courses. CDC issued recommendations to US providers to conduct additional laboratory and radiology testing. Due to concerns of malaria as an etiology, and reports of non-falciparum malaria in this population, treatment for hypnozoites with primaquine (after glucose-6-phosphate dehydrogenase testing) following arrival in the United States was recommended. Pre- and post-malaria treatment total IgM is currently pending. This initial evaluation did not identify a definitive unifying etiology of splenomegaly and while pending results may indicate a likely etiology, further study of this prevalent condition in Congolese refugees in western Uganda is needed.

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IMPROVING THE QUALITY OF CARE FOR COMMON CHILDHOOD ILLNESSES AMONG PATENT AND PROPRIETARY MEDICINE VENDORS IN EBONYI STATE, NIGERIA

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In Nigeria, malaria, pneumonia and diarrhea are the leading causes of death in children under five. As patent and proprietary medicine vendor (PPMV) shops are the origin of a high proportion of treatments, they could be a strategic partner in increasing the proportion of children that receive appropriate treatment for common childhood illnesses. MalariaCare and the Expanded Social Marketing Project in Nigeria, in collaboration with the Federal Ministry of Health (FMOH) and Ebonyi State Ministry of Health, are conducting a pilot evaluation to assess the ability of trained PPMVs to manage cases of common childhood illnesses according to national health standards. The pilot intervention includes integrated community case management training, covering the use of RDTs, ACTs, ORS, zinc, respiratory timers and amoxicillin, followed by on-site mentoring; and targets poor-performing, high-volume PPMV shops for more cost-effective resource allocation. The evaluation is a quasi-experimental study with 2 intervention and 2 control areas in Ebonyi State. At baseline, we conducted household and outlet surveys to determine the quality of care provided by PPMV shops. Household surveys identified 2,614 children with fever, diarrhea or pneumonia symptoms; 83% had fever, 24% percent had diarrhea, and 4% reported pneumonia symptoms. In 37% of cases treatment was received from a PPMV shop. Of these, 13% of fever cases received an ACT, 1% of diarrhea cases received ORS and zinc, and 2% of pneumonia cases received amoxicillin. Among cases treated at a PPMV shop (68%), rather than treating at home with products previously purchased from PPMVs (32%), only 5% of fever cases had a diagnostic test and 9% of pneumonia cases had their respiratory rate checked. Of the 198 PPMV providers included in the outlet survey, 65%, 4%, and 21% knew the correct first line treatment for malaria, diarrhea and pneumonia, respectively; 67% were not aware of RDTs. End line evaluation results that demonstrate whether the pilot was effective in improving the proportion of children under five with common childhood illnesses receiving appropriate treatment will be presented.

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HIGH PROTEIN DIETARY SUPPLEMENT IMPROVES NUTRITIONAL STATUS AND RECOVERY IN CHILDREN WITH BURKITT'S LYMPHOMA: A NON-RANDOMIZED CONTROLLED STUDY

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Each step of the cancer continuum from diagnosis to recovery poses nutritional challenges. In children with cancers, poor nutritional status will lead to faster disease progression, slower recovery and poorer survival. The effect of nutritional intervention using a soya milk powder (SMP) supplement on nutritional status, recovery and mortality among children undergoing chemotherapy for Burkitt's lymphoma (BL) was studied. Sixty-four subjects were recruited for this non-randomised controlled intervention study. The intervention group was provided the supplement measured to provide 80% RDA for protein and was followed for 6 months, taking measurements at the 0, 3 and 6-months follow-up. Baseline characteristics of the study population were similar except for haemoglobin and prealbumin. SMP supplementation was associated with reduced prevalence of malnutrition (<-2 sd BMI-for-age) from 50% baseline up to 0% six months after the intervention (p=0.005). Likewise, the SMP improved anaemia status (100%, 76.9% and 15.8% anaemia between baseline, 3-months and 6-months follow up respectively), serum zinc deficiency (87.5%, 50% and 52.6%, p=0.004) and reduced glutathione deficiency (GSH) (21.9%, 0 and 0, p=0.045). Same cannot be said in the non-intervention group. Recovery from BL 1 year after the intervention was 47% compared with 16% in the non-intervention, whereas mortality was 19% versus 28% between the intervention and non-intervention groups respectively. Dietary supplementation using a high protein-based SMP improved nutritional status, recovery and survival in children with BL hence the need for larger studies to assess the efficacy of nutritional intervention as non-conventional treatment of childhood cancers in limited resource settings.

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DENGUE AND LEPTOSPIROSIS CO-INFECTION IN THE PERUVIAN AMAZON, 2013-2014

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Dengue is a major public health problem associated with high morbidity and mortality rates in developing countries. In Iquitos, the largest city in the Peruvian Amazon, dengue and leptospirosis are responsible for 40% and 30% of acute undifferentiated febrile illness (AUFI) cases, respectively. Despite this data, few studies have discussed about co-infection, which could explain some atypical or severe cases. Passive clinic-based surveillance conducted by NAMRU-6 in 12 Iquitos health facilities, provided an opportunity to evaluate the clinical impact of leptospirosis infection in dengue confirmed cases (co-infections). From January 2013 to December 2014, 4,211 AUFI patients enrolled in our study provided acute and convalescent blood samples, and were evaluated clinically and epidemiologically. A dengue case was defined as any patient where dengue virus or viral RNA was detected through real -time PCR or viral isolation in an acute sample, or demonstrated a seroconversion (4-fold increase IgM antibodies) between acute and convalescent samples. Leptospira infection was defined by seroconversion of IgM antibodies plus the presence of a titer of Microscopic Agglutination Test (MAT) in convalescent sample of ≥1/400 or a titer of MAT≥1/800 in any of the

paired sample. Of the febrile cases where complete dengue and leptospira testing and clinical data was available, 1,533 of 1,572 (97.5%) had a confirmed dengue infection. Of these, 39 (2.4%) cases had leptospira co-infection. None of the clinical findings (constitutional, gastrointestinal and respiratory symptoms) or complications were associated to co-infection ($p > 0.05$, Pearson Chi square test). The hospitalization rate and shock syndrome ($p>0.05$) were similar in both groups with no fatal cases. Asymptomatic infections due to leptospirosis occur commonly in this city and may explain this finding, even though both dengue and leptospirosis have been associated with severe and fatal disease in Iquitos. In dengue and leptospirosis endemic areas, serological results should be interpreted in the context of the clinical presentation.

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A PROSPECTIVE ASSESSMENT OF ANTIBIOTIC PRE-TREATMENT, USING A URINE ANTIBIOTIC BIOASSAY, AMONG PATIENTS ATTENDING AN INFECTIOUS DISEASE HOSPITAL IN MANILA AND THE RELATIONSHIP BETWEEN ANTIBIOTIC USE AND SOCIOECONOMIC STATUS

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The widespread unregulated use of antibiotics contributes to the rising prevalence of antibiotic resistance in Southeast-Asian countries. Antibiotic usage before a medical consultation also reduces the possibility of identifying the casual pathogen due to the reduced sensitivity of bacterial culture. We conducted a hospital-based observational study investigating prior antibiotic usage in patients attending San Lazaro Hospital (SLH) for a medical consulation. SLH is the National Infectious Disease Hospital and provides free-health care to a low-income population in Metro Manila, Philippines. Patients attening the ER with a history of fever were enrolled. A urine bioassay was used to detect antibiotic activity in urine using three organisms: *Bacillus stearothermophilus* (ATCC7953); *Escherichia coli* (ATCC25922); and *Streptococcus pyogenes* (ATCC19615). Patients or caregivers reported their medication history, clinical information and socioeconomic status. During the study period (2nd February 2015 to 2nd July 2015) 410 patients were enrolled and provided a urine. The median (IQR) age was 14 (7 to 23) years and 158 (39%) reported prior antibiotic use, predominantly a beta-lactam antibiotic. A total of 164 (40%; 95%CI 35 to 45) patients were positive by urine bioassay with any of three organisms. The Bacillus assay detected 162 (99%; 95%CI 96 to 100) cases. Many patients with a positive urine bioassay were clinically considered to have dengue (n=91, 55%; 95%CI 48 to 63). Patients with a positive bioassay were significantly more likely to be from the lowest-income group (AOR 1.7; 95%CI 1.1 to 2.6) and require hospital admission (AOR 2.1; 95%CI 1.3 to 3.5). Antibiotics are widely used in the community setting in Manila by fever patients before the medical consultation, and this antibiotic use is significantly more common among those with the lowest-income.

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DIGITAL GANGRENE DUE TO RICKETTSIAL VASCULITIS - UNCOMMON MANIFESTATION OF AN UNDERAPPRECIATED DISEASE

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Rickettsiae are a common but underdiagnosed cause of acute febrile illness in India. Indian tick typhus caused by *Rickettsia conorii indica* belongs to the spotted fever group of *Rickettsiae* and is less frequently reported than scrub typhus (caused by *Orientia tsutsugamushi*). A healthy 45-year-old woman presented with fevers, chills, dysuria, vomiting, and headache. She was admitted to a community hospital and started on broad spectrum antibiotics. After failing to improve, she was transferred to our institution. On presentation she was febrile, hypotensive, tachycardic and tachypneic. She appeared critically ill with physical examination significant for periorbital edema, conjunctival suffusion and bibasilar rales. She was admitted to the ICU. Laboratory values showed anemia, thrombocytopenia, abnormal LFTs, proteinuria and lactic acidosis. Initial workup was negative for bacteremia, malaria, dengue, leptospira, typhoid fever and HIV. Weil-Felix titers were inconclusive. A tentative diagnosis of rickettsial infection was made and doxycycline was added. After 48 hours the patient improved and was transferred to the medical floor, but began to develop gangrene of the toes and fingers. Repeat testing showed persistent thrombocytopenia, abnormal LFTs and prolonged APTT. Repeat Weil-Felix OX-2 titer was 1:160, supporting a diagnosis of spotted fever group rickettsial infection. The patient was discharged home but there was no improvement in the condition of her digits on follow-up. *Rickettsiae* invade endothelial and smooth muscle cells of the microcirculation causing increased vascular permeability and microthrombi with resulting multi-organ dysfunction and thrombosis. While multi-organ dysfunction is common, gangrene is a rare complication. The epidemiology of Indian tick typhus is poorly defined, but serological surveys and case reports suggest widespread occurrence across the Indian subcontinent. It is characterized by a purpuric rash and unlike scrub typhus, an eschar is rarely seen. Early diagnosis and treatment with doxycycline is crucial to reduce morbidity and mortality due to *Rickettsiae*.

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ADVERSE EVENTS FOLLOWING PURIFIED CHICK EMBRYO CELL (PCEC, RABAVERT®) VACCINE IN THE VACCINE ADVERSE EVENT REPORTING SYSTEM, 2006 - 2015

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In 1997, the Food and Drug Administration licensed Purified Chick Embryo Cell (PCEC, RabAvert®) vaccine against human rabies. A previous post-licensure study in the Vaccine Adverse Event Reporting System (VAERS) during 1997-2005 did not find any safety concerns. This study was undertaken to assess the safety of PCEC vaccines in VAERS during 1/1/2006–12/31/2015. We searched the VAERS database for US reports of adverse events (AEs) among persons who received PCEC during 1/1/2006–12/31/2015. We reviewed all serious (those resulting in death, life-threatening illness, hospitalization, prolongation of existing hospitalization, or permanent disability) and accompanying medical records. Physicians assigned a primary clinical category to each reviewed report. During the study period, VAERS received 490 reports following PCEC vaccination; 38 (7.8%) were serious. No deaths were reported. Females accounted for 301 (61.4%) reports. PCEC was given alone in 407 (83.1%) reports. The median age was 28 years (range 0 - 88 years). The median time from vaccination to onset of an AE was ,<1 day. The most frequently reported AEs were headache (99; 20.2%), nausea (19.0%), pyrexia (91; 18.6%), dizziness (65; 13.3%), and pain (59; 12.0%). Among serious reports, the most common diagnostic categories were general disorders and administration site conditions (18;47.3%), and nervous system disorders (10; (26.3%). In conclusion, a review of VAERS reports did not identify any new or unexpected safety concerns for PCEC vaccines.

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TRICHOSTRONGYLUS INFECTION IN ITALY: REPORT OF FOUR AUTOCHTHONOUS OUTBREAKS DIAGNOSED IN A SINGLE CENTER

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Trichostrongylus spp are nematodes of herbivores, with a worldwide distribution. Humans get occasionally infected through the ingestion of vegetables and water contaminated with the larvae. Hence, the infection is more frequent in people in close contact with livestock and/or with vegetable gardens fertilized with organic manure. In industrialized countries, human infection has been rarely reported. At the Center for Tropical Diseases of Negrar (Verona), Italy, four outbreaks of trichostrongyliasis were diagnosed between August 2010 and July 2015. The four clusters occurred in three different Italian regions: Lombardy (Varese province and Brescia province), Piedmont, and Veneto. All outbreaks affected several/all members of the same household. Of the 12 patients involved, four had no symptoms. The others reported symptoms of different intensity, mostly abdominal pain (8 of 12 patients, 67%) and diarrhea (5 patients, 42%). Some also complained of myalgias (three), pruritus (two), nausea (one), and fever (one). Eosinophilia was present in all subjects, with or without symptoms, and was severe (>5000 eosinophils/mmc) in 5 patients. Medical history revealed in all cases the ingestion of vegetables exposed to sheep/goat manure. *Trichostrongylus* eggs were found at stool examination of only 4 patients. All patients from Piedmont were negative at stool examination, but the goat manure resulted positive for *Trichostrongylus* larvae. The patients were treated either with pyrantel pamoate (750 mg tablets, 4 tablets stat dose) or albendazole 400 mg x 2 for 10 days. Three patients with no symptoms preferred to defer treatment. All treated patients but one (complaining mild symptoms one year and a half after treatment) reported resolution of symptoms. A decrease in the eosinophil count was observed for all patients, including the ones who were not treated. Although not common in areas of temperate climate, *Trichostrongylus* infection should be considered in case of eosinophilia, in particular when present in different members of the same household.

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CLINICAL CHARACTERISTICS OF EBOLA SURVIVORS 40 YEARS POST INFECTION IN THE DEMOCRATIC REPUBLIC OF CONGO

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Ebola virus disease (EVD) is associated with a mortality rate ranging from 25 to 90% and to-date no cure or approved vaccine is available to the general public. The first cases of EVD were reported in 1976 in Yambuku, the north-eastern part of Democratic Republic of Congo (DRC-former Zaire) in the current province of Mongala. During this outbreak, 318 cases of EVD were recorded with 280 deaths, and 38 confirmed survivors. EVD is hypothesized to put suvirors at increased risk of adverse health courses, however, there is limited information regarding long-term health consequences .We enrolled 11 survivors 40 years after the Yambuku outbreak based on original line listings and case data from the DRC Ministry of Health. After informal consent was obtained, we collected information on clinical profiles at 3 times points: prior, during, and present day. The youngest survivor (15 at time of outbreak) is now 55 years old, and the oldest (46 during the outbreak) is 86 years old, with a mean age of 67.25 years. Four survivors were women and 7 men. The mean heart rate was 92 beats per minute with a peak of 128 beats per minute. The average systolic blood pressure was 142mmHg with a peak of 162mmHg. The most common symptoms reported were: muscle pain 82%, headache 64%, joint pain and fatigue 55%, continual cough 36% and ocular problems 27%. Our results add to the small body of the scientific literature that suggest EVD survivors may be at increased risk for long-term sequelae. Additional research with age and sex matched controls is needed to correlate current symptoms with EVD. Understanding the long-term consequences of EVD could lead to improvements in patient care and a better understanding of virus pathogenesis.

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EOSINOPHILIA IN PATIENTS PRESENTING TO A LARGE TRAVEL CLINIC: SPECTRUM OF DISEASE AND IMPLICATIONS FOR A SYSTEMATIC DIAGNOSTIC WORK-UP

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Eosinophilia is an immunological host response to a variety of triggers - ranging from allergens and malignancy to helminthic infections. Patients presenting to travel clinics with eosinophilia present a challenging task to physicians, as the underlying disease spectrum is as heterogeneous as the patient population and no standardized diagnostic work-up exists. In this study, we describe the spectrum of diseases in patients presenting to our travel clinic with eosinophilia. Additionally we assessed whether additional patients' characteristics or laboratory work-up could inform in order to define a more rational and effective diagnostic work-up. We analyzed data from 6,622 consecutive patients between September 2007 and May 2014. Eosinophilia, defined as an absolute eosinophil count of >500 /µl, was present in 2,4% (155/6,622). The median age was 33 years (range: 5-77 years) and 40% (60/155) were female. Most patients presented as ill-returning travelers (78%, 121/155), others were classified as immigrants, expatriates or tourists visiting Germany. An infectious cause was detectable in 57% (89/155) - with the most common specific infections being schistosomiasis (19%, 29/155) and strongyloidiasis (8%, 12/155). Atopic disease and asthma accounted for 10% (16/155), while no specific cause could be identified in 14% of patients (21/155). Patients with a confirmed infectious cause of eosinophilia had slightly higher eosinophil counts (835 vs 712 /µl, p=0.04) but equal levels of IgE (152 vs 176 kU/L, p=0.70) compared to those without an infectious cause. In travelers who visited friends and relatives and in immigrants, an infectious cause was identified more often than in classical tourist travelers (p<0,01). In conclusion, eosinophilia is an important condition in patients presenting to a travel clinic. Our data show that IgE did not yield any added diagnostic value. Instead a systematic diagnostic approach could help to identify the majority of underlying conditions.

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MALARIA AND LASSA FEVER VIRUS CO-INFECTION IN SOUTHERN MALI

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Lassa Virus (LASV) was unknown in Mali until an exported case of Lassa fever (LF) was reported in 2009. Since then, multiple rodent surveys have been conducted and shown evidence of LASV infected *Mastomys natalensis* in several communities restricted to the southern tip of the country near the border of Côte d'Ivoire. LF has similar clinical manifestation with malaria and maybe misdiagnosed. To date only a single case of LF has been confirmed in Mali and little is known about the

prevalence of LASV exposure in human population. The goal of this study is to determine the prevalence of LASV exposure and malaria parasite prevalence in three villages in southern Mali, where infected rodents have been documented and where malaria is endemic. About 1 ml of blood was drawn by technicians for haemoglobin measurement and *Plasmodium* detection by standard microscopy of blood smears from 600 participants under a light microscope for evidence of malaria infection and parasite quantification and an enzymelinked immunosorbent assay (ELISA) was used to screen serum samples for the presence and quantification of Lassa fever virus IgG and IgM. The overall IgG sero-prevalence of LFV was 33.2% and the IgM 1.27% (n =600). The IgG sero-prevalence was as high as malaria parasite prevalence in Bamba (44.0%, vs 40.0%) and soromba (41.0% vs 48.5), and lower in Banzana (14.5 vs 45.0). The majority of malaria infection was due to *P. faciparum* (95.1%). Our results show for the first time that LASV is circulation in human population of Southern Mali and the prevalence of LASV exposure is as high as malaria parasite prevalence. More investigation is needed to identify and monitor hot spot areas which are potential epidemic prone areas.

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PROGNOSIS PREDICTION FOR PATIENTS WITH CONFIRMED EBOLA VIRUS DISEASE IN SIERRA LEONE AND LIBERIA: CLINICAL IMPLICATIONS AND FUTURE APPLICATIONS

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We used a computational framework called FMA to derive prognosis prediction models for confirmed Ebola Virus Disease (EVD) patients, with demographic information, clinical symptoms, and Cycle Threshold (CR) values from RT-PCR as covariates. Our goals are (1) to determine which are the factors that better prognosticate patient survival upon presentation, and (2) to explore the possibility of improved patient triage in emergency settings based on the predicted risk scores. We obtained retrospective cohort data from a total of 476 confirmed EVD patients admitted to five Ebola Treatment Units (ETU) in Sierra Leone and Liberia, between 2014 and 2015. Data was recorded as part of routine clinical care at each ETU, and was combined and deposited in International Medical Corps' secure database. The overall mortality in this cohort is 58%, and univariate regression analysis yields the following variables with a P-value under 0.05: CT measurement in first day (P=8×10-9, OR=0.28), Age (P=9×10-3, OR=1.15), Jaundice (P=10-2, OR=3.9), and Hemorrhagic eyes (P=4.5×10-2, OR=0.65). We trained a Logistic Regression model with Elastic Net regularization on these variables, augmented with a number of additional clinical factors above P=0.05: Coma (P=6.2×10-2, OR=undefined as all patients with coma died), Confusion (P=7.1×10-2, OR=3.1), Breathlessness (P=7.7×10-2, OR=1.5), and Headache (P=10-1, OR=0.7). The CT, Coma, and Confusion variables have missing entries for 60% of the patients. We addressed this issue by using Multiple Imputation (MI) to complete the records, and observed that mortality of patients with missing values is similar to that of the entire dataset, which indicates that the data is Missing Completely At Random (MCAR). Our best model has non-zero coefficients for CT (OR=0.89), Age (OR=1.006), Jaundice (OR=2.7), Hemorrhagic eyes (OR=0.67), Coma (OR=3.7), and Confusion (OR=3.2). The AUC of this model is 0.74, with a 95% CI of (0.74, 0.86), and it shows low overfitting and good calibration. Decision curve analysis suggests that interventions based on this model would be better than a treat-all policy for decision thresholds above 0.45.

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COMMON FINDINGS AND EXCLUSIONS DURING ENROLLMENT OF ADULT MALIAN VOLUNTEERS FOR MALARIA VACCINE STUDIES

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For malaria vaccine testing, volunteers must be enrolled from a suitable site. Screening is a critical step to identify and enroll healthy volunteers. We conducted two malaria transmission blocking vaccine studies in Malian adults in Bancoumana and surroundings from 2013 to 2015. Once informed consented is obtained, each individual undergoes clinical and laboratory assessment. This study aimed to assess the frequency of different conditions or findings that preclude the enrolment of adult subjects into vaccine studies. In 2013, we screened 277 and enrolled 120 volunteers into the malaria vaccine study of Pfs25H-EPA/Alhydrogel®. The eligibility rate was 43.3 % (120/277), and 14.1% (39/277) of volunteers withdrew their consent before or at the time of enrollment. The most frequent reasons for screening failure were positive Hbs antigen (6.9%, 19/277) and neutropenia (6.1%, 17/277). HIV frequency was 3.6% (10/277). No differences were seen among villages for causes of screening failure. In 2015, we screened 478 volunteers and the eligibility rate was 47.1 % (225/478), with 21.3% (103/478) withdrawing consent before or at the time of enrollment. The most frequent reasons for screening failure were positive Hbs antigen (8.8%, 42/478), HIV (7.5%, 36/478) and positive HCV (4.0%, 19/478). Frequencies of HIV (15.9% (7/44)) and hepatitis C (6.8% (3/44)) were higher in Djoliba village than in other villages. In this area, more than half of volunteers failed to be enrolled. Positives Hbs antigen, HCV and HIV are the most frequent laboratory screening failure reasons, and public health authorities should investigate the high rates of these infections in these study communities.

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THE SNAKEBITE ATLAS: A GROUND-BREAKING, OPEN-ACCESS PORTAL FOR SHARING AND GATHERING GLOBAL, COUNTRY-SPECIFIC INFORMATION ON SNAKEBITE DEATHS, ANTIVENOM AVAILABILITY AND VENOMOUS SNAKES

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Venomous snakebites are medical emergencies that annually kill over 95,000 people residing in some of the most disadvantaged, rural and remote tropical communities, and leave 2-300,000 surviving victims with permanent physical disabilities/disfigurements. Victims require instantly-available First Aid information and rapid access to effective treatment. Attending physicians require immediately-available information as to the most effective, locally-available antivenom. Ministries of Health and medical charities require data and information to plan antivenom-provision and snakebite-management strategies. Acquiring this essential life-saving information is currently laborious, problematic and overly dependent upon personal contact networks. The Snakebite Atlas is a free, open-access resource providing geographically-specific information on the venomous snake fauna (including images aiding snake identification), snakebite incidence, morbidity and mortality data, the brand name and manufacturer details of recommended antivenoms, and links to

recommended First Aid and clinical snakebite-management protocols. The system will also allow data capture, and as such, will be a growing resource. The Snakebite Atlas will comprise a database with Geographic Information System (GIS), a visually rich web interface optimized for mobile, an API for 3rd party integration, and an online/offline smartphone app. The provision of the Atlas as a mobile-optimized website and smartphone app will meet the needs of all users, irrespective of their location. Most rural tropical communities have very limited fixed-line internet access, but good mobile coverage. The online/offline app will allow users to access the information even when mobile coverage is not available, and the app will sync with the central database whenever connectivity is sufficient. The Snakebite Atlas therefore offers a much-needed information-sharing tool for clinical and public health practitioners, biologists and the public.

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RESPONSE TO FEVER AND UTILIZATION OF STANDBY EMERGENCY TREATMENT (SBET) FOR MALARIA IN TRAVELERS TO SOUTHEAST ASIA: A SURVEY-BASED COHORT STUDY

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Guidelines in several European countries recommend standby emergency treatment (SBET) for travellers to regions with low or medium malaria transmission (e.g. Southeast Asia (SEA)) instead of continuous chemoprophylaxis. For this approach travellers are advised to seek for medical assistance within 24 hours in case of onset of fever and to self-administer SBET only if they are not able to consult a doctor within the time period specified. Data on health care seeking behaviour of febrile travellers and utilization of SBET is however scarce as only two studies were performed in the mid-1990s. Since tourism to SEA is constantly increasing and malaria epidemiology has dramatically changed in the meantime more knowledge is urgently needed. For this study 876 travellers to destinations in SEA were recruited in the travel clinic of the University Medical Center Hamburg-Eppendorf. Demographic and travel-related data were collected by using questionnaires, pre-travel advice was carried out and SBET was prescribed in accordance to national guidelines. Post-travel phone interviews were performed to assess health incidents during travel and individual responses of travellers to febrile illness. Out of 714 patients who were monitored, 130 (18.2%) reported onset of fever during travel or 14 days after return. Of those travellers who reported fever, 100 (76.9%) carried SBET during travel. The vast majority of 79 (79%) of febrile travellers did not seek for medical assistance. Overall, 16 (16%) of febrile patients who carried SBET and 6 (20%) of patients who did not carry SBET took the correct measure (doctor visit or SBET intake) as a response to febrile illness, respectively. Only 2 travellers self-administered SBET, but both of them applied the wrong regimen. In view of declining malaria transmission and improving medical infrastructure in most countries of SEA and obvious obstacles concerning SBET as shown in this study we propose to re-evaluate the current strategy. Pre-travel advice for travellers to SEA should focus on the simple message to immediately see a doctor in case of febrile illness.

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MORTALITY AMONG EXTREMELY LOW BIRTH WEIGHT INFANTS IN PERU

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Infant mortality has decreased in recent years given improvements in health care policies all over the world. However, neonatal mortality continues to be a major public health issue, especially among very low birth weight and extremely low birth weight (ELBW) infants. There is no data regarding mortality in ELBW infants in developing countries. The aim of the study was to determine the mortality in ELBW infants and to describe the most common etiologies in three neonatal units in Lima, Peru. We enrolled 77 ELBW (<1000g); 21 with a birth weight of 500-750g and 56 with 751-1000g as part of an ongoing clinical trial in three neonatal units in Lima. All patients were followed until death or discharge. Mean birth weight was 831.9 ± 123g, mean gestational age was 27.4 ± 2.3 weeks and length of hospitalization was 43 days (IQR 13-67). Patients with a birth weight ≤750g had an overall mortality of 85.7% while patients with 751-1000g had an overall mortality of 44.6%. Mortality for infants ≤750g was 23.8% within the first 7 days, 42.9% within the first 14 days and 76.2% within the first 28 days of life. For infants 751-1000g, mortality rates were 8.9%, 21.4% and 28.6% within 7, 14 and 28 days, respectively. Neonatal sepsis was the leading cause of death in both groups (50% for infants ≤750g and 76% for infants 751-1000g). Other causes of deaths included intraventricular hemorrhage, extreme prematurity and respiratory distress syndrome. Mortality was high among ELBW infants, especially in those with a birth weight less than 750g. The greatest risk of neonatal death occurred within the first two weeks of life. More studies focusing on mortality and morbidity in ELBW infants in developing countries are needed. This would help to establish prevention strategies that reduce the risk of sepsis and sepsis-related deaths.

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MANAGING THE FEBRILE CHILD IN THE ERA OF SPREADING ANTIBIOTIC RESISTANCE: DEVELOPMENT OF E-POCT, AN ELECTRONIC ALGORITHM THAT USES HOST BIOMARKER POINT-OF-CARE-TESTS

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The objective was to review the available knowledge on epidemiology, diagnosis, and management of acute infections in children aged 2 to 59 months in the outpatient setting and develop an evidence-based electronic algorithm suitable for resource-poor settings that uses available point-of-care tests to achieve optimal clinical outcome while increasing the rational use of antibiotics. Through a structured literature review in Medline, Embase and the Cochrane Database of Systematic Review targeting outpatients aged 2-59 months, we searched for i) available disease prevalence in resource-poor settings, ii) accuracy of clinical predictors, and iii) performance of point-of-care tests for targeted disease management strategies (biomarkers of inflammation, hemoglobin (Hb), blood sugar, and oximetry). A novel electronic algorithm for the management of childhood illness (e-POCT) was designed based on evidence retrieved. The major

changes compared to IMCI (2014 version) are the following: i) use of vital signs (in particular oxygen saturation and heart rate), Hb and glycemia for classification of severe disease, ii) automated temperature- and age-correction of heartrate and respiratory rate, iii) replacement or elimination of clinical signs with low accuracy, iii) classification of bacterial pneumonia based on a combined respiratory-rate and C-reactive protein cutoff (CRP), iv) antibiotic prescription based on CRP and procalcitonin in fever without source patients, v) use of Hb for depiction of severe disease, vi) increased resources for management of skin infections. This novel smartphone-run algorithm based on new evidence and two point-of-care tests should improve the quality of care of under-fives and lead to more rational use of antibiotics.

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INCREASING PREVALENCE OF HUMAN *DIROFILARIA*SIS IN THE UNITED STATES AND EUROPE

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*Dirofilaria*sis is a mosquito-borne filarial infection of carnivores. Since the zoonotic seroprevalence of dirofilariasis has increased, the objectives of this study were to determine human prevalence rates of dirofilariasis and compare them for significant increases over the period, 1999-2012. Internet search engines identified reports of human dirofilariasis in the United States (US) and Europe with cases defined by positive histopathology. Proportional increases in disease prevalence were stratified by nations and compared for statistically significant differences by chi squares (X2) with significance defined by p-values < 0.05. By 2012, 372 cases of human pulmonary dirofilariasis caused by *Dirofilaria immitis* had been reported worldwide representing a 121% increase since 1999. The greatest increases occurred in Italy and the US with the most significant increase in the US (X2=6.4, p=0.011). By 2012, 1,410 cases of subcutaneous and/or ocular dirofilariasis, caused by *Dirofilaria* repens had been reported worldwide representing a 67% increase since 1999. The greatest increases in cases occurred in Russia (X2=66.4, p <0.0001) and Italy (X2=185.9, p<0.0001). Dirofilariasis is an emerging parasitic disease of dogs and man resulting from a combination of factors including warmer year-round global temperatures with shorter winters extending vector transmission cycles; failing regional mosquito control programs; increasing seroprevalence of *Dirofilaria* infections in wild carnivores; increasing parasite resistance to chemoprophylaxis in domestic dogs with macrocyclic lactones, especially ivermectin; and more frequent international travel to *Dirofilaria*-hyperendemic regions, especially the Southern US, Eastern Russia, and the Italian Piedmont. Residents and vacationers in these high-risk regions need to protect themselves from dirofilariasis with mosquito repellents. More effective chemotherapeutics and improved immunodiagnostics and are needed to control and monitor sentinel animal reservoirs. More frequent regional mosquito control will interrupt prolonged vector-transmission cycles.

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DETERMINATION OF BREAK IN TRANSMISSION IN VECTORS OF LYMPHATIC FILARIASIS GHANA

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Since the implementation of the Global Programme for the Elimination of Lymphatic Filariasis (GPELF) in 2000, MDA has been on-going in many LF endemic countries. Post-MDA monitoring of parasite transmission is to assess the efficacy of MDA, when to stop MDA and for the certification of elimination of the disease. Monitoring of the transmission pattern in the mosquito vectors is as essential as detecting levels of infection the human population, since mosquitoes offer real time estimates of transmission. This study aims to provide evidence of break in transmission in vectors of lymphatic filariasis in some endemic areas of Ghana. A total of 7,072 mosquitoes were collected from 53 communities in two selected districts in Ghana in 2013 and 2014. A total of 4,733 (66.9%) *Anopheles* sp. (comprising of *An. gambiae* s.l, *An. funestus* and *An. pharoensis*), 2,274 (32.2%) *Culex* species and 65 (0.9%) Mansonia species were identified and tested. Mosquitoes were tested in pools of 1 to 20 with an average pool size of 15 using Loop-mediated Isothermal Amplification LAMP). All LAMP positive samples were confirmed with PCR. Three pools (2 *Anopheles* and 1 *Culex*) and 2 pools of *Anopheles* tested positive for W. bancrofti in 2013 and 2014, respectively. Infection rates for *Anopheles* and *Culex* mosquitoes for 2013 were found to be 0.97 and 0.86, while that for 2014 were 1.35 and 0.00, respectively. The average biting rates for both years did not show any significant difference (p > 0.99). Surveillance in humans has shown low levels of microfilariae prevalence but in areas where there is residual infection; xenomonitoring offers real time estimates of transmission in areas where very low levels of microfilaremia may not be detected in humans. Therefore the detection of infection in mosquito vectors is an indication that there may be positive individuals in the area of interest.

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EVALUATION OF ONCHOCERCIASIS TRANSMISSION IN TANZANIA: RESULTS FROM THE TUKUYU FOCUS, 2015

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Onchocerciasis, or river blindness, is the second most prevalent infectious cause of blindness in Sub-Saharan Africa. Tanzania implemented annual ivermectin mass drug administration (MDA) in 2000 in the Tukuyu focus, which had pre-control endemicity as high as 63%. Recent MDA coverage was 69-86%. World Health Organization (WHO) guidelines require Ov-16 antibody positivity to be <0.1% in children at risk before stopping MDA. This study compared diagnostic tests in the Tukuyu focus in relation to the guidelines and examined age-group specific differences in prevalence. Eleven villages near vector breeding sites were selected, and an age-stratified random sample was performed. Participants underwent a questionnaire, skin examination, skin snips for microfilaria count and PCR (≥5 years-old only), and blood draw for: rapid Ov-16 antibody test (RDT), Ov-16 ELISA, immunochromatograph (ICT) filariasis rapid test, and daytime blood smears. A total of 695 households (HH) were selected; 617 (98%) HH participated yielding 948 individual participants. A total of 499 (52.7%) participants were male; the median age was 12 years (interquartile range: 6-26 years). Past-year ivermectin use was reported by 522 (65.7%) of eligible participants; itchy skin was reported by 207 (21.9%). Only 12 (1.3%) participants had nodules; manifestations of onchodermatitis occurred in <1% of participants. All skin snips, ICT card tests, and daytime blood smears were negative; 38 (5.5%) participants had a positive RDT. Weighted, adjusted age group specific prevalence was: 0-5 years, 0.5%; 6-10 years, 0.4%; 11-15 years, 0.8%; 16-20 years, 2.2%; >20 years, 10.5%. The low burden of symptomatic disease and few positive RDTs demonstrates that annual MDA has had a significant impact on the disease in the Tukuyu focus. However, the Ov-16 positivity in children failed to meet the WHO guidelines for stopping MDA. Results of skin snip PCR, OV-16 ELISA, and a simultaneous vector collection will

add to the data presented here. Further consideration is needed to assess if the 0.1% threshold is too strict and if extended age groups (≥10 years-old) should be included in future assessments.

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NEW METHODS TO MEASURE CHANGES IN INFECTIOUS DISEASE TRANSMISSION FROM QUANTITATIVE ANTIBODY MEASUREMENTS: EXAMPLES USING *WUCHERERIA BANCROFTI*, *PLASMODIUM FALCIPARUM* AND ENTERIC PATHOGENS

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Global elimination efforts for neglected tropical diseases and malaria rely on accurate estimates of pathogen transmission intensity to target control programs and evaluate their effectiveness. Serological antibody levels have proven to be a sensitive marker of pathogen exposure, and advances in multiplex serological assays have created enormous potential for large-scale, integrated infectious disease surveillance. We developed a novel, nonparametric method using recent advances in ensemble machine learning and statistical estimation to measure changes in transmission from quantitative antibody levels that can be applied to diverse pathogens of global importance. We compared age-dependent immunoglobulin G curves in intervention (Nigeria, Cook Islands) and observational (Haiti, United States) settings with differences in transmission intensity for multiple pathogens, including: lymphatic filariasis (*Wuchereria bancrofti*), malaria (*Plasmodium falciparum*), enteric protozoans (*Cryptosporidium parvum, Giardia intestinalis, Entamoeba histolytica*), enteric bacteria (enterotoxigenic *Escherichia coli, Salmonella* spp.), and norovirus groups I and II. Age-dependent antibody curves followed a characteristic shape across pathogens that aligned with predictions from basic mechanisms of humoral immunity. Changes in pathogen transmission led to shifts in fitted antibody curves that were remarkably consistent across pathogens, assays, and populations. Summary differences between curves provided a robust and sensitive measure of changes in transmission, with greatest sensitivity among young children. Summary *P. falciparum* antibody measures correlated strongly with the entomological inoculation rate (Spearman's $\rho = 0.75$). We will illustrate easy to use, open source software to implement the approach. The method generalizes to pathogens that can be measured in high-throughput, multiplex serological assays, and scales to estimation problems requiring high spatiotemporal resolution -- features that make the approach well-suited to integrated surveillance of global infectious disease elimination efforts.

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THE FIRST SUCCESSFUL CONFIRMED ELIMINATION OF AN ONCHOCERCIASIS FOCUS IN AFRICA: ABU HAMED, SUDAN

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Mass treatment with ivermectin for onchocerciasis was stopped in 2012 in Abu Hamed, an isolated focus on the River Nile in northern Sudan. A three year post-treatment surveillance (PTS) ensued, at the end of which an evaluation was conducted in 2015 following the current WHO guidelines for verification of onchocerciasis elimination. Vector black flies were collected from sentinel breeding sites and fingerprick bloodspots were collected from children ≤ 10 years old resident in 35 communities within the focus. O-150 PCR screening of 19,191 flies from 4 sites found no flies carrying *Onchocerca volvulus* larvae (0%, 95% Upper Confidence Limit = 0.16), and serological testing of 5266 children identified only one Ov16 seropositive child (0.019%, 95% UCL = 0.074); who was negative when screened by O-150 PCR assay. These results indicate that for the first time in Africa, onchocerciasis elimination has been verified following a successful PTS in Abu Hamed.

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USABILITY, ACCEPTABILITY, AND IMPLICATIONS OF UTILIZING THE SD BIOLINE ONCHOCERCIASIS IGG4 RAPID TEST IN ONCHOCERCIASIS SURVEILLANCE IN SENEGAL

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Global efforts toward control and elimination of onchocerciasis have made significant progress through community-directed treatment with ivermectin (CDTI). After years of successful CDTIs, control programs need to determine whether *Onchocerca volvulus* transmission has been interrupted and therefore treatment can be stopped. In many communities, the current testing method is skin snip microscopy; however, this method is less acceptable and has declining sensitivity in low-prevalence settings. The 2016 World Health Organization "Guidelines for Stopping Mass Drug Administration (MDA) and Verifying Elimination of Human Onchocerciasis" recommend using Ov16 serology tests, in addition to entomological evaluations, for post-treatment and post-elimination surveillance. The SD BIOLINE Onchocerciasis IgG4 rapid test (Standard Diagnostics, South Korea) is a rapid Ov16 serological diagnostic test (Ov16 RDT) that is field friendly, noninvasive, simple to use, and low cost. Our hypothesis is that the Ov16 RDT is an improved tool over skin snip microscopy for country programs to monitor their progress toward stopping MDA and reaching elimination. The study incorporates the Ov16 RDT in ongoing onchocerciasis surveillance activities in Senegal in 15 villages among 1,250 individuals over the age of 5 years. The study compares age-prevalence curves, workflow, and cost analyses of the Ov16 RDT and skin snip microscopy. Additionally, usability and community acceptance of the Ov16 RDT are assessed using a mixed methods research design, and a mobile phone-based data collection tool is piloted along with traditional data collection systems. This study provides key evidence of the feasibility of implementing the Ov16 RDT to make critical decisions about whether to continue, halt, or re-initiate MDA efforts in communities. The results of this study may be informative to other country programs interested in adopting this new tool, particularly as these country programs quickly move from control to elimination of onchocerciasis.

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THE FEASIBILITY OF A 'RE-MAPPING' PROTOCOL FOR LYMPHATIC FILARIASIS IN AREAS WHERE TRANSMISSION IS UNCERTAIN IN ETHIOPIA

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Lymphatic filariasis (LF) is one of the world's leading causes of permanent disability. WHO proposed a comprehensive strategy to eliminate LF by 2020, interruption of transmission through MDA and morbidity management. The global program to eliminate lymphatic filariasis (GPELF) recommends mapping as an initial step to determine the need of MDA in Implementation units (IUs). The existing WHO guideline recommends two sites per IU should be selected for mapping and a sample of 100 adults should be tested for antigenaemia. In low transmission setting this strategy has limitations. An alternative complementary mapping method that could resolve this situation is useful. This study was, therefore, designed to assess the Lf endemicity level of IUs in Ethiopia which have low transmission setting. The 2013 mapping in Ethiopia resulted in 45 IUs with antigenemia result not enough for programmatic decision making. To solve this gap the school based re-mapping study was conducted in two phases; phase I was conducted last year in 8 IUs, to evaluate the protocol itself. The study proceeded to Phase II after the result of the phase I re-mapping was analyzed and interpreted. In this survey, schools were selected by either systematic or cluster sampling, based on the number of schools in the IUs. From each selected school children of grade 4 to 8 were sampled systematically and tested for antigenemia. The number of positive result was compared against the critical value. From 41 IUs involved in second phase re-mapping survey, antigenesimia was tested from 16,365 children of target grades in selected schools. In 39 of the IUs, the number of antigen positive identified in the re-mapping surveys was below the critical cut off, suggesting transmission of LF is not ongoing in these IUs. Where as in two of the IUs, the number of antigen positive identified was above the critical value suggesting that the LF transmission is ongoing. In low prevalence areas, where the current WHO protocol has several limitations, this re-mapping study design will provide enough information on the LF transmission situation which may help programs to make evidence based decision.

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LONGITUDINAL EVALUATION OF ONCHOCERCIASIS 2012-2015 IN THE MID NORTH FOCUS IN UGANDA

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Onchocerciasis is a neglected tropical disease that is targeted for elimination. Uganda implemented annual mass drug administration (MDA) with ivermectin (IVM) in this focus in 2009 and began twice yearly MDA in October 2012. Late in 2012 it also implemented a 1-year vector control program. We conducted an initial survey of 500 people in September 2012 and a follow-up survey in September 2015. All participants underwent questionnaires, skin examination for *Onchocerca*-associated lesions, two skin snips and a venous blood draw. Skin snip microscopy, PCR and OV-16 ELISA were performed on the collected specimens. A total of 343 (68%) people re-enrolled in the 2015 study; 209 (60%) were female, and the median age was 36 years (range 10-90 years). The use of IVM was high at both time points (86% vs. 88%). Comparisons between 2012 and 2015 showed that significantly fewer people at follow up had skin nodules (54% vs 24%), positive skin snip results (25% vs 6%), as well as skin lesions: acute papular onchodermatitis (3% vs. 0.3%), chronic papular onchodermatitis (6.5% vs 0.6%), lichenified onchodermatitis (6% vs 0%), and skin depigmentation (9.7% vs 1.6%) (McNemar's test, $p<0.05$). Significant reductions in microfilarial density in skin snips (2.3 vs 0.2 microfilariae/2 snips/person) and OV-16 ELISA optical density (OD) values (2.08 [SD=1.58] vs 0.92 [SD=1.14]) (paired t-test, $p<0.05$) were also observed; however, the prevalence of OV-16 positivity did not change (85% vs 79%). Taken together, these results show that a significant reduction in disease morbidity occurred in North Uganda after three years of twice per year IVM MDA and one year of vector control. Both skin snip microscopy and quantitative OV-16 ELISA provided important information on MDA program impact. Correlating OV-16 ELISA results to other markers of infection might allow for the differentiation of on-going versus suppressed transmission. Furthermore, the decline in OV-16 ELISA values suggest its potential use as an alternative to skin snip PCR when assessing those few individuals with OV-16 positive results in program evaluations to stop MDA.

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DETECTION AND EVALUATION OF ANTI-OV-16 ANTIBODIES FOR ONCHOCERCIASIS SURVEILLANCE IN THE CENTRAL ENDEMIC ZONE OF GUATEMALA

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Current WHO guidelines recommend testing for OV-16 serologic responses in children to determine when it is appropriate to stop mass drug administration (MDA) for onchocerciasis. Understanding the decrease in antigen-specific seropositivity over time might allow the inclusion of older age groups for these assessments or post-treatment surveillance (PTS). In the Central Endemic Zone (CEZ) of Guatemala, interruption of onchocerciasis transmission was observed in 2011 and confirmed in 2014. A follow-up study was conducted in October 2014 to assess the serological response to onchocerciasis among people tested between 2003 and 2009, while transmission was ongoing. Comparisons were based on a normalized OV-16 ELISA, with a positive cutoff of 40 Activity Units (AU). Results from participants with positive serology at baseline were used to conduct a preliminary estimation of temporal antibody decay rates using a mixed effects linear regression model. A total of 230 people (120 female, 52%) were enrolled, 85 with previous positive OV-16 ELISA results and 145 who were negative. The 85 positives contributed 93 retrospective data points with mean AUs of 86 (n=11), 174 (n=59), 108 (n=19) and 82 (n=4) in years 2003, 2006, 2007 and 2009, respectively, and 40 [95% CI 23.8-55.8] in the 2014 follow up. Those considered negative contributed 155 data points, with mean AUs of 30 (n=18), 19 (n=59), 10 (n=67) and 0.1 (n=11) in 2003, 2006, 2007 and 2009, respectively, and 6 [95% CI 3.9-7.7] in the 2014 follow up. Additionally, none of the 77 study participants under the age of 20 years had a positive serologic result. Temporal analysis of AUs showed a mean decay rate of 0.31/year (SD= 0.20) and an average half-life of 2.25 years. These results concur with previous assessments that onchocerciasis transmission had been interrupted in the CEZ. The antibody responses to OV-16 appear to have decreased over time, presumably due to the lack of exposure to viable adult worms. These findings also highlight the importance of conducting further studies to determine if people ≥10 years of age could be included in evaluations for stopping MDA, PTS, or post-elimination surveillance.

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A DELPHI CONSULTATION TO ASSESS INDICATORS OF READINESS TO PROVIDE QUALITY HEALTH FACILITY-BASED LYMPHEDEMA MANAGEMENT SERVICES

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The World Health Organization (WHO) in collaboration with partners is developing a toolkit with resources to guide lymphatic filariasis (LF) morbidity management and disability prevention (MMDP) implementation and evaluation. Assessment of the readiness of programs to provide quality lymphedema management services is recommended via a direct facility inspection. As part of tool development, a Delphi consultation was implemented to gain consensus on the proposed themes and tracer indicators to measure readiness to provide quality health facility-based lymphedema management services. A seven-point Likert-type scale was used to rank the importance of proposed themes and tracer indicators. Consensus for inclusion of the indicator was defined a priori as 70% or more of respondents ranking the proposed indicator in the top three points (5-7). Purposive sampling was used to select 43 representative experts including neglected tropical disease (NTDs) country representatives, program implementers, and technical experts. A 55.8% response rate (n=24) was achieved for the first round of the survey. The majority of respondents had ten or more years of expertise (n=17, 70.8%) in MMDP or NTDs. Analysis of the first round of data demonstrated that consensus for inclusion had been reached across all proposed indicators including trained staff (mean=6.9, standard deviation (SD)=0.34), case management and education materials (mean=6.1, SD=0.65), water infrastructure (mean=6.3, SD=0.81), medications and commodities (mean=6.3, SD=0.69), patient tracking system (mean=6.3, SD=0.85), and staff knowledge (mean=6.5, SD=6.5, SD=0.66). The results from this analysis were used to inform revisions of the direct inspection which will be piloted in several countries to further refine tools to assess readiness to provide quality lymphedema management services.

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REEXAMINATION OF AREAS WITH PERSISTENT LYMPHATIC FILARIASIS 9 YEARS AFTER CESSATION OF MASS DRUG ADMINISTRATION IN SRI LANKA

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Sri Lanka was one of the first countries to initiate a lymphatic filariasis (LF) elimination program based on WHO guidelines. Following several years of mass drug administration (MDA) with DEC alone, the Anti-Filariasis Campaign (AFC) provided 5 annual rounds of MDA with DEC plus albendazole in all endemic districts in the country from 2002-2006. The AFC and other groups have conducted extensive surveillance activities since 2006. Microfilaremia (Mf) rates have been consistently <1% in all sentinel and spot check sites since that time, and all 11 evaluation units passed school-based transmission assessment surveys (TAS) in 2013. We have previously reported results from comprehensive surveillance studies conducted in 2011-2013 that documented low-level persistence of LF in 19 high risk Public Health Inspector areas (PHI, mean population 25,000) spread across 8 endemic districts. We now present results from repeat comprehensive surveys conducted in 2015 (8 to 9 years after the last round of MDA) in 5 PHI areas that had the strongest LF signals in the prior study. These surveys assessed community CFA and Mf rates, CFA and anti-filarial antibody rates in school children (ages 6-8), and filarial DNA rates in *Culex quinquefasciatus* collected with gravid traps. Two areas had encouraging results with improved LF parameters (Pw and KN), but three other areas (Uw, Amb, Wg) showed no significant change. Our study also identified a new hotspot in Galle district with alarmingly high LF parameters (community CFA 3%, Mf 1%, anti-Bm14 antibodies in school children 5.7%, and a filarial DNA rate of 5.2% in the vector). Thus areas with persistent LF in Sri Lanka appear to be close to the transmission breakpoint; LF is likely to disappear without further intervention in most areas, while other areas may require more work. We think that LF elimination programs should consider using methods other than school-based TAS to identify areas with persistent LF following completion of MDA. In addition, long term surveillance may be needed to verify that LF has been eliminated, and this may be especially true in areas like Sri Lanka where the parasites are transmitted by *Culex* mosquitoes.

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DEFINING AND DETECTING SUBOPTIMAL RESPONSES TO IVERMECTIN IN PATIENTS WITH ONCHOCERCIASIS

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Mass drug administration (MDA) with ivermectin is the cornerstone of global efforts to eliminate onchocerciasis (river blindness). Several epidemiological studies in Ghana and Cameroon have reported so-called suboptimal or atypical responses to ivermectin in patients infected with *Onchocerca volvulus*, the causative filarial parasite of onchocerciasis. These responses are characterised by a faster than expected rate of skin repopulation by parasite microfilariae following treatment and have been interpreted as warning signs of decreased efficacy of the anti-fecundity effects of ivermectin on adult female worms, potentially caused by emerging (reproductive) resistance. Yet, there is currently no clear and objective definition of what constitutes a suboptimal response nor any reliable method for detangling the true underlying drug response from the high degree of statistical sampling error incurred when counting microfilariae in skin snips. Here we tackle this problem using an individual-based statistical model which we fit in a Bayesian framework to individual patient data from the first set of clinical trials of ivermectin against human onchocerciasis conducted in the mid 1980s, before the widespread use of ivermectin for MDA. We use the fitted model to define predictive distributions of typical responses to ivermectin in drug-naïve patients and validate these using both censored data from the same set of (historical) trials and contemporary data from ivermectin-treated control patients who participated in the recent phase II clinical trial of moxidectin. We discuss how the analytical framework can be used to identify and monitor suboptimal responses to ivermectin in populations undergoing long-term MDA.

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THE EFFICACY OF PREVENTATIVE CHEMOTHERAPY DRUGS FOR THE TREATMENT OF LYMPHATIC FILARIASIS: A SYSTEMATIC REVIEW AND MODEL-BASED META-ANALYSIS

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The principal intervention strategy to control and eliminate lymphatic filariasis (LF) is so-called preventative chemotherapy (PCT) by mass drug administration (MDA) with combinations of albendazole and either ivermectin or diethylcarbamazine. These therapies, although of uncertain

efficacy against adult parasites (macrofilariae), suppress numbers of blood-borne microfilariae for approximately one year after treatment. Because microfilariae are infectious to the mosquito vectors of lymphatic filariae, if enough infected people are treated, transmission between treatment rounds will be markedly reduced or interrupted completely. Local elimination is possible if this can be maintained for at least as long as the natural life-span of the macrofilariae. While compelling, a key uncertainty in this elimination algorithm, is for how long following treatment microfilariae are sufficiently suppressed such that individuals adhering to MDA are essentially removed as contributors to transmission. Indeed, the efficacy of PCT drugs is currently incorporated into LF transmission models (that are used to predict timeframes for elimination) with considerable uncertainty, based on expert opinion and semi quantitative ultra-sonographic data on macrofilariae. Here, we present a literature review to identify clinical and field trials of the efficacy of the PCT drugs used to treat LF and extract relevant data on numbers of microfilariae at different times following treatment. We develop a simple mathematical model to describe the population dynamics of microfilariae following treatment and fit this to the available data. We use the fitted model to characterise the efficacy of PCT combinations against LF and discuss the application of our results to mathematical transmission models of LF and to the detection of suboptimal or atypical drug responses.

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IMPACT OF IVERMECTIN MASS TREATMENT ON THE BURDEN OF *ONCHOCERCA*L SKIN AND EYE DISEASE: DETAILED MODEL PREDICTIONS UP TO 2025

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The African Programme for Onchocerciasis Control (APOC) coordinated from 1995-2015 annual ivermectin mass treatment to control morbidity of onchocerciasis (river blindness). These efforts should be maintained even after 2015 to achieve elimination in 80% of all endemic countries by 2025, although this may not be achievable everywhere due to late onset of infection and/or low treatment coverage. Even if elimination is realised, a considerable chronic disease burden remains due to earlier infection. To understand the need for alternative interventions and new drugs, we predict trends in infection and onchocercal morbidity over time up to 2025, stratified by age and sex. We use the individual-based model ONCHOSIM to predict trends for a range of scenarios, varying by type of onchocerciasis (forest / savannah), baseline endemicity, history and future of control. The model was extended to make detailed predictions for a wide spectrum of forms of onchocercal skin disease, which so far were considered to only include itch. Model parameters were quantified to reproduce association between infection and morbidity using data from a TDR-funded multi-country field study on onchocercal skin disease as well as literature on visual impairment and blindness. The prevalence of infection, morbidity and excess mortality decline progressively over time up to 2025. The prevalence of reversible skin disease (e.g. troublesome itch, acute and chronic papular, and lichenified onchodermatitis) declines rapidly with waning infection prevalence, with the rate of the decline depending on achieved therapeutic coverage. Irreversible manifestations i.e. visual impairment, blindness, atrophy, depigmentation, and hanging groin decline much more gradually. This study provides better insight in expected trends of infection and onchocercal morbidity. We discuss expected trends in disease burden for endemic countries and Africa as a whole, which will be useful to policy makers and national onchocerciasis control programmes.

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APPLYING A MOBILE SURVEY TOOL FOR ASSESSING LYMPHATIC FILARIASIS MORBIDITY IN MTWARA MUNICIPAL COUNCIL OF TANZANIA

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A number of methods have been used to estimate lymphatic filariasis (LF) morbidity, including: routine programmatic data, cluster random surveys and the "town crier" method. Currently, few accurate data exist on the global LF morbidity burden. We aimed to estimate prevalence of lymphedema and hydrocele in Mtwara Municipal Council using mobile phone based survey. A cross-sectional survey was conducted among adults of Mtwara municipal council with access to mobile phones. A sample size of at least 384 completed surveys was required to estimate prevalence of lymphedema (both males and females) and hydrocele (males only) morbidity of 50% within a 5% error margin given a 5% level of significance and 95% confidence level. Eligible mobile phone users received a short message text (SMS) requesting consent to participate in the survey. A total of 10 questions were administered via interactive SMS through GeoPoll, a survey platform developed by Mobile Accord (research.geopoll.com). The survey was completed over a period of 4 days. A total of 8,759 surveys were sent to mobile phone subscribers of whom 1,330 (15.2%) opted-in to complete the survey. A total of 492 (37.0% or those opted-in, 384 male and 108 female) people completed the survey. Lymphedema and hydrocele signs were reported by 20.9%; (95% confidence interval [CI] 17.4 - 24.8) and 20.6%; (95% CI 16.6-25.0) of respondents, respectively. Majority of hydrocele patients (59.5%) and 46.6% of lymphedema patients reported having sought treatment. The proportion of patients reporting similar symptoms among friends are relatives was 35.8% and 70.9% for lymphedema and hydrocele, respectively. The findings suggest that mobile phone based surveys are a practical and rapid approach of undertaking morbidity surveys. While further methods of clinical examination are needed to verify the findings, this approach can be expected to encourage identification of lymphedema and hydrocele morbidity at community level and provide evidence where morbidity management services are warranted.

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STEPS TOWARDS ELIMINATION: RE-EVALUATION OF LYMPHATIC FILARIASIS PREVALENCE IN TANZANIA

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Despite positive strides made in the control of lymphatic filariasis (LF), this disease continues to cause morbidity and mortality in Tanzania. In order to inform targeted and effective mass drug administration (MDA) in the country, the national neglected diseases program (NTDCP) conducted remapping in 2015. The purpose of the re-mapping surveys was to to assess LF prevalence levels and to identify new LF transmission hotspots in areas where MDA had not been implemented before. The 2015 LF remapping exercise was conducted in nine regions covering 63 districts in the Lake, Western and Northern zones in Tanzania, with support from USAID through the ENVISION Project and from the Task Force for Global Health. The 9 regions included Geita, Simiyu, Mwanza, Arusha, Shinyanga,

Mara, Kagera, Kigoma and Kilimanjaro. This was a randomized 30-cluster school survey design, in which 30 primary schools were randomly selected from each district. Fifteen children aged from ≥10 years were selected randomly from each school. A total of 1,770 primary schools were randomly sampled and 29,054 students aged ≥10yrs old were tested for LF. Each child was tested using the immunochromatographic card test (ICT) for LF. Of these, six positive LF tests were confirmed, equivalent to 0.021% of the total number of students tested. The confirmed positive LF tests were found in Magu DC, Ukerewe DC, Misenyi DC, Moshi DC and Bariadi TC. The results of the re-mapping indicated that these districts do not require MDA. This is an important step in scaling down MDA interventions in Tanzania and now the NTD program will focus on the remaining districts to achieve elimination.

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MOSQUITO BITE HETEROGENEITY INFLUENCES LYMPHATIC FILARIASIS PREVALENCE, INTENSITY AND OPPORTUNITIES FOR CONTROL

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Global efforts to eliminate lymphatic filariasis have achieved many successes in the local elimination of this debilitating neglected tropical disease. An emerging challenge to the elimination program are heterogeneities in village-specific characteristics within district-level interventions. One important question is how aggregated exposure to infective bites and aggregated worm burden impact the choice of intervention and the optimum coverage needed to achieve elimination and how this varies spatially. We test the hypothesis that heterogeneous disease patterns are derived primarily from the distribution of infective bites received by an individual over their lifetime. We also test the hypothesis that vector control results in more heterogeneous exposure which may influence the time to local elimination. We employed a dataset from five villages in Papua New Guinea characterized by moderate to high transmission of LF. These included spatially resolved anopheline densities surrounding the bednet distribution, and individual antigenemia and microfilaremia. We calculated the heterogeneity of biting density and mf by the fitting of a negative binomial distribution at both village-level and at the level of individuals. This was complimented with a full geospatial model of filariasis infection based on the underlying distribution of bites. We found that the heterogeneity of bites at the village level is a very poor indicator of heterogeneity in the mf count (correlation less than 0.1). We observed a significant increase in bite risk heterogeneity, however the decrease in biting density achieved by bednets more than offset the increase in bite aggregation, resulting in a shorter recommended course of mass drug administration. At the individual level, the biting density was a stronger indicator of mf burden, although there was a significant variation in the distribution unaccounted for. This highlights the need for further investigation on how the population-level distribution of parasites arises from environmental, geographic and individual factors.

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ONGOING TRANSMISSION OF ONCHOCERCIASIS IN THREE COMMUNITIES IN MASSANGAM DISTRICT IN WEST CAMERON AFTER 18 YEARS OF MDA OF IVERMECTIN

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The West Region of Cameroon has been under annual ivermectin mass distribution (MDA) for more than 15 years but transmission is on-going. High *Onchocerca volvulus (O.V)* infections have been identified through studies conducted by Sightsavers in collaboration with the Ministry of health of Cameroon, in the Massangam health district and Makoupsap village in particular. There was therefore a need to clearly delineate the boundaries of this potential high transmission focus. We conducted epidemiological and entomological surveys to evaluate the prevalence of Onchocerciasis in the communities around Makoupsap, map out the breeding sites of *Simulium damnosum* s.l. and thus delineate the boundaries of such a potential focus. Nodule prevalence in communities within 20 Km of Makoupsap were determined through clinical examination and prevalence of *OV* microfilaria was determined in children up to 10 years using the IgG_4 (Ov 16) and positive children to OV-16 were skin sniped . Breeding sites were prospected for blackfly larvae and adult blackflies were collected on Esperanza Window traps using hand-held battery powered aspirators. In total 2375 persons participated in the study. The nodule prevalence was 3.4% with children of 6-10 years having nodules in two communities. 898 persons were skin snipped and 115 were positive giving a microfilaria rate of 12.9%. 1530 children were assessed using OV-16 and 148 were positive giving a prevalence of 1.5%. 4598 blackflies were caught during the 9 days of collection. Morphological identification revealed that *S. squamosum s.s.* was the only vector in this region. 3162 females were dissected. Of these, 633 (20.02%) were parous, while 8 (0.25%) were infected and 2 (0.06%) were infective. Mbam River is probably the most important source of biting *S. squamosum s.s.* during the high biting season. These surveys showed an on-going transmission of onchocerciasis in 3 communities despite 18 years of Ivermectin MDA.

1105

IMPLEMENTATION OF A FACILITY-BASED INSPECTION TOOL TO ASSESS QUALITY OF LYMPHEDEMA MANAGEMENT SERVICES IN VIETNAM

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Lymphedema (LE) management activities in Vietnam were initiated in 2004, when staff were trained to provide facility-based services for patients with LE. With the support of USAID's MMDP Project, Vietnam piloted a WHO-developed direct inspection tool to measure the quality of health facility-based LE management services. A list of all commune health stations (CHS) in areas with known LE patients was compiled. Patients were reported from 213 CHS in the Northern region, 2 CHS in Central region, and 2 CHS in Southern region. About 10% of facilities in the north were randomly selected, whereas all facilities with patients were selected in the Central and Southern regions. A standardized questionnaire was administered at each facility capturing data on 14 equally-weighted tracer

indicators across six quality themes: trained staff, case management and education materials, water infrastructure, medications and commodities, patient tracking system, and staff knowledge; as well as patient knowledge. Scores were generated for the 32 CHS surveyed, as well as national scores for each tracer indicator. The average facility score was 8.8 out of 14.0 possible points (62.9%), and ranged from 4.0 (28.6%) to 13.0 (92.9%). The national average score for each of the tracer indicators was: staff trained in last two years (0.0%); availability of LE management guidelines (56.3%), availability of information, education, and communication materials (15.6%); reliable improved water infrastructure (93.8%); availability of antiseptics (81.3%), antifungals (43.8%), analgesics or anti-inflammatories (96.9%), oral/injectable antibiotics (93.8%), supplies for LE and acute attack management (100.0%); LE patients recorded in last 12 months (9.4%); staff knowledge about LE signs/symptoms (62.5%); staff knowledge about LE management strategies (71.9%); staff knowledge about signs/symptoms of acute attacks (81.3%); and staff knowledge about acute attack management strategies (75.0%). Attrition of trained health staff and depletion of education materials are some areas where Vietnam is planning to reinforce to ensure quality LE services.

1106

ASSESSING AN IMPORTANT BARRIER TO ONCHOCERCIASIS ELIMINATION: DETERMINANTS AND CHARACTERISTICS OF *LOA LOA* INFECTION AND INTENSITY IN CAMEROON AND GABON

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As the 2020 deadline for elimination of onchocerciasis approaches, it is essential to determine the mapping and treatment needs of areas with untreated hypo-endemic onchocerciasis (<40% prevalence) currently ineligible for mass drug administration (MDA) with ivermectin due to co-endemicity of *Loa loa* infection. Intensity of *L. loa* infection is associated with likelihood and severity of serious adverse events (SAEs) to ivermectin MDA. To inform guidelines for future testing and treatment decisions in 10 *L. loa* endemic countries, we used existing *L. loa* prevalence and intensity data from Gabon (10214 individuals tested in 2014-2015) and Cameroon (5574 individuals tested in 2012-2013) to describe demographic predictors of *L. loa* infection. We used the following guidelines to characterize intensity of *L. loa* infection: no infection detected (0 mf/mL), low intensity (<8,000 mf/mL), medium intensity (8,000-<30,000 mf/mL), and high intensity (>=30,000 mf/mL). In Gabon, 8355 (82%) had no infection, 1503 (15%) had low-intensity infection, 265 (3%) had medium-intensity infection, and 91 (1%) had high-intensity infection. In Cameroon, 3929 (70%) had no infection, 1346 (24%) had low-intensity infection, 215 (4%) had medium-intensity infection, and 44 (2%) had high-intensity infection. Males had a higher prevalence of infection in both Gabon (21% vs. 16%, p<0.0001) and Cameroon (34% vs. 25%, p<0.0001). In both countries, *L. loa* prevalence increased with age. In Gabon, 5% of individuals under age 15 were infected compared to 26% of individuals ages 60 and older. In Cameroon, 13% of individuals under age 15 were infected compared to 37% of individuals 60 and older. High intensity infections were rare but found in all age groups in both countries. These results suggest that *L. loa* testing targeting males and older individuals would be most likely to detect *L. loa* infection in a community.

1107

LOSS OF CROSS-REACTIVE FILARIAL ANTIGENEMIA IN PERSONS WITH LOIASIS IN CENTRAL CAMEROON

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Recent reports have shown that some persons with loiasis have positive *Wuchereria bancrofti* antigen tests, and this problem is more common in persons with high *Loa loa* microfilaria (Mf) counts. False-positive antigen tests present a challenge for mapping and monitoring of LF elimination efforts in central Africa. We collected blood samples from adult volunteers in *L. loa*-endemic areas in central Cameroon to obtain material for research on cross-reactive filarial antigen(s). We collected blood samples from 183 persons living in the Akonolinga and Awae health districts. Eighty-nine (49%) of these participants had tested positive for loiasis in prior studies, and 18 (10%) had tested positive for *W. bancrofti* antigenemia by ICT in 2013 or 2015. None of the new blood samples ICT positive, and only 3 of 183 plasma samples from the same participants were weakly positive by Alere FTS. *L. loa* Mf counts in the 18 persons previously ICT positive were slightly higher during the present study (median 17, 540, IQR 12,120 - 36,620) than in the prior studies (median 11,870, IQR 5,240 - 32,540). Loa Mf counts were lower among participants with previously negative ICT results (median 2,000, IQR 340 - 4,480), and comparable to their counts in the prior studies (median 2,720, IQR 840 - 6,900). No participant had *W. bancrofti* Mf in night blood smears. These results suggest that persons with loiasis may spontaneously clear a cross-reactive filarial antigen detected by ICT card tests and that this is independent of their clearance of Mf. Our results may also help to explain why many areas in Africa with loiasis do not report falsely positive filarial antigen tests. This variability may be related to differences in infection intensity and/or variable clearance of filarial antigenemia in different regions or seasons.

1108

PREVALENCE OF ANTIBODIES TO WB123 SIX YEARS AFTER ELIMINATION OF LYMPHATIC FILARIASIS AS PUBLIC HEALTH PROBLEM IN TOGO

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Togo has successfully eliminated lymphatic filariasis (LF) as a public health problem. The last mass drug administration (MDA) targeting LF was in 2009. Since then, LF surveillance has included lab-based screening of nighttime blood films for microfilaria in patients tested for malaria and regular testing of a convenience sample of persons across Togo using the Binax Now® ICT, with follow-up blood films in those who test positive. Togo has also passed two post-MDA transmission assessment surveys. During six years of surveillance, only 8 individuals have tested positive for active infection, and only 3 of those were residents of Togo. In 2015, Togo employed the InBios Filaria Detect IgG4 ELISA to establish the prevalence of antibodies to Wb123 six years after interrupting LF transmission and to assess the utility of the Wb123 ELISA for LF surveillance. The survey was integrated with an integrated NTD impact assessment. At two schools in all 157 peripheral health units of the 8 districts previously endemic for lymphatic filariasis, a convenience sample of 8 school-going children age 6 to 9 years old provided blood spots on filter paper (DBS) for testing by Wb123 ELISA. DBS were obtained from 2344 children. Wb123 ELISA testing is ongoing. All samples run to date appear to be negative for Wb123 antibodies but interpretation of test results is challenging; negative and positive cut-off values are not established and results are

best interpreted using the expectation maximization algorithm (EMA). ELISA directions recommend testing 100 confirmed LF-positive samples, 100 known LF-negative samples, and 100 samples from individuals with other known filarial infections or non-filarial febrile illness. This proves challenging in the setting of LF elimination, and limits utility of the test. Once all samples have been run, the EMA should yield interpretable results. The Wb123 ELISA may be useful for tracking antibody prevalence over time as a means of surveillance for resurgence of LF in Togo, but the need for skilled technicians and difficulty with interpretation pose challenges.

1109

A BIOINFORMATICS APPROACH TO ASSESS PARASITE KINASES AS DRUG TARGETS USING ANTI-CANCER DRUGS

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The role of human kinases in carcinogenesis has been largely demonstrated. Such knowledge has allowed the development of a variety of kinase inhibitors that target mutated kinases in their kinase domains. At the contrary, protein kinases expressed by parasites have been less studied and their participation in infection remains poorly understood. The present work aimed to determine similarities and differences, at sequence and structure levels, in a set of human 21 kinases and their orthologs from 9 parasites. Microorganisms were divided in carcinogenic parasites (i.e. *Schistosoma hematobium, Ophistorchis viverrini, Clonorchis sinensis*) and non-carcinogenic parasites (i.e. *Plasmodium falciparum*, *Taenia solium, Trypanosoma cruzi, Fasciola hepatica, Leishmania donovani,* and *Echinococcus granulosus*). By applying sequence alignment, phylogeny algorithms and 3D-structure analysis, the comparison of human kinases and their counterparts in parasites was established. Human cancer-related kinases had homologs in parasites, with up to 69% amino acid sequence identity. Such level of conservation was considerably high given the large phylogenic distances among the species analyzed. The human cytosolic kinases showed higher amino acid sequence conservation than human membrane kinases when compared to their homologs in parasites. The cytosolic kinases BRAF, AKT-1, ABL-1, c-SRC, and CDK8 had the higher level of conservation and were present in carcinogenic and non-carcinogenic organisms. A coevolution of kinases in both the host and the parasite is plausible to explain the highly conservation observed among kinases. Residues involved in binding of inhibitors to the active site were inspected in human BRAF, AKT-1, ABL-1, c-SRC, CDK8 and found that most of them were conserved in the corresponding sequences of parasite orthologs. This observation can be exploited and taken as an advantage to repurposing human kinases inhibitors into their homologues in parasites.

1110

DEVELOPMENT OF IMMUNOCOMPETENT ANIMAL MODELS FOR SIMULTANEOUS AND SEPARATE TESTING OF DRUGS ON *ONCHOCERCA* AND *LOA LOA* MICROFILARIAE, AND *ONCHOCERCA* ADULT WORMS

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Onchocerciasis is the second leading infectious cause of blindness globally, with over 99% of all patients residing in tropical Africa. The only currently recommended drug for treatment of the disease, ivermectin, kills the microfilariae (mfs) of the causative parasite, *Onchocerca volvulus*, but also *Loa loa* mfs in the blood of co-infected patients, resulting in severe adverse events and fatalities in some cases. Ivermectin does not kill the adult worms, which can linger on for more than 14 years, aggravating the burden of the disease. The search for new drugs against onchocerciasis has been seriously hampered by the lack of suitable animal models. The present study was aimed at developing immunocompetent small animal models that can better mimic the natural infection and that can be used to simultaneously or separately test new drugs on *L. loa* and *Onchocerca* ochengi mfs and adult *O. ochengi* worms. The co-infection model would permit selection for drugs that kill only *Onchocerca* and avoid fatalities in *L. loa* co-endemic areas during mass drug administration with current microfilaricides. Of several animals tested, the Mongolian gerbil (*Meriones unguiculatus*) was the only one permissible to both parasite species, with good parasite recoveries and excellent viabilities recorded on day 30 post experimental infections. Syrian hamsters were highly permissible to *Onchocerca* mfs and adult worms, but not to the *L. loa* mfs. Treatment of the gerbil co-infection with ivermectin at 150 µg/kg body weight resulted in complete elimination of *L. loa* mfs in blood and *O. ochengi* mfs in skin, and viability reduction of *L. loa* mfs in the peritoneum. Further development of the models is on-going, but so far we have developed and validated a new small animal co-infection model for the development of onchocerciasis drugs that do not kill *L. loa* mfs, and established suitable small animal hosts for adult *Onchocerca* worms.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 7-AMINO PYRAZOLOPYRIMIDINE COMPOUNDS POSSESSING POTENT ANTI-*WOLBACHIA* ACTIVITY FOR THE TREATMENT OF ONCHOCERCIASIS AND LYMPHATIC FILARIASIS

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Filarial nematodes are a group of human pathogens that affect more than 157 million people worldwide, contributing to serious public health and socio-economic challenges. These parasites are responsible for the Neglected Tropical Diseases lymphatic filariasis and onchocerciasis, which is the second leading infectious cause of blindness. The main causative agents of these diseases are the nematodes, *Wuchereria bancrofti and Onchocerca volvulus* respectively. These infections are currently treated using mass drug administration programmes with chemotherapeutics donated by large pharmaceutical companies. Elimination however, remains hampered by insufficient activity against adult worms and serious adverse effects. The nematodes responsible for causing filarial diseases, share an essential endosymbiotic relationship with the bacterium, *Wolbachia*. Although the exact nature of this relationship is not understood, Anti-*Wolbachia* therapy has been identified as a viable treatment for filarial diseases, which delivers safe macrofilaricidal activity with superior therapeutic outcomes compared to current anti-filarial drugs. Doxycycline is the current gold standard for Anti-W*olbachia* activity, but requires treatment for at least four weeks and is contraindicated in children under 9 years of age and pregnant women. The Anti-*Wolbachia* (AWOL) drug discovery and development programme aims to identify alternative drugs which are suitable for a wider patient range and shorter treatment plan. This work describes the development of Anti-W*olbachia* agents of the pryazolopyrimidine chemotype. Despite high potency demonstrated by the original hit, DMPK experiments highlighted poor metabolic stability. Organic synthesis has enabled functionalization of key positions within our template, generating a broad library of compounds of which many analogues possess nanomolar activity against *Wolbachia in vitro* as well as display improved DMPK parameters. Further work is in progress to achieve our goal of providing a candidate that can achieve a 90% *Wolbachia* reduction in fewer than 14 days of treatment in the *in vivo* model system.

1112

ECONOMIC COSTS AND BENEFITS OF SCALING UP DISABILITY PREVENTION FOR LYMPHATIC FILARIASIS ACROSS INDIA

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Lymphatic filariasis (LF) is endemic in 73 countries, with 68 million people infected, of whom 36 million suffer serious disability (17 million with lymphedema, 19 million with hydrocele). Repeated acute attacks of fever and disabling pain (acute dermatolymphangioadenitis or ADLA) aggravate lymphedema and prevent work for 4-7 days per attack. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) has two goals: interrupting LF transmission by 2020, and caring for people already infected through morbidity management and disability prevention (MMDP). By 2014, 60 countries had ongoing mass drug administration to end LF transmission, but only 24 had begun MMDP, in part due to its perceived high cost and low return. Simple, low-cost interventions at the community level, including instruction in limb washing and provision of soap, topical antibiotics, and antifungals can reduce ADLA and slow progression of lymphedema. MMDP programs attenuate disability and productivity loss. For Khurda District, Odisha State, India, we estimated lifetime medical costs and earnings losses due to chronic lymphedema and acute dermatolymphangioadenitis (ADLA) with and without a community-based limb-care program. The program would reduce economic costs of lymphedema and ADLA over 60 years by 55%. Savings of US$ 1 648 for each affected person in the workforce are equivalent to 1 258 days of labor. Per-person savings are more than 130 times the per-person cost of the program. We then estimate the costs of scale-up for all Indian states for community-based programs of limb care for lymphedema. India has great diversity in levels of wages (and thus foregone earnings from disability that prevents working), prevalence of lymphatic filariasis, health systems, NGO involvement, and other factors that influence community health programs. In spite of the diversity of conditions, our cost estimates demonstrate the long-term economic benefits of simple limb care and provide an economic rationale in addition to the ethical mandate for MMDP, the second pillar of GPELF.

1113

APPLICATION OF ULTRASONOGRAPHY TO DETECT PERITONEAL FILARIAL DANCE SIGN IN PRECLINICAL RODENT *BRUGIA MALAYI* MACROFILARICIDAL DRUG SCREENING MODELS

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Ultrasonography (USG) has been successfully used in placebo-controlled clinical trials to evaluate macrofilaricidal (curative) drug efficacy in onchocerciasis and lymphatic filariasis. Here we describe the application of a portable ultrasound machine (SonoSite MTurbo) to detect 'filarial dance sign' (FDS) in preclinical *Brugia malayi* rodent drug screening models. In these models, defined numbers of *B. malayi* adults were implanted into the peritoneum or, alternatively, variable *B. malayi* adult burdens were established from a unit intraperitoneal inoculum of infectious stage larvae either within inbred Severe-Combined ImmunoDeficient mice or outbred *Meriones unguiculatus* (Mongolian) gerbils. USG successfully detected FDS of mixed sex or single sex adult worm burdens to a degree of sensitivity of a single female worm or 2 male worms. USG could also be applied to semi-quantify worm loads based on strength and multiplicity of FDS signal within different peritoneal anatomical locations. In both non-blinded and blinded preclinical drug studies, USG detection of peritoneal FDS has subsequently been utilised to accurately predict macrofilaricidal outcome. This technique could therefore be highly beneficial in refining and reducing the number of animals used during drug screens and accelerating preclinical macrofilaricidal drug by being able to more rapidly detect drug efficacy by longitudinal exam of the same study group without the necessity of invasive surrogate filarial viability sampling.

1114

INVESTIGATING EARLY INFECTION STATUS OF THE FILARIAL PARASITE *BRUGIA MALAYI* IN THE CAT, THE LABORATORY MODEL FOR LYMPHATIC FILARIASIS

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Human lymphatic filariasis (LF) is a mosquito-borne disease primarily caused by the parasitic nematodes *Wuchereria bancrofti* and *Brugia malayi*. These parasites are a major cause of morbidity globally, with an estimated 120 million people infected. *Brugia malayi* is the preferred laboratory model for LF due to *W. bancrofti* requiring the use of primate hosts. Currently, the domestic cat is utilized as the primary non-rodent animal model for *B. malayi*. However, on average only 25%-50% of felines become patent, so a method of early detection would be invaluable. Currently, the only test to determine infection status is the detection of circulating microfilariae, which are usually detectable 4-6 months post-infection. In other filarial parasites such as *Dirofilaria immitis*, the Enzyme Linked Immunosorbent Assay (ELISA) is used to detect circulating female uterine antigen. Recently, it was suggested that heat treatment of serum or plasma may dissociate the antibody-antigen complex, potentially releasing the antigen so that it may be detected. Due to the close relationship of these filarial worms, there could be detectable cross-reactivity after heat treatment for *B. malayi* antigen in these capture-antibody tests. We hypothesized that we would be able to detect circulating antigen after heat treatment in the serum of these infected cats. Ten male domestic cats were infected by subcutaneous injection of 400 *B. malayi* third-stage larvae. Serum was collected at key time points post-infection. Both heat-treated and room temperature serum was tested for circulating antigen using the DiroCHEK® ELISA kit. Of the six cats that became microfilaremic, five tested antigen-positive, whereas only one cat with a low microfilaremia tested antigen-negative. These data may indicate a methodology other than microfilarial counts may be used to detect *B. malayi* infections in cats. Furthermore, heat treatment of serum could expose epitopes that cross-react with the antibody used in commercial *D. immitis* tests.

1115

CELLSCOPE-*LOA*: DISTRICT-WIDE DEPLOYMENT OF A POINT OF CARE TOOL FOR THE PREVENTION OF POST IVERMECTIN SERIOUS ADVERSE EVENTS IN *LOA LOA* ENDEMIC AREAS

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Because of the marked adverse effects (functional impairment) and serious adverse events (SAEs, occasionally fatal but more often with potentially irreversible neurologic manifestations) that can occur when

Loa loa microfilariae (mf) levels exceed 8,000 mf/mL and 30,000 mf/mL, respectively, implementation of ivermectin (IVM)-based elimination programs for lymphatic filariasis (LF) and onchocerciasis in areas where loiasis is co-endemic has been extremely problematic. Identifying those individuals "at risk" for such SAEs would allow them to be excluded from IVM community treatment and prevent SAEs. This strategy, termed "Test and not Treat" (TNT), relies on the development of a rapid field-friendly test to quantify *L. loa* mf in peripheral blood. To this end, we developed a mobile phone-based video microscope (CellScope-Loa) that automatically quantifies *L. loa* mf in whole blood in less than 2 minutes without the need for conventional sample preparation or staining. Between August and October 2015, a field evaluation was conducted in a health district of Central Cameroon to assess the performance of the Cellscope-Loa in comparison to examination of a calibrated blood smear (the current standard method to assess *L. loa* mf densities). Among the 15,298 participants, 226 (1.5%) had mf densities above 30,000 mf/mL, when assessed by calibrated thick smear. There was a strong correlation (rho=0.84, p<0.0001) between mf densities estimated by the CellScope-Loa and those measured by the calibrated thick smear. Receiver operating characteristic (ROC) analysis demonstrated that the CellScope-Loa could identify individuals harboring > 30,000 mf/mL with 94.0 and 99.6% sensitivity for CellScope-Loa thresholds set at 20,000 and 10,000 mf/mL, respectively. Most importantly, it had a negative predictive value (probability that the mf density is actually below 30,000 mf/mL) of 99.9 and 100% for the same threshold values. The TNT strategy based on the Cellscope-Loa is an extremely promising and practical approach to the safe implementation of large-scale treatment for LF and onchocerciasis in *L. loa* co-endemic areas.

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SYNERGY OF ALBENDAZOLE AND RIFAMPICIN COMBINATION THERAPY IN A MURINE INFECTION MODEL OF HUMAN LYMPHATIC FILARIASIS

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An estimated 120 million people are infected by lymphatic filariasis throughout the tropics leading to a profound public health and socio-economic burden in severely affected communities. Wolbachia is an essential endosymbiont of the filarial nematodes *Wuchereria bancrofti*, *Brugia malayi* the causative agents of lymphatic filariasis. Doxycycline is currently the gold standard for the targeting of Wolbachia in lymphatic filariasis chemotherapy. However, the current drug regimen is a 100-200 mg/day doxycycline dose given for 4 to 6 weeks to patients. The A·WOL consortium plan to reduce the current treatment time to 7 days or less to improve drug regimen adherence and to reduce drug resistance and costs of treatment. To achieve a rapid 7-day or less kill rate of Wolbachia, a number of drug combinations will be employed. These include different tetracyclines (Doxycycline and minocycline) rifamycins (Rifampicin or Rifapentine), Moxifloxacin as well as anti-helminthic drugs. The complexity of multiple drug combinations necessitates a rational approach in the identification and choice of the best treatments in in-vivo models and translating the animal treatments in the lab into clinical trials on the field. In this current study we apply a rational drug development approach using our on in our murine infection model of *B. malayi* and pharmacokinetic (PK) analysis to investigate the synergy of Albendazole and Rifampicin combination therapy on the macrofilaridal and anti-Wolbachia efficacy. Pharmacokinetic modelling and simulation allowed the administration of rifampicin dosages equivalent to a standard 10 mg/Kg or 600 mg dose or a 35 mg/Kg super-dose and albendazole equivalent to a 400-800mg clinical dose in our murine infection model of *B. malayi*, making drug exposure and efficacy results clinically relevant in comparison to traditional efficacy studies. We have found synergistic interaction between rifampicin and albendazole for both macrofilaricidal and anti-Wolbachia activities and have used PK analysis and parasitological methods to dissect the origins of these interactions.

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FACTORS PREDICTING TRANSMISSION ASSESSMENT SURVEY OUTCOMES FOR LYMPHATIC FILARIASIS

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National programs are progressing towards elimination of lymphatic filariasis (LF) as a public health problem. Nearly 300 transmission assessment surveys (TAS), population-based cluster surveys to determine whether prevalence has been lowered to a level at which mass drug administration (MDA) can be stopped, supported by USAID have been implemented in 14 countries. Since both failing TAS and continuing to implement MDA have financial and opportunity costs, TAS should be conducted at an appropriate time. A key question, which has not yet been analyzed using survey data, is therefore which factors increase the likelihood of passing TAS. We performed logistic regression analysis to examine whether the odds of passing TAS was related to baseline prevalence, number of MDA rounds implemented, or median epidemiological coverage. The analysis included data from 14 countries implementing 296 stop-MDA TAS between 2012-2015. Of these TAS, 90% of districts passed. We found that passing TAS was significantly associated with both baseline prevalence (OR 0.945, CI 0.915-0.976) and median epidemiological coverage (OR 1.044, CI 1.008-1.082) at alpha =0.05. While the number of MDA rounds was not significantly associated with passing TAS, it was important to control for as otherwise it confounded the relationship between baseline prevalence, median coverage, and passing TAS. The R-square value was low (0.0714), however; this indicates that this model does not include all of the factors that affect the likelihood of passing TAS. Ongoing analysis will incorporate additional factors that may affect the likelihood of passing TAS, such as vector species, diagnostic tests used to determine eligibility for TAS, and consecutive versus missed rounds of MDA, among others. These results confirm that it is important to achieve high coverage when implementing MDA, especially in districts with high baseline prevalence, and additional rounds of MDA may be necessary. National programs can increase the likelihood of passing TAS—and therefore achieving elimination—by implementing high-quality MDA throughout the program, rather than only in response to a failed TAS.

1118

THREE-DIMENSIONAL VISUALIZATION OF THE INTERNAL ARRANGEMENT OF ONCHOCERCAL (*ONCHOCERCA VOLVULUS*) NODULES USING HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING

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Adult stages of *Onchocerca volvulus* live in subcutaneous or deep nodules. For descriptive biology or drug effect assessment purpose, the nodules are generally processed using either histology (fixation and section, followed by staining) or enzymatic digestion (incubation in collagenase to eliminate host tissue and isolate adult worms). Non-invasive detection of adult *O. volvulus* using ultrasound has also been used, but has little indications

because of the low optical resolution of the nodule content. None of these techniques enable to have a tridimensional view of how an onchocercal nodule is organized, and how the different worms arrange themselves relative to each other. Here, we had the opportunity to examine nodules using high-resolution magnetic resonance imaging (MRI). The nodules had been placed in a fixative just after their collection, and stored in the latter for about 20 years before the present study. To reduce the background noise and artifacts during image acquisition, nodules were immersed in Fluorinert FC-77 liquid, which is a proton-free fluid with low water solubility and similar magnetic susceptibility to the tissue. MRI experiments were done using a 9.4 Teslas apparatus equipped with a MAGNEX TS1276D, a Quadrature Volume Coils 400 MHz RF43 and associated with a VnmrJ Imaging acquisition system. 3D gradient echo images were acquired during14 hours with 100 ms repetition time, 4.44 ms echo time, 8 averages, a 30° flip angle, a 40 x 20 x 20 mm3 field-of-view and a 512 x 256 x 256 matrix. 3D reconstruction was processed using Myrian 1.21.1 (Intrasense, Montpellier, France) on the basis of DICOM data, in both Maximum Intensity Projection and average rendering modes. This study is a proof of concept that MRI can provide clear images of adult worms in onchocercal nodules fixed for many years. These results warrant further developments including adapted MRI coil and fine image analysis to assess the worm's viability. Studies could be conducted with recently collected nodules that have not been stored in a fixative, as well with small animals (rodents) naturally or experimentally infected with various filarial species.

1119

IDENTIFICATION OF NEW MACROFILARICIDAL COMPOUNDS FOR TREATMENT OF ONCHOCERCIASIS

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Current efforts to control and eliminate onchocerciasis are hindered by the lack of compounds that target the adult worm stage. In a joint collaboration with DNDi, academia and Celgene, a pipeline was established to identify macrofilaricidal compounds. To date, more than 400 compounds have been screened *in vitro* against *Onchocerca gutturosa* adults, identifying 120 compounds with EC_{50} <1μM 40 of which having EC_{50} <100nM. From this set of 400 compounds, a select set of 160 compounds were tested against both *O. lienalis* microfilariae and *Onchocerca gutturosa* adults, identifying 43 compounds with specific activity against the adult parasites *in vitro*. Active compounds with EC_{50} in the 0.015-1μM range and suitable pharmacological profiles were prioritized for *in vivo* testing. 23 lead candidates were tested by oral gavage in mice that harbored adult worms of the rodent filarial nematode *Litomosoides sigmodontis*. Two compounds significantly reduced the *L. sigmodontis* adult worm burden by 98 and 93% after 10 days of TID treatment and 1 day of BID treatment, respectively. Presence of microfilariae in the treated animals suggest that both compounds do not have a strong microfilaricidal effect. Current efforts to further assess the impact of both compounds on microfilariae in the *L. sigmodontis* jird model are scheduled. The current study demonstrates the successful establishment of a screening cascade which resulted in the identification of two promising novel macrofilaricidal compounds. The identification of such macrofilaricidal compounds which lack microfilaricidal effects are ideal candidates for the treatment of onchocerciasis, as they have a reduced risk for microfilariae-driven adverse events.

1120

COMPARISON OF THE ONCHOCERCIASIS OV16 IGG4 RAPID TEST AND OV16 ELISA AMONG CHILDREN IN TOGO: EXPERIENCES WITH A NEW SURVEILLANCE TOOL

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The Alere SD BIOLINE Onchocerciasis IgG4 rapid test (RDT) is a new field tool for on-site identification of antibodies to the Ov16 protein of *Onchocerca volvulus,* the parasite that causes river blindness. WHO recommends using Ov16 ELISA to decide when to stop mass treatment with ivermectin. In 2015, in preparation for a move towards onchocerciasis elimination, the Ministry of Health of Togo used the Ov16 RDT in a national survey to obtain preliminary data on the prevalence of antibodies to Ov16 in school-age children and to compare Ov16 RDT to Ov16 ELISA. The survey was integrated with an NTD impact assessment. At each of 1126 schools serving as NTD sentinel sites, a convenience sample of 8 children age 6 to 9 years had finger-stick blood drawn for Ov16 RDT. A subset of children provided blood spots on filter paper (DBS) for testing by Ov16 ELISA. In total, 9007 children were tested by RDT, of whom 60 (0.7%) were positive. DBS were obtained from 2600 children. Ov16 ELISA testing is ongoing; of 294 RDT-negative samples tested to date, 50 of 294 (17%) were positive by ELISA. The significant discrepancy between RDT and ELISA results prompted additional investigations. Confirmatory Ov16 ELISA testing will be conducted at a US laboratory. The protein glutathione S-transferase (GST) is fused to the Ov16 protein. To assess whether Ov16 ELISA positives may be due to antibody cross-reactivity with GST, a GST-specific ELISA will be run on a subset of samples. To assess whether the RDT was properly conducted in the field, it will be repeated using the same DBS samples as for ELISA, using a modified protocol for testing DBS on Ov16 RDT. Application of the expectation maximization algorithm to our ELISA findings may improve classification of results. The 60 children who tested positive by RDT and a subset of those who are RDT-/ELISA+ will be revisited to document residency and travel history, repeat the RDT, and conduct skin snip testing with treatment if indicated. Resolution of these test discrepancies is important for onchocerciasis elimination in Togo. These findings highlight some of the challenges of employing these tests and our results should illuminate where pitfalls lie.

1121

DESIGN AND EVALUATION OF A HEALTH EDUCATIONAL BOARD GAME FOR THE CONTROL OF SOIL-TRANSMITTED HELMINTHIASIS AMONG PRIMARY SCHOOL CHILDREN IN ABEOKUTA, NIGERIA

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Despite repeated annual treatment with anti-helminthic drugs, soil-transmitted helminthiasis (STH) remains an important factor in school children morbidity in sub-Saharan Africa as school children are rapidly re-infected within 3 months after treatment. We designed a health education board game "Worms and Ladders" inscribed with health education and STH preventive messages and evaluated its potential for promoting good hygiene practices among school children for the integrated control of STH during mass drug administration (MDA). The evaluation employed a randomized control trial across six primary schools in Abeokuta, Nigeria. A total of 372 pupils were enrolled in the study, of which 212 were in the intervention group in three schools, and 160 were in the control group in three schools. Baseline knowledge, attitude and practices (KAP) relating to STH were obtained with a questionnaire followed by the collection

of fresh stool samples for STH diagnosis. All the participants were then treated with Albendazole according to their height. The designed "Worms and Ladders" board game were introduced and distributed to the intervention group to play for six months under the supervision of their class teachers. No game was given to the control group to play. Prevalence of STH dropped from 25.0% to 10.4% in the intervention group and 49.4% to 33.3% in the control group at three months' post treatment. The prevalence further dropped to 5.6% in the intervention group but increased to 37.2% in the control group at six months' post treatment. There was a significant difference ($p<0.05$) in post-treatment prevalence among the two groups. Knowledge, attitude and practices on transmission, control and prevention of STH significantly improved ($p<0.05$) from 5.2% to 97.9% in the intervention group compared to (6.2% to 7.1%) in the control group. The "Worms and Ladders" board game have shown its potential to promote good hygiene behaviour among school children and should be integrated into Mass deworming programme to prevent reinfection.

1122

RISK FACTORS ASSOCIATED WITH PREDISPOSITION TO SOIL-TRANSMITTED HELMINTH INFECTION IN SOUTHERN MYANMAR

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Southeast Asia has a substantial burden of soil-transmitted helminths (STH). In Myanmar, a mass drug administration (MDA) programme targeting STH in school-aged children (SAC), in conjunction with a community-wide MDA programme targeting lymphatic filariasis, has been implemented for the last 3-5 years and coverage has been consistently high. Past STH studies have identified the phenomenon of predisposition to STH infection in human hosts; individuals predisposed to STH infection may act as persistent reservoirs of infection. Parasitological data were analysed in conjunction with epidemiological data, collected during two MDA rounds in two villages in southern Myanmar (n=584). Baseline STH prevalence was 27.05%; 5.14% for *Ascaris lumbricoides*, 16.95% for *Trichuris trichiura* and 8.9% for hookworm. There was no statistical difference in presence of predisposition to STH infection (defined here as positive STH infection in both rounds) between the two villages. Preliminary analysis suggests that predisposition to STH infection is associated with individual adults' main form of employment ($P<0.0001$), if the main toilet is shared with other households ($P=0.003$) and household income ($P=0.03$). There was no evidence to suggest that predisposition was associated with age or gender. Aggregation of predisposed individuals was observed at a household level. It is concluded that predisposition to STH infection is associated with socioeconomic and water and sanitation hygiene (WASH) factors. Further analysis will include identifying factors associated with predisposition to single STH species infections.

1123

IMPLEMENTATION AND EVALUATION OF A QUALITY AND SAFETY TOOL FOR AMBULATORY STRONGYLOIDIASIS PATIENTS AT HIGH RISK OF ADVERSE OUTCOME

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Although simple intestinal strongyloidiasis is curable, infections are frequently asymptomatic and unknown, leading to potential adverse patient outcomes upon immunosuppression. Given the potential complexity of care of patients with strongyloidiasis, a safety tool may help to improve patient outcomes and standardize care for strongyloidiasis patients. We developed a novel safety tool, and implemented it in June 2015. Our aim was to evaluate the utility of the tool using a retrospective chart review. Patients diagnosed with strongyloidiasis were identified through our clinic "Special Access Programme" log from January 1, 2013 to December 31, 2015. Patients were categorized as treated for strongyloidiasis pre-implementation of the tool (prior to June 2015), or post-implementation of the tool (June 2015 to December 2015). Outcome measures included loss to follow-up; documentation of seroreversion post-treatment; documentation of stool clearance post-treatment, if positive at baseline; and screening for factors known to confer risk of hyperinfection and dissemination (e.g, HTLV1 infection) During the study period, 37 patients were treated for strongyloidiasis: 23 males (62%), and 14 females (38%). Median age was 44 yrs (range 5-85 yrs). 24 patients were treated pre-implementation of the tool, while 13 were treated after implementation. Loss to follow-up after treatment occurred in 25% of patients pre-implementation, and for no patients in the assessible post-implementation group ($p=0.148$). Proof of seroreversion occurred in 47% of assessible patients pre- implementation, and 66% of assessible patients in the post implementation group ($p=0.635$). Proof of stool clearance and seroreversion occurred in 50% (2/4) of patients pre-implementation, and 50% (1/2 assessible patients) post implementation ($p=1.000$). Evaluation of HTLV-1 co-infection occurred in 33% of patients pre-implementation, and in 69% post-implementation ($p=0.021$). Our findings suggest that a safety tool may of benefit in preventing future adverse outcomes due to strongyloidiasis, though a larger prospective evaluation is warranted.

1124

STRONGYLOIDIASIS IN ONTARIO: INFORMING THE DIAGNOSTIC EVALUATION BY ESTABLISHING THE NUMBER NEEDED TO EXAMINE (NNE)

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In order to provide a diagnostic strategy that offers sensitivity, specificity, as well as larval staging and quantification, clinical guidelines suggest using a combination of serologic and microscopic diagnostic tests for confirmation of strongyloidiasis. We aimed to evaluate the performance of stool microscopy, serology, and real time PCR (qPCR) for the optimal diagnosis of strongyloidiasis at our reference laboratory. We included all specimens submitted for O&P examination and *Strongyloides* serology between April 1, 2014 and May 31, 2015. All stool specimens positive for any stage of *Strongyloides stercoralis*, as well as 5-times that number of random stool specimens negative for *Strongyloides* were included in our verification of a *Strongyloides*-specific qPCR assay. Positivity rates were calculated, and the total number of examined specimens divided by the number of positive specimens was calculated as the "Number Needed to Examine" (NNE). During the enrolment period, 17,933 stool specimens were processed for O&P examination, 14 of which were positive for *Strongyloides* larvae, yielding an overall NNE for stool microscopy of 1281. During the enrolment period, 3258 specimens were processed for *Strongyloides* serology, 200 of which were reactive (6.1%), 210 indeterminate (6.5%), and 2848 non-reactive (87.4%), yielding an NNE for reactive serology of 16. Two patients shedding larvae and known to the laboratory as undergoing iatrogenic immunosuppression had negative serology. qPCR was positive in 10 of 12 (83.3%) stool specimens containing larvae, and negative in all stool specimens without larvae by microscopy. There was no cross-reactivity of *Strongyloides*-specific qPCR to other common stool protozoa or helminths. In the absence of immunosuppression, larval burden in strongyloidiasis is low, limiting the utility of microscopy for diagnosis, and favoring serologic testing. However, false negative

serology can occur in those with hyperinfection necessitating a combined diagnostic approach. The qPCR assay was insufficiently sensitive to replace microscopy for detection of larvae.

1125

EOSINOPHILIA, ANEMIA AND INTESTINAL PARASITES IN CHILDREN FROM RURAL COMMUNITIES OF VENEZUELA

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A cross-sectional epidemiological survey was conducted in four rural communities in the north of Venezuela. One stool sample of school-age and unschooled children between 0 and 15 years old was requested (n=438/909) and examined for ova and parasites, using direct smear (428/438) and Kato-Katz techniques (n=400/438). Hemoglobin (Hb), hematocrit and relative eosinophil value (REV) were also determined (n=803/909). A questionnaire was performed before processing the samples. Eosinophilia (REV ≥ 5%) was detected in 90,6% (n=763/842) and was more prevalent in UBP (94,5%) and Palo Negro schools (95,1%) p <0,001. Anemia (Hb < 11,5 g/dl) was demonstrated in 7% (n= 56/803) with the highest prevalence in TK (21,7%) and EH schools (30,4%) p <0,001. *Giardia intestinalis* (n=86/428; 20,1%), *Ascaris lumbricoides* (n=26/400; 6,5%) and *Trichuris trichiura* (n=19/400; 4,8%) infections did not show a significant statistical association with anemia (Fisher's exact p=0.284; p=0.532; p=0.167 respectively). Mean parasitic loads for both helminths were low according to WHO cut offs. We reccomend that in settings of developing countries, with high prevalence of eosinophilia and low prevalence of intestinal nematodes according to stool examination, the burden of soil-transmitted helminthiasis may also take in consideration other variables suchs as unsatisfied basic needs and undiagnosed strongyloidiasis, to assess the most adequate therapeutic intervention in order to reduce the associated morbidity.

1126

PREVALENCE OF STH AT A COASTAL AREA IN INDIA - ROLE OF STUDENTS' HYGIENE PRACTICES, SCHOOL AND HOME SANITATION FACILITIES

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Soil transmitted helminth infestation is a global health concern affecting two billion population worldwide. Mainly three species viz. *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm inflict considerable morbidity and mortality amongst infected persons. Present study was conducted among school children of Allepey city, Kerala state, India after having prior consent from respective authority. Sample size was estimated according to WHO guidelines as 200-250 children per ecological zone. Children were informed about the purpose of study. Information regarding their social and personal hygiene practices was recorded with the help of semi structured questionnaire and they were provided with a container to bring stool sample on the following day. Samples collected were subjected to examination for helminthic eggs using Kato-Katz technique. Statistical analysis was done by using Chi-square test. Total 219 samples were collected in which 79 (36%) were positive. *A. lumbricoides* infection was found in all samples. 76 (95%) samples had monotypic infection. data was analyzed to find out the factors associated with occurrence of STH infection. The factors like not having household latrine, not washing hands before meal and practice of eating food fallen on ground/unwashed vegetables/fruits were found associated with having STH infection among children and this was found statistically significant. Significant association was found between presence of anaemia and having STH infection. Preventive chemotherapy along with social awareness about good hygienic practice go hand in hand in reducing morbidity associated with STH. Hand washing and in-house sanitary latrine qualify as the most important preventive measures.

1127

HIGH PREVALENCE RATES OF SOIL-TRANSMITTED HELMINTHS IN CHILDREN WHO RECEIVE MASSIVE DRUG ADMINISTRATION IN A REMOTE AMAZONIAN COMMUNITY IN PERU

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Following the recommendations from the WHO to control soil-transmitted helminth (STH) infections, a school-based deworming program with albendazole 400mg oral single dose every 3 months was recently implemented in the Amazon rainforest of Peru. In order to evaluate the prevalence of STHs in children from a community within the program's scope, we collected stool samples from 2-14 years old children from *Padre Cocha*, Loreto. All samples were analyzed for the presence of *Ascaria lumbricoides, Trichuris trichiura,* hookworm *and Strongyloides. stercoralis*; by using the following techniques: spontaneous sedimentation in tube, Kato-Katz, modified Baermann and agar plate culture. Stool samples of their mothers were also collected and examined. Additional information including weight, height, sociodemographic and epidemiological risk factors (i.e. water supply, sanitation and hygiene practices) were collected by interview. Out of 124 children, 32 (25.8%) were infected with one or more STH. Twenty (16.1%) had *A. lumbricoides;* 2 (1.6%), hookworm; 2 (1.6%), *T. trichiura;* and 13 (10.5%) had *S. stercoralis.* Malnutrition was present in 72 (60.8%) of the children, although no association was found with STH infection (OR:1.02; IC:0.41-2.63). Among risk factors, walking barefoot was associated with any STH (OR:3.47; IC:1.16-12.5). Prevalence of STHs was higher in the mothers from the children infected (36.4%) compared with the mothers from those uninfected (14.1%) (p<0.02). In conclusion, children from this particular Amazonian community have high prevalence rates of STHs even after an intensive MDA program. The mothers infected with STHs could play an important role in the dissemination of the eggs and larvae (*S. stercoralis*) from these parasites, which could eventually contribute to reinfections. High prevalence of *S. stercoralis* prompt further evaluation of the inclusion of ivermectin within the local MDA program. Integration of more control measures for STHs -including clean water supply, adequate sanitation services and hygiene education- should be taken into account to develop a successful program, particularly in remote populations from this region in Peru.

1128

AN AUTOCHTHONOUS CASE OF GNATHOSTOMIASIS ACQUIRED IN QUEENSLAND, AUSTRALIA

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Gnathostomasis is an uncommon foodborne zoonosis, which is caused by infection with the larvae of *Gnathostoma* spp, most commonly *Gnathostoma spinigerum*. In Australia, *G. spinigerum* has been identified in cats and bandicoots, and *G. hispidum* in wild pigs. Only two locally acquired gnathostomiasis cases have been reported from Australia. We present the case of a previously well 30-year-old man presenting to a Darwin Hospital with left forearm swelling and eosinophilia, positive

gnathostomiasis immunoblot and an epidemiological plausible link to infection from undercooked mudcrabs caught in Yeppoon, Queensland after heavy flooding.

1129

MODELING COGNITIVE DEFICITS IN SOIL-TRANSMITTED HELMINTHIC INFECTION USING GOLDEN SYRIAN HAMSTER

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Soil-transmitted helminthic (STH) infection, which includes *Ascaris*, whipworm, and hookworm (*Ancylostoma duodenale*, *Necator americanus, and A. ceylanicum*), remains a significant public health issue today. Previous studies in humans, both retrospective and prospective, have linked STH infections with anemia, nutritional deficiency, growth stunting, and impaired memory and cognition, potentially leading to lower socioeconomic status and perpetuation of poverty. However, the results to date have been conflicting with regard to the nature of cognitive deficit and benefit of anthelmintic therapy. Using Gold Syrian hamsters, which are susceptible to acute *A. ceylanicum* infection, we wanted to isolate, observe, and study potential cognitive defects from confounding factors normally present in work with humans. Hookworm infection did not impair the hamster's ability to recognize previously encountered objects (Novel Object Recognition task), but did impair performance on a spatial memory task (Displaced Object Recognition task; control vs infected, p=0.02). Further, the severity of deficit was dependent on infection burden (control vs severe infection, p=0.01) and the impairment appeared to be reversible with clearance of infection. Accordingly, acute hookworm infection resulted in deficits in cognitive function, which resolved with the clearance of STH infection. It will be important to determine if the cumulative effects of repeated infections produce long-term cognitive deficits.

1130

SOIL TRANSMITTED HELMINTHS IN BENIN: EVIDENCE OF COUNTRYWIDE HOOKWORM PREDOMINANCE

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From 2013 to 2015, mapping of soil-transmitted helminths (STH) was conducted in all 77 of Benin's communes as part of the baseline surveys for schistosomiasis and STH. The aim of the mapping was to provide epidemiological data needed to develop a national strategy for the control of neglected tropical diseases (NTDs) in Benin by 2020. In each commune, 5 schools were purposively selected; and in each school 50 children (25 girls and 25 boys) ages 8 to 14 were randomly selected. In total, 19,250 stool (from 9,625 girls and 9,625 boys) from 385 schools were examined using Kato-Katz technique. STH are present in all districts. National prevalence of STH is 22.74% (95% CI 2.00% - 62.80%) and 58.44% of the communes (45/77) have prevalence of ≥20% and therefore require mass drug administration (MDA) for STH. Four species of STH (Hookworm, *Ascaris, Trichuris* and *Enterobius*) were observed with intra-specific and inter-specific variation in the prevalence and density of the parasites. Hookworm constitute the highest proportion of STH parasites and the prevalence was 17.40% (95% CI 0.40% - 60.00%; n=76); *Ascaris* 5.35% (95% CI 0.40% - 26.40%; n=62); *Trichuris* 1.15% (95% CI 0.40% - 9.60%; n=37); and *Enterobius*: 1.92% (95% CI 0.40% - 18.80%; n=32). Hookworm was present in 100% of the surveyed communes with a national mean prevalence of 17.14% (95% CI 0.40% - 60.00%). Most infections were of light density except in the communes located in the department of Atacora. This mapping provides a global view of the epidemiological pattern of STH needed for the implementation of a control strategy (which could potentially include MDA and the provision of potable water, sanitation and health education). Multiple infections with several STH are commonplace among the school-age children surveyed, possibly due to poor hygiene and sanitation. In Benin, the high prevalence of hookworm and its predominance in all communes calls for a strengthening of maternal and child health policy through health education and routine screening of pregnant women. In addition, STH MDA should be tailored to target not only school-age children, per the standard guidance, but also women of child-bearing age.

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REPEATED ROUNDS OF MASS DEWORMING ADMINISTRATION STILL LEAVE HOUSEHOLD CLUSTERING OF SOIL-TRANSMITTED HELMINTH INFECTIONS

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Kenya is one of the many countries endemic for soil-transmitted helminth (STH) infections. Since 2012, a national school-based deworming programme has provided preventive anthelminthic treatment to over 6 million children annually. While this control strategy reduces overall infection levels, infection bounces back soon after treatment administration. In order to improve the efficiency of control programmes, further knowledge on the factors driving reinfection is still required. A study conducted in 2014 in western Kenya investigated the clustering of STH infections at the village and household levels. A cross-sectional survey was conducted in four rural villages near Bungoma Town, targeting over 1000 residents from 2-81 years of age. Epidemiological data were collected at two time-points, at study baseline and three months post-treatment with 400mg albendazole. Treatment was administered to all study participants to simulate a mass drug administration campaign. At study baseline, *Ascaris lumbricoides* and *Necator americanus* infections had an overall prevalence of 9.8% and 6.7% (n=763), respectively, and *A. lumbricoides* was significantly more prevalent in one of the villages (17.7% vs. 6.0%, 4.0% and 3.9%; Pearson X^2=35.7, p<0.001). Three months post-treatment, levels of *A. lumbricoides* and *N. americanus* infection were reduced to 1.8% and 1.4%, respectively, with no significant difference between villages. Clustering at household level was observed for *A. lumbricoides*, with 1.3 and 1.75 persons infected per house at the first and second time-point, respectively. This clustering was found to be associated with predisposition to *A. lumbricoides* infection, with 62.5% of the infected households at the second time-point also having participants infected at the first time-point. This study highlights the importance of household clustering and predisposition to infection in the maintenance of *A. lumbricoides* infection in endemic communities, a factor to take into account if elimination of STH infections is to be successful.

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UNDERSTANDING THE EPIDEMIOLOGY OF HOOKWORM INFECTION IN A LOW-TRANSMISSION SETTING IN SOUTHERN INDIA: ANALYSIS OF DATA FROM A CLUSTER-RANDOMIZED MASS DEWORMING TRIAL

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Hookworms are a leading cause of malnutrition and anemia in resource poor settings. Periodic mass deworming of at-risk populations (particularly school-going children) with anthelminthic drugs remains the cornerstone of hookworm control efforts worldwide. Reinfection rates following treatment are high, suggestive of an untreated reservoir of transmission. Also, recent modeling-based estimates suggest that school-based deworming may have limited impact in interrupting the community transmission of hookworm infections. In a recently concluded cluster-randomized community-intervention trial of a modified population-based mass deworming strategy, 8681 participants aged 2-70 years, residing in 45 tribal villages in southern India were randomized into 3 groups: one received one round of treatment with albendazole (400 mg) at month 1, the second received two rounds of treatment at months 1 and 2, and the third received four rounds of treatment - two rounds at months 1 and 2, followed by another two at months 8 and 9. Stool samples collected from a subset of participants pre- and post-intervention were tested for hookworm by microscopy to evaluate the effect of the treatment with albendazole and at 3-monthly intervals for one year to test for re-infection. The baseline prevalence of hookworm infection ranged from 2-44% (overall prevalence: 19%; 95% CI: 16-21%); majority of infections (90%) were of low intensity (<2000 epg). The prevalence and intensity of infection increased with increasing age. Following deworming, hookworm prevalence decreased after the first two doses, but remained stable thereafter. Data from this trial will be used to estimate the key parameters for hookworm transmission models. Deterministic, age-structured models will be fitted to assess the transmission dynamics of hookworm infection. The effect of individual, household and village-level predisposition to hookworm infection will be explored. The models derived from this study will help identify the drivers of hookworm transmission in a low-transmission setting and can be used to further refine the end-game strategy for hookworm control.

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MODELLING THE EFFECT OF PATTERNS OF ADHERENCE AND NON-ADHERENCE TO TREATMENT IN PURSUIT OF HELMINTH ELIMINATION BY MASS DRUG ADMINISTRATION

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In mass drug administration (MDA) aimed at elimination of disease and/or disease, sufficient treatment coverage is essential for success. Non-adherence to treatment is a barrier to achieving adequate coverage. A critical question concerns the likelihood of non-adherence at one round of treatment predisposing to non-treatment at subsequent rounds. In addition the transmission dynamics may be affected by patterns of treatment or non-treatment over multiple rounds - for example, individuals untreated over multiple rounds of MDA may act as a reservoir of infection. We address the importance of these issues through the construction and analysis of a stochastic computational model in which the effects of systematic non-adherence on coverage and treatment pattern are examined in detail and conclusions drawn about the importance of non-compliance to achieve policy goals.

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TO WHAT EXTENT IS PREVENTIVE CHEMOTHERAPY FOR SOIL-TRANSMITTED HELMINTHIASIS 'PRO-POOR'? EVIDENCE FROM THE 2013 DEMOGRAPHIC AND HEALTH SURVEY, NIGERIA

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Health equity is a guiding principle for the control and elimination of neglected tropical diseases (NTDs), including those addressed through so-called 'preventive chemotherapy' (PC), such as soil-transmitted helminthiasis (STH). NTD advocacy messages frequently emphasize the 'pro-poor' potential of PC, with the aim of 'rescuing the bottom billion.' Available evidence suggests that poverty, lack of education, and residence in rural areas are all significant risk factors for STH. Little information is available, however, on the extent to which PC reaches those at highest risk within STH-endemic communities. To identify demographic and socioeconomic factors associated with drug coverage for STH, we analyzed data from the 2013 demographic and health survey from Nigeria. In this nationally-representative survey, mothers were asked whether their young children received deworming medication during the previous 6 months. We conducted multivariable logistic regression that controlled for child age, gender, immunization status and having received vitamin A supplementation in the previous 6 months. Overall, 19.9% of children 6-59 months of age were reported to have received deworming medication in the previous 6 months. Reported six-month deworming prevalence was 15.2% in rural areas, compared to 28.4% in urban areas. Prevalence of deworming increased linearly with level of maternal education (9.4% for children whose mothers had no formal education, compared to 42.5% with more than secondary education) and wealth quintile (7.9% for the lowest wealth quintile, compared to 39.1% for the highest). Deworming prevalence remained significantly associated with maternal education (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.8-2.7), wealth (OR 2.3, CI 1.9-2.7), and urban residence (OR 1.6, CI 1.3-2.0) in the multivariate analysis. These results highlight systemic challenges to actualizing a 'pro-poor' NTD policy and raise questions about the degree to which current NTD policies and practices, particularly for STH, actually reach those at greatest risk.

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THE SECOND GLOBAL NGO DEWORMING INVENTORY: ASSESSING SOIL-TRANSMITTED HELMINTHIASES TREATMENT REPORTING

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Affecting nearly one billion children globally, soil-transmitted helminthiases (STH) is the most common parasitic infection. To combat the disease, the World Health Organization (WHO) target for 2020 is to reach ≥75% of children at-risk of STH with regular preventive chemotherapy (PC). Ministries of Health (MoH) provide routine STH treatment reports to the WHO PCT Databank to monitor treatment coverage. In 2014, 47% of at-risk children were reported to receive PC. Non-governmental organizations (NGOs) also play a key role in administering PC. However, according to the first Global NGO Deworming Inventory (DI) for data of 2009 and 2010, over a third of the NGO administered treatments were unreported to WHO in 2010. To assess progress made in improving coordination of NGO-MoH-WHO reporting of STH treatments, a second DI was conducted after a 5

year period. From August to October, 2015, 40 NGOs were surveyed, of which 17 (43%) reported administered STH treatments in 2014. NGO-delivered treatments were again compared with those reported by MoHs to WHO. Comparing 2014 to 2010, the total number of reported STH treatments increased from 261 million to 441 million globally; treatments delivered by NGOs increased from 65.4 million (25%) to 187.2 million (42%); and the number of NGO treatments unreported to WHO decreased from 23.3 million (36%) to 10.5 million (6%). The NGO unreported treatments constitute 2.4% of the global total in 2014, compared to 8.9% in 2010. These findings demonstrate improved NGO-MoH data reporting and collaboration at the country level. Only six countries accounted for >90% of NGO unreported STH treatments in 2014. While the DI is not intended to provide an alternative data collection process, periodically comparing the DI and PCT Databank can further strengthen reporting by prioritizing support to countries with large gaps in reporting. Combining data from these two sources highlights important reporting gaps, demonstrates the effect of systematized efforts to reduce them, and helps to increase confidence in the accuracy of national treatment coverage reporting to the global level of children at-risk of STH infection.

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GUIDANCE IN DESIGNING SURVEYS FOR MONITORING SURVEYS FOR MONITORING THE PROGRESS OF SCHOOL-BASED DEWORMING PROGRAMS TO CONTROL SOIL-TRANSMITTED HELMINTHIASIS

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There is a worldwide upscale in school-based deworming programmes to control the morbidity caused by soil-transmitted helminths (STH). However, there is a lack of guidance in designing surveys to verify whether these programmes progress as anticipated. We expanded an existing 2-level hierarchical model that accounts for variation in egg counts within individuals due to the egg counting procedure (level 1; Poisson distribution) and between individuals within a school due to host-parasite interactions (level 2; negative binomial distribution (NB)), to a 3-level model that also accounts for clustering of STH infections between schools (level 3; NB or zero-inflated NB distribution). In addition, we adapted the model for variation in the effectiveness of deworming programmes at both the individual and the school level. To maximize the flexibility in survey design, the framework was worked out for the examination of both individual and pooled stool samples. From the derived formulae to estimate the variance, we updated the methodology to calculate the number of schools and the number of individuals per school required for assessing (i) the intensity of infections, (ii) the effectiveness of programmes and (iii) the absence of infections for any scenario of disease epidemiology, diagnostic strategy and programmatic effectiveness. To bridge the gap between this mathematical framework and the end-users we further developed an online interface that guides the user in designing an appropriate survey without the need of prior mathematical or statistical knowledge. At the meeting we will briefly outline the underlying mathematical framework. Subsequently, we illustrated its applications using available data on the effectiveness of deworming and the related costs to diagnosis STH infections in epidemiological surveys in Eastern Africa. Finally, we will demonstrate selective features of the online tool.

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IMPACT OF HELMINTH INFECTIONS DURING PREGNANCY ON HUMORAL VACCINE IMMUNOGENICITY IN INFANTS

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Infection with helminths is considered as a neglected tropical disease and is a major public health problem especially in the tropics. The influence on cognitive and physical development as well as on the immune system is well recognized. Recent studies showed that individuals infected with helminths have a reduced antibody response to vaccination. Furthermore, there is evidence that infants born to helminth-infected mothers display changes of their immune system that might lead to a reduced antibody response towards vaccines. In this ongoing study we investigate the influence of maternal helminth infection on the immunogenicity of vaccines administered within the national Expanded Program on Immunization (EPI) in Gabon. Infants of mothers either with or without helminths are compared (NCT02714348; BMBF 01KA1307). More than 300 mothers have been enrolled and helminth status assessed prior to delivery. Blood has been collected at delivery from the mother and the cord, and additionally from the infants at 9 months and 12 months of age. The antibody profile to the vaccines are measured with ELISA. Here we present preliminary study data.

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INTESTINAL PARASITIC INFECTIONS IN HIV INFECTED AND NON-INFECTED PATIENTS IN A HIGH HIV PREVALENCE REGION, ADAMAOUA-CAMEROON

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The magnitude of intestinal parasitic infection in acquired immunodeficiency syndrome patients requires careful consideration in the developing world where poor nutrition is associated with poor hygiene and many tropical diseases. Studies have addressed this issue in Cameroon, mainly in the low HIV prevalence settings. This study aimed to determine the prevalence of intestinal parasites in HIV/AIDS patients in Adamaoua (with HIV prevalence 5.1%) Stool and blood specimens from HIV/AIDS patients and control group were screened respectively for intestinal parasites and for HIV antibodies. Intestinal parasites were identified using direct microscopy, formalin-ether concentration, Ziehl Neelsen and giemsa stains methods. Out of 235 participants recruited among patients consulting at hospital, 69 (29.24%) were HIV positive, Thirty-one of them treatment naïve (44.93%). The prevalence of intestinal parasites was 32.34%. Out of 69 HIV/AIDS patients, 31.88% (22/69) were infected with intestinal parasites, while 32.53% (54/166) of the HIV negative patients were infected with intestinal parasites. The parasites detected in the population included: *Blastocystis hominis* (18.30%), *Entamoeba histolytica* (6.36 %), *Entamoeba coli* (5.96 %), *Endolimax nanus* (3.83%), *Iodamoeba buetschlii* (2.13%), *Crystosporidium* spp (2.98%), *Trichomonas intestinalis* (1.70%), *Embadomonas intestinalis* (0.43%), *Cyclospora cayetanensis* (0.43%), *Ascaris lumbricoides* (0.43%). There was no difference between the prevalence of intestinal parasites

amount people living with HIV and people living without HIV. The parasitic density instead was higher in the group of HIV positive patients compared to HIV seronegative people. 38 out 69 HIV infected patients were on ARV and 31 were still treatment naïve. Being on treatment or not did not affect infection by intestinal parasites. Poor hygiene conditions were associated to parasites infections (p=0). In conclusion, HIV patients should be screened routinely for intestinal parasites and treated for their overall well being. Emphasis should be placed on their hygiene as well.

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OLDER AND FORGOTTEN; SEXUAL BEHAVIOR AND PERCEIVED HEALTH STATUS AMONG HIV POSITIVE AND NEGATIVE MENOPAUSAL WOMEN IN NIGERIA

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Not only are people living longer with the Human Immunodeficiency Virus, but there is also a significant increase in older individuals becoming infected. Women in the menopausal transition may constitute a group that is vulnerable to HIV infection with less likelihood of using a condom and low perception of the risk of HIV infection with inadequate knowledge of HIV transmission and prevention. This study assessed sexual behavior and perceived health status among HIV positive and negative menopausal women in Ibadan, Nigeria. Focus group discussions were conducted among HIV positive and negative menopausal women attending the ARV and General Outpatient clinics at the University College Hospital Ibadan, Nigeria with the use of a focus group discussion guide. Opinions of discussants on condom use, having multiple sexual partners, knowledge of HIV transmission and prevention and perceived health status were explored. Ten focus group discussions were conducted among women aged 40 and 60 years in each of the two groups. Data was analysed thematically. A total of 90 HIV positive and 92 HIV negative women aged between 40 to 60 years were sampled. While all the women opined that condom use protects against STIs and unwanted pregnancy, condom use was low among both groups. More HIV negative women opined that having multiple sexual partners was unbecoming and any older woman with multiple sexual partners is promiscuous, however, HIV positive older women strongly affirmed that men often run away when they disclose their HIV status to them, hence the need for multiple sexual partners. Knowledge of HIV transmission and prevention was poor among both groups. Interestingly, more HIV positive women perceived their health status as good, compared to HIV negative women. Coping strategies include belonging to a support group and seeking information from health care workers. Menopausal women are vulnerable to HIV infection and its impact on this group should not be ignored. There's a need for risk reduction strategies and health promoting interventions that will help these women in coping with the double burden of HIV infection and ageing.

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PREVALENCE OF PREECLAMPSIA AMONG HIV-POSITIVE PREGNANT WOMEN AS COMPARED TO HIV-NEGATIVE WOMEN IN IBADAN

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Preeclampsia is a common complication of pregnancy and a major cause of maternal morbidity. Pathogenetic explanations for preeclampsia include; maladaptation of the immune system to paternal antigens and exaggerated maternal inflammatory response to trophoblastic tissue. Immune deficiency, induced by HIV or any other cause, could therefore inhibit a tendency to immune hyper-reactivity and thus theoretically prevent the development of preeclampsia. The study aimed to explore the role of the immune theory of pre-eclampsia by comparing the prevalence of preeclampsia among HIV-positive and HIV-negative pregnant women. The study is a cross-sectional survey of pregnant women, beyond 28 weeks gestation, who delivered at the University College Hospital, Ibadan, Nigeria between 1st October 2011 and 31st December 2011. Data was collected using a pre-specified proforma. Analysis was done using SPSS version 17.0 and p-value was set at <0.05. A total of 766 women who gave birth during the period of the study met the inclusion criteria. Among the cohort, HIV prevalence rate was 7.2% while preeclampsia was 10.7%. None of the HIV-positive women had preeclampsia. This study concluded that the prevalence and perhaps, risk of developing preeclampsia is reduced among HIV positive women. This is similar to other studies done in various countries in the world.

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HTLV AND HIV CO-INFECTION AMONG KEY POPULATIONS, DOMINICAN REPUBLIC

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HTLV and HIV coinfections are not well characterized among most at-risk populations. Overall, there has been a decline in HTLV research in the past 24 years with few studies reporting current data on its prevalence in endemic countries. Past studies have shown that HTLV-1 and HIV coinfection causes increased HTLV-1 seropositivity and subsequent risk for tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM) and other neurological diseases in addition to reduced survival time. Based on the fact that HTLV and HIV share the same modes of transmission, the purpose of this investigation was to estimate the seroprevalence of HTLV IgG and HIV antibodies and to establish the prevalence of coinfection among two key populations, transactional sex workers (SWs) and drug users. A demographic, stratified sample of 200 sera was randomly selected in four high burden regions of Santo Domingo, Dominican Republic. Informed consent was obtained from each participant and each received pre- and post-counselling about HIV and HTLV transmission. Blood samples were drawn from each participant and screened for HIV and HTLV-1/2 IgG antibodies using ImmunoComb®II (Orgenics, Israel) products. Overall weighted seroprevalence of HTLV-1/2 IgG antibodies was 13.91% (CI: ±6.32%) in men and 10.59% (CI: ±6.54%) in women and for HIV-1 was 13.91% (CI: ±6.32%) in men and 17.65% (CI: ±8.10%). Of those HTLV positive, 50% of those men and 44.44% of those women were coinfected with HIV and half of whom were SWs. Seroprevalence of both HTLV and HIV antibodies detected among heterosexual SWs (33.33%) appears to be the most important route of transmission. Results call attention for more public health preventive strategies among key populations in the Dominican Republic and further investigation on the neurological complications experienced and clinically relevant effect of HTLV-1 on HIV positive patients in endemic regions.

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FACTORS ASSOCIATED WITH DEFAULTING FROM CARE AMONG ADULTS ON ANTI-RETROVIRAL TREATMENT PROGRAM IN ONDO STATE, NIGERIA, 2015

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Nigeria has one of the highest burden of Human Immunodeficiency Virus (HIV), with a prevalence of 3.4%, and over 700,000 on antiretroviral therapy (ART). Defaulting from care is an emerging threat to successful control of HIV. This study explored factors associated with default among adults on ART in Nigeria. An unmatched 1:2 case control study was conducted at Federal Medical Centre, Owo, Ondo State. Cases were

adults who defaulted clinic visit at least three consecutive times and have not returned to care, while controls were consistent in clinic visit for at least 6 months. Defaulters identified from the clinic register were interviewed at home. Controls were selected from the ART clinic using systematic sampling technique. Semi-structured questionnaire was used to collect data on respondents' socio demographics, disclosure status and knowledge on ART treatment. Four in-depth interviews (IDI) with defaulters were conducted to document the barriers to retention in care. A total of 102 cases and 204 controls were enrolled. Respondents mean age was 41.4±10.3 years and 118(38.6%) were males. Defaulting from treatment was associated with non-disclosure of status to partner (AOR: 2.8; CI 95%: 1.6-4.9), receiving fewer counselling sessions (AOR: 2.3; CI 95%: 1.3-4.2), perception that quality of service received was poor (AOR: 2.6; CI 95%: 1.4-4.7), and sub-optimal quality of life (AOR: 2.7; CI 95%: 1.5- 4.8). Major reasons for defaulting included: traveling out of base 10(67%) and lack of support from workplace 9(50%). IDI revealed clinic not operating on weekend as a cause of defaulting. In conclusion, the clinic management team increased the number of patient counselling sessions and reviewed its content to include training on disclosure techniques. Commencing weekend clinic days was recommended.

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MOLECULAR AND CLINICAL IMMUNE STATUS OF HIV EXPOSED BUT UNINFECTED (HIV EU) INFANTS COMPARED TO CONTROL HIV UNEXPOSED (HIV UU) INFANTS: A COHORT STUDY IN KISUMU DISTRICT, KENYA

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Kenya has one of the world's greatest HIV burdens; nearly 1.5 million adults are infected. Due to increased access to antiretroviral therapy and mother to child transmission interventions implemented in Kenya, the number of babies infected with HIV is low. But as the number of HIV positive adults in Kenya remains steady and transmission to infants is decreased, there is now a growing population: HIV exposed but uninfected (HEU) infants. These infants, while healthier than HIV positive infants, have increased morbidity and mortality compared to HIV unexposed uninfected (HUU) infants. We hypothesized that *in utero* exposure to HIV and/or the chronically activated maternal immune environment resulting from HIV infection affects the fetal immune system leading to prolonged elevation of pro-inflammatory biomarkers, decreased antibody production, and increased clinical events of infants. This study is investigating the following aims: (1) Determining the magnitude and duration of elevated pro-inflammatory biomarkers in HEU vs. HUU infants using MagPix analysis of plasma samples at birth, 6, 10, 14, 18 weeks, and 6, 9, and 12 months (2) Determining the prevalence and magnitude of antibodies against multiple *Plasmodium falciparum* antigens by serology up to two years of age and (3) Characterizing the clinical events (such as pneumonia, meningitis, malaria) experienced by HEU vs. HUU infants over the first two years of life. Preliminary results suggest that there is no significant difference in the levels of pro-inflammatory biomarkers present in plasma of HEU vs. HUU infants at all of the time points tested between birth and one year. These results suggest that perhaps the immune system of HEU infants is actually more stable than initially hypothesized. This finding is further supported by preliminary results from the clinical database that suggest there is no significant difference in the number of sick visits, severe infections, or hospital admissions between the HEU and HUU infants.

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HIV EPIDEMIOLOGY AND COVERAGE OF HIV HEALTH SERVICES IN GEM COUNTY, SIAYA COUNTY, WESTERN KENYA, 2013-2014

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According to the Kenya AIDS Indicator Survey (KAIS) of 2012, the former Nyanza province of Kenya had the highest HIV prevalence among persons aged 15-64 years; 15.1% (against the country's national average of 5.6%) with 18.3% among females and 13.9% among males. In the same survey, 71.3% and 79.9% of persons had ever been tested for HIV in the past country-wide and in Nyanza province respectively. Among all males, 91.2% were circumcised country-wide and 66.3% in Nyanza. HIV prevalence in uncircumcised and circumcised men was 16.9% and 3.1% and 25.9% and 8.1% in Kenya and Nyanza respectively. Among the HIV infected, 89.3% were enrolled in HIV care countrywide of whom 88.6% were on Cotrimoxazole Preventative Therapy (CPT); CPT coverage was 90.0% in Nyanza. We present more recent results of a home based HIV counseling (HBCT) survey in Gem Sub-County, Siaya County (one of the five counties in the former Nyanza province). We reviewed data for persons aged between 15 and 64 years of age who participated in the HBCT Survey, between June 2013 and August 2014. We compared HIV prevalence and coverage of selected HIV health services for former Nyanza province in KAIS 2012 to HBCT. Of 21,879 persons who participated in the survey; 63% were female. Among all participants, 19,417 (89%) had ever been tested for HIV in the past of whom 2084 (10.7%) tested positive; majority (98%) of HIV positive persons had been enrolled into HIV care and were on CPT (98%). Among the larger group (89.3%) who had tested negative for HIV in the past, HIV prevalence during survey testing was 4.1 % (n=704) and 7.1 % (n=171) among those who had never been tested. The overall HIV prevalence was 13.8 %. HIV prevalence was significantly higher among females compared to males (16.4% vs. 9.4%). Among all men, 64.5% had been circumcised. HIV prevalence was significantly higher among circumcised compared to uncircumcised men (4.9% vs. 11.8%). The current HIV prevalence in this region reflects the country's downward trend in HIV prevalence and maybe due to increased coverage of HIV health services. More comprehensive comparisons should routinely be made to illustrate trends in the HIV response.

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USING THE LIVERPOOL HIV ICHART TO PREDICT THE SPECTRUM OF DRUG-DRUG INTERACTIONS IN A COHORT OF HAART- EXPOSED PERSONS LIVING WITH HIV (PLHIV) IN A TREATMENT CENTRE IN SOUTH-SOUTH NIGERIA

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Drug-drug interaction (DDI) occurs where two or more drugs interacts in a manner that alters their therapeutic effects. HAART may interact with co-medications in HIV patients and present severe complications. Objective We used the Liverpool iCHART application to describe the pattern of drug-drug interactions between HAART and other medications in a cohort of HAART-exposed PLHIV at the University of Port Harcourt Teaching Hospital. This was a review of client records at the HAART clinic of the University of Port Harcourt Teaching Hospital in the South-South region of Nigeria conducted in September 2014. Folders of 480 patients who reported for clinic consultations and drug refills were selected via systematic sampling over a 20 day period. We used simple random sampling to identify two drug prescriptions from client folders. A data extraction form was used to record data on socio-demographic details, co-morbidities, co-prescribed drugs as well as the specific HAART regimen employed. The Liverpool HIV iChart Application was used to screen for possible interactions such

as potential drug interactions and clinical significant drug interactions (CSDI) between the ARV drugs and co-medications. Results The study involved record from 157(33.1%) male and 321 (66.9%) female PLHIVs with mean age of 38.82±9.68 years with ages ranging from 20 to 84 years. Prevalence of potential drug interactions (PDI) was as high as 463 (96.5%) while the prevalence of CDSI was 216 (45%). All client prescriptions reviewed using the app had elements in the green indicating no interactions, 464 clients (96.7%) had elements in amber indicating presence of potential interactions for which caution was needed while 48 clients (10%) of elements of their drug treatments in the red/danger zone indicating an absolute contra-indication to co-administration of HAART and the particular co-medication. In conclusion, the Liverpool HIV ICHART is an inexpensive and useful resource for predicting drug-drug interactions for PLHIV on HAART. Its routine use is advocated in HIV treatment centres especially in resource poor settings.

1146

DIAGNOSIS OF TOXOPLASMOSIS REACTIVATION IN HIV PATIENTS IN URINE USING NANOPARTICLE TECHNOLOGY

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The most devastating opportunistic diseases associated with HIV are those that affect the central nervous system (CNS). Their nonspecific presentation makes diagnosis difficult even in the best-resourced settings. In many cases, diagnosis by exclusion is the only option. *Toxoplasma gondii* is one such malady. Thus we present a point of care western blot for the detection of *T. gondii* antigen, SAG1. *T. gondii* seroprevalence varies by continent and socioeconomic status, but is estimated to be highest in Latin America ranging from 39-90%. An estimated 33% of patients with advanced immunosuppression and previous seropositivity for *T. gondii* will develop toxoplasmic encephalitis (TE). Diagnosis of *T. gondii* in HIV positive patients is difficult without CT or MRI in resource-poor settings. PCR of cerebral spinal fluid (CSF) has a sensitivity of 12-to-70%. Safe collection of CSF is difficult in locations without medical facilities and expertise. Obtaining a culture of the parasite is possible, but requires at least 6 weeks for completion, rendering results diagnostically irrelevant. When TE is treated early, the disease boasts a 90% clinical response rate. Thus, a rapid point of care test with high sensitivity and specificity, using an easily obtained body fluid is absolutely necessary if LMIC treatment is to surmount the aforementioned diagnostic challenges. Nanoparticle-concentrated urinary-antigen diagnostic assays are noninvasive, safe, and inexpensive; they provide a rapid, accurate, and precise parasitological test in resource-constrained zones where PCR is not readily available. Sensitive and specific urinary tests combined with clinical assessment will aid in the diagnosis and treatment of TE in HIV-infected patients. Briefly, nanoparticles were circulated in murine or human urine samples, collected, and the contents eluted. Said contents were separated by polyacrylamide electrophoresis and detected by western blot. Results illustrate detection of all positive and negative samples in accordance with previous qPCR results. We are intrigued by these results and will continue pilot testing this assay as patient samples become available.

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COULD ACCELERATION TOWARDS GLOBAL 90:90:90 HIV TARGET ALONE END TB BURDEN AMONG UNDIAGNOSED PEOPLE LIVING WITH HIV? A FOUR YEAR PRE- AND POST-ISONIAZID PREVENTIVE THERAPY IMPLEMENTATION COMPARATIVE DATA FROM COMPREHENSIVE HOSPITAL IN NORTHWESTERN NIGERIA

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Early access to HIV testing and counselling provides opportunity to start antiretroviral therapy (ART) and Isoniazid Preventive Therapy (IPT) for eligible people living with HIV (PLHIV). There is paucity of data that demonstrate comparative programmatic analysis of the impact of IPT intervention on the incidence of TB among PLHIV on ART and those not on ART. In August 2013, the PRO-ACT project funded by USAID and implemented by Management Science for Health started implementation of 6 month of IPT in General Hospital Koko, northwestern Nigeria. The objective of the study is to assess and compare impact of IPT in reducing TB incidence among PLHIV on ART and those previously undiagnosed and not on ART. Using the Hospital TB register between July 2011 to September 2015, TB/HIV co-infection cases were extracted into 2 groups i.e. group 1/pre-IPT (July 2011-July 2013) and group 2/post-IPT implementation era (September 2013-September 2015). TB/HIV co-infected cases in each group were then categorized into 2 cohorts each. Cohort 1 are those not on ART, not on IPT, not previously diagnosed as HIV positive until they develop TB. Cohort 2 patients are those previously diagnosed HIV positive, not on IPT but on ART before they develop TB. Cohort 3 was on IPT, not previously diagnosed as HIV positive until they develop TB and not on ART. Cohort 4 was on IPT, previously diagnosed as HIV positive before they develop TB and on ART. Data from the 4 cohorts were then compared to demonstrate impact of IPT and ART in reduction of TB burden and incidence among PLHIV. The lowest incidence (23.4%) of new TB cases was found in post-IPT era among cohort 4 while the worst incidences of new TB cases of 53.3% and 76.6% were found among cohorts 2 and 3 respectively. The study demonstrates the combined multiplier effects of both IPT and ART in reducing the incidence of TB among PLHIV and increased TB incidence among previously undiagnosed HIV cases in Northwestern Nigeria. In line with global 90:90:90 target, scaling up HIV testing and counselling will ensure early diagnosis as entry point for improved access to lifesaving ART and IPT thereby reducing the incidence of TB among undiagnosed HIV cases.

1148

THE GENETIC VARIATION WITHIN SUB-SAHARAN POPULATIONS ENDEMIC TO HUMAN AFRICAN TRYPANOSOMIASIS

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Human African trypanosomiasis (HAT) is one of the neglected tropical diseases that affect thousands of individuals in sub Saharan Africa. Within these populations, some individuals are highly susceptible to infection whereas others remain asymptomatic. The TrypanoGEN consortium was setup to study the Human genetic determinants of disease susceptibility

and trypano-tolerance in 6 African countries. In order to identify loci that are associated with disease, whole genome sequencing was carried out on 250 individuals from five populations; Guinea (GUI), Ivory Coast (CIV), Cameroon (CAM), Democratic republic of Congo (DRC) and Uganda (UGA) to discover SNPs for a planned Genome wide association study (GWAS). Approximately 2 million SNPs within the TrypanoGEN population samples were called. Principal component analysis (PCA) and Admixture analysis were used to identify population structure that could confound the GWAS. The samples clustered into 4 distinct groups; West African Bantu (CIV & GUI), Central African Bantu (DRC), Ugandan Bantu (UGB) and Ugandan Nilotics (UGN). Further population structure analysis showed that the Uganda Bantu (UGB) had substantial admixture with the Nilotic (UGN) ancestry (approximately 50%), were as the Nilotic are a distinct population with no Bantu admixture. There is some evidence that HAT is a relatively recent infection associated with agriculture and livestock domestication. Consequently, loci such as APOL1 associated with disease response may show signs of positive selection. Preliminary Fst analysis has already identified loci with high Fst which have known associations with malaria or methotrexate toxicity. An analysis of loci under positive selection that may be associated with response to trypanosomiasis will be presented.

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EVIDENCE OF AUTOCHTHONOUS CHAGAS DISEASE TRANSMISSION IN SOUTH TEXAS

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Chagas disease (*Trypanosoma cruzi* infection) is one of the most significant neglected tropical diseases affecting the Americas. There are an estimated 8-9 million prevalent cases worldwide with an estimated 300,000 infected people residing in the United States. Chagas disease is often referred to as the 'silent killer' due to its long (up to 3 decades) asymptomatic period. During this period, progressive cardiac damage can occur in up to one-third of infected individuals. In fact, sudden cardiac death is the first presenting symptom in 35% of those with cardiac manifestations. Due to concern for transmission of the parasite from infected blood products, national blood donation screening became mandatory in the United States in 2007. Since screening started, 47 seropositive donors have been identified in the greater San Antonio area. From this convenience sampling, we aimed to gain a better understanding of the transmission sources for Chagas positive donors in south Texas. Our case investigation found 71% (12 out of 17) of enrolled donors had evidence of acquiring the infection locally. Risk factors for disease in those with autochthonous transmission included rural residence, outdoor occupations, and outdoor hobbies. Of most concern, 58% (5 out of 12) had evidence of Chagasic cardiac disease as detected on electrocardiogram. This study adds to the growing body of evidence for autochthonous Chagas disease transmission in the southern United States. In fact, from this population, we identified the largest percentage of autochthonous cases to date. This has important implications for public health officials and clinicians as our understanding of the global epidemiology of this disease changes. Following this presentation, the audience will have a better understanding of the epidemiology of Chagas disease in the southern United States.

1150

PAN-AMERICAN MIGRATION PROMOTES THE SPREAD OF PATHOGENIC *TRYPANOSOMA CRUZI* HYBRID STRAINS

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The principal reproduction strategy of *Trypanosoma cruzi*, the aetiological agent of Chagas disease, is the subject of an intense, decades-old debate. Despite the existence of two recent natural hybrid lineages (TcV and TcVI), which are sympatric with severe disease in southern endemic areas, a pervasive view is that recombination has been 'restrained' at an evolutionary scale and is of little epidemiological relevance to contemporary parasite populations. With improved sampling strategies, the geographical distribution of TcV and TcVI appears to be expanding. High resolution nuclear and mitochondrial genotyping of potential hybrid isolates from domestic vectors and human infections in Colombia was undertaken, in comparison to representative strains from across South America, to resolve their putative status as novel recombinants. All suspected Colombian hybrids were highly heterozygous, minimally diverse and possessed intact parental alleles at each loci. Compared to local Colombian isolates, hybrids were distinct from, but more closely related to, those identified in southern reference TcVI strains. Based on independent inheritance patterns of microsatellite loci, our data support the hypothesis that two recombination events led to the formation of TcV and TcVI. However, more private alleles among Colombian hybrids and the sharing of mitochondrial haplotypes between southern TcV isolates and a Colombian TcVI strain, suggests the evolution of these recombinant lineages may be more complicated than previously assumed. The origin of these Colombian hybrids is unclear; they are unlikely to be predecessors of southern TcVI strains, but were also not clear descendants, and may instead represent a sibling group, which diverged and anthroponotically dispersed northwards, following a single hybridization event between heterozygous southern TcII and TcIII isolates. We discuss the important implications the geographical range expansion of TcVI has for emergent human Chagas disease in Colombia, considering the successful, epidemic establishment of this low-diversity genotype among domestic transmission cycles in the South.

1151

EVIDENCE AND IMPORTANCE OF GENETIC EXCHANGE AMONG FIELD POPULATIONS OF *TRYPANOSOMA CRUZI*

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Many eukaryotic pathogenic microorganisms that were previously assumed to propagate clonally have retained cryptic sexual cycles. The principal reproductive mode of *Trypanosoma cruzi*, the aetiological agent of Chagas disease, remains a controversial topic. Strong linkage disequilibrium, deviations from Hardy-Weinberg allele frequencies and structuring of parasite populations into stable, distinct genetic clades have been used to argue that recombination has been restrained at an evolutionary scale and has little influence on contemporary field populations. However, with improved sampling strategies and the development of higher resolution nuclear and mitochondrial genotyping techniques, mounting evidence now indicate that natural hybridization in *T. cruzi* may be frequent, non-obligatory and idiosyncratic; potentially involving independent exchange of kinetoplast and nuclear genetic material as well as canonical meiotic mechanisms. Asymmetric mitochondrial introgression is emerging as a common feature of some transmission cycles, which given their crucial role in growth, development and metabolism, satisfies the elevated necessity to escape from Muller's ratchet, and may be exploitable as a method of host range extension. A clear understanding of the implications of genetic exchange for the ecological and geographical distributions and

pathological characteristics of *T. cruzi* strains is crucial to establish the epidemiological risk associated with hybrid genotypes, with respect to virulence, transmissibility and drug susceptibility. We discuss the growing number of field studies which now challenge the traditional paradigm of preponderate clonal evolution in *T. cruzi*, the caveats underlying why detecting genetic exchange is inherently complicated, given that parasites most likely to be recombining may be closely related and potentially indistinguishable, and describe experimental strategies which must be adopted to resolve these fundamental biological phenomena in trypanosomatids as we enter the post-genomic era.

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CHAGAS DISEASE IN PREGNANT WOMEN AND SCREENING BY PCR IN NEWBORNS FROM GUANAJUATO, MÉXICO

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Chagas disease is caused by an infection with the protozoan hemoflagellate *Trypanosoma cruzi*, and it is a major endemic health problem in Latin America. The congenital route is one of the main non-vectorial pathways of transmission, which can arise either in the chronic or acute phase of maternal infection. Serological screening of *T. cruzi* infection was performed in 520 pregnant women and newborns at the Hospital General Regional de León, Guanajuato, Mexico, between 2014 and 2015. Anti-*T. cruzi* antibodies were detected in 20 mothers (4%) by ELISA and HIA with four PCR-positive newborn cases. Risk factors were identified according to an epidemiological survey, and the most significant ($P < 0.050$) factors associated with *T. cruzi* infection were the building materials of dwellings, the presence of pets and dwellings located in rural areas. This study constitutes the first systematic study on congenital Chagas disease and the epidemiological risk factors in Guanajuato. Our results represent the probability of an incidence of 770 cases per 100,000 births during a period of 12 months, with a vertical transmission rate by 0.8%, which highlights the necessity to establish reliable serological and PCR tests in pregnant women to prevent vertical transmission. However, it is also important to follow-up the newborns from seropositive mothers for one year, which is necessary, as many children yielded negative results.

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TRYPANOSOMA CRUZI PREVALENCE AND SEROPREVALANCE IN A COHORT OF U.S. SERVICE MEMBERS IN SOUTH TEXAS

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Although the vast majority of the estimated 300 thousand U.S. residents infected with *Trypanosoma cruzi*, the causative parasitic agent of Chagas disease, are among immigrants from endemic areas of Latin America, autochthonous transmission is possible in some parts of the United States. A study is being conducted at Joint Base San Antonio-Lackland, Texas, to determine the prevalence and seroprevalence of Chagas disease among military members who may be at increased risk due to field training activities in an area where a large number of *T. cruzi*-infected triatomines have been identified. We offered voluntary enrollment to U.S. Air Force technical training students graduating from security forces training, Basic Military Training field instructors, and military working dog instructors. Volunteers completed a questionnaire regarding risk factors for Chagas disease and had their blood drawn. Real-time polymerase chain reaction (PCR) and two serologic tests (enzyme-linked immunosorbent assay [ELISA] for IgG and IgM and immunofluorescence assay [IFA] for IgG) were conducted on the collected samples. Descriptive statistics were used to analyze the prevalence and seroprevalence of *T. cruzi* and risk factors. A total of 473 individuals have been enrolled to date. Of the tests conducted (PCR [N=460]; ELISA [N=465]; IFA [N=465]), all have been negative for *T. cruzi*. The participants reported a mean of 7 weeks spent in a triatomine-endemic field environment, 273 weeks living or traveling in the Southwest United States and Latin America, and 15 weeks camping or hunting in the Southwest United States and Latin America. Chagas disease does not constitute a significant operational risk to service members who conduct or undergo field training in south Texas. The lack of positive cases may demonstrate the effectiveness of countermeasures that prevent triatomine bites (e.g., trainees are issued insect repellent and permethrin-treated bed nets) and/or the poor efficacy of stercorarian transmission of *T. cruzi*.

1154

TRANSMISSION DYNAMICS OF VISCERAL LEISHMANIASIS IN THE INDIAN SUBCONTINENT - A SYSTEMATIC LITERATURE REVIEW OF THE ROLE OF ASYMPTOMATIC LEISHMANIAL INFECTION, POST-KALA-AZAR DERMAL LEISHMANIASIS AND RELAPSE RATES

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As Bangladesh, India and Nepal progress towards visceral leishmaniasis (VL) elimination, it is important to understand the role of asymptomatic *Leishmania* infection (ALI), VL treatment relapse and post kala-azar dermal leishmaniasis (PKDL) in transmission. We systematically reviewed evidence on ALI, relapse and PKDL as potential reservoirs of infection. We searched multiple databases to include studies on burden, risk factors, biomarkers, natural history, and infectiveness of ALI, PKDL and relapse. After screening 292 papers, 98 were included. ALI, PKDL and relapse studies lacked a reference standard and appropriate biomarker. The prevalence of ALI was 4-17-fold that of symptomatic VL. The risk of ALI was higher in VL case contacts. Most infections remained asymptomatic or resolved spontaneously. The proportion of ALI that progressed to VL disease within a year was 1.5-23%, and was higher amongst those with high antibody titres and those who had a VL case in the family. The natural history of PKDL showed variability; 3.8-28.6% had no past history of VL treatment. About 49% of PKDL resolved spontaneously without treatment. The infectiveness of PKDL was 32-53%. Relapse following VL treatment occurred in 0.14-20% and the risk was higher with HIV co-infection. Modelling studies produced a range of scenarios. One model predicted that early diagnosis was unlikely to eliminate VL in the long term. Another model estimated the infectiveness of ALI to be 1-3% and that ALI contributed to 82% of the overall transmission, VL to 10% and PKDL to 8%. In contrast, another model predicted that VL cases were the main driver for transmission. Another model predicted that VL would be eliminated if the sandfly density was reduced by 67% by killing the sandfly or by 79% by reducing their breeding sites. Another model predicted VL elimination with 4-6y of optimal IRS or 10y of sub-optimal IRS and only in low endemic setting. There is a need for xenodiagnostic and longitudinal studies to understand the potential of ALI and PKDL as reservoirs of infection.

1155

MOLECULAR DETECTION OF *LEISHMANIA (VIANNIA) PANAMENSIS* IN ANTHROPOPHILIC AND ZOOPHILIC SANDFLIES FROM AN ENDEMIC FOCUS OF CUTANEOUS LEISHMANIASIS IN PANAMA

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Cutaneous leishmaniasis (CL) is a parasitic zoonosis prevalent in many rural areas of Panama. *Leishmania Viannia panamensis* is considered the main involved etiologic agent. The transmission of this parasitic disease is conditioned by the bite of infected sandflies, most of them belonging to the genus *Lutzomyia*. The abundance and diversity of these vectors in Panama is high with about 76 described species. However, only six of these species feed on human blood frequently (anthropophilic), and therefore have been considered important vectors. Little is known about the infection rates with confirmed *Leishmania* species in these putative vectors and even less in those considered zoophilic vectors, although the latter are abundant in many foci of transmission. In this study, sandflies were collected using light traps HP inside and around 24 houses from Trinidad de Las Minas, a rural community where CL transmission is high. More than 5,600 sandflies were collected. The most abundant anthropophilic especies were *Lu. panamensis* (967), *Lu. gomezi* (1,146) and *Lu. trapidoi* (1,151). Among the zoophilic vectors, *Lu. dysponeta* (490) and *Lu. triramula* (1,150) were the most frequently species found. Female sandflies were pooled in 5 to 10 individuals per species. *Leishmania* infection and species discrimination was performed by ITS-1 and kDNA PCR and by HSP70 PCR-RFLP and sequencing analysis respectively. The results confirm the high infection rate with *L. (V.) panamensis* in the anthropophilic vectors, predominantly *Lu. trapidoi*. Interestingly, it was also demonstrated the infection in the zoophilic *Lu. triramula* and *Lu. dysponeta* pools. This is the first molecular detection and identification of *L. (V.) panamensis* within naturally infected *Lu. triramula* and *Lu. dysponeta* from an endemic focus of CL in Panama. This finding concluded that *Lu. triramula* and *Lu. dysponeta* are susceptible to L. (V.) panamensis infection and suggest that more attention should be paid to zoophilic sandflies vectors regarding the ecoepidemiology of CL.

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EFFECT OF GEOGRAPHICAL DIFFERENCES, *TRYPANOSOMA CRUZI* INFECTION AND BLOOD MEAL ON MICROBIOME OF *TRIATOMA INFESTANS*

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The protozoan parasite *Trypansoma cruzi* causes Chagas disease, which is considered one of the neglected tropical diseases by the WHO. Chagas disease is primarily transmitted by triatomine bugs, which bites a human for a blood meal and defecates near the bite site. Infection occurs when the person rubs feces containing the parasite into the bite wound or a mucous membrane. We examined the fecal microbiome of *Triatoma infestans* bugs captured in Arequipa, Peru during vector control campaigns in 2011 and 2014-2015. Frozen, ethanol-preserved bugs were thawed, and fecal contents were expressed onto filter paper. DNA was extracted from the fecal spots using a modified phenol chloroform technique. Quantitative real time polymerase chain reaction (qPCR) was used to test for *T. cruzi* infection. Blood meal source for each bug was identified using conventional PCR targeting a 355-bp segment of the cytochrome B gene followed by Sanger sequencing. Sequences were run through the BLAST database on the NCBI website to identify the species of the bug's last blood meal. MEGA was used to align sequences and QIIME to examine genetic diversity and relatedness between samples. 16S ribosomal rRNA was amplified using universal primers and deep sequenced using Illumina technology. 90 insect fecal samples were extracted and sent for 16S sequencing and cytochrome B could be amplified from 58 of those. From the samples that amplified cytochrome B 74% (43/58) of those were found to have human mitochondrial DNA, 12% (7/58) had various rodent DNA, 9% (5/58) had dog DNA and 5% (3/58) had chicken DNA. We will compare diversity and composition of triatomine gut microbiome by *T. cruzi* infection status, bug stage, geographic location, and blood meal source. These findings may have implications for the development of new non-traditional vector control interventions.

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OUTCOMES OF A COMMUNITY INTERVENTIONAL-EVALUATIVE MODEL FOR NEGLECTED DISEASES IN EAST POKOT, KENYA

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Neglected tropical diseases (NTDs) are the primary barriers for low-income individuals to escape poverty. Population based cross-sectional surveys conducted in 2012 and 2013 in East Pokot, Kenya showed high seroprevalence of visceral leishmaniasis (VL) with 23 rK39-confirmed cases out of 1,324 screened, compounded by high rates of poverty, hunger, illiteracy and conflict. This necessitated the need to develop an interventional program using community strategies. Focusing on three administrative locations in the East Pokot sub-county, the ongoing model is comprised of public health education, provision of rapid diagnostics, screening and treatment, training of clinicians and community outreach workers, environmental control and operations research. Between 2015-2016, 552 rk39 rapid diagnostic kits (Bio-Rad) were distributed to seven health facilities. As a result, 326 individuals were screened for VL, of which 60 displayed rK39 positive results. A community-based screening of 441 individuals who meet clinical case-definitions identified 14 rk39-positive individuals. Seven coordination meetings were held with national, regional and local stakeholders. Ten health workers (laboratory technicians, nurses and clinicians) were trained on recognition, treatment, management and referral of potential VL cases. Fifteen community health volunteers were trained on recognition, referral of suspected VL cases and health education. Integrated public health education campaigns on VL and trachoma prevention and treatment were conducted in nine villages and six schools. Additionally, 200 VL educational posters were distributed to nearby schools, churches, health facilities and market areas. Integrated mobile clinics reached 516 patients. Vector control activities were conducted in five villages. An entomology assessment was conducted to investigate the distribution of the sandfly vector and the relationship between the ecology and socio-cultural context impacting disease. A mixed model for research and community-based interventions can be a successful approach in impacting NTDs in hard-to-reach populations.

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PREDICTORS OF CHAGAS INFECTION AMONG INDIGENOUS COMMUNITIES IN THE SIERRA NEVADA DE SANTA MARTA IN COLOMBIA

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Chronic Chagas cardiomyopathy is the main contributor to mortality in endemic regions and is caused by the protozoan parasite *Trypanosoma cruzi*. Many factors affect the susceptibility to the infection, including environmental, genetic, parasite-driven and vector-mediated. However, additional clinical features contribute to the determination of infections, and the aim of this study was to rank the importance of these factors for classifying participants as Chagas positive or negative in an indigenous community in Sierra Nevada de Santa Marta, Colombia. A cross-sectional case-control study was implemented, with 232 patients with positive dual Chagas serologies and 261 negative serologies enrolled. Among study participants residing in areas with greater than 10% infestation by *Triatoma dimidiata* (TD), 64% were positive for Chagas disease compared to 46% in areas with less than 10% infestation (chi-square p<.001). Variables associated with positive Chagas serologies were chest pain (37% vs. 18%, p<.001), paroxysmal nocturnal dyspnea (PND) (20% vs. 8%, p=0.02), syncope (24% vs. 9%, p<.001), edema (20% vs. 9%, p=0.05) and abnormal EKG (28% vs. 17%, p=.02). Participants with Chagas positivity were significantly older than participants that were negative for Chagas (33 years vs. 25 years, respectively, p<.001). Random forest classification was implemented by fitting 500 bootstrap aggregated trees with 5 variables randomly chosen among a list of 16 possible at each node. The top five variables according to the mean decrease in accuracy were infestation by TD, age, chest pain, syncope and PND. The top five variables with respect to mean decrease in Gini were age, infestation by TD, chest pain, syncope and edema. Abnormal EKG was in the top 10 for both importance measures. Older age, higher infestation of TD, chest pain, PND, edema, syncope and abnormal EKG are important indicators of potential Chagas infection in this region. These findings highlight the critical importance of vector-driven factors for infection rate and useful and practical clinical variables that can increase the pre-test probability of Chagas infection in low-resource settings.

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LONGITUDINAL CHANGES IN VECTOR BORNE DISEASE PREVALENCE IN A UNITED STATES DOG POPULATION

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Zoonotic vector-borne diseases, such as Lyme disease, have increased in prevalence in both animals and humans over the past decade. While these diseases spread due to various factors, little is understood about the progression of these diseases over time in animals with other co-morbidities, such as leishmaniasis. Within a cohort of approximately 600 dogs enrolled in a phase-III clinical trial of an experimental vaccine for leishmaniasis, a subset of 200 dogs were included in a longitudinal study to assess long term changes in ehrlichiosis, anaplasmosis, borreliosis, and heartworm infection status and to determine if there is a causal relationship between these comorbid infections and presentation with clinical leishmaniasis. The cohort included dogs from the Western, Midwestern, Eastern, and Southern regions of the United States. Dogs were tested by serology and PCR both pre- and post-primary vector season. Diagnostics used to assess these changes in vector borne diseases included the IDEXX SNAP® 4Dx® Plus Test and PCR to identify specific species of *Anaplasma*, *Ehrlichia*, *Borellia* and *Dirofilaria immitis* (dog filarial heartworm). At 6 months, a small geographic subset was also assessed for acute infection with *Anapaslma phagocytophilum*, *Anaplasma platys*, and *Ehrlichia canis*. All dogs were evaluated for clinical signs of erhlichiosis, anaplasmosis, Lyme disease, and heartworm at enrollment and at 6 months via physical examination. Additional information, including information regarding each dog's age, sex, *Leishmania* status (combination of PCR, serology, and clinical signs), and leishmaniasis vaccination status were assessed to determine how vector borne comorbidities affect progression of leishmaniasis in a dog population endemic for leishmaniasis. Initial results from trial enrollment indicated that 100% of dogs symptomatic for leishmaniasis and 65% of asymptomatic dogs had a co-infection with at least one of four other vector-borne diseases. This prospective cohort study will help to better understand the potential causal relationship between co-infection with vector borne diseases and progression of leishmaniasis.

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SERIAL EVALUATIONS OF THE PARASITE LOAD OF *LEISHMANIA (VIANNIA)* SPECIES BY QPCR (QUANTITATIVE POLYMERASE CHAIN REACTION) OF NATURAL INFECTED WILD AND SYNANTHROPIC RODENTS FROM AN ENDEMIC AREA OF SOUTH FOREST ZONE OF PERNAMBUCO, BRAZIL

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This study was undertaken to evaluate parasite levels of *Leishmania (Viannia*) species in wild and synanthropic rodents from an endemic American Cutaneous Leishmaniasis (ACL) foci in the South Forest Zone of Pernambuco, Brazil and assess their importance in the enzootic cycles. Wild and synanthropic rodents were captured tagged released and recaptured between May 2012 and August 2014. *L. (Viannia*) infections were evaluated by qPCR of skin and blood samples. Xenodiagnosis was performed with *Nyssomyia. whitmani* and *Lutzomyia longipalpis*. A total 603 rodents were marked with microchips. 40.6% (245/603) were *Nectomys squamipes*, 24.5% (148/603) were *Rattus rattus*,13.8% (83/603) were *Necromys lasiurus.* Of these 186 animals were monitored at 394 recaptures (Recapture 1 (R1) = 186, R2 = 97 R3 = 52 R4 = 27 R5 = 18, R6 = 6, R7 = 3, R8 = 2, R9 = 2 and R10 = 1). 29.2% (176/603) showed natural *L. (Viannia*) infections. The infection rates determined by qPCR were as follows*: N.squamipes* 43.8%, *N.lasiurus 30.1%, R.rattus* 16.2%, *Oxymycterus angulares* 16.3%, *Holochilus sciureus* 25%, *Akodon arviculoides* 9.4%. The infections in *Rattus rattus* – a synanthropic rodent – was 4.2%, 54.2% in plantations and 41.7% in houses. The only species recaptured 5 times was *N. squamipes*. The parasite load of rodents during recaptures (0- 50060.71 fg DNA) and remained high being highest during October and November 2012 and June 2013 and January 2014. Parasitamia fell in animals kept in the laboratory. There was no difference in xenodiagnoses positivity between the two sand fly species nor was there a positive association between parasite load and positive xenodiagnoses. In conclusion, the results reinforce the hypothesis that the enzootic is maintained in a mosaic rodent species and that parasitemia levels are maintained by re-infections. The presence of infected *R.rattus* in plantations and houses strongly supports peri-domestic transmission, especially as *Ny. whitmani* populations are highest in these niches. We consider that the detected infections were *L.(V.) braziliensis* as this species has previously been isolated from wild animals, sand flies and man in this very same area.

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ESTIMATING THE COSTS AND COST-EFFECTIVENESS OF EARLY DIAGNOSIS AND TREATMENT OF CHAGAS DISEASE IN COLOMBIA

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Chagas disease still remains an important public health problem in Latin America. Early stage treatments for curbing the progression of the disease have proved effective. However, access to Chagas disease diagnosis and treatment still remains very low in most endemic countries. In Colombia it is estimated that 5 million people are at risk of acquiring the infection, 436,000 people are already infected and 30% of these are prone to develop heart complications, yet access to diagnosis is estimated at <1% of the at-risk population. In Colombia the costs and cost-effectiveness of preventive and treatment strategies have not been quantified. We estimate the unit costs of (i) preventing Chagas by mass screening school-aged children and (ii) treating inpatient and outpatient episodes of those with Chagas (according to disease stage). Costs are presented in 2014 USD and based on (i) primary data collected from a provider perspective at national, departmental and municipality levels; (ii) in-depth interviews from Ministry of Health officials and municipal and departmental secretaries of Health in Boyacá, Casanare, and Santander and, (iii) a third-payer perspective, using the National Registry of Health Services between 2008 and 2014 for 7,227 patients. Having calculated unit cots as median and interquartile range (IQR), cost-effectiveness is modelled using the authors' previously developed burden of disease model, to estimate the incremental cost per DALY averted by scaling up mass screening. Early diagnosis was costed at $18 (IQR: 4-46) per school-child screened. Average treatment cost per patient per year was estimated at $29 (IQR: 15- 94) for mild Chagas and $211 (IQR: 104-541) for severe Chagas. On average a hospital admission for a patient with a primary diagnosis of Chagas cost $340 (IQR: 310-882, and maximum $16,685). However, outpatient clinic services, (doctor visits and ambulatory procedures) were the main cost driver, at 86% of total Chagas treatment costs. Preliminary modelling results suggest that mass screening for Chagas amongst school-aged children is cost-effective in a variety of epidemiological contexts.

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UNDERSTANDING LONG-TERM CYCLES OF VISCERAL LEISHMANIASIS IN BIHAR

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Visceral leishmaniasis (VL) is a vector-borne disease of public health importance in India, with the highest burden of disease in the states of Bihar, Jharkhand, West Bengal and Uttar Pradesh. VL is currently targeted for elimination by 2017; the primary interventions used for elimination are indoor residual spraying, active case detection and treatment. Historically the disease trend in India has been regarded as cyclical with case resurgence characteristically occurring every 15 years. However, the cause of this pattern remains unclear and as the Bihar VL programme nears the elimination target, explaining previous trends to use within predictive tools to avoid future epidemics has become essential. To interpret observed cyclical trends, annual climatic indicators including rainfall, temperature and humidity over time periods known to influence disease and vector trends over the year were compared with annual VL case incidence data. Rainfall was found to have a strong association with annual VL case patterns during the monsoon season (June to September) (p=0.0383) and prior to sand fly peaks (February to May, September and October) (p=0.0253). Whilst annual rainfall was also found to have a close association with annual case incidence (p=0.0398), rainfall during the sand fly peaks (March to June, October and November) was not significant (p=0.0911). No association between humidity or temperature and VL incidence was detected (all values p=>0.05). The VL programme in Bihar has made significant progress in recent years, adopting improved practices for vector control, diagnostics and treatment strategies: changing from DDT and stirrup pumps to alpha-cypermethrin and hand compression pumps, introduction of the rk39 test and wide-scale availability of amphotericin B. Such concerted efforts may lead to short term success, however to achieve and sustain elimination, a better understanding of external causative factors is required.

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CHAGAS DISEASE PREVALENCE AND RISK FACTORS IN WORKING DOGS ALONG THE TEXAS-MEXICO BORDER

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Chagas disease is a neglected tropical disease caused by the protozoan parasite *Trypanosoma cruzi* and transmitted by hematophagous triatomine vectors. Chagas disease is estimated to affect 6 million people throughout Latin America and is increasingly recognized in humans and dogs across the southern U.S., where studies have found that exposure of shelter and stray dogs ranges from 3.6-22.1%. Our objective was to assess the prevalence and distribution of canine Chagas disease in dogs along the Texas-Mexico border, a suspected focus for local transmission of the parasite. Department of Homeland Security (DHS) working dogs play important security roles including detection of narcotics and concealed humans, and may be at high risk due to prolonged work outdoors in borderland regions with established kissing bug populations. From fall 2015 to summer 2016, we collected blood samples from dogs in five different geographical management areas, including dogs along the geopolitical border as well as north of the border. Canine plasma was screened for anti-*T. cruzi* antibodies by rapid immunochromatographic serological tests, and positivity was confirmed by indirect fluorescent antibody testing and an independent immunochromotagraphic assay. To test for active infection, buffy coat samples were tested by qPCR to amplify *T. cruzi* satellite DNA. The preliminary results (n=528) indicate over 11.9% [9.2, 14.7] of dogs are positive for anti-*T. cruzi* antibodies by two or more serology assays, and parasite DNA was detected in three blood samples. Seropositivity did not differ across age, sex, breed, geographic location or canine discipline. Ongoing work aims to track canine infection over time in relation to clinical status and vector occurrence. Understanding the epidemiology of Chagas disease along the border is a prerequisite for implementing vector control measures to protect the health of not only these high value working dogs, but also local human populations.

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EPIDEMIOLOGICAL EVIDENCE OF CANINE VISCERAL LEISHMANIASIS IN IÑAPARI-PUERTO MALDONADO, PERU, BORDER WITH BRAZIL AND BOLIVIA

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Visceral Leishmaniasis (VL) is lethal when it is not detected and treated promtly. In Latin America, it is caused by *Leishmania (L.) chagasi* being endemic in 11 countries such as Colombia, Bolivia and Brazil, neighbouring countries of Peru, where still not reported cases of LV. The aim of this study was to verify the presence of epidemiological risk factors involved in the transmission of LV at Iñapari locations, border district with Brazil and Bolivia. An exploratory cross-sectional descriptive study was conducted in two stages: i) Serological search using the Inmunocromatográfico Dual Path Platform and Indirect Immunofluorescence tests, to detect specific

antibodies against *L. (L) chagasi* in canine population of: a) Iñapari, urban locality b) Villa Primavera, rural location, c) Belgium, native rural location; ii) entomological survey with CDC traps and taxonomic identification with Young & Duncan's keys. Data and clinical signs of dogs were recorded in a Veterinary Protocol Field. We sampled 134 dogs, detecting specific antibodies against I in 7/134 (5.22%) of the population in study; the percentage distribution by localities was 2/28 (7.14%) for Belgium, place where it was observed a close coexistence between the settlers and their similar Brazilian beyond right of the Acre River; 4/87 (4.6%) for Iñapari and 1/19 (5.26%) in Villa Primavera; general clinical condition was fair to poor with eczematous pictures, alopesia and oncinogrifosis in 12% of dogs. Sampling of sand flies were captured in the three locations highlighting the identification of *Lutzomyia nevesi,* belonging to *Lu verrucarum* group, near *Lu. evansi,* vector of LV. This is the first study of LV performed in Peru, in which we bring a prevalence of 5.22% for canine visceral leishmaniasis in Iñapari, district border with Brazil and Bolivia; this finding, is significant because up to now Peru is considered to be a country free of LV. Therefore it is recommended to implement epidemiological surveillance studies in search of the vector and the etiologic agent of the LV in high risk living borders in Peru, in order to control the spread of LV into new geographic areas in Latin America.

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THE IMPACT OF TEN-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) ON *STREPTOCOCCUS PNEUMONIAE* NASOPHARYNGEAL CARRIAGE RATE: PHENOTYPIC AND GENETIC DIVERSITY OF ISOLATES FROM VACCINATED CHILDREN IN ADDIS ABABA, ETHIOPIA

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Streptococcus pneumoniae (*Pneumococcus*) among the most important human pathogens, with high morbidity and mortality rates. Nasopharyngeal colonisation is the necessary first step in the pathogenesis of associated invasive pnuemococcal diseases. Ethiopia, introduced the ten-valent pneumococal conjugate vaccine (PCV110) since October, 2011, there is nevertheless lack of adequate baseline information on epidemiological factors for subsequent impact assessment. The aim of this study was to determine phenotypic and genotypic diversity nasopharyngeal isolates of *Streptococcus pneumoniae*. A total of 789 newborn babies were enrolled at the age of six weeks when they came for the first PCV10 vaccine, and 206 were re-sampled at the age of nine months and 201 at two years after final dose of PCV10. Nasopharyngeal swabs were taken for bacteriological analysis before vaccination at the age of six weeks, and after completion at the age of nine months and two years. Isolates were tested for commonly used antibiotics by disc diffusion method and those that isolates showed resistance for penicillin and erythromycin the minimum inhibition concentration were determined by E-test A total of 325 pneumococcal isolates were serotyped and characterized by Pulsed Field Gel Electrophoresis and 12 isolates were analyzed by multilocus sequence typing. The carriage rate of *S. pneumoniae* at the age of six weeks, nine months and two years was 26.6%, 56.8% and 47.6% respectively. A total of 61 serotypes of *S. pneumoniae* were identified from 325 isolates, and 6A, 11A, 15B, 23F,15A and 19F dominated in decreasing order. The proportion of serotypes covered by PCV10 vaccine among the isolates at 6 weeks and 9 months were 20.2% and 11.1% respectively. Molecular typing further showed a presence of high genetic diversity.The antibiotic test indicated that resistance rates were ranging from 4.3% for chloramphenicol to 27.7% for Trimethoprim/sulfamethoxazole. In conclusion, this study highlights the presence of very diverse serotypes in the country, and PFGE and MLST result indicates case of a possible capsular switching event.

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ASSESSING THE BURDEN OF STIGMA AMONG TUBERCULOSIS PATIENTS IN A PASTORALIST COMMUNITY IN KENYA

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Tuberculosis (TB) epidemic is one of the important global humanitarian and development challenges. Stigma associated with TB has been termed as a barrier to prompt diagnosis and treatment compliance. Although TB stigma is recognised as a serious problem, it has been difficult to describe the magnitude and therefore the public health importance of the problem due to lack of quantitative measures of stigma in the African context. Due to lack of an instrument to measure TB stigma in Kenya at the time of our study, we examined the adaptability of the TB stigma scales previously developed and validated in Thailand. The purpose of this study was to assess and quantitatively measure TB-related stigma as well as identify factors associated with it among patients in rural Kenya. This was a mixed method study. Data were collected using questionnaires, four focus group discussions and ten patient's narratives. A questionnaire containing socio-demographic characteristics and scales measuring perceived TB stigma and experienced/felt TB stigma, was administered to 220 patients on TB treatment in the period between July-December 2015. Assessment of psychometric properties of the scales included basic statistical tests, evaluation of Cronbach's alpha and factor analysis. Multiple linear regressions were performed to determine factors associated with higher TB stigma scores. The study showed that internal consistency reliability coefficients were satisfactory with Cronbach alphas of 0.87 and 0.86 for the 11-item and 12-item scale. The investigation revealed that experienced TB stigma was high and symptoms similar to those of AIDS, as well as fear of infection through casual contact, such as eating with friends and touching others were significant determinants of TB stigma. Low level of education (mean difference of 1.85; 95% CI: 0.09, 3.62) and female gender (mean difference of 3.61; 95% CI: 2.11, 5.11) were significantly associated with higher stigma scores while age, marital status, occupation and the patient's religion were not. There is need to implement stigma reduction interventions to mitigate the impact of stigma and improve TB program outcomes.

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PREVALENCE OF PNEUMOCOCCAL CARRIAGE AND ANTIMICROBIAL SUSCEPTIBILITY AMONG CHILDREN TARGETED BY VACCINATIONS PROGRAM IN BURKINA FASO

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In Western Africa *Pneumococcus* is the most common pathogen isolated in purulent meningitis. In Burkina Faso the fatality rate remains high (up to 46%) among *Pneumococcus* infected patients treated with Penicillin or ceftriaxone which are the most common drugs used in this country. This study aims to describe the prevalence of pneumococcal carriage and antimicrobial susceptibility among children targeted by pneumococcal vaccinations program in Burkina Faso. The data were collected during the baseline assessment of an interventional cluster randomized controlled study (SMC-AZ project) evaluating the impact of Sulfadoxine-Pyrimethamine (SP)+Amodiaquine (AQ) combined with azithromycin (Z) on children mortality rate years in the district of Hounde (located in the Western Region of Burkina Faso). In August 2014 nasopharyngeal swabs were collected among 430 children aged 0-5 years old before they have been randomized to receive either "Sulfadoxine-Pyrimethamine

(SP) + Amodiaquine (AQ) combined with azithromycin (Z)" or "SP + AQ + placebo". We used pneumococcal positive cultures to determine resistance profile. The pneumococcal identification was made from morphology and conventional characterization methods. (Azythromycin, Oxacillin, Ceftriaxone, Norfloxacin, Vancomycin, Gentamicin, Erythromycin. Resistance to penicillin and macrolides will be confirmed by E-test strips. Among 430 nasopharyngeal specimens collected, 189 (43.96 %) had positive cultures of pneumococcus. The prevalence of pneumococcal resistant strains was 26.46 % (16/189) and 1.06% (2/189) for penicillin and ceftriaxone respectively: This resistant prevalence for azithromycin was 4.23% (8/189). In conclusion, due to the emergence of penicillin resistance as shown by our study, ceftriaxone becomes the most suitable antibiotic for the treatment of pneumococcal infections. However the presence of Pneumococcal strains resistant to ceftriaxone highlights the need to closely monitor this cephalosporin antibiotic.

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EFFECT OF OVEREXPRESSION OF *MYCOBACTERIUM TUBERCULOSIS* RPSA PROTEIN IN MOLECULAR MECHANISM OF RESISTANCE TO PYRAZINAMIDE IN *M. SMEGMATIS*

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Tuberculosis remains a major cause of illness and death worldwide causing 1.6 millions of deaths annually, being exacerbated by the epidemic co-infection of HIV-TB and the emergence of multidrug-resistant strains and extremely resistant in developing countries like Peru. Pyrazinamide (PZA) is one of the most important drugs used in the combined anti-tuberculosis therapy, drug that is used as a first option to treat Tuberculosis. After the drug enters *Mycobacterium tuberculosis* (MTB) is hydrolyzed by the pyrazinamidase to the bactericidal molecule, pyrazinoic acid (POA). A recent study identified a target of pyrazinoic acid, ribosomal protein S1 (RpsA). RpsA is a protein involved in the process ribosomal trans-translation, which has been associated with bacterial survival in stress conditions, nutrient starvation and virulence. Despite its importance, some of PZA action mechanism involved are still poorly understood. *M. smegmatis* presents highly POA active efflux pumps, 900 times faster than *M. tuberculosis*, largely explaining part of their natural resistance to PZA. To further understand *M. smegmatis* PZA action mechanism, we evaluate the role of *M. tuberculosis*-RpsA overexpression in *M. smegmatis*. To evaluate this effect, *M. tuberculosis*-RpsA recombinant protein was expressed in *M. smegmatis* system, followed by a PZA- drug susceptibility test using the minimum inhibitory concentration. Our results showed a phenotypic change from naturally resistant *M. smegmatis* (MIC: > 15 mg/ml) to sensitive (MIC: 0.468 mg/ml). This evidence suggests that *M. tuberculosis*-RpsA proteins, which are part of ribosomes might be binding POA in *M. smegmatis*, therefore inhibiting trans-translation system and its viability.

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TB OR NOT TB? A MODEL FOR INTEGRATING PARAGONIMIASIS SURVEILLANCE AND CONTROL WITH TUBERCULOSIS CONTROL PROGRAM

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Misdiagnosis of paragonimiasis as pulmonary tuberculosis (TB) due to similar clinical manifestations results in continuing morbidity and loss of productivity. Integration of surveillance and control of paragonimiasis with the TB control program may be important especially in co-endemic areas to prevent misdiagnosis. This study aimed to describe the prevalence of paragonimiasis, TB, and coinfections in six municipalities in Zamboanga Region, Philippines using a model for integrating paragonimiasis surveillance and control with tuberculosis control program, as well as to analyze the cost of implementing the aforementioned model. Active surveillance for TB and paragonimiasis was conducted in nine barangay clusters, while passive surveillance was implemented in two rural health units (RHUs) for at least three months. A simple cost analysis compared the cost of implementing the model with the National Tuberculosis Control Program (NTP). Four hundred patients were included in the active surveillance, seven of whom had paragonimiasis (2%), while three had TB (1%). Out of the 54 patients included in the passive surveillance, one (2%) had paragonimiasis. A simple cost analysis showed that the marginal cost of implementing the model is lower than the average cost of implementing the NTP. The study showed that the integration of surveillance and control of paragonimiasis with the TB control program is feasible and contributed in describing new paragonimiasis foci, as well as finding and treating misdiagnosed paragonimiasis and TB cases. Optimization of the model and scaling up of its implementation are recommended prior to its proposed integration with NTP.

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TUBERCULOSIS OUTBREAK INVESTIGATION IN A COLONY OF *AOTUS* MONKEYS: DIAGNOSIS, EPIDEMIOLOGY AND CROSS-SECTIONAL RANDOMIZED SCREENING USING ANTIBODY AND WHOLE-BLOOD *IN VITRO* INTERFERON-γ RELEASE TESTING

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Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is a devastating and terminal disease in non-human primates (NHPs). Regular TB screenings using the intradermal tuberculin test (TST), despite its low specificity, have been the mainstay of TB surveillance and control in NHPs. However, the lack of a reliable source of old tuberculin has hampered TB screening programs in NHP colonies around the world. Historically, *Aotus* monkeys have been considered less susceptible to TB than Old-World NHPs. Here we present the diagnosis and epidemiology of a TB outbreak in a colony of ~400 *Aotus* monkeys at The Gorgas Memorial Institute in Panama during the first half of 2015 that killed 7 animals and the results of two cross-sectional randomized TB screening studies, using antibody (Ab) and IFN- γ release assay based testing, eight years apart. The outbreak started on January 6th, 2015, with the death of a lab-bred 9 year-old 600 g male splenectomized *Aotus* that died with signs of a chronic wasting disease (index case). *M. kanssasi* was isolated from a lung tubercle of this animal. Between January-June, 2015, six additional TB cases occurred, three confirmed with MTB isolation and three suspicious by histopathology. Control measures included, quarantine, disinfection and TST screening of all personnel. In the Ab based screening study of 2008, only one animal out of 50 tested, reacted weakly to the Immunochromatographic PrimaTB STAT PAK® assay. This reaction was considered a false positive. In the second study in 2016, 34/34 animals of a total adult population of 313 *Aotus* resulted negative in the Primagam® IFN-γ release assay. TST screening was negative in all animal handlers after the outbreak. The source of infection was not identified, though human to monkey transmission is suspected. Genotyping of MTB isolates and a screening program based on the Primagam® IFN- γ release assay are underway. This is considered to be the first *Aotus* TB outbreak reported at the Gorgas Memorial Institute *Aotus* monkey colony since its inception in 1976.

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DETERMINATION OF PLASMA LEVELS OF LEVOFLOXACIN BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY FOR USE AT A MULTIDRUG-RESISTANT TUBERCULOSIS HOSPITAL IN TANZANIA

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Therapeutic drug monitoring may improve multidrug-resistant tuberculosis (MDR-TB) treatment outcomes. Levofloxacin demonstrates significant individual pharmacokinetic variability. Thus, we sought to develop and validate a high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection for levofloxacin in patients on MDR-TB treatment. The HPLC-UV method is based on a solid phase extraction and a direct injection into the HPLC system. Human plasma was loaded onto Oasis SPE cartridges, conditioned, washed and eluted. The assay parameters of accuracy, precision, recovery and limits of quantification were determined using human plasma spiked with known concentrations of levofloxacin. This method was then utilized to measure levofloxacin concentrations from patients' plasma samples from a retrospective cohort of consecutive enrolled subjects treated for MDR-TB at the national TB hospital in Tanzania during 5/3/2013- 8/31/2015. Plasma was collected at 2 hours after levofloxacin administration, the time of estimated peak concentration (eCmax), after 2 and 4 weeks of treatment. Forty-one MDR-TB patients had plasma available and 39 had traceable programmatic outcomes. Only 13 (32%) patients had any plasma concentration that reached the lower range of the expected literature derived Cmax of 8 µg/mL. In patients with an eCmax ≥ 7.0 µg/mL compared to those with eCmax <7.0 µg/mL, the time to sputum culture conversion was 37.6 ± 22.1 days vs. 48.7 ± 26.8 days (p=0.19) but a trend was observed in greater proportion of cure in 10 out of 17 (58.8%) vs. 6 out of 222 (27.3%) (p=0.05). Furthermore, one patient with an eCmax/minimum inhibitory concentration (MIC) of only 1.13 µg/ml acquired extensively drug resistant (XDR)-TB while undergoing treatment. The HPLC-UV methodology for determination of levofloxacin concentrations achieved excellent accuracy and reproducibility along a clinically meaningful range. The individual variability of levofloxacin concentrations in MDR-TB patients from Tanzania supports further study of the application of onsite therapeutic drug monitoring and MIC testing.

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MOLECULAR CHARACTERIZATION OF CIRCULATING STRAINS OF INFLUENZA A BETWEEN 2014-2015 IN EGYPT

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Influenza viruses are continuously evolving with the potential for new subclades with altered antigenicity. Hence, tracking genetic changes is crucial for selection of effective vaccine strains, detection of drug resistance and determination of virulence markers. Herein, we analyzed the hemagglutinin (HA) and neuraminidase (NA) genes of influenza A/ H3N2 and H1N1 pdm09 circulating in Egypt during the winter of 2014/15. Patients were considered to have influenza-like illness (ILI) if they met the WHO criteria. Oropharyngeal swabs in viral transport media collected from ILI patients from seven sites within Egypt were tested by real-time PCR to determine influenza subtypes. Positive influenza A samples were inoculated in MDCK cells and representative isolates chosen for HA and NA sequencing. Phylogenetic analysis of the HA gene obtained from 13 H3N2 viruses showed that nine clustered within genetic subgroup 3C.2a, and four clustered within clade 3C.3 with three in subgroup 3C.3b. All sequences showed 97.6 - 98.3% nt similarity to clade 3C.1 vaccine strain of 2014/15 season (A/Texas/50/2012), and 98.4 - 98.9% nt similarity to clade 3C.3a 2015/16 candidate vaccine strain (A/Switzerland/9715293/2013). Of note, viruses in which HA genes clustered within subgroup 3C.3b had three distinct mutations in their NA protein (Y155F, D251V, and S315G) that define a distinct cluster with other recently collected viruses. The HA gene sequences obtained from four Influenza A H1N1 isolates clustered within clade 6B, with a notable observation in one sequence of a D222G mutation previously reported to be associated with severe disease outcome. The NA gene sequences of A/H3N2 and H1N1did not reveal mutations previously reported to be associated with resistance to NA inhibitors. Sequence analysis results of influenza A/H3N2 revealed that more than 60% of sequences clustered within the 2014/15 3C.2a subgroup. Clade 6C clustering was not observed among A/H1N1 viruses. Representative influenza A strains analyzed during this season remain susceptible to NA inhibitors. We report the first observance of a severe disease marker (D222G) among H1N1 viruses.

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UNDERSTANDING THE IMMUNE RESPONSE TO *STREPTOCOCCUS PNEUMONIAE* FROM VACCINATION AND CARRIAGE ON A PROTEOME SCALE

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Antigenic diversity presents a challenge for pneumococcal vaccine development. Technological limitations have hindered characterization of immune responses to the diverse protein repertoires observed within pneumococcal populations. Proteome microarrays permit exploration of the antibody response against entire proteomes. We profiled IgG responses against a *S. pneumoniae* (*Sp*) whole cell vaccine (SPWCV) in a Phase I trial with 42 U.S. adult participants, and against nasopharyngeal colonization in a longitudinally-sampled birth cohort of 63 infants residing in the Maela refugee camp near the Thailand-Myanmar border under natural exposure to pneumococci. We used the TIGR4 core proteome and 90 isolates from Massachusetts, United States to construct a "pan-genomic" *Sp* whole proteome microarray and probed serum samples. Large differences in the IgG response to Sp array proteins were reproducible between individuals. Protein traits significantly associated with elevated immunogenicity included increased length, signal peptides for secretion, and cell surface attachment domains. IgG responses to 166 unique *Sp* proteins increased after vaccination with SPWCV, and a dose response was observed. In the Maela infant cohort, the antibody kinetic profile against hundreds of *Sp* proteins followed a trend of sharply declining antibody levels between birth and 6 months of life, followed by a gradual increase during the following 18 months of follow-up. Both variable antigens, including zinc metalloproteases and choline binding proteins, and more conserved peptidoglycan synthesis machinery and transporters elicited high IgG responses. Proteome microarrays can facilitate vaccine development and test hypotheses relating to bacterial evolution, population genetics and epidemiology.

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EXPANSION AND EVALUATION OF TUBERCULOSIS MICROSCOPIC-OBSERVATION DRUG-SUSCEPTIBILITY ASSAY (TB-MODS) IN EGYPT, 2014-2015

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Microscopic-Observation Drug-Susceptibility (TB-MODS) assay is a liquid culture-based test that detects *Mycobacterium tuberculosis* and assesses isoniazid (INH) and rifampicin (RIF) resistance directly from sputum samples. Like Mycobacteria Growth Indicator Tube (MGIT) culture, the method markedly reduces growth time compared to solid media and enables detection of multidrug-resistant tuberculosis (MDR TB). However, TB-MODS is less expensive and has produced faster results than MGIT in low-resource settings. Our objectives were to implement TB-MODS in Egypt for routine TB diagnosis and treatment decisions, compare it to MGIT, and expand its use in high-TB burden governorates. Between October 2014 and September 2015, TB-MODS was implemented at the central and three high-TB burden governorate laboratories in Egypt where MGIT culture and drug susceptibility testing (DST) are used. Test characteristics of TB-MODS were compared to MGIT using the results of sputum samples from presumptive TB patients. There were 521 sputum samples cultured by both TB-MODS and MGIT techniques. Compared to MGIT, the sensitivity and specificity of TB-MODS in detecting TB was 99.5 % and 97.1%, respectfully. The time from specimen processing to DST results was 11.3+6 days for TB-MODS and 18.9+13.9 days for MGIT ($p<0.01$). The proportion of samples tested by TB-MODS with cultures resistant to INH was 31.0% (118/381), RIF was 28.1% (107/381), and both (i.e. MDR TB) was 22.9% (86/376). Compared to MGIT, the sensitivity and specificity of TB-MODS in detecting resistance to INH was 86.8% and 94.9%, to RIF was 86.5% and 95.9%, and to both drugs was 88.1% and 95.9%, respectfully. TB-MODS appears to be a reliable and more rapid alternative to MGIT for detecting TB and performing first-line DST, including for MDR TB, in Egypt.

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THE SPATIAL-TEMPORAL DISTRIBUTION OF *ONCOMELANIA HUPENSIS* ALONG YANGTZE RIVER AFTER IMPLEMENTATION OF AN INTEGRATED CONTROL STRATEGY IN JIANGSU, P.R. CHINA

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Using spatial-temporal analysis to explore the distribution and of *Oncomelania hupensis*, the intermediate host of *Schistosoma japonicum*, along Yangtze River under an integrated control strategy in Jiangsu, P.R.China,. The density and spatial location of live and infected snails from 2001 to 2013 were collected in fields. Descriptive analysis and mapping were respectively used to detect the changes and distribution of live and infected snail in different years. Global and local spatial autocorrelation analysis were carried out to find the trend and area of spatial cluster at different years. The spatial-temporal scan analysis was used to identify the risk area and temporal during the study period. The number and area of habitats, densities of live and infected snails were increasing before 2004, then went into a rapid decreasing after implementation of an integrated control strategy, and went into a relatively slow declining after 2009. The distribution map showed the number of high density habitats was declining, and the location was transferring from west to east. Global spatial autocorrelation showed there were spatial clustering of live and infected snails when the density was relatively high at the province scale. Local spatial autocorrelation revealed that the number of specific clustering area were declining and transferred to the middle reaches of Jiangsu province. Two high risk area of live snails located in upper and middle reaches of Yangtze river, and one high risk area of infected snail located in upper reach. In conclusion, the integrated control strategy was more effective in Jiangsu province. Next, more control resource should be settled in the middle of Yangtze river, Jiangsu.

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THE SEROLOGICAL DIAGNOSIS METHODS OF SCHISTOSOMIASIS AT DIFFERENT PREVALENCE: A META-ANALYSIS

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Use meta-analysis of diagnostic tests to comprehensive evaluation of indirect hemagglutination test (IHA), enzyme-linked immunosorbent assay (ELISA) and dipstick dye method (DDIA) in the diagnosis of schistosomiasis japonica at different prevalence. Through literature reveiw according with the inclusion and exclusion criteria to establish a database, and use Meta-disc and R software to make Meta-analysis of threshold test, heterogeneity test, weighted by the quantitative effect of merger and SROC curve fitting, etc. Results A total of 84 papers were included in the final analysis. The sensitivity of IHA respectively were 0.84, 0.76 and 0.94 in heavy, medium and low endemic areas, and specificity were 0.73, 0.64 and 0.73; sensitivity of ELISA respectively were 0.88, 0.80 and 0.93 in heavy, medium and low endemic areas, and specificity were 0.59, 0.59 and 0.62; sensitivity of DDIA respectively were 0.93, 0.81 and 0.93 in heavy, medium and low endemic areas, and specificity were 0.66, 0.69 and 0.59. Weighted sensitivity of IHA, ELISA and DDIA were 0.83, 0.87 and 0.90; The weighted specificity was 0.69, 0.60 and 0.62. The areas under the curve of SROC respectively were 0.89, 0.96 and 0.92 in the IHA, ELISA and DDIA. In conclusion, in different prevalence, there is some differences effectiveness of methods for serological diagnosis of schistosomiasis. The method of IHA, DDIA and ELISA is relatively high effectiveness in low, moderate and severe endemic areas, respectively. The sensitivity and specificity of all diagnostic methods of schistosomiasis are required further improved.

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A PILOT STUDY ON HUMAN SCHISTOSOMIASIS IN A RURAL COMMUNITY OF FIANGA, REPUBLIC OF CHAD

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Schistosomiasis, a water-associated parasitic disease and part of neglected tropical diseases (NTDs), still poses a significant public health threat in many part of Africa. In recent years there have been increasing national control programs against schistosomiasis and other NTDs. This was encouraged by the World Health Assembly resolution WHA 54.19. Human schistosomiasis is an important public health problem in Cameroon and Chad but the control program is only implemented in Cameroon. Dacheka (Cameroon) and Fianga (Chad) are 2 neighboring sub-divisions located across the border of the 2 countries. People from both sides constantly move across the border and this can affect the epidemiology of schistosomiasis in both sides. The aim of this study is to assess current schistosomiasis situation in villages in the Chadian side and how it might impact the situation in Cameroon. Here we present preliminary results concerning the parasitological survey and environmental characterization on potential transmission sites. This study was conducted in December 2014 and 5 schools were selected in Fianga, based on the geographic localisation. In each school, 50 schools children were randomly selected to be part of the survey. Upon receiving approval of parents and local authorities, selected children were asked to provide stool and urine specimens which were examined using the Kato-Katz and sedimentation techniques, respectively. Overall, only *Schistosoma haematobium* eggs were found in urine samples: prevalence of infection of 53.4% ±0.5 and an average of 13±23 eggs/20µl of sediment. Prevalence of infections in Kiriou, Tchangbele and Deheing were ≥ 50% whereas in Gabra and Kaski they were between 10% and 49%. From our investigation we observed

that villages were very poor and relied mostly on temporary water bodies for their daily activities. In kiriou, population create natural reservoirs to retain rainfall water during rainy period to help cultivation during the dry season. Urinary schistosomiasis is a real public health problem in Fianga and poor life and environmental condition seem to be important factors to be considered for future control plan.

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EFFICACY AND DRUG ACTION MECHANISM OF ARTESUNATE AND A SYNTHETIC ENDOPEROXIDE COMPOUND N-89, AGAINST ADULT STAGE *SCHISTOSOMA MANSONI*

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Treatment and morbidity control of schistosomiasis largely relies on a single drug, praziquantel (PZQ), thus creating concerns about the selection of resistant worms due to repeated therapy. PZQ is also known to kill only adult *Schistosoma* worms and shows inability to abort early infection or prevent re-infection and its lack of prophylactic effect demands the need for novel drugs. N-89 a synthetic compound based on the endoperoxide structure of artemisinin has been previously shown to have anti-schistosomicidal effects against *S. mansoni* in both larvae stages and adult stages. In a murine model infected with *S. mansoni*, oral administration of 300 mg/kg of N-89 and artesunate showed significant worm burden reduction, hepatomegaly reduction and inhibiting granuloma formation at 2 weeks post-infection and a significant reduction in fecundity, egg burden and a significant reduction in body length for the N-89 treated group at 5 weeks post-infection. Scanning electron microscopy results revealed no tergumental damages suggesting that the drug targets may be internal. *In vitro* assessment of the survivability of *S. mansoni* worms cultured with 50 µM to 6.25 µM concentrations in 2-fold dilutions of N-89 and N-251 (a derivative of N-89) revealed IC_{50} values of 6.1±3.6 µM and 10.72±2.5 µM respectively. Artesunate however did not have any effects *in vitro* at the same concentrations. These results suggest that N-89 and artesunate may be possible drugs for schistosomiasis. This study therefore explores the exact biochemical action mechanism related to worm killing and fecundity reduction using molecular and immune-chemical techniques.

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DRUG DISCOVERY: *IN VITRO* EVALUATION OF EXTRACTS FROM MEDICINAL PLANT *BALANITES AEGYPTIACA* (LINN) DEL FOR ANTI-*SCHISTOSOMA* CERCARIAL PROPERTIES

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Schistosomiasis is a parasitic disease caused by schistosomes which manifests mainly in two forms; intestinal schistosomiasis caused by *Schistosoma mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi* which is associated with bloody stool, and urinary (or urogenital) schistosomiasis caused by only *S. haematobium* with by bloody urine. Schistosomiasis continues to persist in many endemic communities with at least 261 million people need treatment in 2013. Successful control effect would largely depend on prevention of cercarial penetration of the human skin at the point of water contact. There is scarce information on preventive drug that is topically applied to prevent schistosomal cercaria from penetrating the human skin. Medicinal plants offer unique platforms for novel drug discoveries for treatment and prevention of many diseases including Neglected Tropical Diseases. The aim of this work was to screen medicinal plant extracts for anti-schistosomal cercaria activities. Aqueous (Aq), 70% (70EtoH) and absolute ethanol (Abs) extracts were prepared from *Balanites aegyptiaca* stem-bark and tested against cercariae at concentrations of 1000 to 10,000 ppm in 24-well culture plate at room temperature. The cytotoxic activities of the extracts on CHANG, PC-3 and MCF-7 cell lines were assessed by MTT assay. The Aq at 10,000 ppm demonstrated high anti-cercarial activity by killing the cercariae (20 to 80/test) within 7 mins and up to 36 mins at 1,000 ppm. However, the cercariae incubated with deionized water only had a mortality rate of 10.4% even after 240 mins. The Abs extract had IC50 values of >1000 µg/ml on PC-3 with 31.76 and 26.57 on MCF-7 and CHANG cells respectively. While the 70EtoH recorded 40.01, 60.80 and 64.25 against PC-3, MCF-7 and CHANG cells respectively. The IC50 for Aq were 44.96, 40.90 and 32.45 accordingly. While the curcumin control had 4.69, 15.22 and 11.67 against PC-3, MCF-7 and CHANG cells respectively. Extracts showed promising anti-cercarial activities that can be explored further for development of novel anti-cercarial drug that could be topically applied on the skin of population at risk to prevent cercaria penetration.

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OUTBREAK OF URINARY SCHISTOSOMIASIS IN A SCHOOL FOR MIGRANT CHILDREN, GYALLESU WARD, ZARIA, KADUNA STATE, NIGERIA. JANUARY 1ST-MAY 15TH, 2015

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Urinary schistosomiasis is a disease of poverty that leads to chronic ill health more than 700 million people live in endemic areas worldwide. The disease infects 240 million people globally with over 50% in African countries. School age children in regions with poor sanitation and contact with fresh water constitute the majority of cases in endemic areas of Nigeria. Urine mapping using rates of blood in urine of school age children showed multiple areas of endemicity in Kaduna state. We investigated to identify the cause of heamaturia among students and the associated risk factors. A descriptive study and a 1:1 unmatched case control study with 100 respondents were conducted to identify the source of infection. Cases were students with a history of visible heamaturia or with possible reagent slip for heamaturia residing in the school hostel, 1st January-15th May 2015. Ten Urine specimens and two water samples from the Galma River were sent for laboratory testing. We identified 50 cases (Overall attack rate 13.3%, CFR: 0%). Male: female ratio (1:0) between January-June, 2015. Mean age of cases was 10.2 years ± 1.4 years; mean age of controls 10.0 years ± 1.3 years. The attack rate was highest among 10-13 year old (35%). Compared with controls, the cases did not differ in terms of state of origin and environmental exposure. Cases were more likely to Swim in the river (odds ratio: 36; 95% CI: 7.3-241.4) and wash with contaminated water (OR: 7.4; 95% CI: 2.8-20.0). 30% of 10 Urine specimens tested positive for Ova, 50% of 2 water samples from Galma River were positive for cercariae of *Schistosoma haematobium*. The outbreak was confirmed to be Urinary schistosomiasis. The risk factors associated with the outbreak were: Swimming in the river and washing with contaminated water. We provided mass chemotherapy with Praziquantel and albendaxole, health education using community health teams and facilitated provision of portable water to the school. Findings will be used in mapping endemic areas for planned mass chemoprophylaxis, disseminated to stakeholders for use in planning public health policy and utilized for health education to populations at risk.

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ASSESSMENT OF THREE SCHISTOSOMIASIS ENDEMIC AREAS USING KATO-KATZ TECHNIQUE AND ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) ANTIGEN AND ANTIBODY TESTS

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Schistosomiasis is endemic in 12 out of the 16 administrative regions of the Philippines and undertaking surveillance to monitor endemic areas is necessary. The Department of Health (DOH) Philippines currently undertakes surveillance through parasitological examination using Kato-Katz technique. However, in areas where there is low level of endemicity, case detection through Kato-Katz technique may pose a major challenge due to the low sensitivity of the test. This study aimed to determine the prevalence of schistosomiasis in selected schistosomiasis-endemic provinces using Kato Katz technique and ELISA Antigen (Ag) and Antibody (Ab) tests. Areas identified as endemic and near elimination level for schistosomiasis were purposively selected. School-based collection of stool and blood samples was conducted and samples were examined using Kato-Katz technique and ELISA Ag and Ab tests, respectively. Results showed zero prevalence of schistosomiasis in Davao City, 0.5% in Davao del Sur, and 3.6% in Compostela Valley using Kato-Katz technique. Higher prevalences of schistosomiasis were observed for Davao City, Davao del Sur, and Compostela Valley with 5.0% and 34.4%; 3.0% and 19.2%; and 14.4% and 56.5% using ELISA Ag and Ab tests, respectively. Results of the study showed that the use of Kato-Katz technique in highly endemic areas is still helpful in diagnosis of infected individuals. In low endemic areas, surveillance of schistosomiasis using ELISA Ab test may provide a better evaluation of the transmission status of the infection at population level necessary in the policy formulation for appropriate surveillance and implementation of control measures. ELISA Ag test, on the other hand, may provide more accurate diagnosis of the infection in low transmission areas necessary in the treatment of the infection that could contribute to the control of transmission of the infection in the community. Further studies are needed to support the use of these diagnostic techniques in a stratification scheme to be utilized by Schistosomiasis Control and Elimination Programs in light of the other strategies being implemented at the community level.

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DETERMINING THE IMPACT OF *SCHISTOSOMA MANSONI* INFECTION ON PUBLIC HEALTH IN A HIGH PREVALENCE REGION IN REMOTE MADAGASCAR

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Schistosomiasis is widespread in Madagascar but many treatment campaigns are unable to reach some of the more rural and remote regions of the country. The aims of our research expeditions were to determine the prevalence and level of disease burden of schistosomiasis in the Marolambo district of Eastern Madagascar (one of Madagascar's most remote regions), to provide treatment for schistosomiasis and initiate a health education program. We screened school aged children (five to fourteen years of age) for schistosomiasis from six schools along the Nosivolo River in Marolambo, using circulating cathodic antigen (CCA) testing and Kato-Katz procedures. We found an overall prevalence of 94% attributed to *Schistosoma mansoni* infection, and a mean of 482 eggs per gram of stool. The preliminary results from this study have revealed an extremely high prevalence of *Schistosoma mansoni* infection in Marolambo, and high parasite loads are indicative of significant disease morbidity. A repeat research expedition in May-June 2016 aims to assess the impact of schistosomiasis on this remote population using anthropometrics, questionnaires, tests for anaemia and assessing cardiovascular fitness.

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EVOLUTION OF IMMUNOLOGICAL MARKERS OF INFECTION WITH *SCHISTOSOMA MANSONI* IN PATIENTS TREATED WITH PRAZIQUANTEL IN THE KOU VALLEY (BURKINA FASO)

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The parasitic diagnosis of infection with *Schistosoma mansoni* using the Kato-Katz technique lacks sensitivity in zones with low prevalence of infection or after chemotherapeutic treatment. The present study aims to evaluate the evolution of immunological markers of *Schistosoma mansoni*'s infection in patients following treatment with praziquantel in the Vallée du Kou. In 2007, 980 subjects having at least 6 years old have been screened at Vallée du Kou (Burkina Faso). Among them, 216 having positif *S. mansoni* stools samples using Kato-Katz test method received a single dose of praziquantel of 40mg/kg, and were followed up from February 2007 to March 2008. During the screening and at each follow-up visits (days 45, 3, 6 and 12 months) stools and blood samples were collected. Subjects found positive were treated with the same single dose of of praziquantel. Kato-Katz test method was used to detect schistosome eggs in stools and the ELISA test was used to detect in the serum antibodies (IgG, IgM, IgA, IgG1, IgG2, IgG3, IgG4), targeting the antigens of schistosome eggs. Results A total of 980 subjects were screened. Their mean age was 23,29±19,42. *Schistosoma mansoni* prevalence in stools samples was 22%. This prevalence significantly decreased overtime (11,4% at 12 month, p=0.001). We observed a regular and significant decrease (p=0.001) of the level of immunoglobulin IgG4. We observed a non-significant reduction in the levels of immunoglobulin IgA et IgG1. There was a positive linear correlation between parasitic load and immunoglobulin IgG4 level before treatment (r=0, 82). During the follow-up this IgG4 immunoglobulin level was significantly lower in subjects having negative Kato-Katz results. In conclusion, the study demonstrated a good efficacy of praziquantel in reducing parasitic infection in treated patients. Immunoglobulin IgG4 is the best marker associated with the therapeutic efficacy of praziquantel in treating *S. mansoni* and could be a possible cure marker.

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RELIABILITY OF COMMUNITY HEALTH WORKER REPORTED TREATMENT COVERAGE FOR SCHISTOSOMIASIS IN WESTERN KENYA-THE SCHISTOSOMIASIS CONSORTIUM FOR OPERATIONAL RESEARCH & EVALUATION PROJECT

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Community health workers (CHWs) are key drivers in mass drug administration programs (MDA). Although the community-directed treatment approach has shown good results in the control of onchocerciasis and lymphatic filariasis,some reports from CHW's treatment coverage have in the past been shown to be inaccurate. We compared CHW reported and household survey coverage for schistosomiasis

to identify factors that may influence CHW reporting. We employed CHWs to conduct community-wide treatment (CWT) in 75 villages in western Kenya. A census was done prior to the MDA to collect demographic data, and all the treatments were recorded in treatment booklets to determine the reported treatment coverage. A household survey was carried out to determine the compliance coverage rates. A structured questionnaire was used to determine treatment coverage levels as well as levels of drug-related side effects.Twenty-four villages were randomly selected for the survey where 1479 households covering 6183 persons were visited in 2012, 2013 and 2014. The eligible population was 5551. Up to 62.9% (53.9-71.9%) reported having been treated compared to CHW's reported coverage of 88.9% (84.2-93.7%) in the same villages (P<0.0047). 33.9% reported being absent during the treatment with 51.3% reporting that the CHW did not visit their homes to offer treatment. More females (50.7%) compared to males (49.2%) complied with treatment. Few people declined treatment for fear of side effects (5.0%). About 2.5% of the population surveyed reported having not heard about the program. Only 1.8% felt they were not sick hence didn't need drugs, while 1.6% reported were pregnant, 1.4% did not take drugs for religious reasons, and 0.05% were influenced by rumors. Of the total population surveyed, only 25.9% experienced side effects with abdominal pains being most frequent (46.0%) followed by diarrhea (31.7%) and dizziness (25.0%).We noted a significant difference between CHW-reported and house-hold survey coverage. The CHW coverage (as validated by the household surveys) improved over time probably attributable to the additional training of the CHWs over the years.

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MODELING THE WITHIN-HOST DYNAMICS OF *SCHISTOSOMA MANSONI*: THE CONSEQUENCES OF INCONSISTENT TREATMENT EFFICACY FOR DISEASE CONTROL

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Schistosomiasis is a neglected parasitic disease caused by various trematode species of the genus *Schistosoma*, for which 249 million people needed treatment in 2012. Substantial variability in treatment efficacy has been observed despite comparable *Schistosoma mansoni* prevalence between populations prior to treatment. Praziquantel is the most common pharmaceutical used to control schistosomiasis, due to its applicability over several species and its negligible side effects. However, Praziquantel is not very effective against juvenile schistosomes in humans. This limited efficacy on the juvenile life-stage of the parasite may be an important factor in the persistence of the disease, yet when forecasting the impacts of control measures this factor is usually neglected. We developed a stochastic model to investigate the consequences of inconsistent drug efficacy among parasite life-stages and variation in parasite population structure within the human host. These results were used to parameterize a population-level model to explore control options, including alternatives to the prevalent annual treatment strategy. The effects of anti-helminths on schistosome population age and sex composition within the human host may obfuscate the effectiveness of chemoprophylactic control strategies. Furthermore, we found the effectiveness of the treatment to be heavily dependent on the force of infection to humans, the initial schistosome population size and structure, and the frequency at which pharmaceuticals are administered. Ultimately our results can be used to design optimal control treatments under differing risk scenarios.

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SYSTEMATIC REVIEW OF ANTISCHISTOSOMAL TREATMENT EFFICACY STUDIES AND THE SIGNIFICANCE OF INDIVIDUAL-LEVEL PARTICIPANT DATA FOR META-ANALYSES

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Schistosomiasis control mainly relies on preventive chemotherapy with praziquantel distributed through mass drug administration. With a target of 260 million treatments a year, reliably monitoring efficacy is all-important. We performed a systematic review of published literature to identify studies that included investigation of antischistosomal drug efficacy, performed since 2000. Out of 914 unique references, we identified 90 studies involving an outcome assessment within 60 days post-treatment, enrolling a total of 20,517 participants infected with *Schistosoma* spp., treated mostly with praziquantel. We extracted study-level characteristics (*Schistosoma* species, treatment, country, methods used for diagnosis and reported estimates of drug efficacy, etc.). This has allowed us to depict the landscape of schistosomiasis research reporting on anthelmintic efficacy assessment, and to highlight the associated diversity in methodological and reporting approaches. We complete this descriptive exercise by meta-analyses, exploring spatial and temporal heterogeneity among estimates of antischistosomal drug efficacy. We will discuss our results in the context of global efforts to control schistosomiasis. Our work highlights the general limitations of aggregate-data meta-analyses. We argue that individual participant-level data (IPD) would allow application of standardised analytical approaches to efficacy and safety assessments, and more powerful investigation of treatment effects in target sub-populations (as demonstrated by our prior IPD meta-analyses on a subset of up to 4,740 participants). This leads us to discuss the importance of initiating and sustaining efforts to collect and share clinical and epidemiological data, and the potential benefits of this approach to the effective monitoring of antischistosomal drug efficacy.

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OUTBREAK OF GASTROENTERITIS ASSOCIATED WITH BORE WELL WATER - GANESHPUR VILLAGE, BIDAR DISTRICT, KARNATAKA STATE, INDIA, 2015

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Diarrhea and foodborne outbreaks account for half of outbreaks in India but few investigations identify the source. On October 9, 2015, Bidar district of Karnataka state, India, reported a gastroenteritis outbreak in Ganeshpur village. We investigated to identify risk factors and provide recommendations. We defined a case as ≥3 loose stools within 24 hours between September 3 and November 3, 2015 in a Ganeshpur village resident. We conducted a retrospective cohort study to assess risk factors and collected stools for Vibrio cholerae culture. We collected one water sample from bore well A and six water samples from bore well B to

test for faecal contamination. We interviewed 947/1040 villagers (91% response rate) and identified 180 cases (attack rate=19%) and 2 deaths. Among 180 cases, 90% were admitted. The outbreak occurred between September 5 and November 1 and peaked October 5-8. Having family members with diarrhoea (RR=4.9, 95% CI=3.5 – 7.1) and using water from bore well A for drinking or cooking (RR=2.6, 95% CI=2.0 – 3.4) were associated with illness. Using water from bore well B for drinking or cooking (RR=0.4, 95% CI=0.3-0.5), drinking filtered water (RR=0.4, 95% CI=0.3 – 0.6), washing hands before eating (RR=0.6, 95% CI=0.4 – 0.7) and having a toilet at home (RR=0.2, 95% CI=0.1 – 0.6) were protective against illness. Stool cultures from four case-patients were negative for Vibrio cholerae. Water from bore well A was positive for faecal contamination by most probable number test. All other water sources were potable. This gastroenteritis outbreak was likely due to consuming contaminated water from bore well A. We recommend avoiding bore well A, using bore well B water, promoting hand washing practices, and improving access to indoor toilets.

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QUANTITATIVE ASSESSMENT OF EXPOSURE TO FECAL CONTAMINATION FOR YOUNG CHILDREN IN A CROWDED, LOW-INCOME URBAN ENVIRONMENT IN THE SANIPATH STUDY OF ACCRA, GHANA

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Diarrheal diseases are a leading cause of death for children under five globally. In the developing world, lack of adequate sanitation results in fecal contamination of the environment and poses a risk of enteric disease transmission via multiple exposure pathways. To better understand how different sources and transmission routes contribute to overall exposure to fecal contamination, we identified eight different fecal exposure pathways for children under five years old in four high-density, low-income neighborhoods in Accra, Ghana, and quantified the contribution of each pathway to oral intake of fecal contamination. Data collection for the SaniPath study was from 2011 to 2012, and comprised 500 hours of structured observations for behaviors of 156 children, questionnaires from 800 households, and 1855 environmental samples for microbiological testing. Data were analyzed using Bayesian models, estimating the environmental and behavioral factors associated with exposure to fecal contamination. These estimates were applied in exposure models simulating sequences of behaviors and transfers of fecal indicators from the environment to oral ingestion. This approach allows us to identify the contribution of any sources of fecal contamination in the environment to child exposure and use dynamic fecal microbe transfer networks to track fecal bacteria from the environment to oral ingestion. Exposure pathways were categorized into four types (high/low by dose and frequency), as a basis for prioritizing pathways by their potential to reduce fecal exposure. Although we observed variation in exposure (magnitude ranged from 108 to 1016 CFU/day for E. coli) between different age groups and neighborhoods, the greatest contribution consistently was through the food pathway (contributing >99.9% to total exposure) in Accra, Ghana. Hands played a pivotal role in fecal microbe transfer from the environment to ingestion. The fecal microbe transfer network provides a systematic approach to study the complex interaction of poor sanitation infrastructure and human behavior on exposure to fecal contamination.

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OBSERVATIONAL AND LABORATORY HYGIENIC ANALYSIS OF RESTAURANTS IN IQUITOS, PERU

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Poor sanitation contributes to foodborne infections associated with food consumption. Specific risk factors associated with contamination include unsafe handling and preparation of food, hygiene, sanitation, and water quality. Fifteen restaurant owners in Iquitos, Peru participated in a study to assess sanitation and hygienic practices. The study included an observational survey and laboratory analysis of samples collected from food, water, and the restaurant environment. Participants were given a final report of the findings. Survey questions included food handling and preparation, restaurant cleanliness, sanitation, and standardized hygienic practices. Observations were numerically graded and an average sanitation score was calculated. Restaurant contact surfaces, food, and beverages were cultured for enteric bacterial pathogens via sample collection onto rayon or polyester swabs in Stuart's transport media with same day culture according to standard microbiology protocols. Water samples were collected for fecal coliform testing. Statistical significance was determined using a chi-square analysis. There was no significant correlation between average sanitation scores and the presence of enteric pathogens found on contact surfaces or food samples. The sanitation scores for the 15 restaurants ranged from 26 to 43.38. Presence or absence of enteric bacteria was assessed and results ranged from none isolated to one or more present. Coliform counts ranged from to <1 to 21 UFC/100mL. The restaurant with the lowest sanitation score average (26) yielded no growth of enteric pathogens and no fecal coliforms. Conversely, the restaurant with the highest sanitation score average (43.38) yielded enteric pathogens but no fecal coliforms. Overall, no statistical significance was noted between bacterial growth and the presence of fecal coliforms in the cooking water. Additionally, there does not appear to be a correlation between In observational analysis and results of coliform analysis or enteric bacterial culture. Future studies may include a resurvey of restaurants to assess reproducibility and potential interventions.

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LATRINE LEARNING: USING CONDITIONAL INFERENCE TREES TO EXPLORE HOW LATRINE CONDITIONS CAN PREDICT LATRINE USE IN RURAL BANGLADESH

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Global public health efforts to eliminate open defecation specifically on the Indian subcontinent have recently begun focusing on improving latrine use. In this study, we attempt to identify a latrine's likelihood of use based on observations of physical characteristics of the latrine and the surrounding premises (i.e., latrine spot-check indicators [SCIs]). Recursive partitioning algorithms, often called decision trees, are typically used in machine learning and data mining because they do not require the assumptions made by traditional regression models. Conditional inference trees (CIT) specifically apply unbiased statistical inference tests as a method of variable selection based on a priori partitioning criteria. Unlike other regression trees, the selected partitions are conditional of all other covariates in the model. In this study we measured latrine usage in rural Bangladesh in 2014 using average daily 'likely defecation events' recorded by a motion sensing device called a passive latrine use monitor (PLUM). Using this continuous distribution, we dichotomized the

measurement along its median so that we had a "Most used" group (≥ median) and a "least used" group (< median). We then employed CIT to separately predict the continuous and dichotomous forms of the outcome using 15 SCIs as independent variables. After implementing a Bonferroni correction for multiple tests of significance, the CIT analysis identified a tree with three partitions using three SCIs for the dichotomous outcome. The primary partition was the presence/absence of water for the purpose of flushing or anal cleansing with two secondary partitions being 1) the presence/absence of flies and 2) having a wet floor. The primary partition shows the strongest SCI but the secondary partitions show that a latrine with water for cleansing that does not attract flies and latrines that do not have water for this purpose but keep a dry floor draw the most use from their users. This interaction suggests a latrine's cleanliness and structural maintenance is an important indication of its use. The CIT for the continuous outcome could indicate some measurement error within the PLUMs.

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WOMEN AND WATER USE IN THE EASTERN REGION OF GHANA: A QUALITATIVE APPROACH

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Despite efforts to expand access to improved water sources in sub-Saharan Africa, countries like Ghana continue to face significant heterogeneities in water source coverage and quality. When multiple water sources are available for use, it is critical to understand the decision-making process in water source selection. Given the key role played by women in Ghana with respect to household water resources management, we interviewed 50 women from 11 communities in the Eastern Region of Ghana and asked about preferences for improved and unimproved water source use. Data was used to compare water source coverage with actual water use and women's water source preferences; questions relate to perceptions of "good" and "bad" water, availability and accessibility, and seasonality of water sources. Concepts such as "improved water" do not always match the definitions women have of "good" water. Women assess water appropriateness for various domestic tasks using a complex set of factors, such as contextual indicators, social conceptualizations of "good" and "bad" water, organoleptic assessments, and seasonally-determined quality and availability. Distance to the water source plays a key role in source acceptability. While rainwater is overwhelmingly preferred for domestic use and is used by all participants during the rainy season, source preferences change in the dry season. Women can articulate their water source preferences, but many find it challenging to consistently access a water source that provides "good" quality water. This is due to factors like distance, unmaintained or unavailable infrastructure, and visible and/or biochemical contamination. Water source availability is partially determined by the season and impacts women's water source use year-round. Our research contributes to a qualitative, community-based approach to assessing the need for improvements in water quality and accessibility in a schistosomiasis-endemic part of Ghana.

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IDENTIFICATION OF CAUSAL PATHWAYS DETERMINING THE RELATIONSHIP BETWEEN PATHOGEN-SPECIFIC INFECTION AND IMPAIRED GROWTH AMONG CHILDREN < 59 MONTHS IN MIRZAPUR, BANGLADESH

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The burden of childhood diarrhea and malnutrition remains high in South Asia due to inadequate household sanitation, lack of access to improved water and poor hygiene practices. We evaluated causal pathways linking household factors, enteric pathogen infections (EPI) and impaired growth using data from Mirzapur, Bangladesh that is part of the Global Enteric Multicenter Study. Stool specimens collected at enrollment from children with moderate-to-severe diarrhea and matched controls were screened for bacterial, viral and protozoa EPI. Height measurements of children were taken of children at enrollment and information was collected on sanitation facilities, water sources, and household animals, cooking fuel type, caretaker education and hand washing practices. Structural equation models tested pathways directly linking household factors with stunting (< - 2 height-age-Z score) or indirectly through their effects on EPI transmission. The modifying effects of hand washing behaviors, water sources and caretaker education were also tested. *Giardia lamblia* and *Cryptosporidium* infections were associated with increased stunting among older children. In turn, a higher prevalence of *Cryptosporidium* was associated with cow dung fuel use when caretakers reported no hand washing before eating. Traditional latrine use was associated with a greater prevalence of *G. lamblia* and *Cryptosporidium* infections when caretakers reporting no hand washing before cooking. A higher prevalence of *Cryptosporidium* was also associated with child feces disposal when caretaker had no formal education. Increased caretaker education had the greatest effect on stunting through direct associations with reduced stunting and indirectly through effects on *Cryptosporidium* and *Giardia* infections. Overall, causal pathways were identified that linked animal and environmental reservoirs with childhood stunting that were modified by distinct hygiene-related behaviors. These results can be used as tools to inform the design, implementation and evaluation of different interventions to more effectively reduce diarrhea burden and stunting.

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HIGH PREVALENCE OF *BLASTOCYTIS* SP IN POPULATION LIVING IN URBAN AREAS OF GABON

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Intestinal parasitic infections (IPIs) are one of the major public health problems, especially in the rural area of developing countries with low socio-economic status and poor sanitation. The aim of the study was to establish the profile of intestinal parasites diagnosed at the Department of Parasitology-Mycology (DPM) of the Faculty of Medicine in Gabon over a period of 10 years. A retrospective study was carried out. Socio demographic and clinical/biological data of patients, who consulted at the DPM between 2004 and 2014 and who benefited of stool examination, have been collected from archived files. During the survey, 1251 patients have been selected; 81% of them were adults. Half of them lived in urban areas, a quarter (25.1%; n=118) in slums and 20.4% (n=96) in rural

and semi-rural areas. IPIs have been found in 39.8% (497/1251) of the patients, mostly Protozoan: 84.9% (n=422/497) vs 15.1% (n=78/497) of helminths. Overall, 13 parasites species have been identified, the predominant was sp (45.1%; n=224/497) followed by *Entamoeba (E.) coli* (42.5%; n=211/497). *Blastocystis* sp (41.6% (n=42/101), *E. coli* 32.7% (n=33/101) and *E. nanus* 27.7% (n=28/101) were more frequently detected among populations living in slums (p=<0.0001). Prevalence of intestinal parasites increased between 2004 and 2014 (p<0.01) ranging from 34.1% to 65.3% between 2011 and 2014; due to the elevated frequency of Protozoan. None *Blastocystis* sp was found in samples collected in 2004, but its prevalence rose significantly from 2010 reaching 23.7%, in 2013 and 22.3% in 2014. Soil Transmitted Helminths prevalence varied during the study period. A decrease of the prevalence was observed being below 10%. An increase of the Protozoan frequency was found among patients living in urban areas and slum compared to populations living in rural areas (p<0.01). These data showed a non negligible rise of frequency of *Blastocystis* sp infections in populations living in urban areas of Gabon. Integrated efforts, such as improving infrastructure to provide clean water source and educating the inhabitants for appropriate hygienic lifestyle are needed.

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FORMATIVE RESEARCH TO INFORM DESIGN OF A BEHAVIOR CHANGE INTERVENTION FOR THE "F" AND "E" COMPONENTS OF THE SAFE STRATEGY FOR TRACHOMA CONTROL IN OROMIA, ETHIOPIA

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Trachoma, caused by *Chlamydia trachomatis,* is thought to be transmitted from eye to eye via hands, fomites and eye-seeking flies which breed in human faeces. Little research has been conducted to understand hygiene and sanitation-related behavioural risk factors for trachoma transmission or how these might be addressed through the "F" and "E" (face washing and environmental change) components of the SAFE strategy. This impedes progress towards the 2020 trachoma elimination goal. A study was carried out in a trachoma hyper-endemic area in Oromia, Ethiopia to identify behaviours potentially associated with trachoma risk, namely: water use for hygiene purposes; defecation and stool disposal practices; sleeping arrangements and laundry. Data were collected in five communities in January 2016 through direct observation in households with young children (n=10), semi-structured interviews with caregivers (n=10), focus groups with mothers (n=3), grandmothers (n=1) and fathers (n=1) and stakeholder interviews (n=4). Data collection and analysis were guided by an ecological model of the determinants of behaviour: "Evo-Eco". A range of sub-optimal hygiene practices were documented, but none were consistently poor across households. Open defecation within or next to a compound was a normative practice, particularly for young children. Latrines, when present, had been built under threat of a fine, and were unhygienic and poorly constructed. Faces were washed with hands and feet, occasionally in response to a cue (food or dirt) or for refreshment. Frequency of face washing differed within and between households and soap was intermittently used. Children's dirty faces with visible discharge were not viewed to be disgusting and were rarely wiped by mothers who felt the ideal behaviour was unattainable for them. Families slept closely together and shared bedding. Laundry was done infrequently. Laundry and bedding were not thought to transmit germs. Behaviour change activities should focus on making face washing feasible and a priority for all family members, generating demand for sanitation and promoting use and laundry of affordable pillows.

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INCORPORATING WASH INDICATORS INTO NATIONAL CONTROL PROGRAM SURVEYS FOR SCHISTOSOMIASIS AND STH IN MADAGASCAR

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Access to clean water, sanitation and hygiene (WASH) has been recognised as a key element of socio-economic development, and has been adopted as one of the Sustainable Development Goals. Recent studies show interesting links between access to WASH and the reduction of transmission of schistosomiasis and soil-transmitted helminthiasis (STH); however, reports also highlight the need for more data collection to better understand the factors involved. In October 2015, a baseline study was conducted in the western half of Madagascar prior to scale-up of the schistosomiasis and STH control programme. Primary outcomes were to determine the prevalence and intensity of schistosomiasis and STH in the treatment area. Indicators of access to, and use of, WASH facilities as defined through consensus-defined observed and reported factors were included as secondary outcomes in order to determine the feasibility of incorporating collection of school-level data on access to WASH, and to determine the relationship between access to school-level WASH and schistosomiasis and STH. A total of 1,958 children were tested from 29 primary schools across the treatment area. The prevalence of *S. haematobium* infection and heavy-intensity infection was 30.5 % and 15.1 %, respectively. The prevalence of *S. mansoni* infection and heavy-intensity infection was 5.0 % and 0.9 %, respectively. The prevalence of any STH was 4.7%. Of a total WASH score of 12, 75% of schools scored less than 3, and the maximum score was 7. This study demonstrates the feasibility of including WASH indicators in monitoring and evaluation surveys for neglected tropical disease control programmes. The results show an extremely limited access to WASH in the study sites. No significant relationships were observed between WASH score and school level infection rates, perhaps due to sample size limitations. The national control programme will aim to integrate interventions to improve access to WASH alongside mass treatment of infection.

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ESTIMATING THE GLOBAL RISK OF DIARRHEAL DISEASE ATTRIBUTABLE TO INTERMITTENT WATER SUPPLIES

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Approximately 925 million people globally are served by an intermittent water supply (IWS). These supplies are often fecally contaminated and are associated with increased risks of gastrointestinal illness. The global burden of disease associated with such supplies however is unknown. A quantitative microbial risk assessment (QMRA) was performed using Monte Carlo techniques to estimate the risk of infection for three reference pathogens (*Campylobacter*, *Cryptosporidium*, rotavirus) attributable to consuming contaminated tap water supplied by an IWS. The stochastic model utilized *E. coli* measurements in intermittent distribution systems along with reference pathogen to indicator bacteria ratios in three potential sources of contamination (sewage, surface water, groundwater) to characterize risks of infection. These risks of infection were then used to calculate the annual diarrheal cases, DALYs, and deaths that might plausibly be associated with IWS. Results indicate that when considering contamination of an IWS by sewage, the daily risks of infection are 1 in 480 for *Campylobacter*, 1 in 885,000 for *Cryptosporidium*, and 1

in 61,000 for rotavirus. Collectively, these reference pathogens and their median daily risks of infection are estimated to lead to approximately 143.5 million cases of diarrhea annually and cause 1.98 million associated DALYs and 31,250 deaths. Calculated DALYs and deaths associated with IWS in this analysis account for 6.6% and 7% respectively of the total diarrheal DALYs and deaths attributable to inadequate water according to recent burden of disease estimates. This is the first attempt to estimate the risk of specific enteric infections, and global diarrheal disease burden expressed in cases, DALYs and deaths, associated with intermittent water supplies using QMRA. These results suggest that there may be significant health risks associated with intermittency of water supplies to which almost 1 billion people are exposed.

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IMPACT OF COMMUNITY HEALTH CLUBS ON DIARRHEA, ANTHROPOMETRY AND WATER QUALITY IN WESTERN RWANDA

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The Community-Based Environmental Health Promotion Programme (CBEHPP) is a cluster-randomized controlled trial that covers 150 villages in Rusizi district, western Rwanda. The intervention was community health club meetings led by trained facilitators. Villages were randomly assigned to one of 3 study arms: control (no intervention), Lite (8 meetings), or Classic (20 meetings). We aimed to evaluate the impact of the community health club approach on diarrhea among children <5, anthropometry among children <2, and household water quality. The CBEHPP endline survey collected data in late 2015 on diarrhea in the previous 7 days for children <5 (N=10,261), anthropometry for children <2 (N=3,179), and water quality for a random sub-sample of households (N=1,085). To analyze impact on diarrhea, we used log-binomial regression with a log link function and generalized estimating equations (GEE). For anthropometry, we calculated length-for-age and weight-for-length z-scores (LAZ and WLZ) then used linear regression with GEE. For water quality, we measured colony forming units of thermotolerant (fecal) coliforms (TTC) per 100ml water then used linear regression with GEE. All analyses accounted for clustering at the village level and the household level as appropriate. The prevalence of caregiver-reported diarrhea for children <5 in the previous 7 days was 14.2%, 14.2%, and 14.3% in the control, Lite, and Classic arms respectively. Mean (SD) LAZ among children <2 was -1.54 (1.26), -1.59 (1.28), and -1.61 (1.32) in control, Lite, and Classic respectively. Mean (SD) WLZ among children <2 was 0.18 (1.11), 0.18 (1.09), and 0.10 (1.11) in control, Lite, and Classic respectively. Mean (SD) TTC was 139.8 (230.9), 165.4 (251.1), and 155.5 (243.7) in control, Lite, and Classic respectively. The differences between study arms were not statistically significant for any outcomes (p=0.96, 0.20, 0.83, 0.47 for diarrhea, LAZ, WLZ, and TTC respectively). The community health club model, as implemented in this setting in western Rwanda, had no impact on prevalence of diarrhea or anthropometry among children or on household water quality.

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THE ROLE OF PUBLIC-PRIVATE PARTNERSHIPS FOR NEGLECTED TROPICAL DISEASES (NTDS) PREVENTION AND CONTROL: THE SUPER SCHOOL OF FIVE TRACHOMA PROGRAM

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Public Private Partnership (PPP) is an increasingly popular model for implementing important public health intiatives. Sighstavers international through its partnership with Unilever launched a school-based trachoma program that integrates face washing into the existing Unilever's Lifebuoy brand school of five handwashing programs, towards the prevention and control of trachoma. This program is delivered in collaboration with local ministries of health and education in-country. The super-school of five (SS5) program seeks to increase hygiene behaviors and in particular the practice of hand and face washing with soap among school children and their mothers/caregivers. Specifically, it addresses the facial cleanliness component of the SAFE strategy for trachoma control. This program adopts the Unilever behavioral change model and takes school children through a four-step journey of awareness, commitment, reinforcement and reward/recognition. Each step on the behavioral change pathway has a corresponding communication material. The SS5 program has been rolled out in 41 primary schools in the trachoma endemic county of Turkana in Kenya. Currently, the SS5 is being scaled-up across trachoma endemic countries in the region. Pre-and post-evaluation comparisons following the roll out of the SS5 showed marked improvements in facial washing and handwashing events (21.2% vs. 75.6%) and face and handwashing events using soap (0 vs. 75.4%). Public private partnerships have the potential for meaningful benefits to be gained for the public partner and the overall health sector. The super school of five program demonstrates that partnerships with the private sector can also be particularly valuable as a method of leveraging on existing models and technical expertise all of which can lead to the ultimate goal of trachoma elimination. The super school of five model and adapted materials along with results from the current ongoing programs is briefly presented.

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RELATIONSHIP OF INFANT DIET TO CHILDHOOD HEALTH: ROUTES OF PARASITIC INFECTIONS FROM CONTAMINATED WEANING FOODS

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There is a deficit of published data on the prevalence and intensity of gastrointestinal parasitic infections in Honduras and routes of parasitic transmission especially in infants and young children. Historically, many of the surveys of water-borne, vector borne and soil-transmitted parasites were published more than 30 years ago. Transmission of parasitic infections in Honduras are the result of many factors which include zoonotic transmission, contaminated water and foods, direct transmission from child care providers, food handlers, and agricultural workers; each playing a contributing role in the transmission of parasitic diseases. From November 2014 through February 2015, the Department of Microbiology, VCOM, conducted a preliminary 3 month-long study in Honduras where 175 mothers were extensively interviewed. This study investigated weaning practices used by mothers when transitioning infants from breast milk to complementary foods and the role these foods have in the transmission of gastrointestinal parasites. Of those surveyed, 98.9% of mothers reported at least one of their children infected with a gastrointestinal parasite. Out of the 322 children of the mothers surveyed, 42% of the children had been previously diagnosed with a gastrointestinal parasitic infection. In

this study routes of infection of protozoan and helminth parasites could have resulted from contaminated complementary foods and water given to infants while still breastfeeding or from contaminated foods after breastfeeding was completed. Contaminated water is a likely source of protozoan parasites. Contaminated water was fed to infants directly, used to mix with formula or complementary foods, or to wash bottles for infant feeding. There was an absence of hand washing by children and mothers before eating or while preparing foods. The major source of soil transmitted helminth infections was the result of environmental contamination, unwashed or uncooked complementary foods, unpasteurized animal milk, unsanitary food storage, poor living conditions with exposed dirt floors, and exposure to roaming domestic animals.

1201

DETERMINANTS OF LIFE-THREATENING DIARRHEAL DISEASE AT HOSPITAL PRESENTATION: EVIDENCE FROM 22 YEARS OF ADMISSIONS IN BANGLADESH

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To take advantage of emerging opportunities to reduce morbidity and mortality from diarrhoeal disease, we need to better understand the determinants for life-threatening disease in resource-poor settings. We analyzed records of patients admitted with acute diarrhoeal disease over twenty-two years at the International Centre for Diarrhoeal Disease Research, Bangladesh (1993-2014). Patients presenting with and without severe dehydration (SD) were compared by multivariable logistic regression models, which included socio-demographic factors and pathogens isolated. Generalized additive models evaluated non-linearities between age or household income and SD. Among 55,956 admitted patients, 13,457 (24%) presented with SD. *Vibrio cholerae* was the most common pathogen isolated (12,405 patients; 22%), and had the strongest association with SD (AOR 5.88; 95% CI: 5.52-6.27); detection of multiple pathogens did not exacerbate SD risk. The highest proportion of severely dehydrated patients presented in a narrow window only 4-12 hours after symptom onset. Patients between 10-15 years had the highest probability of presenting with SD, with dramatic increase per year of life up to age 10. Adult women had a 38% increased odds (AOR 1.38; 95% CI: 1.30-1.46) of SD compared to adult men. The probability of SD increased sharply at low incomes. These findings were consistent across pathogens. There remain underappreciated populations vulnerable to life-threatening diarrhoeal disease that include children 10-15 years-old and adult women. In addition to efforts for children under 5 years, there is an urgent need to develop interventions for these older sub-populations that are accessible within 4 hours of symptom onset.

1202

BISMUTH SUBSALICYLATE REDUCES ANTIMICROBIAL USE AMONG ADULT DIARRHEA PATIENTS IN PAKISTAN: A RANDOMIZED, PLACEBO-CONTROLLED, TRIPLE-MASKED CLINICAL TRIAL

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The World Health Organization has declared antimicrobial resistance a global crisis. Antimicrobial medications are used inappropriately for many of the 2 billion annual cases of diarrhea. We assessed whether providing bismuth subsalicylate (BSS) to adults with acute diarrhea could reduce antimicrobial use in a setting where antimicrobials are easily obtained. We included adult outpatients from 22 clinics in Karachi, Pakistan, who presented from Apr - Oct 2014 with acute diarrhea and who had not taken antimicrobial or antidiarrheal medications during the present illness. Twenty patients from each clinic were randomized 1:1 to BSS or placebo. We requested stool specimens for bacterial culture upon enrollment and assessed antimicrobial use during 5 days of follow-up. We present unadjusted odds of antimicrobial use by intervention because we did not detect interactions with clinic, age, sex, wealth, or diarrhea severity. We concealed group assignment from patients, healthcare providers (HCPs), field staff, and the principal statistician. Among 440 participants, those who received BSS were less likely than those who received placebo to use antimicrobials (odds ratio [OR] 0.55, 95% confidence interval [CI] 0.30 - 0.98), particularly when ≥1 pathogen was detected (OR 0.26, 95% CI 0.09 - 0.81). Fifty-four (12%; BSS, 20; placebo, 34) participants took antimicrobial medications; all received them from a HCP, 36 (67%) began taking them within 1 day of enrollment, 25 (46%) were treated with >1 antimicrobial agent (mean 1.6 ± 0.7 oral and 0.6 ± 0.8 intravenous agent), and nitrofurantoin (n=46 [85%]) and ciprofloxacin (n=28 [52%]) were the most commonly used agents. Six (1%) patients were hospitalized (BSS, 3; placebo, 3); no patients died. Providing BSS to adults with acute diarrhea reduced antimicrobial use by 45% in a setting with high rates of diarrhea and antimicrobial usage for diarrhea. Encouraging HCPs and pharmacists in similar settings to recommend BSS as front-line treatment for adults with diarrhea, and promoting BSS for diarrhea self-management, may reduce antimicrobial use and rates of antimicrobial resistance globally.

1203

CONTINUED FEEDING DURING DIARRHEA MANAGEMENT AT HOME AND GROWTH FALTERING: SECONDARY DATA ANALYSIS OF THE KENYA GLOBAL ENTERIC MULTICENTER STUDY (GEMS) OF DIARRHEAL DISEASE IN INFANTS AND YOUNG CHILDREN IN DEVELOPING COUNTRIES

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In 2013, 587,000 child deaths were attributed to diarrhea. WHO guidelines recommend commercially available oral rehydration salts (ORS), zinc, and continued feeding of an age-appropriate diet for diarrhea. From 2006-2011, 34% of children in sub-Saharan Africa received continued feeding and ORT during diarrhea. Among case data from the Global Enteric Multicenter Study (GEMS) Kenya site, we investigated the association between continued feeding at home during a moderate-to-severe diarrhea episode (MSD) in children< 5 years old (reported at enrollment by a caregiver) and growth faltering 50-90 days after enrollment. At enrollment, caregivers were asked about feeding practices at home during the MSD episode, with continued feeding defined as offering a usual or more than usual amount of food during MSD. Weight and height were measured at enrollment and at follow-up 50-90 days later. Growth faltering was defined as a *reduction* in weight-for-height Z-score (WHZ) category by >1 SD from enrollment to follow-up. We evaluated the association between continued feeding during MSD and growth faltering using log binomial regression analysis. Data from 1,363 of 1,476 enrolled children with MSD (92%) was complete; 20% received continued feeding and 26% experienced growth faltering. The mean age of children provided continued feeding was higher (20 months, SD 13) than of those who had feeding discontinued (17 months, SD 13). Vomiting 3 or more times a day was inversely associated with continued feeding (RR=0.69, 95% CI=0.58, 0.82). Caregiver's wealth and education were not associated with continued feeding. In bivariate analysis, children

reported to have received continued feeding during MSD had 25% lower risk of growth faltering (267, 20%), compared to those who had feeding discontinued (1096, 80%) (RR=0.75, 95% CI=0.59, 0.97); the association was confounded by age (RR=0.86, 95% CI=0.67 - 1.09). Kenyan children with MSD were rarely provided continued feeding but age-adjusted analyses suggested that continued feeding did not significantly alter the risk of growth faltering. Barriers to feeding during diarrhea include young age and frequent vomiting.

1204

DISRUPTIONS OF THE HUMAN GUT MICROBIOME DURING DIARRHEA INFECTIONS CAUSED BY ROTAVIRUS AND ENTERO-PATHOTYPES OF *ESCHERICHIA COLI*

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Little is known about the disturbances that enteropathogens cause in the ecology of the normal gut during diarrheal infections. For example, it is unclear whether viral and bacterial pathogens produce similar or distinctive alterations in the structure of the human gut microbiome and it remains undetermined whether pathogen-specific signatures in the sick gut microbiome exist that discriminate among different pathotypes. In this study we report on an analysis of 74 cases of human diarrhea in Northern Ecuador where six different pathotypes of *Escherichia coli* were identified as the probable causative agent and compare these to 11 cases of diarrhea where rotavirus was detected. We compared these samples to those from 54 healthy samples and 13 samples from other cases of diarrheal disease of undefined etiology, from individuals living in the same geographical locations. We used 16S rRNA taxonomic profiling combined with metagenomic sequencing to assess OTU richness, evenness and diversity in both diarrhea and healthy samples and evaluated the effects of additional demographic variables in the variation observed at the taxonomic and functional level. Our preliminary results have shown a significant reduction in OTU richness and diversity in individuals with diarrhea of undefined etiology when compared with healthy samples (paired *t*-test, $p = 0.01$) and that when the causative agent was specified, such as in rotavirus and *E. coli* infections, the diarrheal samples were distinguishable from healthy ones based on distinct taxonomic and metabolic differences. We have also observed that geographical location and age (but not sex or ethnicity) are important factors determining the structure of the healthy gut microbiome in individuals from Northern Ecuador and play a significant role in the response of the gut microbiota to perturbations generated during diarrheal disease. Together, our results advance our understanding of how the ecology of the healthy gut microbiota is disrupted during pathogen-specific diarrheal infections and provides insight into the role of demographic factors in determining gut microbiome response to enteric infections.

1205

THE FECAL MICROBIOME ASSOCIATED WITH SMALL INTESTINE BACTERIAL OVERGROWTH IN BANGLADESHI CHILDREN

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Small intestine bacterial overgrowth (SIBO) has been associated with intestinal inflammation, linear growth delay, and poor sanitation in children from low-income countries. Neither the microbiota that comprises SIBO in this setting nor association with enteric pathogens has been reported. We tested for SIBO via glucose hydrogen breath testing at 2 years of age in a cohort of 90 Bangladeshi infants. These children had their stool microbiome assessed via 16s rDNA sequencing and analyzed via linear discriminant analysis (LDA) effect size (LEfSe) to determine the influence of the fecal microbiome on presence of SIBO. Additionally, multiplex PCR for 30 enteric pathogens was conducted utilizing a Taqman array and analyzed via Fisher's Exact Test. 15 (16.6%) of the 90 children tested were SIBO positive. Children with SIBO had a statistically significant increase in Lactobacillus spp. (LDA score 3.46, p value 0.03) and a decrease in Megasphaera spp. (LDA score 2.38, p value 0.04). There was no difference in Shannon Diversity indices between SIBO positive and negative children. Pathogen carriage did not differ between the two groups for any of the pathogens studied. However, SIBO positive children carried more pathogens on average in their stool than the SIBO negative group (4.2 vs 3.75 pathogens, p value 0.037). Although changes in the stool microbiome were noted, the duodenal microbiome needs further investigation. No association with a particular pathogen was found and increased asymptomatic pathogen burden is likely a marker of poor sanitation, which is known to predispose to SIBO.

1206

EVALUATION OF THE TEST-NEGATIVE CASE-CONTROL DESIGN TO ESTIMATE ROTAVIRUS VACCINE EFFECTIVENESS IN LOW-INCOME SETTINGS

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The test-negative case-control study design (TND) is an epidemiologic method currently used to measure rotavirus vaccine (RV) effectiveness. In this design, vaccination status is compared between rotavirus-positive cases and rotavirus-negative controls presenting to the clinic and meeting a pre-defined case definition for acute gastroenteritis. Despite the use of this study design in low-income settings, the TND has not been validated to measure rotavirus vaccine effectiveness. This study builds upon prior methods to evaluate the TND for influenza vaccine by using a randomized controlled clinical trial database. Similarly, test-negative vaccine effectiveness (VE-TND) estimates were derived from three large

randomized placebo-controlled trials (RCTs) of monovalent (RV1) and pentavalent (RV5) rotavirus vaccines in sub-Saharan Africa and Asia. Derived VE-TND estimates were compared to the original RCT vaccine efficacies (VE-RCTs). VE-TND and VE-RCT estimates were almost identical during the first year of life (RV1: VE-TND (95% Confidence Interval): 58.2% (35.5-72.9), VE-RCT: 61.2% (44.0-73.2); RV5- sub-Saharan Africa: VE-TND: 66.9% (42.7-80.9), VE-RCT: 64.2% (40.2-79.4); RV5- Asia: VE-TND: 44.4% (-13.2-72.2), VE-RCT: 51.0% (12.8-73.3)). Point estimates were also comparable using additional diarrheal surveillance into the second year of life, though the VE-TND overestimated the VE-RCT in the RV5 trial in sub-Saharan Africa. Analyses restricted to the second year of life replicated the limited vaccine efficacy demonstrated in the RCTs. In conclusion, TND vaccine effectiveness estimates were nearly equivalent to original RCT vaccine efficacies, with some country-specific differences. In the RV1 and RV5 trials there were challenges in case capture and varied methods of surveillance between study sites. Limitations of the original RCTs should be considered when comparing derived effectiveness and primary efficacy results. Nevertheless, this study supports the feasible and efficient TND as a valid study design to measure rotavirus vaccine effectiveness in low-income settings.

1207

A PHASE 1 OPEN-LABEL, DOSE ESCALATING STUDY OF ARTIFICIAL *SHIGELLA FLEXNERI* 2A INVAPLEX ADMINISTERED INTRANASALLY TO HEALTHY, ADULT VOLUNTEERS

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An efficacious *Shigella* vaccine is a coveted public health intervention. The intranasal (IN) route of mucosal delivery has shown promise for subunit vaccine administration. The *Shigella* artificial invasin complex (termed, InvaplexAR) contains IpaB, IpaC and *S. flexneri* 2a LPS. The primary objective of this study was to evaluate the safety of InvaplexAR given by IN immunization (without adjuvant) assessed by active monitoring during the vaccination stage and for 28 days following the third vaccine dose. The secondary objectives were to evaluate immune responses and thus identify a safe and immunogenic dose of InvaplexAR for advancement to preliminary efficacy studies or expanded Phase 1 trials. The study is an open-label, dose-escalating first-in-human trial in which volunteers received one of four vaccine doses (10, 50, 250 or 500 µg). We have immunized all four cohorts enrolling 37 subjects with safety data available for the first three cohorts (27 volunteers). The vaccine was administered on Days 0, 14, and 28 in a total volume of 200 µL split equally between both nostrils and delivered with a nasal spray device (VaxINator ™ distributed by Teleflex). Blood, stool, saliva and ocular secretions were collected at specified intervals to examine systemic and mucosal immune responses directed to Invaplex, LPS, IpaB and IpaC. Peripheral blood mononuclear cells were also collected to determine IgA antibody secreting cells and antibody lymphocyte supernatant responses. IN immunization with InvaplexAR was well tolerated. The overall safety and tolerability profiles were consistent with prior IN immunizations. There were no adverse events (AEs) that met the vaccination stopping criteria. Most vaccine-related AEs were of mild severity. Only three subjects reported AEs of moderate severity. The most commonly observed AEs were rhinorrhea (0-33%), nasal congestion (11-33%), nasal tenderness, itching and burning (0-33%). The VaxINator ™ consistently delivered 200 µl ± 10% of InvaplexAR. Immunological assessments are currently underway and will help inform future clinical evaluations of the subunit *Shigella* vaccine.

1208

ASSESSMENT OF THE NEEDS FOR THE NEGLECTED TROPICAL DISEASE (NTD), NON-COMMUNICABLE DISEASE (NCD) AND THE EYE HEALTH PROGRAMS IN LIBERIA FOLLOWING THE OUTBREAK OF EBOLA VIRAL DISEASE

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The outbreak of Ebola Virus Disease (EVD) in Liberia in 2014-15 infected about 10,675 and claimed the lives of more than 4,809 individuals. During this period the NTD, NCD and Eye health programmes were suspended. By June 2015 the EVD outbreak was under control, the Ministry of Health conducted an assessment of communities, health facilities and county health teams to understand their perception and readiness to resume programmes. The assessment was conducted in all counties including surveys of communities and health facilities affected and unaffected by EVD. All 36 communities surveyed reported they were ready and anticipating the resumption of programmes, especially MDA. All the communities desired increased engagement in the programme when it restarts as they recognized the benefits it presented. The survey also revealed disparities between individual programmes, though there is a high degree of acceptance of the lymphatic filariasis programme, the awareness and acceptance of the schistosomiasis programme was limited. Awareness for leprosy and Buruli ulcer is increasing but is limited. The number of trained personnel for these programmes, particularly at local health facilities, was found to be very low. This challenge has been exacerbated by high turnover of staff, during and following the EVD outbreak. Communities which were aware of one or more NCDs (22%) wanted treatment but felt they did not have access. Furthermore, eye care was very limited with 39% of communities reporting no access while the rest reported sporadic visitations by health workers or NGO groups over the last 5 years. The assessment highlighted the magnifying role that EVD had on the existing gaps within the NTD, NCD and Eye health programme, the desire within communities to resume NTD preventative treatment and also identified opportunities to build on the lessons learned during the outbreak for community mobilisation. The assessment also identified key recommendations related to leadership and governance, management and coordination, and planning and implementation to enable the programme to successfully move forward and increase its impact in post-EVD Liberia.

1209

EFFECT OF THE NATIONAL SCHISTOSOMIASIS CONTROL PROGRAM ON *TAENIA SOLIUM* TAENIOSIS AND PORCINE CYSTICERCOSIS IN RURAL COMMUNITIES OF TANZANIA

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Taenia solium is found throughout sub-Saharan Africa and co-endemic with schistosomiasis in many regions. *T. solium* leads to taeniosis and neurocysticercosis - the leading cause of preventable epilepsy globally. This study aimed to assess the effects of the National Schistosomiasis Control Programme (NSCP) on prevalence of *T. solium* and porcine cysticercosis over a four year period in Tanzania. School-based mass

drug administration (MDA) of praziquantel was carried out based on schistosomiasis endemicity. Four human and five porcine cross-sectional surveys were carried out from 2012 to 2015 in Mbozi and Mbeya district in Tanzania. Three rounds of school-based MDA of praziquantel were delivered in Mbozi and two in Mbeya by the NSCP. The prevalence of taeniosis and porcine cysticercosis was estimated annually. Stool samples were collected from humans and prevalence of taeniosis estimated by copro-Ag-ELISA. Blood samples from pigs were collected to estimate cysticercosis prevalence by Ag-ELISA. "Track and treat" of taeniosis cases were carried out after each survey. In total 12,082 stool samples and 4,579 porcine serum samples were collected. There was a significant higher prevalence of taeniosis in Mbozi compared to Mbeya prior to the intervention, but no difference at the end of the study. Significantly fewer children (≤15) from Mbozi were infected throughout the study than children from Mbeya who showed a significant decrease in copro-Ag prevalence after the first treatment only. During the final survey in Mbozi the prevalence of taeniosis in adults was significantly lower (p=0.031, OR 0.40, CI: 0.17-0.89), compared to baseline. The prevalence of porcine cysticercosis had also dropped significantly (p=0.002, OR 0.49, CI: 0.32-0.76) in this district compared to baseline, whereas no significant difference was seen in Mbeya. The study suggests that three rounds of MDA targeting schistosomiasis in school aged children contributed to a reduction in prevalence of infection with *T. solium* in this population, and also had a spill over effect on adults in treated areas as well as reducing the prevalence of *T. solium* in the pig population.

1210

USING A DOOR-TO-DOOR MASS DRUG ADMINISTRATION CAMPAIGN TO IDENTIFY TRICHIASIS AND HYDROCELE IN TOGO

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The Togolese Ministry of Health (MOH) utilized their highly successful Integrated Neglected Tropical Diseases (NTD) Control Program to identify and treat people with trachoma and hydrocele. Every year, Community Drug Distributors (CDDs) distribute medication to treat soil-transmitted helminths, onchocerciasis, and schistosomiasis. In 2015, the MOH received funding from the Bill & Melinda Gates Foundation to pilot a program to identify and treat individuals with trichiasis or hydrocele. CDDs identified persons with suspected trichiasis or hydrocele while conducting their drug distribution activities. A total of 5,665 suspected cases of trichiasis and 3,573 suspected cases of hydrocele were identified by CDDs nationwide. Funding for surgeries was limited, so case confirmation was performed first in the districts with the highest numbers of suspected cases. Trichiasis confirmation rates were low. Among the 3,269 cases reported in the Kara and Savanes regions, 2,143 were examined by ophthalmology technicians and only 17 (0.8%) were found to have trichiasis. The most common ocular issues identified were conjunctivitis (52%) and cataracts (17%). Sixteen of the 17 individuals with trichiasis were successfully treated, and one refused surgery. Among the 479 people with suspected hydrocele, surgeons examined 121, plus another 81 suspected cases that were identified in the field. A total of 202 suspected cases of hydrocele were examined, of which 101 were confirmed (50%). The most common finding among individuals who did not have hydrocele was hernia (99/101, 98%). All 101 individuals with confirmed hydrocele had surgical repair, with an average hospitalization period of eight days. Togo's integrated NTD drug distribution platform can be an effective means of identifying people in need of surgery for trichiasis and hydrocele. CDDs were better at identifying hydrocele than trichiasis, and better training of the CDDs is needed to help them correctly identify trichiasis. The approach should be repeated in subsequent years to identify additional individuals who warrant surgery.

1211

PROXY RESPONSES FOR MASS DRUG ADMINISTRATION COVERAGE SURVEYS: THE INDIVIDUALS REQUIRING THEM AND THE POTENTIAL FOR RECALL BIAS

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The success of mass drug administration (MDA) for neglected tropical diseases is dependent upon achieving adequate drug coverage, which is validated through household coverage surveys. Coverage surveys rely on respondent recall and often permit proxy responses, whereby another household member is allowed to respond on behalf of an absent individual. This study used data from coverage surveys for lymphatic filariasis in Malawi, Burkina Faso, and Uganda to determine the demographic characteristics of individuals for whom a proxy response was required and the extent to which a proxy response was associated with reported drug coverage. According to our results, teenagers and young adults (10 - 25 years) were more likely to be absent during the coverage survey and require a proxy response, compared with older adults (OR 1.96, p<0.001). Similarly, males were more likely to require a proxy response than females (OR 1.76, p<0.001). Adults who were eligible to receive MDA for lymphatic filariasis (i.e. everyone, excluding women who are pregnant or in the first week of breastfeeding and the severely ill) were more likely to be absent and require a proxy response than individuals who were ineligible for MDA (OR 2.86, p<0.001). A multivariate analysis found that individuals for whom a proxy response was provided had 1.52 times the odds of being recorded as having swallowed the drugs compared to self-reporting individuals, controlling for age and sex (95% CI (1.03, 2.24)). This finding is unexpected given that individuals who are unavailable at the time of a coverage survey may also have been unavailable at the time of MDA, and suggests that proxy respondents may be inflating drug coverage. While this finding could be explained in part by the fact that self-reporting individuals are more likely to have been ineligible to receive MDA and thus are expected to have lower coverage, this does not account for the entire increase in odds. This study highlights the possibility for recall bias in proxy responses to MDA coverage and suggests that further research is necessary to determine the best method for obtaining information on drug coverage when individuals are absent.

1212

FEASIBILITY AND SAFETY OF MASS CO-ADMINISTRATION OF AZITHROMYCIN AND IVERMECTIN MASS DRUG ADMINISTRATION: THE AIM STUDY

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Mass drug administration (MDA) has made a major contribution to the public health control of neglected tropical diseases across the world. The practical benefit of linking programs to increase efficiencies is well recognised, but limited in practice by uncertainties about the practical

and biological implications of co-administration of drugs. In the Solomon Islands, trachoma MDA with azithromycin was implemented in nine out of 10 provinces. When a decision was made to extend the program to the province of Choiseul, we had an opportunity to investigate the feasibility, safety and efficacy of co-administering ivermectin to control scabies and impetigo, diseases that were recognised as endemic in a number of countries of the Pacific region. The drug delivery infrastructure was established using the framework for trachoma. The MDA regimen was a single dose of oral azithromycin combined with a single dose of oral ivermectin. A second dose of ivermectin was given a week later to ensure elimination of scabies eggs that may have been present at first visit. Participants in 10 randomly selected villages were asked to undergo skin examination to collect scabies and impetigo baseline data. The study enrolled 26,188 participants, 99.3% of the total resident population. Of those, 98.2% received azithromycin and 98.5% received a first dose of ivermectin. A second dose of ivermectin was received by 83.7% of participants. In the survey villages, baseline scabies prevalence was 18.7% and highest in children aged 5-9 years (34%). Impetigo was present in 24.8% of participants, and highest in the 5-9 age group (46.4%). There were no serious adverse events. Adverse events were noted in 2.6% of the entire study population and 4.3% of participants in the more closely monitored skin survey sites. At present, this is the world's largest scabies MDA and the first large scale co-administration of Ivermectin and Azithromycin. Co-administration of ivermectin and azithromycin appears to be safe, well tolerated and feasible.

1213

ADDING TSETSE CONTROL TO MEDICAL ACTIVITIES ALLOWS CONTROL OF SLEEPING SICKNESS IN THE MANDOUL FOCUS (CHAD)

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Gambian sleeping sickness or HAT (human African trypanosomiasis) is a neglected tropical disease caused by *Trypanosoma brucei gambiense* transmitted by riverine species of tsetse. A global programme aims to eliminate the disease as a public health problem by 2020. The Mandoul area of Chad is a persistent focus of Gambian sleeping sickness where more than 100 HAT cases are still diagnosed and treated annually. Up to 2013, control of HAT relied solely on case detection and treatment, and did not lead to a clear and consistent decrease in the annual incidence of HAT despite annual screening of the population. We assessed whether the addition of vector control to case detection and treatment could reduce annual incidence of HAT in Mandoul. In particular, we investigated the impact of deploying 'tiny targets' which attract and kill tsetse. Before tsetse control commenced, a census of the human population was conducted and their settlements mapped. A pre-intervention survey of tsetse distribution and abundance was implemented in November 2013 and 2600 targets were deployed in the riverine habitats of tsetse in early 2014 and 2015. Impact on tsetse and on the incidence of sleeping sickness was assessed through six tsetse monitoring surveys and four medical surveys of human population in 2014 and 2015. The census indicated that a population of 26600 inhabitants lived in the vicinity of the Mandoul focus. Within this focus, the vector is *Glossina fuscipes fuscipes* and the mean catch of tsetse from traps was 0.7 flies/trap/day (range, 0-26). The catch of tsetse from 44 sentinel biconical traps declined after target deployment with only five tsetse being caught in five surveys giving a mean catch of 0.009 tsetse/trap/day. Simultaneously, HAT transmission declined from a mean of 127 cases/year between 2009 and 2013, to 52 cases in 2014 and only 25 new cases in 2015 with a similar medical effort.

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THE IMPACT OF MASS DRUG ADMINISTRATION ON REDUCTION OF NTD PREVALENCE IN RWANDA

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Worldwide an estimated 6 billion of the world's most impoverished people, including 875 million children are affected by Neglected Tropical Diseases (NTDs) which cause severe pain, long-term disability, and are the cause of death for over 500,000 people per year. In 2008, 65.8% of Rwandan schoolchildren were affected by Soil-Transmitted Helminth (STH) infections. Rwanda Ministry of Health in collaboration with its partners had started to implement large-scale NTD control through regular Mass Drug Administration (MDA) against these infections as per World Health Organization guidelines. Two national mapping surveys were conducted in 2008 and 2014 in order to assess schistosomiasis and STH prevalence at national level and geographic distribution. In 2008, a total of 8,313 schoolchildren aged between 10 and 17 years were tested for STH and schistosomiasis using Kato-Katz method. Prevalence of urinary schistosomiasis was established by testing for micro-haematuria using dipsticks and urine filtration technique. In 2014, a total of 9,250 schoolchildren aged between 8 and 18 years were tested for STH and schistosomiasis using Kato-Katz method while 19,371 schoolchildren were tested for schistosomiasis also using Circulating Cathodic Antigen (CCA) urine Assay. We carried out trend analysis for schistosomiasis and STH data from 28 schools that were randomly selected in both mapping surveys. All 28 schools are located in districts that reached at least 75% MDA therapeutic coverage for all treatment campaigns. For schistosomiasis, eleven (11) schools are located in areas that received praziquantel. Of these 11 schools 7 had 100% reduction in prevalence; three (3) had reduction between 39.4% and 93.0%. The comparison for STH infections showed a remarkable reduction in prevalence for only hookworm with 10 schools having 100% reduction and 17 schools with a reduction between 39.4% and 96.4%. These data demonstrate an encouraging quick impact of MDA in controlling schistosomiasis and STH and call for continuous support to NTD control programs of endemic countries.

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TARGETTING MALARIA HOTSPOTS IN SENEGAL: RESULTS OF A CLUSTER-RANDOMIZED TRIAL

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In Senegal scaling-up of control measures has reduced the incidence of malaria but transmission persists and new tools are needed to move towards elimination. We evaluated a targeted approach, employing IRS and chemotherapy implemented in transmission hotspots, on a large scale. 40 clusters (health posts) were randomized. In 30 clusters, hotspot villages were targeted to receive IRS with Actellic 300CS in July, followed

in 15 clusters by MDA with dihydroartemisinin-piperaquine (DHA-PQ) administered to all persons except pregnant women and children under 3 months of age, at the end of August and again in October. In the other 15 clusters, persons were screened using a malaria RDT and positives treated with DHA-PQ. 10 clusters served as controls. In all three arms, health promotion encouraged care seeking for fever, and a free LLIN was provided to each malaria patient at health facilities. The intervention strategy was delivered over two years. Primary outcomes were malaria incidence, and the prevalence of parasitaemia just after the main peak of transmission, in year 2. Adherence to treatment, and adverse events, were monitored after each round. Acceptability was investigated using in-depth interviews, and provider costs of the interventions were assessed. The year before intervention, malaria incidence was 11 per 1000, and parasitaemia prevalence by microscopy 1.9%. Interventions reduced annual incidence within hotspots by 46% (IRS+MDA) and by 52% (IRS+MSAT). Incidence in non-target communities within 2km of treated hotspots reduced by 41% (IRS+MDA) and 24% (IRS+MSAT). The overall efficacy against malaria (including target and non-target villages) was 37% (95% CI 31%,44%) in the IRS+MDA arm and 44% (38%,49%) in the IRS+MSAT arm. The strategies were well accepted and achieved high coverage. The cost of MSAT was 30% higher than for MDA. Adding IRS approximately doubled the cost. Where scaling-up of existing policies has reduced malaria transmission but additional measures are needed for elimination, targeted control with IRS and MDA or MSAT could be used to reduce transmission, but MDA was cheaper and slightly more effective than MSAT.

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COMPARISON OF MASS DRUG ADMINISTRATION VS. MASS SCREENING AND TREATMENT HIGH-RISK, MILITARY MOBILE POPULATIONS TO SUPPORT MALARIA ELIMINATION IN CAMBODIA

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The Cambodian government has set a goal for malaria elimination by 2025. However, the effectiveness of elimination strategies in hard-to-reach mobile populations, including the military, is largely unknown. We are conducting a two-arm, controlled, cluster-randomized, open-label pilot study to determine the effectiveness of monthly malaria prophylaxis (MMP), using dihydroartemisinin-piperaquine (DP) and weekly primaquine (22.5 mg), compared to monthly focused screening (microscopy and PCR) and treatment (FSAT) of malaria positive subjects according to the national treatment guidelines. After 3 months of interventions, both arms will be actively followed for 3 more months to assess malaria incidence in the rainy season when malaria usually peaks. Of 1,114 active duty military and dependents screened in Oddor Meanchay province near the Thai-Cambodian border, 1,050 volunteers were enrolled into 8 clusters. We noted reductions of malaria incidence within 2 months in both arms from a baseline prevalence of 53/516 (10.3%; 39 cases of *Plasmodium falciparum* (*P.f)*, 13 cases of *P. vivax* (P.v) (*P.v,* 1 cases of mixed) and 91/534 (17.0%; 45 cases of *P.f*, 38 cases of *P.v,* 8 cases of mixed) malaria positive at screening in the FSAT and MMP arms, respectively. In the first month, 8/509 (1.6%) subjects from the FSAT arm and 2/529 (0.4%) from the MMP arm had a *P. falciparum* requiring an unscheduled visit, with an additional 10/509 (1.9%) in the FSAT and 16/529 (3.0%) in the MMP being malaria positive on the day 30 follow-up visit (p=0.906). On day 60 follow up, only 6/489 (1.2%; 0 cases of *P.f* and 6 cases of *P.v*) and 2/504 (0.4%; 1 cases of *P.f*, 0 cases of *P.v*) subjects were malaria positive by microscopy or PCR in FSAT and MMP arms, respectively, showing low parasitemia in both treatment arms (p=0.172), reaching statistical significance by month 3 follow-up, with 20/472 and 0/502 cases of malaria in FSAT and MMP arms, respectively (p<0.001). The number of subjects withdrawn or lost to follow up remains low at around 3% in each arm. Most malaria cases in the MMP arm occurred within 1 month of follow-up and likely represent *P.f* treatment failures of DP. Final outcome data from 6 months of follow-up will be presented.

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RELATIVE CONTRIBUTION OF GENERALIZED EARLY DIAGNOSIS AND TREATMENT AND OF TARGETED MASS TREATMENT TO ELIMINATION OF *PLASMODIUM FALCIPARUM* MALARIA IN EASTERN MYANMAR

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Plasmodium falciparum (PF) malaria elimination is on the agenda of 19 countries. In the Greater Mekong Sub-region, elimination is of particular interest and urgency because of the threat of spreading artemisinin resistance. In coordination with community-based health organizations and the Myanmar National Malaria Control program, the Malaria Elimination Task Force was set up to develop strategies and to implement a regional approach towards PF elimination in 4 districts of Eastern Myanmar. Malaria Posts (MP) were deployed in each community of the target area to provide access to early diagnosis and treatment of malaria. MP reported PF and *P. vivax* (PV) case data weekly. Village-level malaria prevalence was measured in surveys analyzed by ultrasensitive qPCR. Hotspots of asymptomatic malaria prevalence were defined by malaria prevalence > 40% with PF representing >20% of all malaria infections. Hotspots were addressed by 3 rounds of targeted mass treatment (TMT) using dihydroartemisin-piperaquine. A generalized linear mixed model adjusting for season and location was used to analyze PF case counts, monitor trends in PF incidence and determine the relative contribution of MP and TMT to malaria elimination. From May 2014 to April 2016, >800 villages were equipped with MP and reported weekly data. Out of 218 surveys performed, 43 hotspots were identified and addressed with 3 consecutive months of TMT between January 2015 and March 2016. The probability of an MP declaring ≥1 PF case during its first month of operation was 26% and decreased to below 10% after 18 months, while the probability of declaring ≥1 PV case remained stable around 30%. The PF incidence rate ratio (IRR) for 10 additional weeks of MP operating in a village was 0.78 (95%CI=0.74-0.82). Before TMT IRR for hotspot villages compared to non-hotspot villages from the same area was 2.6 (95%CI=1.3-5.0). After TMT incidence in hotspot villages was similar to non-hotspot villages (IRR=1.4; 95%CI=0.6-3.5). Over 24 months of follow-up, the deployment of an MP network in 4 districts triggered a strong decrease of PF incidence rate. TMT proved to accelerate the decrease in high prevalence villages.

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IMPACT OF MASS DRUG ADMINISTRATION WITH DIHYDROARTEMISININ-PIPERAQUINE ON MALARIA TRANSMISSION IN A HIGHLY SEASONAL TRANSMISSION SETTING IN THE GAMBIA

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There is renewed interest in mass drug administration (MDA) as a strategy to interrupt malaria transmission in settings approaching elimination. Data on its impact in areas with seasonal and heterogeneous transmission are limited. The objective of the study is to evaluate the impact of MDA with Dihydroartemisinin-Piperaquine (DHA/PPQ) on *Plasmodium falciparum* carriage in low-moderate transmission settings in The Gambia. In June 2014, the start of the transmission season DHA/PPQ was administered using weight based dosing to residents between ≥6 months and <75 years of age in twelve villages across the five regions of the country. A baseline community survey was conducted prior to MDA. Participants were followed up with monthly surveys from July to December. Finger prick blood samples were collected for parasite detection using diagnostic PCR. A total of 3888/4677 (83.1% of the population) were eligible and received DHA/PPQ. All pregnant participants or elderly participants over 75 years were excluded (4.2%, 172/4060). The prevalence of *P. falciparum* post-MDA was 5.43% (170/3130; 95%CI 4.6-6.2%). The villages in the eastern region where transmission is moderate had a 44.03% reduction in prevalence (12.9%, 327/2527 in 2014 vs 23.1%, 1185/5141 in 2013) while in the rest of the country where transmission is low villages in the central and western regions there was a 17.0% reduction in infection prevalence 3.9% (81/4691) in 2014 and 4.6% (637/13727) in 2013. Preliminary results show, the overall incidence rate of *P. falciparum* parasitemia was 0.2 (95%CI: 0.2-0.2) episodes per person-year at risk in the 2014 transmission season. The risk of *P. falciparum* decreased with increase in age; children 5-15 years (HR=1.7, 96%CI: 1.3-2.2) and adults 15-29.9 years; HR=1.4, 95%CI: 1.10-1.9). The risk of infection increased with severity of anaemia (severe anaemia; HR=3.1, 95%CI: 1.6-6.4). The most significant impact of MDA on *P. falciparum* carriage was in communities located in areas with moderate transmission compared to areas with very low prevalence. MDA might be considered as an additional intervention in areas of on-going moderate malaria transmission.

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FREEDOM FROM INFECTION: MEASURING THE INTERRUPTION OF MALARIA TRANSMISSION

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Good malaria surveillance is the foundation for effective malaria elimination efforts and should generate timely and actionable information for decision makers. Measuring elimination poses a specific challenge in that it involves proving a negative: when a country shifts into the scenario of zero-malaria reporting, improved strategies are required for identifying areas where there is more or less certainty in having achieved elimination. Here, we present quantitative tools by which the probability of having achieved freedom from malaria infections can be calculated. These tools are applied to the malaria context in order to provide accessible and actionable tools for countries engaging in malaria elimination and are evaluated against the current WHO guidelines. Assuming a single population of 100,000 people (i.e. a health facility catchment area), reporting zero cases per month over three years, results suggest we can achieve a 95% probability that there are in reality fewer than 100 cases. We can be sure that there are fewer than 50 cases with a probability of 80% or 95% in 5 or 15 years of monthly zero reporting, respectively if relying solely on passive surveillance. To improve the probability of freedom achieved within 3 years, programs have the option for supplementing passive surveillance with active 'freedom' surveys that will increase the system sensitivity for that reporting month. To achieve a high probability of achieving freedom within 3 years, at least 2 population-based 'freedom surveys'. Therefore, the freedom tools can be used for estimating the level of confidence that has been achieved in asserting a malaria-free status and for informing programs where and how to target efforts to boost to the desired level of certainty that elimination has been achieved. Such an approach is particularly important in settings that are accelerating the timeline to elimination where it is paramount to measure the absence transmission on a shortened timeline.

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THE NATURAL HISTORY OF MALARIA ELIMINATION IN SOUTHERN ZAMBIA

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As areas transition from malaria control to elimination, targeted interventions will be needed. Knowledge of changing spatial and temporal patterns of transmission and parasite genetic structure and divergence can guide elimination efforts. This study describes the natural history of malaria elimination in the catchment area of Macha Hospital in Choma District, Southern Province, Zambia. Passively-detected, symptomatic cases of malaria were reported from six rural health centers from August 2008 to September 2015. Seasonal malaria incidence was estimated for each catchment area and spatial patterns were evaluated. Asymptomatic, infected individuals were identified through active case detection using rapid diagnostic tests and PCR for *Plasmodium falciparum* in population-based, longitudinal and serial cross-sectional cohort studies conducted from February 2008 to October 2013. Spatial clusters of asymptomatic cases were estimated and seasonal overlap was assessed. A 24 single nucleotide polymorphism molecular barcode was used to determine the genetic relationship between *P. falciparum* parasites from symptomatic and asymptomatic cases. Genetic relatedness was analyzed using phylogenetic trees and genomic divergence was calculated for each season. After the 2009-2010 transmission season, the incidence of symptomatic cases shifted from an annual to a biannual pattern and parasite prevalence by active case detection decreased substantially. A fractured spatial pattern was observed for symptomatic cases after the 2010-2011 transmission season. Phylogenetic trees showed independent clustering of symptomatic and asymptomatic cases, suggesting asymptomatic infected individuals were not contributing substantially to on-going transmission. Genetic complexity was high in asymptomatic cases, consistent with a chronically-infected reservoir, and low in symptomatic cases. Parasite genetic divergence decreased among asymptomatic cases, indicating loss of parasite diversity in this chronically-infected reservoir, but remained high in symptomatic cases, consistent with some degree of parasite importation.

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GENOMIC TOOLS REVEAL TRENDS IN *PLASMODIUM FALCIPARUM* PARASITE DIVERSITY ACROSS TRANSMISSION GRADIENTS WORLDWIDE

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Recent progress in malaria control and elimination has underscored the need for development of new tools and methodologies to assess progress towards programmatic milestones and signal program reorientation. The renaissance of genomic approaches to complement epidemiological tools has offered unparalleled opportunities to better assess the parasite population underlying characteristic epidemiological signals, such as transmission intensity. However, there are few data relating the signals of parasite diversity to transmission intensity levels from global populations. The current study assessed the correlation of genetic-based signals of parasite populations to determine their usefulness as a proxy for relative transmission levels. *Plasmodium falciparum* complexity of infection (COI), relatedness, and clonality from a worldwide population of parasites from Southeast Asia (Bangladesh and Cambodia), the Americas (Panama, Peru, and Haiti), and Africa (Zambia, Mozambique, Malawi, Burkina Faso, Uganda, and Senegal) were assessed using the molecular barcode. The results of this analysis showed clear trends in parasite populations along the gradient of transmission intensity, both within and between countries. Samples from regions with relatively low intensity, such as those from the Americas, showed increased clonality and a clear ability to track individual parasite lineages during epidemic outbreaks. In contrast, areas with high transmission had reduced clonality and overall relatedness compared to low transmission settings. Furthermore, sampling of 6 surveillance sites within Senegal also demonstrated that relative transmission intensity was associated with characteristic population diversity, as well as several instances of parasite lineages shared between regions, suggestive of importation. The findings of this study support the usefulness of genomic tools such as the molecular barcode for programmatic surveillance. These tools require sampling a small number of individuals to provide real-time, informative data with operational applications and the potential to impact national and regional policies.

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HOST EXPOSURE TO EARLY LIFE STAGES OF *SCHISTOSOMA HAEMATOBIUM* DOES NOT ALTER THE BLADDER RESPONSE TO EGGS

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Despite the significant impact of urogenital schistosomiasis (*Schistosoma haematobium* infection) in endemic regions, relatively little is known regarding the pathophysiology of this disease. Primate models remain a powerful tool to approximate human schistosomiasis, yet many technical reasons prevent widespread use of these models, including high costs, low availability, and ethical considerations. Infecting rodents percutaneously with *S. haematobium* cercariae, the route of natural human infection, results in low or no involvement of the urogenital system. Previously, we have developed a mouse model of urogenital schistosomiasis that bypasses this limitation via microinjection of viable *S. haematobium* eggs directly into the bladder wall. This model recapitulates many relevant sequelae found in human disease, including granuloma formation, urinary tract fibrosis and dysfunction, and systemic Th2 responses. However, it is unclear whether the absence of host exposure to the early parasite life stages (cercariae, schistosomules, and worms) prior to egg deposition in the bladder affects the resulting systemic and local immune response. We addressed this question by comparing mice that underwent bladder wall injection with *S. haematobium* eggs to mice that were percutaneously infected with *S. haematobium* cercariae followed 8 weeks later by microinjection of their bladder walls with *S. haematobium* eggs. Portions of these mouse cohorts were also treated with praziquantel following bladder wall injection. Based on worm counts, histology, and cytokine analyses, we conclude that while subtle differences exist, bladder wall injection with *S. haematobium* eggs alone may be sufficient to model urogenital schistosomiasis in mice. These findings also have implications for understanding chronic egg-induced bladder inflammation in people who have been cured of schistosomiasis by drug therapy and/or acquired immunity. Namely, the absence of continued antigenic stimulation by early parasite life stages may not impact ongoing bladder inflammation triggered by previously deposited *S. haematobium* eggs.

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MATERNAL *SCHISTOSOMA MANSONI* INFECTION ALTERS THE IMMUNE RESPONSE OF OFFSPRING TO TETANUS AND DIPHTERIA IMMUNIZATION

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Maternal helminth infections have been implicated in the reduced efficacy of critical life saving neonatal and childhood vaccines. Approximately 40 million women of childbearing age are at risk for schistosomiasis and at least 10 million women in Africa have schistosomiasis during pregnancy, yet little is known about the impact of prenatal exposure on the immune responsiveness of offspring. Findings from previous studies indicate that a fetus can be exposed to helminth antigens *in utero*, so the high frequency of schistosomiasis in this population represents a significant potential public health problem. The underlying mechanisms through which maternal infection with helminths, such as *Schistosoma mansoni*, function to negatively impact neonatal vaccine responses, however, remain to be discovered. We sought to determine the immunological mechanism(s) through which responses to immunization with tetanus/diphtheria are altered following prenatal *S. mansoni* infection in an experimental mouse model of *S. mansoni* infection. Interestingly, offspring from infected mothers exhibited smaller germinal centers after immunization with Tetanus/Diphteria than pups born to uninfected mothers. In addition,

the offspring from infected mothers presented decreased numbers of IL-4 secreting TFH cells and decreased expression of B cell co-stimulatory markers in comparison to age-matched offspring of uninfected mothers. These profound alterations suggest a possible mechanism for the previously reported reductions in vaccine specific titers in offspring born to helminth infected mothers in endemic countries.

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RECOMBINANT PARAMYOSIN IN MONTANIDE ISA 206 PROTECTS WATER BUFFALO FROM *SCHISTOSOMA JAPONICUM* INFECTION

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Schistosomiasis japonica is a zoonosis and a major disease risk for more than 40 million people in China and 7 million more in the Philippines. Because water buffalo play a critical role in transmission to humans, a veterinary vaccine would have a significant impact on prevalence and incidence of human infection while also improving animal health and economic output. Paramysin (Sj97) is a 97 kDa myofibrillar protein with a coiled-coil structure found only in invertebrates. We successfully produced pilot-scale recombinant full-length paramyosin (rSj97) and assessed its safety and efficacy in vaccine challenge experiments in water buffalo. A three-dose regimen with 250 or 500 mg rSj97/dose in ISA206 was well tolerated with no severe adverse events, no differences in body condition score and no differences in serum chemistry assays compared to controls. In our first challenge trial, buffalo were immunized three times at 4-week intervals with 250 mg /dose rSj97 in ISA206 (n=7) or ISA206 alone (n=6). Buffalo were challenged with 1,000 *S. japonicum* cercariae and perfused 8 weeks post challenge. Worm burdens were reduced by 51.5%, but this reduction did not achieve statistical significance, likely due to small sample size. In a second vaccine-challenge experiment of similar design, buffalo immunized with 500ug/dose of rSj97 in ISA206 had 60.9% lower worm burdens compared to adjuvant controls (p=0.05). A similar reduction (57.8%) was observed with animals immunized with 250ug rSj97/dose. Egg recovery from liver tissue was positively correlated with worm burden (R^2=0.4876, p<0.001), while anti-rSj97 specific IgG_2 titers at 4 weeks after 3rd immunization were negatively correlated with worm burden (R^2= -0.275, p=0.03). Moreover, rSj97 stimulated markedly increased IFN-gamma levels in whole blood cultures from rSj97-ISA206 immunized animals compared to controls. These findings indicated that rSj97 is a safe and promising schistosomiasis veterinary vaccine and mandate further evaluation of rSj97 based vaccine safety and efficacy.

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A MICROFILTRATION DEVICE FOR DIAGNOSIS OF UROGENITAL SCHISTOSOMIASIS

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Urogenital schistosomiasis, infection of the urinary tract by *Schistosoma haematobium* worms, is a cause of urologic disease in over 112 million people worldwide. The diagnostic standard of care, counting eggs in urine, is slow, making it difficult to use as a point-of-care test for infection. This is a major barrier to mass drug administration campaigns seeking to eliminate *S. haematobium*. Herein we describe the development of a microfiltration device for trapping, isolation, and on-chip fluorescence characterization of schistosome eggs toward rapid diagnostics of urogenital schistosomiasis. The device comprises a linear array of microfluidic traps to immobilize and separate eggs of *S. haematobium* from urine. The trap array allows sequential loading of individual eggs by flow resistance to facilitate observation and enumeration of samples with low-abundance targets. Computational fluid dynamics modeling and experimental characterization are performed to optimize the trap design for enhancing the trapping efficiency and throughput. The microfiltration device is capable of isolating schistosome eggs from urine and the trapped eggs can be recovered for downstream analysis. The trapping efficiency of the device is 100% with 300 µl/min and 83% with 3000 µl/min. The filtration procedure can be finished within 10 min. The microfiltration device is capable of isolating schistosome eggs from urine and the trapped eggs can be recovered for downstream analysis. On-chip staining is demonstrated in the microfiltration device for fluorescence analysis of schistosome eggs. In conclusion, our results are proof of concept that a microfluidics device can be used to more efficiently trap and separate *S. haematobium* eggs in urine. Further optimization of this device may lead to a point-of-care diagnostic suitable for use in the field.

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AN EGG PROTEIN FROM *SCHISTOSOMA MANSONI* IS PROMISING FOR DEVELOPMENT OF HIGH-SPECIFICITY DIAGNOSTICS IN THE ERA OF INTENSIFIED CONTROL

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Schistosomiasis is a serious global public health problem. The standard for diagnosis is the Kato-Katz method, which has low sensitivity and therefore does not work well on patients with low-level infections, representing the majority of cases. Adding tests such as ELISAs using soluble egg antigens (SEA), increases diagnostic accuracy in low burden areas of Minas Gerais, Brazil. However, crude SEA antigens have low-specificity and cross-react with other helminthes. Therefore, the goal of this work is to identify SEA proteins with high schistosomiasis specificity, as well as the sensitivity to differentiate between active (acute and chronic) and cured (post-treatment phase) infections, in order to develop point-of-care (POC) tests as well as improve others diagnostic methodologies. To complete these studies, SEA was generated from mice 45 days after infection with *Schistosoma mansoni*. Using a protocol approved by the Brazilian Ethical Committee, human serum was obtained in Minas Gerais from each group: healthy volunteers (negative controls); schistosome acute, chronic and post-treatment patients; and patients infected with other helminthes. The sample from each group were submitted to two-dimensional Western blot (2D-WB) using native and sodium metaperiodate (SMP) treated SEA. The immunoreactive spots were identified by mass spectrometry and analyzed by bioinformatics tools. A total of 23 spots were identified by serum from Schistosoma infected patients. Among these, 22 spots were identified by serum from patients infected with other helminths, and 9 by negative control samples. One spot was uniquely recognized by sera from Schistosoma-infected patients and detection remained after sugar denaturation by SMP treatment, suggesting serum antibodies were binding to peptide epitopes. We identified a potential egg protein from this unique spot, for which we are developing monoclonal antibodies, toward the development of POC immunodiagnostic test and highly specific ELISAs. Further, the fast, simple POC assay requires minimal equipment and will be an accurate screening tool for epidemiologic surveying in low resource regions.

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MAPPING OF SCHISTOSOMIASIS IN RWANDA: USE OF POC-CCA VERSUS KATO-KATZ

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Worldwide an estimated 240 million of the world's most impoverished people are affected by schistosomiasis. Classic severe schistosomiasis-related morbidities include periportal fibrosis in intestinal schistosomiasis caused by *Schistosoma mansoni* and *S. japonicum*, and bladder deformity and hydronephrosis caused by *S. haematobium*. However, the more subtle, but nonetheless disabling morbidities of anemia, growth stunting, and, cognitive impairment likely represent the wider public health challenge. In 2008, the Rwanda Ministry of Health in collaboration with its partners began implement large-scale NTD control, including schistosomiasis, through regular mass drug administration (MDA) against these infections as per WHO guidelines. A national NTD mapping survey was carried out from June to mid-July 2014, using both the Kato-Katz and the Point-Of-Care Circulating Cathodic Antigen (POC-CCA) assays for detection of *Schistosoma mansoni*. Fifty children of the required age (primarily 13-14 years) were randomly selected in each of 399 schools. For diagnosis of *S. mansoni* duplicate fecal Kato-Katz thick smears and the urine POC-CCA test were performed. A total of 19,934 pupils were included, with 19,371 from 388 schools tested with POC-CCA and 9,250 from 186 schools tested with Kato-Katz. There was an approximately equal number of boys and girls sampled in each school. Ages of the sampled children ranged from 8 to 18 years, although 88% of children sampled were 13 or 14 years, and 98% of children were in the range of 10-14 years. When POC-CCA Traces readings were considered negatives, overall schistosomiasis prevalence was 7.4% (95%CI: 5.7%-9.5%) with 0.6%-16.7% as range in mapping units; when POC-CCA Traces readings were considered positives, overall schistosomiasis prevalence was 36.1% (95%CI: 32.6%-39.8%) with a range of 10.8%-63.8% in mapping units; With Kato-Katz overall schistosomiasis prevalence was 1.9% (95%CI: 1.1%-3.3%) with a range of 0.0%-9.4% in mapping units. Results from this mapping survey demonstrate issues in the use of POC-CCA in the implementation of national program and the need for related WHO guidelines.

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A NOVEL CELL FREE DNA DETECTION ASSAY FOR THE DIAGNOSIS OF SCHISTOSOMIASIS JAPONICA

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Accurate diagnostics play a pivotal role in achieving current schistosomiasis control and elimination goals. Lack of accuracy and inability to detect pre-patent infections are major limitations of current diagnostic procedures. We have optimised a novel droplet digital PCR duplex assay for the diagnosis of schistosomiasis japonica which provides improved detection sensitivity and specificity. The assay involves the amplification of two specific and abundant target gene sequences in *Schistosoma japonicum*; a retrotransposon (*SjR2*) and a mitochondrial gene (*nad1*). The assay detects target sequences from different schistosome lifecycle stages (adult worms, schistosomules and eggs) and exhibits a high level of specificity, representing an ideal tool for the detection of low levels of parasite DNA in different clinical samples. Following optimization, the assay was validated using a *S. japonicum*-infected mouse model. It detected both pre-patent and patent infections using serum, urine and faecal DNA collected at different time points. There was a positive correlation between the gene copy numbers and the intensity of infection determined by egg and worm counts. The assay is quantitative and can be used to determine parasite infection intensity and will be an important diagnostic tool, particularly for the detection of low intensity infections in low prevalence schistosomiasis-endemic areas.

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MATURATION OF FLAVIVIRUSES AND ROLE IN DISEASE

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Many viruses are initially assembled in host cells in a non-infectious immature form and are converted to their mature infectious state through a series of coordinated events requiring specific triggers. This prevents premature disassembly of these viruses during egress from host cells. For flaviviruses, the maturation process involves pH-driven structural rearrangements of precursor Membrane (prM) and Envelope (E) glycoproteins and furin protease-mediated cleavage of prM during transit through the trans-Golgi network. Despite the cleavage of prM being crucial for virus infectivity, this process is inefficient for dengue virus (DENV). Virus preparations comprise a continuum of particles with variable maturity from immature 'spiky' (having high prM content) to fully mature 'smooth' particles (having low or zero prM content) determined using cryo-electron microscopy. The consequence of inefficient maturity is structural heterogeneity that may be advantageous for the virus for immune evasion and pathogenesis. We have developed sensitive biochemical and biophysical tools to quantitate the maturity of DENV and other flaviviruses and explore the role of prM in virus dynamics, disease pathogenesis and vaccine design/quality control. We have developed a mass spectrometry-based selected reaction monitoring assay and use it in tandem with cryo-electron microscopy to probe prM content/ maturity of different serotypes of DENV produced in cell culture and are currently developing protocols to study virus produced from natural infection of mosquitoes (vector) and humans (host). Using these methods, we have detected differences in the cleavage efficiency of prM among different serotypes of DENV that have implications in virus breathing, structural dynamics and specific infectivity. These studies have been broadened to examine this cleavage and its effect on virus structure using other flaviviruses.

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FLAVIVIRUS NS1 PROTEINS DIFFERENTIALLY INDUCE HYPERPERMEABILITY IN HUMAN ENDOTHELIAL CELL MONOLAYERS FROM DISTINCT TISSUE TYPES

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Dengue (DENV), Japanese encephalitis (JEV), West Nile (WNV), yellow fever (YFV) and Zika (ZIKV) viruses belong to the *Flavivirus* genus, *Flaviviridae* family. Severe dengue disease is characterized by increased vascular leakage leading to pleural effusion, causing hypotension and death. In contrast, WNV and JEV infections can result in neurological diseases, including encephalitis. ZIKV appears to cause pathology in both the placenta and the fetal brain. Evidence suggests that disruption of physiological barriers such as the microvascular endothelium or the blood brain barrier can play a critical role in flavivirus pathogenesis. Recently, we described a direct effect of DENV non-structural protein 1 (NS1) in triggering endothelial barrier dysfunction in human pulmonary

microvascular endothelial cells (HPMEC) *in vitro* and systemic vascular leakage *in vivo*. Here, we examined the ability of flavivirus NS1 proteins to interact and modulate endothelial barrier function of different endothelial cell (EC) types: HPMEC, human dermal EC (HMEC-1), brain microvascular EC (HBMEC), and umbilical vein EC (HUVEC). We show that flavivirus NS1 proteins interact with the surface of human EC and alter the barrier function, as measured by Trans-endothelial Electrical Resistance (TEER), in a cell-type dependent manner. DENV2 NS1 induced permeability in all endothelial cell types tested. However, WNV and JEV NS1 only significantly reduced TEER of HBMEC. ZIKV increased permeability only in HUVEC. YFV NS1, a flavivirus that causes severe hepatic injury, moderately increased permeability of only HPMEC. Ongoing TEER experiments using hepatic endothelial cells will further explore this specificity. These *in vitro* EC permeability results appear to reflect the tropism of the disease caused by each virus. Our findings propose a mechanism by which flavivirus NS1 proteins differentially cause endothelial barrier dysfunction, potentially resulting in increased plasma leakage, inflammation, or virus dissemination through different biological barriers as a part of the flavivirus pathogenesis process.

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DISCOVERY OF SMALL MOLECULE BIOMARKERS THAT PROVIDE METABOLIC SIGNATURES TO DIFFERENTIATE DENGUE, CHIKUNGUNYA AND ZIKA VIRUS INFECTIONS AND DENGUE DISEASE SEVERITY

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Chikungunya (CHIKV) and Zika viruses (ZIKV) are now co-circulating with dengue viruses (DENV) in over 30 countries in the Americas. Accurate diagnoses and prediction of disease severity using acute phase clinical specimens is critical for appropriate triaging and better clinical management of diseases caused by these viruses. We have developed a versatile metabolomics platform to identify small molecule biomarkers (SMBs) in serum that predict dengue disease severity and are currently defining metabolic signatures that differentiate the three arboviral diseases. This platform combines reverse phase ultra-high performance liquid chromatography-mass spectrometry (RP-UPLC-MS) and hydrophilic interaction liquid chromatography (HILIC) -MS and was used to characterize the acute phase serum metabolome of patients from Nicaragua and Mexico who were diagnosed with different grades of dengue disease severity, dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Patients with laboratory-confirmed infections with DENV, CHIKV, or ZIKV contributed serum, urine and saliva samples during the 2015/2016 transmission season, and we have used these samples to validate SMBs for dengue diagnosis and prognosis and explore similarities and differences unique to CHIKV and ZIKV infections. We will discuss the biochemical classes of metabolites identified by the combined platform and highlight SMB signatures that are specific for each disease type. Metabolic markers that are specific to flavivirus (DENV and ZIKV) infections versus an alphavirus (CHIKV), or differentiate between the flaviviviruses could potentially provide important information on differential pathogenesis and could be exploited for development of therapeutics. These comparative studies are particularly important, as the clinical presentation of these diseases in the acute phase can be similar.

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HUMAN DENV2 MONOCLONAL ANTIBODIES TARGET MULTIPLE EPITOPES ON THE ENVELOPE GLYCOPROTEIN

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Dengue virus (DENV) infection causes dengue fever and more severe disease, and it is estimated that a third of the world is at risk for infection. Dengue serotype 2 (DENV2) is widespread, causes severe epidemics, and the recently licensed live tetravalent dengue vaccine was not protective against DENV2, despite protecting against the other three serotypes. DENV2 infections stimulate durable, serotype-specific neutralizing and protective antibodies in people. Previous work from our group has shown that the majority of DENV2 type-specific neutralizing polyclonal antibodies targets a complex epitope containing EDIII of the envelope (E) glycoprotein. While the crystal structure of a single human DENV2 type-specific neutralizing antibody, 2D22, has been solved, it was not known if this epitope is representative of a diverse panel of DENV2 type-specific antibody epitopes. Using a DENV infectious clone system, we have generated a panel of recombinant DENV viruses that were then used in binding and neutralization assays. With these experiments we have mapped the epitopes of additional DENV2 type-specific neutralizing antibodies. While some of these antibodies share a similar epitope to 2D22, others use entirely different domains in their epitopes. Our results reveal that there are multiple epitopes targeted by DENV2 neutralizing antibodies. Future work aims to determine what the proportion of each of these antibody epitopes are in polyclonal immune sera, and test whether antibodies targeting one epitope is more important for neutralization that the other.

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USE OF THE DENGUE HUMAN CHALLENGE MODEL TO CHARACTERIZE THE CLINICAL AND IMMUNOLOGICAL RESPONSE TO SEQUENTIAL HETEROTYPIC DENGUE INFECTION

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Dengue is recognized as the most important mosquito-borne virus worldwide. There are 4 dengue viruses (DENV), each capable of causing the full spectrum of disease which ranges from an asymptomatic or mildly symptomatic infection to a live-threatening illness characterized by vascular leak syndrome. Epidemiologic studies have demonstrated that the greatest risk for developing severe dengue occurs with a second, heterotypic DENV infection. This is thought to be mediated by antibody-dependent enhancement of infection in which antibodies from the primary DENV infection opsonize the secondary, heterotypic DENV but instead of neutralizing the virus, the antibody-virus complex is able to enter target cells through the FcγR2a leading to higher titers of virus. Interestingly, third and fourth DENV infections appear to result in less severe illness. Using our controlled dengue human challenge model, we studied the clinical and immunological response to sequential heterotypic DENV infection to characterize the neutralization and enhancement qualities following primary and secondary dengue infection. Twelve flavivirus-naïve subjects were enrolled and randomized to receive the live attenuated DENV-1 DEN**α**30 (n=9) or placebo (n=3). Nine months later 8 subjects were received the DENV-2 challenge virus DEN2**α**30 (6 had received DEN1**α**30; 2 had received placebo). The treatment assignments remained blinded until

study day 360. Following primary infection, 9/9 subjects were viremic with DENV-1 (mean peak titer = 0.9 $\log_{10}$ PFU/mL), 8/9 seroconverted to DENV-1, 2/9 seroconverted to DENV-2 NGC, 4/9 seroconverted to DENV-3, and 0/9 serconverted to DENV-4. Antibody to DENV-2 decreased to <1:5 by study day 90. Following challenge with DENV-2 9 months later, 6/6 DENV-1 recipients had detectable DENV-2 viremia and 3/6 had rash compared with 2/2 controls with detectable viremia and rash. The virologic and immunologic responses following primary and secondary DENV infection will be discussed.

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HLA DRB1 ALLELIC VARIANTS ARE ASSOCIATED WITH DIFFERENT RESPONSE MAGNITUDE OF DENV SPECIFIC CD4 T CELL RESPONSES AND DISEASE SEVERITY OUTCOMES

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All four dengue virus serotypes are now simultaneously circulating worldwide being responsible for 400 million human infections each year with around 100 million resulting in apparent infections. The observation that only a minority of patients develops severe disease suggests that host genetic factors may play an important role in disease severity. HLA molecules that restrict CD4 and CD8 T cell responses are one of the most polymorphic host factors in humans with several thousand variants thus far known. While DENV-specific CD8+ T cell responses have been extensively studied, the breadth and specificity of CD4+ T cell responses remains to be defined. Here we map CD4 T cell responses in individuals previously exposed to dengue virus. To identify HLA class II candidates, we utilized a panel of algorithms for sixteen common HLA DR molecules representative of the main DR supertypes. These efforts led to the identification of 365 epitopes derived from all 10 DENV proteins. In contrast to CD8 T cell targets, the highest number of epitopes was associated with the structural capsid protein (C), followed by nonstructural NS3, NS2A, NS5 and envelope proteins (E). Similar to CD8 T cell responses we noticed a wide variation in magnitude of T cell responses as a function of the restricting DRB1 allele. To investigate if HLA specific variations in magnitude of response might actually predict as yet unknown associations between DENV disease outcomes and HLA DRB1 alleles we assembled a set of 411 samples from hospitalized patients with confirmed diagnosis of Dengue fever or dengue hemorrhagic fever. We found several HLA alleles that were associated with stronger responses and showed significant OR<1 indicating a lower risk of hospitalized disease (protective effect). Phenotyping of the responding CD4+ T cell subsets revealed a DENV specific T cell subset, specifically expanded in donors carrying an allele associated with protection from severe disease and which is absent in DENV negative donors. Detailed knowledge of phenotype and function of DENV-specific T cells will aid in the establishment of correlates of protection against severe disease.

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ORGAN DAMAGE AND IMMUNOPATHOLOGICAL FEATURES IN FATAL DENGUE CASES

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Dengue is the most common arthropod borne infectious disease worldwide. The infection may be asymptomatic or mild, some subjects develop severe dengue with hemorrhagic manifestations, fluid leakage and organ failure leading to death. The extent of organ involvement in disease and death is not clear. A systematic analysis of the immunohistopathological reactions of these organs will provide important clues on the pathogenesis of severe dengue. 50 fatal dengue cases which underwent autopsy between 2010 and 2015 were analyzed. Most of them positive for dengue by RT-PCR in tissue. FFPE tissues from liver, lung, heart, kidney, brain, spleen, and lymph node were stained with H&E and immunostained for T cells, CD4+ and CD8+T cells, macrophages and dengue antigen. Vascular congestion, hemorrhagic changes and inflammation were prominent in all tissues, being more common and severe in lungs and livers. The livers exhibited acute hepatitis, necrosis and steatosis. Portal space inflammation was characterized by infiltration of T cells and macrophages. Both CD4+ and CD8+T cells were observed however most of them were CD8+, these cells were also found infiltrating parenchyma. Dengue antigen was visualized mostly in macrophages. In lungs alveolar hemorrhage, diffuse alveolar damage, hyaline membrane formation, type II pneumocyte hyperplasia and septal thickening was observed. The alveolar septum showed abundant mononuclear infiltration with macrophages and T cells, predominantly CD8+T cells. Macrophages were abundant also in the alveolar space, some of them with appearance of foamy histiocytes. Dengue antigen was observed in alveolar macrophages and type II pneumocytes. The lungs were the most affected organ, with alveolar diffuse hemorrhagic damage being a prominent pathological feature in fatal dengue. Abundant macrophages and moderate CD8+T cell infiltration were typical features in lung and liver lesions. Dengue antigen was present in alveolar macrophages and type II pneumocytes but rarely present in liver. These results highlight the participation of T cells and macrophages immune mediated responses in dengue induced organ pathology.

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CHRONIC MALNUTRITION DOES NOT IMPAIR THE MEMORY T CELL RESPONSE TO CRYPTOSPORIDIAL INFECTION IN INDIAN CHILDREN

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Approximately 48 % of children <5 years of age are stunted in India, and chronic malnutrition is believed to predispose to impaired immune responses and repeated infections. *Cryptosporidium* spp., an intracellular parasite is responsible for 3.1-7.6 million diarrheal episodes in children <2 years of age in India. Immune response to *Cryptosporidium* is primarily CD4 T cell based, with a poorly defined role for CD8 cells. This study aimed to assess the role of chronic malnutrition on memory T cell responses in children with cryptosporidial infections. In a birth cohort study of the natural history of cryptosporidium infection, infants from a semi-urban slum in Vellore, Southern India, were followed up from birth till 3 years of age, documenting all symptomatic and asymptomatic cryptosporidial infections. Morbidity and monthly anthropometric measurements were recorded, and children's growth classified using WHO guidelines. Peripheral blood mononuclear cells (PBMCs) were isolated at 3 years of age and were stimulated using *Cryptosporidium* oocyst lysate

and stained using florescent tagged antibodies to define the memory component of the CD4, CD8 T cells and markers to define Th1 (IFNγ), Th2(IL-4) and Th-17 (IL-17A) responses. Samples were acquired on a BD Aria III and analyzed. Thirty -four children who had symptomatic cryptosporidial infections were included for this preliminary analysis. Five children were persistently stunted (defined as having a HAZ score <-2SD at 6, 12, 18, 24, 30, 36 month time points) during the 3 year study period whereas 29 children were never stunted. Analysis of memory activated CD4 and CD8 cells expressing either the Th1, Th2 or Th17 phenotypes did not reveal any significant differences between the persistently stunted children compared to the never stunted children (p values not significant). The persistently stunted children had a robust IL-17A and IL-4 CD4 memory response, though they had a slightly lower IFNγ CD8 memory response as compared to the never stunted children. Chronically malnourished children with symptomatic cryptosporidial infections develop and maintain a good memory T cell response.

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GENETIC LINKS BETWEEN SYMPTOMATIC *ENTAMOEBA HISTOLYTICA* INFECTION AND INFLAMMATORY BOWEL DISEASE

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Diarrhea is the second leading cause of death for children globally, causing 760,000 deaths each year in children under the age of 5. Amoebic dysentery contributes significantly to this burden, especially in developing countries. To investigate possible genetic susceptibility to symptomatic *Entamoeba histolytica* (EH) infection in Bangladeshi infants, we conducted a genome-wide association study (GWAS) in two independent birth cohorts of symptomatic EH infection. Cases were defined as children with at least one diarrheal episode positive for EH through either PCR or ELISA within the first year of life, while controls were children without any episodes positive for EH in the same time frame (DBC: 65 cases, 309 controls; PROVIDE: 112 cases, 323 controls). The NIH Birth Cohort and the PROVIDE cohort were analyzed separately, using univariate logistic regression with an additive mode of inheritance. Results were meta-analyzed under a fixed-effects inverse variance weighting model. The top results were found within two neighboring genes on chromosome 10: *CUL2* (cullin 2) and *CREM* (cAMP responsive element modulator). A total of 4 SNPs (single nucleotide polymorphisms) met genome-wide significance (P<5E-08) in the joint analysis. The top SNP was rs2148483 with a P_{meta} of 6.48E-09, with additional risk allele at this locus conferred 2.3 times the odds of a symptomatic EH infection. This SNP is found within an intron of *CUL2* (cullin 2), which has previously been implicated as a susceptibility locus for Inflammatory Bowel Disease and Crohn's Disease. Despite neither individual analyses reaching significance due to their limited power, the meta-analysis of two independent studies shows genome-wide significant results in two genes previously implicated in IBD. These genetic associations reinforce the pathological similarities observed in gut inflammation between EH infection and IBD. Further research is needed to elucidate the underlying mechanisms for the proposed pleiotropy.

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RESPIRATORY TRACT CRYPTOSPORIDIOSIS IS COMMON IN HIV-SERONEGATIVE CHILDREN WITH INTESTINAL *CRYPTOSPORIDIUM* AND COUGH

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We studied respiratory tract cryptosporidiosis (RTC) in children aged 9-36 months presenting to the Acute Care Unit at Mulago Hospital (Kampala, Uganda) with a 2 different chief complaints: A) diarrhea, with cough (n=1023); and B) cough or pneumonia, with or without diarrhea (n=776). Children were screened for *Cryptosporidium* (CR) in stool using RT-PCR. Stool-positive children were selected for further diagnostic tests, including sputum induction. In addition, for every CR stool-positive child in Group B, a CR stool-negative child in this group was selected for further workup. Sputum samples were subjected to RT-PCR for *Cryptosporidium*, bacterial culture and sensitivity, auramine-smear for TB, and RT-PCR for RNA viruses (subject to adequate sample volume). Prevalence of intestinal cryptosporidiosis was 10.7% (89 *C. hominis*, 17 *C. parvum*, 3 *C. meleagridis* or mixed) and 4.8% (27 *C. hominis*, 9 *C. parvum*, 1 mixed) in Group A and B, respectively. Of the stool-positive children that underwent sputum induction, 28/85 (32.9%; Group A) and 8/29 (21.6%; Group B) had RTC. Strikingly, 2 stool-negative children in Group B, neither with diarrhea, also had RTC. All 38 children with RTC were HIV-seronegative. Preliminary data suggests *C. hominis* may have a greater propensity for infection at this site (e.g. RTC occurred in 37.1% of *C. hominis* enteric infections versus 16.7% of C. parvum enteric infections; Group A). Notably, RTC with *C. hominis* occurred even when C. parvum was the species detected in the intestinal tract. No bacterial pathogens were cultured from sputum of 8/28 children in Group A and 6/10 children in Group B with RTC. Results of respiratory virus testing were pending at the time of writing, however at least 3 children in Group B had no alternative explanation for their respiratory symptoms. Clinically, in Group A, children with RTC had significantly lower oxygen saturation SpO2 compared to those who were sputum-negative for *Cryptosporidium* (median 96% vs 98%, p=0.004). Enrolment continues with the aim of further elucidating the clinical and epidemiological significance of RTC.

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AZITHROMYCIN AND DOXYCYCLINE ATTENUATE *ACANTHAMOEBA* VIRULENCE IN A HUMAN CORNEAL TISSUE MODEL

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Amoebic keratitis (AK) is a potentially blinding eye infection caused by the parasite *Acanthamoeba*, a ubiquitous, free-living organism. This organism exhibits resistance to anti-acanthamoebal chemotherapy necessitating long treatment courses; despite this, treatment failures are common. *Acanthamoeba*e isolated from the environment and from the corneas of AK patients have been found to harbour bacterial endosymbionts belonging to Chlamydiales, Rickettsiales, and Legionellales. Previous studies demonstrated that a Chlamydia-like endosymbiont enhanced *Acanthamoeba* virulence *in vitro*, although it is unclear if this translates to a significant effect *in vivo*. We sought to elucidate the potential effect

of *Acanthamoeba*-endosymbiont co-infection in a human corneal tissue model representing clinical AK infection. Several environmental and clinical *Acanthamoeba* isolates from the ATCC were screened for endosymbionts by amplifying and sequencing bacterial 16S DNA. Each *Acanthamoeba* isolate was used to infect EpiCorneal cells, a 3D human corneal tissue model. EpiCorneal cells were then treated with azithromycin (AZT), doxycycline (DOX), or control media to determine if antibiotics targeting common classes of bacterial endosymbionts attenuated *Acanthamoeba* virulence as indicated by a decrease in observed cytopathic effect and inflammatory biomarker production. Infection of EpiCorneal cells with *A. castellanii* 50493 and A. polyphaga 50372 increased TNFα and IL-1 expression. This was attenuated with addition of AZT or DOX. IL-6 and Cu-Zn SOD expression also increased upon infection with either strain, yet attenuation with antimicrobials was only observed in *A. castellanii* 50493. Cytopathic effects on EpiCorneal cells were evident in the presence of *A. castellanii* 50493 and A. polyphaga 50372, and this was reduced with the addition of antimicrobials. Treatment of two *Acanthamoeba* strains with the endosymbiont-targeting antibiotics AZT and DOX, was shown to attenuate inflammatory cytokine production and reduce cytopathic effects. These drugs may present an alternative avenue of therapy in treatment of AK.

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CRYPTOSPORIDIOSIS IN A HUMANIZED MURINE INTESTINAL TRACT

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Cryptosporidiosis is as a major cause of persistent diarrhea worldwide. It has been recently cited as one of only 4 pathogens causing moderate to severe diarrhea in infants and young children in developing countries. Mouse models of enteric infections remain as powerful tools to study host response, susceptibility to disease and response to treatment. However in majority of the models, significant manipulation has been employed to attain infection, including genetic alteration, chemotherapy, irradiation, antibiotic exposure, germ-free condition, infection at neonatal period, or harsh dietary restriction, complicating potential relevance of findings to human disease. We tested the effect of *Cryptosporidium parvum* infection in a humanized murine model attained by gut flora conditioning using a child's fecal specimen. Dams were treated with an antibiotic cocktail and transplanted with human fecal material soon after conception. Control dams were treated with murine feces. Upon weaning, pups were fed with 2% protein diet and infected with *C. parvum* oocysts one week later. Pups were monitored for weight loss and stool specimens were collected up to 21 days post infection. Infected pups from dams transplanted with human feces lost weight, similar to infected pups from dams transplanted with murine feces. Interestingly, infected pups from dams transplanted with human feces shed the parasite longer than the control counterpart. Conditioning the murine intestinal tract with human flora *in utero* may increase susceptibility to cryptosporidial infection and result to prolonged shedding.

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IMPACT OF ENTERIC PARASITES ON INTESTINAL MICROBIOTA DIVERSITY AND METAGENOMIC CHANGES IN RURAL ARGENTINIAN AND ECUADORIAN CHILDREN

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Approximately 30% of children worldwide are infected with gastrointestinal (GI) parasites. Parasites can disrupt intestinal flora affecting nutritional status. We implemented a multi-parallel quantitative real-time PCR and whole genome sequencing analysis for bacterial microbiota and *Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis, Trichuris trichiura*, *Cryptosporidium, Entamoeba histolytica,* and *Giardia lamblia.* Stool samples were collected from 122 asymptomatic children (under 10 years old) from rural Argentina and Ecuador. Separate analyses were done by country for uninfected, *Giardia* only, *Giardia*/helminth co-infections, and helminth only groups. For *Giardia* only infected children, sequencing data showed a decrease in microbiota biodiversity compared to those uninfected that correlated with increasing *Giardia* burden (Spearman $r = -0.5491$, $p = 0.0244$). Clustering was statistically significant using Canonical Correspondence Analysis ordination and shannon alpha diversity (*Giardia* only 2.1; uninfected 2.7, $p < 0.05$). A non-significant increase in diversity was observed for helminth only infections (3.0) with a compensatory decrease in *Giardia*/helminth co-infections (2.3). In *Giardia* only infections, microbiome taxonomy shifted from *Firmicutes* towards increasing proportions of *Prevotella*, with degree of shift related to intensity of infection compared to uninfected (37.1 % versus 23.5%, $p = 0.037$). Abundance of *Prevotella* bacteria was decreased in the helminths only group, but increased for *Giardia*/ helminth co-infections (16.5% versus 38.3%, $p = 0.019$). Metagenomic analysis of the microbiota showed a significant increase in genes required for anaerobic activity among the *Giardia* only group compared to all children without *Giardia* ($p = 0.012$). Our data provides possible evidence for an affect of *Giardia* infections on the intestinal environment allowing permissive growth of anaerobic bacteria such as *Prevotella* and a decrease in microbiota diversity. Future work will explore the contribution of such changes to growth delays in parasite-infected children.

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THE GENOME SEQUENCE OF ANTHROPONOTIC *CRYPTOSPORIDIUM PARVUM*

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Cryptosporidiosis is a life-threatening disease in immune-compromised individuals worldwide, and a major cause of diarrhea-induced death of young children in developing countries. The large Global Enteric Multicenter Study (GEMS) revealed that cryptosporidiosis infections in the developing world are caused primarily by *Cryptosporidium hominis,* followed by *C parvum.* Recent studies revealed that the majority of *C. parvum* infections are due to anthroponotic genotypes. Specifically, it has been observed that, in developing countries, the transmission of *C. parvum* occurs typically from human to human, while zoonotic infections seem to be dominant in developed countries. Until now, *C. parvum* genomic resources have been based on zoonotic isolates, particularly the isolate IOWA II, the source of the reference genome for the species,

and the first *Cryptosporidium* genome to be published. Here, we re-sequenced the genome of the anthroponotic *C. parvum* isolate TU114 using Pacific Biosciences technology, and generated a comprehensive, genome assembly with few sequencing gaps. Comparison between this genome and those of zoonotic isolates will enable a more comprehensive understanding of transmission mechanisms of cryptosporidiosis in humans and animals, and aid vaccine development research against anthroponotic subtypes of *C. parvum*.

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POPULATION GENOMICS OF *PLASMODIUM FALCIPARUM* TO INFORM THE DESIGN AND EFFICACY OF WHOLE ORGANISM MALARIA VACCINES

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The Sanaria® PfSPZ Vaccine is a radiation-attenuated whole-organism vaccine based on the sporozoite stage of *Plasmodium falciparum* (Pf). The vaccine isolate NF54 (West Africa) is the isolate from which the Pf reference 3D7 was cloned. While vaccine efficacy after immunization with moderate doses of PfSPZ is high and similar against controlled human malaria infection (CHMI) with homologous (3D7) and heterologous (7G8 from Brazil) clones, at lower doses protection is higher against CHMI with 3D7 compared to 7G8. Furthermore, at lower doses protection may be lower in the field than against CHMI. These results suggest that while broad efficacy can be achieved by increasing the dose, it may be achieved more efficiently and at lower doses by including additional Pf strains in the vaccine. This goal requires rigorous characterization of NF54 and comparisons to Pf populations in malaria endemic regions so that complementary vaccine strains can be selected. To this end, NF54 was sequenced with PacBio and Illumina platforms resulting in a high-quality assembly and SNP calls. The resulting assembly consists of 24 contigs with a cumulative length of 23.28 Mbp, similar to the 3D7 reference genome (23.26 Mbp). Of the 5,542 genes in the 3D7 genome, all but 15 map completely and accurately to the NF54 genome. Both SNP calls and the assembly indicate that NF54 is very similar to 3D7, with <3K SNP differences between them. We then sequenced and assembled the genomes of 3 additional Pf clones proposed as vaccine constituents: 7G8, NF135.C10 (Cambodia), and NF166 (Guinea). Along with NF54, these were then compared to several hundred Pf clinical isolates from around the globe using whole-genome sequence data. Principle coordinate and admixture analyses based on SNP calls show that cloned and clinical isolates cluster based on geographic origins. Focusing on pre-erythrocytic antigens, we investigate allele and epitope frequency of the four proposed vaccine strains among global Pf populations to inform vaccine design and to interpret the outcome of upcoming vaccine trials.

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GLOBAL LANDSCAPE OF MOLECULAR NETWORKS FOR MALARIA PATHOLOGY REVEALED BY INTEGRATIVE MULTI-OMICS ANALYSIS USING NON-HUMAN PRIMATE ANIMAL MODEL

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Non-Human Primate (NHP) animal models infected with *Plasmodium* pathogens can provide insights into mechanisms and help discover biomarkers for human malarial disease conditions. We adopted a systems biology strategy to comprehensively measure host physiological response to *P. cynomolgi* and *P. coatneyi* infection longitudinally at various molecular layers, including transcriptomics, metabolomics, lipidomics, immunological profiling, proteomics and clinical traits in Peripheral Blood (PB) and Bone Marrow (BM). We developed a novel network biology analysis method, CLR-Directed Bayesian Network Analysis (CDBNA), to integrate Omics data for interrogating differential and common multi-omics network modules perturbed by *P. cynomolgi* and *P. coatneyi* and for deciphering network dynamics in the course of infection. This method integrates the advantages of both information theory-based methods (Context Likelihood Relatedness, CLR) and Bayesian Network Analysis (BNA): CLR empowering genome-scale network reconstruction and nonlinear relationship discovery, with BNA enabling high-resolution focused study of CLR-identified sub-networks. We first applied CLR to integrate Omics data from PB and BM infected with *P. coatneyi* or *P. cynomolgi*, providing a low-resolution overview on genome-scale networks. Then, we applied BNA to derive conditional dependencies between nodes in the network for focused pathways. We illustrate the power of CDBNA by identifying roles of INF-gamma related pathway in malaria. An atlas of species-specific (between *P.coatneyi* and *P. cynomolgi*) and tissue-specific (between PB and BM) network modules of malaria were identified, which highlights tissue-specific mechanisms as well as convergent and divergent mechanisms between *P. coatneyi* and *P. cynomolgi* affecting host network. We illustrate the power of integrative multi-omics analysis by identifying roles of key processes related to immune memory and inflammation in malaria. This global multi-omics map of malaria pathology provides a scaffold for disease mechanism study and potential novel therapeutic targets for prevention and treatment of malaria.

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PIGGYBAC MUTAGENESIS SCREENING OF THOUSANDS OF *PLASMODIUM FALCIPARUM* GENES REVEALS WHAT A MALARIA PARASITE CAN'T LIVE WITHOUT

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Malaria remains an important global health problem and emerging resistance to frontline drugs may reverse recent progress. More robust genomic tools are needed to accelerate progress to identify and validate essential candidate targets to develop the most effective new antimalarial therapies. The efficiency of the *piggyBac* transposon system for insertion within a wide range of genomes and its propensity for random selection of its highly preferred TTAA tetranucleotide insertion site has led to its growing use for functional genomics studies in multicellular eukaryotes. Using Quantitative Insertion-site Sequencing (QIseq), our newly developed next-gen sequencing tool to identify *piggyBac* insertion sites, a high density of insertions revealed a dramatically skewed distribution relative to the frequency of expected genomic *piggyBac* TTAA insertion sites in the

Plasmodium falciparum genome. Through analysis of >5000 new unique insertions generated via a method that primarily produces single-insertion mutant parasites, we can discern genes and pathways essential and dispensable for intraerythrocytic growth of an NF54 clone grown in routine *in vitro* culture. Most importantly, regions significantly void of insertions are calculated to represent regions of genes with essential functions in blood-stage development whereas genes with insertions are considered to be dispensable. Over 1500 insertions are estimated to be lethal in the mutagenesis screen, which was validated by comparison with results for *P. berghei* knock out screens. We will present results from our study that includes analysis to identify approximately 500 high-confidence essential *P. falciparum* genes, representing crucial biological processes associated with core metabolic functions during intraerythrocytic growth. Our results establish *piggyBac* mutagenesis as an effective genetic tool to distinguish essential and dispensable genes that will help accelerate development of new antimalarial therapies.

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WHOLE GENOME SEQUENCING OF *PLASMODIUM FALCIPARUM* MALARIA PARASITES FROM DRIED BLOOD SPOTS: GATEWAY TO HIGH-RESOLUTION GENOMIC SURVEILLANCE

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Plasmodium falciparum malaria is hyperendemic and seasonal in the Kassena-Nankana Districts (KNDs) of the Upper East Region of Ghana, causing significant morbidity and mortality. Medications used for disease control include sulfadoxine-pyrimethamine (SP) prophylaxis during pregnancy, and artemisinin-based combination therapies (ACT). Monitoring the parasite evolutionary response to such measures can inform public health, e.g. by tracking genetic markers that confer or predispose to SP and ACT resistance. But genome-wide epidemiology is limited by technical and logistical difficulties in obtaining sequenceable material from clinical samples. Here, we describe a method for generating *P. falciparum* whole genome sequences from dried blood spots (DBS), collected from finger-pricks (~30µl of blood) in resource-limited rural settings in the KNDs. Using selective whole genome amplification (sWGA), parasite DNA with high (>95%) host contamination was selectively amplified using oligo nucleotides that preferentially bind to the parasite genome. We analysed *P. falciparum* genomes from 156 patients with clinical malaria, including 120 paired DBS and leucocyte-depleted venous blood (VB) samples for head-to-head comparison of sWGA vs genomic DNA. More than 90% of DBS samples produced parasite-enriched DNA with >95% of the core *P. falciparum* genome covered with ≥5x sequence reads, allowing drug resistance loci such as *crt*, *dhfr*, *dhps*, *mdr1*, and *kelch13* to be genotyped. Concordance across ~1 million single nucleotide polymorphisms between VB and DBS samples was >94%, despite there being 50x less blood and no leucodepletion in the DBS samples. Quality sequence data was obtained from DBS down to parasitaemias of 0.03% (~40 parasites per 200 white blood cells). Thus, sWGA makes large-scale, high-resolution genomic epidemiology possible, as DBS collection is better tolerated by most patients and more suitable for remote, resource-limited settings than VB. Genomic data can then inform proactive public health strategies to combat evolving pathogens.

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CULTURE-ADAPTATION OF MALARIA PARASITES IS ASSOCIATED WITH NONSENSE MUTATIONS IN SPECIFIC GENES

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Substantial developments in understanding malaria parasite biology have been derived from studies of *Plasmodium falciparum* cultured *in vitro*. However, culture-adapted laboratory strains may differ from parasites in clinical isolates. To investigate the genetic basis of parasite culture adaptation, 50 new Gambian clinical isolates were introduced to standard *in vitro* culture conditions. Fourteen (28%) of the isolates were successfully grown for at least 48 days, and some were subsequently continued for longer periods. Six of these contained unmixed haploid genotypes at day 0, and were chosen for genome sequence analysis of samples taken during the culture period. In three of the isolates new single nucleotide polymorphism (SNP) variants emerged to frequencies of above 20% during culture, becoming the majority sequences in two isolates. Out of five novel SNPs, four were nonsense mutations resulting in stop codons. Three of these were in the same gene encoding an ApiAP2 transcription factor, with each isolate having a different nonsense mutation, and one was in a serine/threonine protein kinase gene (*SRPK1*). These results prompted survey for nonsense SNP alleles in genomes of eight widely cultured laboratory-adapted parasite strains, revealing four different nonsense mutations in other *ApiAP2* genes, one of which has been previously reported. Remarkably, five of the eight laboratory strains each had a different nonsense mutation in the rap guanine nucleotide exchange factor (*Epac)* gene. A global database of uncultured clinical samples revealed that nonsense mutations were very rare overall, and never found in *Epac*, *SRPK1*, or ApiAP2 genes. In conclusion, loss-of-function mutations in a small number of specific genes are associated with *P. falciparum* growth in culture.

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TRANSCRIPTIONAL AND PROTEOMIC CATEGORIZATION OF THE ETIOLOGY OF PNEUMONIA SYNDROME IN PEDIATRIC PATIENTS IN MALARIA ENDEMIC AREAS

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Pneumonia and malaria are common causes of pediatric respiratory distress in tropical settings. Bacterial pneumonia in particular is a major contributor to morbidity and mortality among children, principally due to delay in antibiotic therapy. Proper clinical treatment requires an actionable and accurate diagnosis. A rapid test that could distinguish between bacterial, malarial, and viral infections would have great clinical utility in directed life-saving antibiotic therapy. We first performed RNA-Seq and analyzed the transcriptomes of 68 pediatric patients with well-characterized clinical phenotype to identify transcriptional features associated with each disease class. Next, we refined those features and used them to create predictive models using elastic net and support vector

machine algorithms. Finally, we validated those models on an independent test set of 37 patients. We developed 4 RNA-based models based on gene expression to distinguish between bacterial, malarial, and viral infections. Support vector machine models fit the training set perfectly utilizing 600 marker genes, suggesting overfitting; elastic net models by contrast had a more uniform performance between train and test sets while utilizing significantly fewer genes. In a second approach, we performed Luminex-based and aptamer-based proteomic analysis and characterized the peripheral blood protein response of 161 pediatric patients from the same population. The pipeline for analysis initially included partial least squares, PAM (prediction analysis for microarrays, a Tibshirani method), random forests, and elastic nets (with genetic algorithms). This study demonstrates that human transcriptional features and proteomic signatures in patients with infectious disease diagnoses recapitulate the underlying biology and provide models for predicting diagnosis. We have identified sets of genes and specific groups of proteins that are expressed in pediatric patients with pneumonia syndrome attributable to different infections and requiring therapeutic interventions. These may provide the foundation for a clinical point of care diagnostic.

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RISK FACTORS FOR SECONDARY HOUSEHOLD TRANSMISSION OF INFLUENZA VIRUS AH3N2 IN THE PERUVIAN NORTHERN COAST

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Influenza virus is associated with 250,000 to 500,000 deaths worldwide and household transmission accounts for approximately one third of all cases. We evaluated risk factors associated with secondary household transmission of influenza virus AH3N2 in a rural community in the northern coast of Peru through a prospective population-based cohort study of influenza-like illness (ILI). We made household visits three times per week to detect cases of ILI, collect nasopharyngeal samples from cases and testing them by RT-PCR. We identified index cases as the first ILI case reported in a household with laboratory-confirmed influenza AH3N2. People residing in the same household as the index case were considered household contacts. Secondary cases were household contacts who developed laboratory-confirmed influenza AH3N2 ILI within seven days after the index case. The household secondary attack rate (SAR) was calculated and generalized linear models were fitted to identify the potential risk factors for transmission, accounting for household clustering, population size, number of primary cases, and other relevant descriptors. The SAR was 6.9% [CI 95% 4.3-10.2] with 22 secondary cases among 321 household contacts. In multiple regression analysis, secondary risk increased 3.6 times in household contacts <5 years old versus those older [Adjusted Prevalence Ratio(PR)=3.6, 95%CI: 1.4-9.3] and risk was increased 4.7 times to siblings of the index case compared to other contacts [Adjusted PR=4.7, 95%CI: 1.4-15.4]. Household transmission of influenza AH3N2 virus was frequent in this cohort, especially to young siblings, who are likely to have especially close contact with the index case. Seasonal vaccinations of children as well as non-pharmaceutical interventions may mitigate this risk. More studies with a better proxy of close contact between household members are recommended.

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DISTRICT TRENDS IN UNDER-FIVE PNEUMONIA MORTALITY IN MALAWI, 2000-2014

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In Malawi, under-5 mortality fell from 247 deaths per 1000 live births in 1990 to 71 in 2013, meeting the target set by Millennium Development Goal 4. This decline was due, in part, to a reduction in pneumonia mortality, which fell from 27.5 under-five pneumonia deaths per 1000 live births to 10.1 from 2000 to 2014. The study objective is to document variability in the decline in under-five pneumonia mortality in Malawi from 2000 to 2014 across 28 districts and describe the contribution of health interventions to this decline. We used the Lives Saved Tool (LiST, version 5.41, Beta 6) to estimate the impact of change in intervention coverage on under-five pneumonia mortality by district from 2000 to 2014. Estimates of intervention coverage were drawn from the Demographic Health Survey (2000, 2004, 2010) and Multiple Indicator Cluster Survey (2006, 2014), and interpolated for years when survey data were unavailable. Populations and cause of death data came from World Population Prospects 2015. We compared the contribution of preventive (breastfeeding, vaccination, nutrition) and curative (antibiotics) interventions on district change in pneumonia mortality. Results for two districts, Blantyre and Kasungu, with different baseline care-seeking, are presented as an illustrative example. The proportion of deaths attributed to pneumonia among children 1-59 months decreased from 17.7% to 15.5% in Blantyre from 2000 to 2014 and from 20.7% to 11.6% in Kasungu. Blantyre had higher care-seeking for pneumonia, 36.2%, while Kasungu was lower at 13.1% in 2000. In 2014, 86.5% of children in Kasungu received 3 doses of PCV while 74.9% did in Blantyre. Vaccination averted >2800 additional pneumonia deaths in Blantyre from 2001 to 2014, accounting for 75% of deaths averted. Vaccination averted 34.2% of additional pneumonia deaths in Kasungu and increase in care-seeking prevented >3000 (30.7%) of pneumonia deaths. Health interventions were scaled up at different rates across districts, which resulted in variations in change in pneumonia mortality over time. Planners should disaggregate data to ensure all districts are served by interventions.

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EPIDEMIOLOGY OF INFLUENZA AMONG SEVERE ACUTE RESPIRATORY INFECTIONS — DAMANHOUR, EGYPT, 2009-2015

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Influenza infections cause substantial morbidity and mortality. We sought to estimate the incidence and describe the characteristics of influenza infections among severe acute respiratory infections (SARI) cases in Damanhour, Egypt. We analyzed surveillance data of SARI cases from 3 public hospitals from June 2009-December 2015. SARI was defined as history of fever or measured temperature ≥38°C, cough with onset in the last 10 days, and requiring hospitalization. Polymerase chain reaction (PCR) of naso/oropharyngeal specimens were tested for influenza A and B viruses, adenovirus, parainfluenza virus, respiratory syncytial virus, human metapneumovirus, and coronavirus. Data from a 2012 healthcare utilization survey were used to estimate incidence. Among 10,431 SARI cases, 9,992 (95.8%) had PCR testing; of these, 3,664 (36.7%) were

positive for one of the tested pathogens and 1,569 (15.7%) for influenza. Among influenza infections, the proportion positive was 57.5% (n=902) for influenza A, 35.9% (n=563) for influenza B, and 6.6% (n=104) for co-infection with other tested viruses. Frequencies for influenza A subtypes were 58.1% (n=524) for seasonal H1N1, 48.9% (n=441) for H3, and 0.8% (n=7) for H5. Overall incidence of influenza infection was 96.9 per 100,000 person-years. The highest proportion of influenza infections occurred during October-February (769/3,409, 22.6 %) compared to other months (206/4,488, 4.6%), (p<0.001). Influenza A infections were 4.9 times more likely between October-November compared to other months. Mean duration of symptoms was 5.17+2.3 days and hospitalization was 4.0+3.1 days; 28 (1.8%) patients were admitted to intensive care for a mean duration of 5.9+5.9 days. Patients with influenza A infection were 2.2 times more likely to be admitted to intensive care compared to patients with influenza B infection. Three cases died, two of whom had influenza A infection. Influenza infection peaked during winter primarily from influenza A seasonal H1N1 and H3. Infection with influenza A was associated with more severe disease and higher mortality. Routine vaccination is essential to decrease influenza burden.

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QUALITY OF CASE MANAGEMENT OF PNEUMONIA AND DIARRHEA IN CHILDREN AGED <5 YEARS: RESULTS FROM A HEALTH FACILITY SURVEY IN SOUTHERN MALAWI IN JANUARY-MARCH 2015

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Globally, pneumonia and diarrhea are leading causes of child deaths. Integrated Management of Childhood Illness (IMCI) is a widely adopted approach to manage these and other childhood illnesses in resource-poor settings, but studies show that many children are inappropriately treated. The objectives of this analysis are to describe case management in Malawi, a malaria-endemic country, in children aged 2-59 months for pneumonia per IMCI and aged <5 years for diarrhea, and to determine factors associated with case management quality. During January-March 2015, we conducted a cross-sectional survey of 95 health facilities (HFs) in southern Malawi using patient exit interviews, healthcare worker (HCW) interviews, and HF assessments. Results were weighted and logistic regression models examined patient, HCW, and HF factors associated with pneumonia and diarrhea case-management quality, using local IMCI guidelines as the gold standard. Of 694 children aged 2-59 months, 132 (19.4%) met IMCI criteria for uncomplicated pneumonia. Of those, HCWs gave correct treatment (cotrimoxazole, amoxicillin, or erythromycin) to 90 (62.8%) and diagnosed pneumonia in 24 (15.1%). Of 724 children aged <5 years, 222 (27.2%) met criteria for uncomplicated diarrhea. Of the 222, HCWs diagnosed 135 (63.7%) and correctly treated 94 (38.2%) with oral rehydration solution (ORS) with or without zinc. Multivariable analyses showed that HCW ascertainment of cough or difficult breathing was associated with correct pneumonia treatment (odds ratio [OR]: 3.1; 95% confidence interval [CI]: 1.01-9.8). Children were more likely to receive correct diarrhea treatment if female (OR: 2.7; 95% CI: 1.3-5.6), if HCWs diagnosed diarrhea (OR: 6.3; 95% CI: 3.1-12.6), or at facilities with ORS in stock (OR: 4.6; 95% CI: 1.8-11.4). Malaria diagnosis was negatively associated with correct management of both pneumonia (OR: 0.4; 95% CI: 0.2-0.8) and diarrhea (OR: 0.3; 95% CI: 0.1-0.7). To improve quality of care, HCWs should be encouraged to solicit patient symptoms systematically and consider alternative common illnesses in children even when malaria is suspected.

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NEGLECTED TROPICAL POPULATIONS: THE BURDEN OF INFLUENZA IN THE ELDERLY, THAILAND

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As the global population ages, infectious diseases of older adults may increase in importance. Influenza virus infections disproportionately affect the very young and the very old, but little attention is given to influenza in the elderly in tropical countries, where influenza was not recognized as an important cause of illness until recently. We used systematic, random sampling to recruit a population-based cohort of persons aged ≥65 years in Nakhon Phanom province, northeastern Thailand, to measure the burden of influenza and the effectiveness of the influenza vaccine to prevent influenza-associated acute respiratory infections (ARI). Participants were contacted weekly to identify those with ARI, and samples were taken by participants at home by self-swabbing their anterior nares. Nasal swabs were tested for influenza viruses using PCR. In May 2015, we enrolled 3,219 elderly persons into the study. Influenza vaccination was offered to the elderly population at large in Nakhon Phanom but was not linked to study enrollment. The cohort contributed 2,512 person-years of observation through the end of March 2016. The median age at enrollment was 71 years (interquartile range, 68-76), 59% of the participants were female and 52% received an influenza vaccine in 2015. There were 1029 ARI cases, with 1013 (98%) samples tested; 42 (4%) samples were positive for influenza, of which 31 (74%) were influenza A/H3N2, 7 (17%) were influenza A/H1N1pdm09 and 4 (10%) were influenza B. Most (83%) of the influenza infections were detected between June and November 2015 (the influenza season), and the incidence of influenza-associated ARI during the influenza season was 3 per 100 p-y (95% confidence interval, 2-4). In this population of Thai elderly with a high influenza vaccination rate, the incidence of influenza-associated ARI was moderate and most illness was associated with influenza A/H3N2. Further analysis will be conducted to determine the burden of hospitalization caused by influenza and the effectiveness of the influenza vaccine in preventing illness in this cohort. This information may be useful to prioritize limited vaccine resources in Thailand.

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ROLE OF NASOPHARYNGEAL PNEUMOCOCCAL DENSITY IN THE EVOLUTION OF ACUTE RESPIRATORY ILLNESSES IN YOUNG PERUVIAN CHILDREN

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Streptococcus pneumoniae commonly colonizes the nasopharynx of young children, with colonization a critical initial step in the development of pneumococcal disease. We analyzed surveillance data from a prospective cohort of young children to examine pneumococcal nasopharyngeal density patterns surrounding acute respiratory illness (ARI) in a rural community setting of the Peruvian highlands. We assessed ARI with weekly household visits and collection of nasal swabs for viral detection. We also collected monthly nasopharyngeal samples to quantify pneumococcal colonization. We defined pre- and post-ARI periods as the

14 days before and after an ARI, and compared pneumococcal densities among samples collected during non-ARI, pre-ARI, ARI and post-ARI periods. Nasopharyngeal samples (n=3,579) from 837 children (median age 1.39 years) were included; 69% of samples had pneumococcal colonization. Relative to non-ARI, median pneumococcal density increased during pre-ARI periods and peaked during ARI. In secondary analyses of samples collected during ARI, both the presence of rhinovirus and persistent detection of colonization (with a new or previously detected serotype) were associated with higher pneumococcal density. These data suggest that nasopharyngeal pneumococcal density is dynamic surrounding episodes of ARI.

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DEVELOPMENT AND CLINICAL PERFORMANCE OF A HIGH THROUGHPUT LOOP-MEDIATED ISOTHERMAL AMPLIFICATION SYSTEM FOR THE DETECTION OF MALARIA

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As malaria prevalence declines in many parts of the world, the accurate and efficient detection of very low density malaria parasite infections is crucial for enabling rapid treatment and interruption of disease transmission. This is increasingly important as more endemic countries move towards elimination with community surveillance and treatment of sub-patent and asymptomatic infections. Common detection methods, based on microscopy and rapid diagnostic tests (RDTs), allow quick and accurate detection but are unable to identify most blood-stage infections below 50 parasites/µl. Nucleic acid amplification techniques (NAATs), such as PCR, are capable of detecting trace amounts of parasite DNA but are costly and complex to establish and maintain in endemic settings. Loop mediated isothermal amplification (LAMP) is a NAAT where amplification occurs in one step under isothermal conditions and is commercially available. The LAMP malaria kit (Loopamp® from Eiken Chemical Co.) was demonstrated to have excellent diagnostic performance in simple laboratories of various endemic countries. However its sample processing and overall throughput was low, limiting the deployment of this technique for large scale screening campaigns. In this study, we evaluate the clinical performance of a newly developed high throughput (HTP) sample processing system to be used in conjunction with the malaria LAMP kit. This system is based on a 96 well format that significantly reduces the need for individual sample pipetting by the use of a simple vacuum system and is compatible with the use of fresh blood and dried blood spots. The turnaround time from sample processing to reading results for 96 samples is less than 2 hours. Our results show that this relatively simple high throughput DNA extraction method for LAMP is capable of detecting low density infections down to 1p/µl, with similar diagnostic accuracy to the gold standard PCR. These characteristics show the HTP-LAMP system is a robust and highly sensitive diagnostic test, with the potential to allow large scale sensitive population screening in the context of malaria elimination campaigns.

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DEVELOPMENT OF HIGHLY ACCURATE QPCR ASSAYS FOR QUANTIFICATION OF SUB-MICROSCOPIC MALARIA PARASITES IN ASYMPTOMATIC POPULATION

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In malaria endemic areas, most infections with the parasite in older children and adults are asymptomatic, and are often characterized by sub-microscopic parasitemia. These often accounts for the majority of the total prevalence of infection as opposed to clinical disease. Asymptomatic malaria inadvertently contributes to malaria transmission due to the long duration of infection and high incidences of gametocyte carriage in both high and low transmission areas. Therefore, the need for highly sensitive malaria diagnostic tools cannot be over emphasized. Here, we describe the development and validation of sensitive plasmodium real time qPCR assays for the detection of low-level malaria parasites in blood. We will also report the prevalence of malaria parasitemia as determined by the assays. Using 700 samples collected in a HIV/malaria co-infection study in a malaria endemic region in western Kenya, the presence of any species of malaria was first determined using an improved assay based on genus-conserved sequences of the *Plasmodium* 18S ribosomal gene. All infections with ≥1 parasite per 50ul sample were detectable by our assay. Second, if positive for malaria, a panel of highly species-specific qPCR assays were developed to determine the presence and quantity of mixed species infections including *P. falciparum, P. ovale* and *P. malariae*. Finally, due to the importance of asymptomatic parasitaemia in malaria transmission, the presence and quantity of gametocytes was determined using stage-specific reverse-transcriptase qPCR. We will report the assay parameters including the limit of detection (LOD) and limit of quantification (LOQ), the linearity of the standard curves over a range of plasmid concentrations, coefficient of variation scores and the PCR efficiency. Overall, these results show sensitive quantitative PCR assays that can be used on samples from malaria endemic areas where high prevalence of sub-microscopic parasitemia have been reported. Such data can be used to inform public health measures aimed at reducing malaria transmission in communities.

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VALIDATION OF ULTRASENSITIVE DETECTION OF ASYMPTOMATIC MALARIA USING DRIED BLOOD SPOTS

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Southeast Asian countries are committed to eliminating artemisinin-resistant *Plasmodium falciparum* malaria in the region by 2030. Recently, ultrasensitive PCR techniques capable of detecting ultralow parasitemias have been used to select target populations for mass drug administration to eliminate malaria infections in asymptomatic carriers who may represent a transmission reservoir. However, these techniques require the use of either venous blood or preserved capillary blood. An ultrasensitive test for malaria infection that can be done using dried blood spots (DBS) would have potential to be scaled up for widespread surveillance. Here we report an optimized method for the highly sensitive detection of *P. falciparum* and *P. vivax* infections using DBS that is both high-throughput and cost-effective, with a similar sensitivity to methods based on whole blood. Laboratory experiments demonstrate a lower limit of detection (LoD) of 20 parasites/mL for DBS collected on Whatman 3MM papers and of 23 parasites/mL for Whatman 903 Protein Saver cards, about 5,000-fold more

sensitive than rapid diagnostic tests and similar to the 16-22 parasites/mL reported for other non-DBS ultrasensitive methods. We validated the sensitivity of the method in two field studies in Myanmar that took place during the wet and dry season. Nearly identical prevalence estimates of subclinical malaria were obtained from DBS samples as with preserved capillary blood samples, as well as with an independent ultrasensitive method using venous blood samples. These data validate the utility of DBS for use in asymptomatic surveillance studies. We are currently using DBS-based ultrasensitive PCR for large-scale surveillance studies across Myanmar in support of malaria elimination.

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DETECTION OF *PLASMODIUM FALCIPARUM* DNA IN SALIVA SAMPLES STORED AT ROOM TEMPERATURE : POTENTIAL FOR A NON-INVASIVE SALIVA-BASED DIAGNOSIS OF MALARIA

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Current malaria diagnostic methods are invasive, requiring blood collection with inherent risk of contracting blood-borne pathogens, pain and poor compliance when repeated sampling is required. On the other hand, the use of saliva, which is a minimally invasive sample for the diagnosis of malaria, has not been widely evaluated. We aim to evaluate the diagnostic test performance of saliva collected and stored at room temperature using the OMNIgene®•ORAL kit, in the diagnosis of malaria. Concurrent blood and saliva samples were collected from 224 febrile patients in Cameroon. Saliva samples were collected in the OMNIgene•ORAL (OM-501) kit and stored at room temperature. Detection of *Plasmodium falciparum* (Pf) DNA was based on amplification of the multicopy 18s rRNA gene using nested-polymerase chain reaction (nPCR). Light microscopy was used to detect Pf blood-stage parasites. Microscopy, nPCR-saliva and nPCR-blood based prevalence of malaria was 22%, 29% and 35%, respectively. When microscopy was used as gold standard, the sensitivity of nPCR-saliva and nPCR-blood in detecting Pf was 91% and 100%, respectively; however, the specificity was 92% and 87%, respectively. When nPCR-blood was used as gold standard, the sensitivity of nPCR-saliva and microscopy was 80% and 68% respectively; whereas the specificity was 99% and 100%, respectively. Nested PCR-Saliva had a "very good" agreement with both microscopy (kappa value 0.8) and blood PCR (kappa value 0.8). Nested PCR-Saliva detected 16 sub-microscopic malaria infections whereas 30 sub-microscopic infections were identified by nPCR-blood. At parasitemia >10,000 parasites/ml of blood, the sensitivity of nPCR-saliva was 100%. Saliva can be used, as an alternative non-invasive sample for the diagnosis of malaria and the OM-501kit is effective at transporting and preserving malaria parasite DNA in saliva at room temperature.

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STIMULATING THE MARKET FOR MALARIA RDTS: NOVEL INSIGHTS FROM REAL-WORLD PROGRAMMING FOCUSED ON PRIVATE SECTOR SERVICE DELIVERY AND MARKET DEVELOPMENT

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Almost 8 out of every 10 suspected malaria patients received a diagnostic test in the public sector in 2014. Estimates of the level of private sector testing are much lower. This is a public health concern given that a significant proportion of patients (estimated at 40%) in many malaria endemic countries seek care for febrile illnesses from private sector providers. Malaria rapid diagnostic tests (RDTs) are considered a viable option for resource-constrained settings. The success of national diagnostic strategies will depend on increased availability and appropriate use of quality-assured RDTs in the private sector. Recent small-scale studies have introduced RDTs into the private sector to estimate their impact on fever case management. Given their controlled settings, these studies offer limited insight into the real world issues of supply chain reliability, RDT affordability, marketing and demand creation among providers and clients, acceptability of test results to providers and clients, post-market quality control of RDTs, and interface with country diagnostic policy and guidance. In response to these knowledge gaps, PSI in collaboration with partners (Malaria Consortium, FIND, and Johns Hopkins School of Public Health) implemented a three-year initiative funded by UNITAID to stimulate a private sector market for RDTs in five sub-Saharan African countries: Kenya, Tanzania, Madagascar, Uganda and Nigeria. Designed as an operations research project, the consortium successfully completed 44 studies across the 5 countries. This presentation will offer an overview of the project design, findings and lessons learned, situating them in relation to results from other interventions in this area. In doing so, the presentation will enable participants to understand to 1) the important role the private sector can play in fever case management in Africa; 2) key market shortcomings, quality concerns and policy challenges related to the scale-up RDTs in the private sector in Africa; and 3) how the new WHO Roadmap for public-private engagement (expected release date of September 2016) can help address these challenges.

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SINGLE CELL FUNCTIONAL ARTEMISININ RESISTANCE IN CLINICAL STRAINS OF *PLASMODIUM FALCIPARUM* MALARIA

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Emergence and spread of artemisinin resistance raises risk of wiping out recent gains achieved in reducing worldwide malaria burden and threatens future malaria control and elimination on a global level. *Plasmodium falciparum* Kelch13 (PfKelch13) and the ring stage survival assay (RSA) respectively provide important tools to screen for and validate the spread of artemisinin resistance. But they fail to detect Kelch-independent mechanisms and a large proportion of clinical strains cannot be adapted for RSA, hampering comprehensive mapping and understanding the global biology of artemisinin resistance, in particular its heterogeneity in individual parasites and clinical infection. Our prior studies have shown that artemisinins target *P. falciparum* phosphatidylinositol-3-kinase (PfPI3K), which binds Kelch13. Kelch13 mutations of artemisinin resistance decrease kinase binding to elevate the lipid product phosphatidylinositol-3-phosphate (PI3P), as reported previously. PI3P increase is predictive of resistance across clinical and engineered laboratory parasites even in absence of PfKelch13 mutations, suggesting that quantitative detection of PI3P in individual parasites may provide a powerful index of resistance. However separation of PI3P from phosphatidylinositol-4-P (PI4P) is challenging since both lipids have identical mass and charge. Here we report on functional assays that quantitatively detect PI3P as well as downstream pathways and distinguish them from PI4P in single *P.falciparum* parasites. Evidence will be presented for rapid measurements of artemisinin resistance applicable to clinical strains eliminating need for culture adaptation and providing powerful mechanistic portals for both the biology of resistance and its heterogeneity in infection.

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DELETIONS OF PFHRP2 AND PFHRP3 IN RDT-NEGATIVE *PLASMODIUM FALCIPARUM* ISOLATES FROM UGANDA

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Malaria rapid diagnostic tests (RDTs) play a key role in malaria case management. The most widely-used RDT identifies *Plasmodium falciparum* based on immunochromatographic recognition of PFHRP2. Deletion of pfhrp2 was reported to be common in *P. falciparum* isolates from Peru and Ghana, and uncommon in isolates from Mali, Senegal, and India. We investigated the presence of deletions in pfhrp2 and the homologous gene pfhrp3 in samples collected from cross-sectional surveys conducted in 3 regions of Uganda in 2012-13. The surveys included annual blood smears and HRP2-based RDTs (SD BIOLINE) in children and adults from randomly identified households. Of 1,493 samples with positive blood smears, 96 were RDT negative and selected for further investigation. DNA was extracted from dried blood samples using Chelex-100. Analysis included amplification of subunit ribosomal DNA for *P. falciparum*-specific sequences, amplification of pfhrp2 and pfhrp3 by nested PCR followed by electrophoresis of PCR products to identify gene deletions, and amplification and electrophoresis of polymorphic regions of msp2 to assess complexity of infection. Of the 96 samples, *P. falciparum* was identified by PCR in 56 (58%). All 56 samples had at least one deletion in pfhrp2, pfhrp3, or flanking regions. Of these samples, 25 (45%) had a deletion in pfhrp2, 39 (70%) a deletion in pfhrp3, and 19 (34%) deletions in both genes. Geometric mean parasite density for the 56 samples was 291/µl and mean complexity of infection was 1.8. Of all positive blood smears in survey subjects, 3.8% appear to have had infections with pfhrp deletions and 1.3% deletions in both pfhrp2 and pfhrp3. Our results suggest that deletions in pfhrp2 or pfhrp3 may explain some false negative malaria RDT results in Uganda, generally in the setting of low parasite densities.

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THE DILEMMAS OF CONGENITAL CHAGAS DISEASE SCREENING IN AN ENDEMIC SETTING

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Chagas disease has shifted from a neglected, endemic parasitic infection of the rural poor to an urbanized chronic disease and now a potentially emergent global health problem. Congenital transmission is estimated to account for 22% of all new *Trypanosoma cruzi* infections. Treatment during infancy is significantly more efficacious and better tolerated, but current diagnostic methods, fail to detect over half of infected neonates and <20% of infants complete 9-months of follow-up. We recruited pregnant women presenting for delivery in two urban hospitals in Santa Cruz department, Bolivia and monitored infants of infected women at birth, 1, 6 and 9 months to evaluate the performance of quantitative PCR (qPCR), IgM Western blots (using TESA-blots) and micromethod (microscopically detectable trypomastigotes) for newborn screening for congenital Chagas disease. Of 518 at-risk infants from 507 seropositive women, unequivocal congenital transmission was identified in 32 infants of 29 mothers, including 3 sets of infected twins (5.7% transmission rate). Vertical transmission was more likely to occur in younger (23.5 years; [CI: 19.6-28.1] vs. [26.9; CI: 22.0-34.0]), first time mothers. Congenital *T. cruzi* infection was significantly associated with severe clinical outcomes including, premature birth (6 vs. 11 infants) and low birth weight (<2500g; 7 vs. 245). Furthermore, uninfected infants of seropositive mothers suffered from respiratory distress (10 vs. 119 infants) and premature labour. In combined birth and 1 month specimens qPCR, TESA-blot and micromethod displayed sensitivity/specificity of 82.8%/97.3% (median of 7143.6 parasites/ml; interquartile range of 5.0-187788.9 parasites/ml), 71.4%/99.5% and 20.7%/100%, respectively. qPCR has the potential to facilitate earlier diagnosis and circumvent loss to follow-up. We critically discuss the technical, logistical and economic obstacles of implementing routine molecular screening for congenital Chagas disease in resource-limited settings and describe the future prospects for improvement.

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TARGETING *TRYPANOSOMA CRUZI* METHIONYL-TRNA SYNTHETASE FOR NOVEL TREATMENT OF CHAGAS DISEASE

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Chagas disease is endemic throughout Latin America infecting approximately 5.7 million people and causing ~7000 deaths per year. New drugs with improved safety and efficacy are needed to replace the antiquated drugs that are currently available. Our group works on a novel drug target in *Trypanosoma cruzi* that is vital for protein synthesis, the methionyl-tRNA synthetase (MetRS). Guided by structure-based drug design, more than 500 novel MetRS inhibitors have been synthesized and tested for activity against recombinant trypanosomal MetRS. The most potent compounds were tested against intracellular *T. cruzi* amastigotes revealing EC50 values as low as 4 nM. The same compounds have minimal toxicity on mammalian cells (selectivity index >5000). Chemical modifications have led to much improved oral bioavailability (up to 80%) and pharmacokinetic properties compared to the parent compounds from which they were derived. A lead MetRS inhibitor was orally administered to mice at 50 mg/kg twice per day for 20 days resulting in no apparent side effects. Experiments testing the efficacy of MetRS inhibitors in the murine model of chronic *T. cruzi* infection are underway. These data support ongoing efforts to develop MetRS inhibitors as novel drugs for Chagas disease.

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NOVEL EXTRACTION PROTOCOL AND RECOMBINASE POLYMERASE AMPLIFICATION ASSAY FOR DETECTION OF *LEISHMANIA DONOVANI* IN 30 MINUTES

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Leishmania donovani (LD) is a protozoan parasite transmitted to humans by sand flies, which causes Visceral *Leishmania*sis (VL). Currently, diagnosis is based on presence of anti-LD antibodies and clinical symptoms. Molecular diagnosis would require real-time PCR, which is not easy to implement at field settings. In this study, we report on the development and testing of a novel extraction protocol in combination with recombinase polymerase amplification (RPA) assay for the detection of LD. The LD RPA assay detected equivalent to one LD genomic DNA. The RPA assay was performed at constant temperature (42°C) and the total assay runtime including the extraction procedure was 30 minutes. The

RPA assay also detected other *Leishmania* species (*L. major, L. aethiopica* and *L. infantum*), but did not identify nucleic acid of other pathogens. Forty-eight samples from VL, asymptomatic and post-kala-azar dermal leishmaniasis subjects were detected positive and 48 LD negative samples were negative by both LD RPA and real-time PCR assays, which indicates 100% agreement. To allow the use of the assay at field settings, a mobile suitcase laboratory (56+45.5+26.5 cm) was developed and operated at the local hospital in Mymensingh, Bangladesh by using a solar-powered battery. DNA extraction was performed by a novel magnetic bead based method, in which a simple fast lysis protocol was applied. Moreover, All reagents were cold-chain independent. The mobile suitcase laboratory using RPA is ideal for rapid sensitive and specific detection of LD especially at low resource settings and could contribute to VL control and elimination programmes.

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SPECTRUM OF BACTERIAL PATHOGENS IN INFLAMMATORY CUTANEOUS ULCERS OF AMERICAN TEGUMENTARY *LEISHMANIA*SIS

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Approximately 10% of New World cutaneous leishmaniasis (CL) ulcers manifest with a severe inflammatory phenotype characterized by pain, erythema, and purulent exudate, leading to near-universal treatment with antibiotics prior to anti-leishmanial therapy. Although these ulcers have a "secondarily infected" appearance, the contribution of potential bacterial co-pathogens in the pathogenesis and natural history of severe inflammatory CL is unknown. Understanding the ulcer microbiome in CL has important implications for antimicrobial stewardship, and evidence-based management strategies. Our objective was to illuminate the represented bacterial species in ulcers of CL manifesting with the severe inflammatory phenotype. Pre- and post-antibiotic treatment filter paper lesion impressions (FPLIs) (n=16) from patients with severe inflammatory CL and baseline FPLIs (n=9) from patients with non-inflammatory CL were evaluated using 16S rDNA end-point PCR, 16S real-time PCR and species-specific real time PCR assays targeting *Streptococcus pyogenes, Escherichia/Shigella* spp, *Citrobacter freundii, Enterobacter/Klebsiella* spp, and *Enterococcus* spp. Confirmation to genus and species-level was performed using Sanger sequencing. Six of 16 (37.5%) FPLIs from inflammatory lesions were positive for bacterial pathogens by real time PCR, versus 2 of 9 (22%) FPLIs from non-inflammatory lesions. Six organisms were confirmed to be Staphylococcus spp (n=2), *S. pyogenes* (n=1), *K. pneumonia* (n=1), *Pseudomonas aeruginosa* (n=1), and *Enterobacter* spp (n=1). Two FPLIs retrieved from patients with inflammatory CL post-antibiotic treatment demonstrated pathogen durability. Our findings suggest that, in addition to usual skin flora, Gram-negative enterobacteriaceae and beta-hemolytic streptococci may contribute to the microbiome of severe inflammatory CL ulcers. It remains unknown if empiric antibiotic treatment of the severe inflammatory CL phenotype changes outcome, however, such regimens should include both Gram-positive and Gram-negative coverage.

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CHAGAS DISEASE: A PROSPECTIVE THERAPEUTIC COHORT WITH 12 MONTHS FOLLOW-UP, ANALYZING ADVERSE DRUG REACTIONS, THERAPEUTIC FAILURE AND SEEKING FOR BIOMARKERS"

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Treatment of chronic phase of Chagas disease with benznidazole (Bz) remains controversial mainly because of its weak evidence allowing its use. Its response is variable and presents, commonly, adverse drug reactions (ADRs). There are few studies, describing the ADRs during the treatment of adult patients with Bz and its failure using molecular methods. We established a prospective cohort study that followed, for 12 months, 87 *T. cruzi* infected adults, (age between 18 – 65 years), with the chronic indeterminate form, mild to moderate cardiac or digestive involvement without advanced forms, during Bz use (5mg/kg/day, up to 300mg/day for 60 days). Patients were evaluated in 5 schedules visits for adhesion, ADRs, blood sample collection (near 15th, 30th, 60th days, 6th month and 1st year after Bz initiation). Blood samples were collected to perform biomarkers identification of failure or cure, to perform transcriptomics and mass spectrometry studies. Of the 87 patients that complete the follow-up (FU), 58 (66.7 %) informed at least one ADR, 63.8% dermatological, 41.4% gastrointestinal and 36.2% neurological related. The majority of the ADRs, 45 (77.6%), occurred in the first 15 days of treatment, mainly dermatological related (55.6%). On the 30th visit, 23 (39.7%) patients related ADRs of which, 60.9% were also dermatological related. On the 60th day visit, 27 (46.6%) patients related ADRs, of which, 48.1% neurological related. Regarding the therapeutic efficacy by the PCR (protein chain reaction) positivity for *Trypanosoma cruzi* was assessed (treatment failure was defined as at least 2 positive PCR out 8 replicates). On 60th day of treatment, 15 (17,9%) patients presented positive (+) PCR; up to 6th month, 37 (44.%) presented + PCR and, on the end of the first year after initiation of therapy, from the PCRs analyzed (70% of the total until this date), 40 (66.7%) patients presented +PCR. Although high failure rate demonstrated by PCR, the gold-standard method for cure still being the serology, that may persists reagent for decades, even after effective treatment. Last FU visit was performed on beginning March, 2016 and data is still on final analysis.

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TOWARDS SENSITIVE AND LESS INVASIVE DIAGNOSIS OF VISCERAL LEISHMANIASIS IN SUDAN USING LAMP

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Confirmatory diagnosis of visceral leishmaniasis (VL) usually requires examination by microscopy of samples collected by invasive means, such as splenic, bone marrow or lymph node aspirates, which cause discomfort to patients, with risks of bleeding and iatrogenic infections, and requires technical expertise. Molecular tests such as PCR have great potential for diagnosis of VL using peripheral blood, but are expensive, require well-equipped facilities and trained personnel. More user-friendly, cost-effective, and field-amenable options are therefore needed. One method that could meet these requirements is loop-mediated isothermal amplification (LAMP): amplification of the target occurs at a constant temperature, the reagents are dried down, can be stored at room temperature, is highly specific, and results can be visualized using simple detection methods. A LAMP assay based on dried reagents, developed by Eiken Chemical Co. (Japan), FIND and partners, was evaluated in the diagnosis of VL at the Institute of Endemic Diseases (IEND), Sudan. A total of 198 VL suspects were tested by microscopy of lymph node aspirates (the reference test) and two serological tests: DAT (produced in house at IEND) and *Leishmania* Ab Rapid Test CE (CTK Biotech, USA). LAMP was performed on peripheral blood previously processed by i) a simple direct boil and spin method, and ii) the QIAamp DNA Mini Kit (QIAgen). The sensitivity and specificity obtained for each of the tests was: *Leishmania* Ab Rapid Test CE 98.96% and 100%; DAT 85.57% and 78.22%; LAMP-boil and spin 97.65% and 99.01%; LAMP-QIAgen 100% and 99.01%. The excellent performance of LAMP on blood indicates that it can be included in the algorithm for diagnosis of VL and eliminate the need for invasive lymph node aspirates. The simplicity of the test makes it a promising candidate for confirmatory diagnosis in settings that are lower than the reference laboratory.

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ASSESSING *IN VITRO* AND *IN VIVO* ACTIVITY OF MILTEFOSINE AGAINST *TRYPANOSOMA CRUZI*

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Chagas disease treatment options are limited to Benznidazole (BZ) and Nifurtimox (NFX). These drugs have high efficacy in acute phase but its use in chronic phases is still under debate, and severe adverse effects are frequent. Alternative treatments are not currently available, in part due to high cost of developing new effective molecules. Drug repurposing is a cost-effective potential solution to fulfill current needs of better and safer therapy for Chagas disease. In primary screening at 10 µM, we found that Miltefosine (MLT; a phosphatidylcholine analog with antineoplastic and anti-*Leishmania* activity) exhibited higher relative anti-T cruzi activity (%RA) against trypomastigotes of *Trypanosoma cruzi* VD strain compared to BZ and NFX, and equal %RA against amastigotes. Consequently, MLT was moved to secondary screening, obtaining a dose-response curve with lytic concentration 50% (LC50) of 14.25 µM (CI95%: 8.23; 24.67) on trypomastigotes and inhibitory concentration 50% (IC50) of 1.44 (CI95%: 0.634; 1.716) µM on amastigotes. These results supported further evaluation in an acute murine model of *T. cruzi* infection. Experimental protocol was approved by Faculty of Veterinary Sciences (UBA) (IACUC#2014/4). BALB/c females were infected with 500 trypomastigotes by intraperitoneal (ip) route and treated orally after 8 days of infection with MLT at 25, 50, 75 or 100 mg/kg for 20 consecutive days. Infected non-treated (NT) and BZ or NFX treated groups (100 mg/kg) were included. MLT treatment decreased parasitemia levels in a dose-response manner, with 100% of survival in mice from 50 to 100 mg/kg dosing. Mice with negative parasitemia were subjected to an immunosuppression cycle (cyclophosphamide 200 mg/kg, ip, 1/week, up to four weeks). Parasitemia reactivation was recorded in 100% of mice in all MLT treated groups, as well as in all mice from BZ group, and in 57% of animals from NFX group. MLT exhibited an excellent *in vitro* parasiticidal effect, especially against amastigotes, but parasitostatic activity *in vivo*. Further studies on combined therapies with BZ or NFX and the evaluation of other repurposed candidates are needed and currently performed.

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OPTIMIZING SEASONAL MALARIA CHEMOPREVENTION (SMC) IN AFRICA: ESTIMATING THE IMPACT OF INCREASING THE NUMBER OF SMC CYCLES ON THE NUMBER OF CHILDREN PROTECTED, THE MALARIA BURDEN AND COST-EFFECTIVENESS

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Seasonal malaria chemoprevention (SMC) is currently recommended by the WHO for malaria control in children in areas of the Sahel and sub-Sahel with highly seasonal malaria transmission. SMC consists of up to 4 monthly cycles of sulfadoxine-pyrimethamine plus amodiaquine (SP-AQ) given to all children between 3 and 59 months of age, and offers highly effective protection against malaria. However, large populations reside in areas with seasonal malaria transmission outside the area where SMC is currently recommended, mainly where the rainy season is slightly longer than in the Sahel. Many of these areas have a high malaria burden, despite scale-up of existing control measures. SMC over a longer period could be an important additional control strategy, but evidence on its likely effectiveness, and delineation of the areas where it would be cost-effective are lacking. We used an individual-based malaria transmission model, fitted to data from SMC trials, to estimate and map the impact of SMC with additional monthly cycles across the African continent. It has previously been estimated that around 25 million children live in areas suitable for SMC in areas with a season up to 4 months in length. Model estimates suggest that a wider area, with a population of about 40 million children, could be protected by four monthly cycles of SMC. The population protected by SMC could be further increased, by about 20 million children, by using 5 or 6 rounds of SMC in areas with a longer season, where approximately 60% of the annual burden occurs within a 5 or 6 month period. This could avert approximately 10.5 million malaria cases in young children per year, and many young deaths. These gains are likely to be highly cost-effective, at less than 10 USD per case averted in many areas, due to the relatively low cost of SMC, its high effectiveness where SP and AQ remain effective, and the high malaria burden. Additional monthly cycles of SMC may also be important within the area where SMC is currently recommended, by allowing national programmes to successfully hit the 'moving target' of seasonal cycles which vary in length and intensity from year to year.

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EVALUATION OF THE IMPACT OF SEASONAL MALARIA CHEMOPREVENTION ON MORTALITY AND MORTALITY IN YOUNG CHILDREN IN NORTHERN GHANA

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Malaria remains a major health concern in sub-Saharan African though global burden has reduced from 262 to 214 million from 2000 to 2015. Across the Sahel sub-region, most childhood morbidity and mortality from malaria occurs during the short rainy season. Seasonal Malaria Chemoprevention(SMC) during this period has been shown to prevent illness and death from malaria in children. WHO recommended SMC implementation in the Upper West region of Ghana due to this seasonal pattern. This evaluation was to determine the impact of this implementation. Fourteen communities (clusters) were selected from Lawra District of Upper West Region with 731 children selected as an intervention area with similar selection in the West Mamprusi District(WMD) in the Northern Region with 711 children without SMC for comparison. Blood samples for hemoglobin and malaria parasitaemia were taken before and after the intervention and parameters of malaria morbidity and mortality were also collected during the intervention. Incidence rates of severe malaria were 0.01 and 0.02 per person years follow up in the Lawra District and WMD respectively with P.E of 45%(p=0.62). For mild malaria, it was 0.22 and 0.17 per person years in intervention and control area respectively with PE of - 25%(p=0.31). For children developing anaemia(Hb< 11.0g/dl) from baseline to endline, there was a reduction of 16%(p=0.000) in Lawra and increase of 12%(p=0.002) in WMD. Mean Haemoglobin reduced by 0. 24g/dl(p=0.000) in WMD and increased by 0.39g/dl(p=000) in Lawra District at the end of SMC. At the end of the intervention, proportion of children with asexual parasites reduced by 19%(p=0.000) in Lawra District and increased by12%(p=0.000) in WMD. Morbidity data collection was a challenge in WMD due to health care seeking behaviour and reduced access to health facilities there due to geographical barriers. In summary, effectiveness of SMC in reducing parasite carriage among children in the intervention area has been demonstrated and its protective effectiveness on the haemoglobin level of children.

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EVALUATING THE COMMUNITY-LEVEL IMPACT OF INTERMITTENT PREVENTIVE TREATMENT OF SCHOOLCHILDREN FOR MALARIA IN JINJA, UGANDA: A CLUSTER-RANDOMIZED TRIAL

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Intermittent preventive treatment (IPT) for malaria in schoolchildren has been shown to benefit individual children, and has the potential to decrease malaria transmission at the community level. To evaluate the community-level impact of IPT of schoolchildren with dihydroartemisinin-piperaquine (DP), a cluster-randomized trial was conducted in Jinja, Uganda. A total of 84 clusters, including one primary school and the 100 closest households, were randomized in a 1:1 ratio to intervention and control. Children were enrolled into the intervention (March-Dec 2014) and monthly IPT with DP was delivered (June-Dec 2014), with participants receiving up to 6 rounds of DP. The evaluation included cross-sectional surveys of schoolchildren (Nov-Dec 2014, N=1092) and community members (Jan-April 2015, N=8922), and continuous entomology surveillance in households from 40 randomly selected clusters (April 2014 – April 2015, N=200). In total, 25,630 students were listed on the 42 intervention school registers; 10,079 (39%) were enrolled in the intervention and received at least one dose of DP. Parasite prevalence by microscopy was lower in the intervention arm than in the control in both the school survey (9.2% vs 44.1%, adjusted risk ratio [aRR] 0.22 [95% CI: 0.16-0.30] p<0.001), and the community survey (19.0% vs 23.1%, aRR 0.85 [95% CI 0.73–1.00] p=0.05). Overall, the annual EIR was lower in the intervention arm than in the control (10.9 vs 18.8 infective bites per person/year) and was significantly lower during October-December 2014, when delivery of DP peaked (7.0 vs 24.7, adjusted incidence RR 0.03 [95% CI 0.001-0.46] p=0.01). Despite not reaching coverage targets, we found that IPT with DP had a positive impact on key malaria indicators measured in individual schoolchildren, and within the community. By targeting a demographic 'hot-pop', IPT of schoolchildren provides an operationally attractive option for malaria control that can benefit school-aged children, and potentially reduce transmission of malaria.

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BASELINE FREQUENCIES OF MOLECULAR MARKERS OF DRUG RESISTANCE BEFORE SCALING-UP ACCESS TO SEASONAL MALARIA CHEMOPREVENTION IN SEVEN COUNTRIES ACROSS THE SAHEL

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A major concern for SMC is that its widespread deployment will lead to the selection of drug resistant parasites with progressive loss of efficacy. It is essential that national SMC programmes incorporate a drug sensitivity monitoring component, using standardised methods so that trends over time can be interpreted and data across countries can be combined. Through the ACCESS-SMC project, we aimed to establish a monitoring system that will continue to be used in the longer term to monitor SMC programmes, through monitoring of molecular markers of resistance, and case-control studies. Surveys were conducted in January and February of 2016, in Burkina Faso, Chad, Gambia, Guinea, Mali, Niger and Nigeria, to establish a baseline for the prevalence of molecular markers associated with resistance to sulfadoxine-pyrimethamine and amodiaquine, using standardised methods. Each survey included two age groups, children under 5 years of age, and a group of older children and adults, aged 10 to 30 years, a group not exposed to SMC drugs, for assessment of the extent of changes in the circulating parasite population. The sample size, 2200 in each age group in each country, was chosen to be able to estimate frequencies of the molecular makers with precision and in order to detect changes in frequency that might give early warning of loss of effectiveness when the surveys are repeated in January 2018 and at future intervals. At monitoring locations in each country, where possible in areas that had not started SMC, probability sampling was used to select participants, a short questionnaire was completed to record date of birth, recent antimalarial treatment and other details, and a finger-prick blood sample taken to

make at least two blood spots onto filter paper. These baseline samples are being genotyped to identify mutations at pfcrt, pfmdr1, pfdhfr and pfdhps known to impact on the efficacy of AQ or SP. The baseline survey results will be presented including PCR-determined prevalence of *P. falciparum* and the resistance genotyping data from each country.

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DIHYDROARTEMISIN-PIPERAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION

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Seasonal Malaria Chemoprevention (SMC) using sulfadoxine-pyrimethamine+amodiaquine (SPAQ) is used in the Sahel to prevent malaria in children. Dihydroartemisinin piperaquine (DHAPQ) is an alternative drug that could potentially be used if SPAQ starts to lose efficacy, and in parts of Africa outide the Sahel with seasonal transmission where there are high levels of resistance to SP. We assessed the effect of DHAPQ dose on efficacy as part of a randomized trial to evaluate the use of DHAPQ for SMC in Burkina Faso. 757 children received DHAPQ on three occasions, in August, September and October. Children were weighed each month to determine dosage, which was rounded to the nearest quarter tablet. PQ plasma concentration was measured in capillary samples in a subset of 159 children on day 7 after treatment with DHAPQ. Mean concentration was 48 ng/ml in August, 52 ng/ml in September, and 60 ng/ml in October. To assess the association between PQ concentration on day 7 and protection against malaria during the same month, these children were divided into three groups according to the tertiles of the day 7 concentration, and the incidence compared using a logrank test for trend. Malaria incidence decreased with increasing concentration. The mean total monthly dose of PQ administered was 50 mg/kg. In linear regression, a 10-mg/kg increase in dose of PQ administered was associated with an increase of 4.7 ng/ml in the day 7 plasma concentration of PQ in August, 5.7 ng/ml in September, and 7.7 ng/ml in October, showing an accumulation of PQ in successive months. Cox regression was then used to assess the relationship between the dose of PQ administered and the incidence of malaria in the subsequent month, in the 757 children who received DHAPQ. An increase in PQ dose administered was associated with a reduction in the incidence of malaria, with a hazard ratio of 0.62 for a 10-mg/kg increase in dose administered in August, 0.52 in September, and 0.85 in October. DHAPQ is effective, with the advantage of a fixed dose combination, but it will be important to ensure children receive an adequate dose. There are limited alternatives for SMC if SPAQ fails.

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COMPARATIVE IMPACTS OF ANTENATAL MALARIA PREVENTION STRATEGIES ON *PLASMODIUM FALCIPARUM* SP-RESISTANCE ALLELES IN MALAWI

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The efficacy of intermittent preventive therapy during pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is continually threatened by parasite resistance to SP. Alternative strategies like intermittent screening and treatment with artemisinin-combination therapies (ISTp) are being considered. We hypothesized that, compared to ISTp with dihydroartemisinin-piperaquine, IPTp-SP would select for higher levels of SP resistance mutations in women infected with *Plasmodium falciparum* at delivery. We analyzed parasites collected from women participating in a randomized trial of ISTp and IPTp-SP at three sites in Southern Malawi, where parasite resistance to SP is high. We pooled *P. falciparum* parasites into populations and sequenced the phenotypically-relevant loci in the parasite genes dhfr and dhps using an Ion Torrent PGM platform. Reads were quality-filtered, aligned to reference sequences, and scored bioinformatically at the loci of interest to compute the frequencies of mutant alleles. Overall, we input 1,410 *P. falciparum* parasitemias into the analysis, comprising 18 pools of between 19 and 104 parasites. After stringent quality-filtering, median read depth was 1,682 at relevant loci in dhfr and 1,552 in dhps. In each population, the frequencies exceeded 97% of the N51I, C59R, and S108N mutations in dhfr and the A437G and K540E mutations in dhps. The I164L mutation in dhfr was absent. The frequency of the dhps A581G mutation was 2.7% in parasites collected at second trimester enrollment. At delivery, the frequency of the A581G mutation in placental parasites was <1% in women who received ISTp and 6.3% in women who received IPTp with SP ($p < 0.001$). This effect was most pronounced at a single study site, where the frequency of A581G in women receiving IPTp-SP increased from 4.3% at baseline to 23.1% in placental parasites ($p < 0.001$). These data indicate that, compared to an ISTp strategy, IPTp-SP promotes the emergence of parasites bearing dhps A581G. Understanding the clinical impact of parasites bearing this mutation on birth outcomes will be critical in areas of East Africa where these parasites circulate.

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EVALUATION OF TARGETED MASS TREATMENT OF MALARIA IN TANINTHARYI REGION, MYANMAR: PRELIMINARY RESULTS

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Targeted mass treatment (TMT) may be a useful intervention for malaria elimination, and is being evaluated for eliminating asymptomatic *Plasmodium falciparum* and *P. vivax* infections detected by active surveillance in malaria endemic populations in eastern Myanmar. A community-based study was conducted in Tanintharyi Region, southern Myanmar to evaluate the feasibility and efficacy of TMT. In preparation, malaria posts were established with trained malaria heath workers, and malaria prevalence was estimated using rapid diagnostic tests (RDT) and ultrasensitive real-time PCR (usPCR) in a total of 35 villages in three rural townships of the Region. Based on the prevalence of subclinical malaria by usPCR, three villages with the highest malaria prevalence were selected to receive TMT, and six control villages were selected. The TMT villages were treated with three daily therapeutic doses of dihydroartemisinin-piperaquine (DHP) and low-dose primaquine, monthly for three months. No treatment was provided in the control villages. Standard diagnosis and treatment for malaria were available in all nine villages. No serious or unexpected adverse effects reported. In pre-TMT screening, only two of 1,750 blood samples collected were positive for *P. falciparum* by RDT, and none were positive for *P. vivax*. By usPCR, the pre-TMT prevalence of malaria ranged from 0-20.8% (*P. falciparum* 0-10.2% and *P. vivax* prevalence 0-18%). The percent reduction for *P. falciparum* was higher in the TMT than the control villages (92.3% versus 72.7%), however the difference was not statistically significant (p-value, xxxxx). The percent reduction in *P. vivax* is significantly higher in the TMT than the control villages (66.7% versus 10.3%, p-value 0.xx). Data for the 12-month follow-up are pending. Results from regression analysis adjusted for a

various covariates will be presented. We conclude that TMT with DHP and low-dose primaquine to eradicate subclinical malaria was well tolerated. The impact of TMT may be greater for vivax malaria than falciparum, but larger studies are needed to differentiate the impact of TMT from seasonal and other variations in prevalence.

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AEDES ALBOPICTUS AT ALTITUDE: WHAT COST FOR CHIKUNGUNYA AND DENGUE TRANSMISSION?

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The spectacular colonization of Europe by *Aedes albopictus* is testimony to its high physiological and ecological plasticity; the species is now present in 27 countries from Spain to Romania and is moving rapidly northward. Although its presence is frequently attributed to importations of used tires in Italy-first detection in 1991-it was already present in Albania in the 1970s. An outbreak of nearly 300 cases of chikungunya in Italy in 2007 and subsequent sporadic autochthonous cases of dengue and chikungunya in other countries confirm the public health significance of the invading species. The strains of the mosquito established in Europe have a marked winter diapause and cold-hardiness, strong evidence that they originated in temperate Asia. If temperature is the limiting factor in its geographic range it could become established as far north as Scandinavia. The critical question is how far north transmission could occur. In this context, the Albanian infestation is of interest because the species is present in isolated mountain villages to at least 1209 m; this allows us to use altitude as a proxy for latitude. We collected eggs at 149, 542, 762 and 1209 m during the summer of 2014 and reared them to F_4 generation. Mosquitoes were orally infected with DENV (serotype 2) and CHIKV (East-Central-South African genotype) at 10^7 FFU/mL and maintained at 28°C, 20°C as well as on a daily cycle of Tmin=15°C and Tmax=25°C. Dissemination and transmission rates were assessed on days 3, 7, 10, 14 and 21 post-infection. We found that titers of CHIKV in saliva compatible with high transmission rates were attained on days 7 and day 10 at 28°C and 20°C respectively. Interestingly, transmission rates for low-altitude strains were higher at 28°C than at 20°C whereas populations collected at high altitude had higher transmission rates at 20°C. By contrast, although all populations became infective with DENV at 28°C, no infection occurred at 20°C. Mean temperatures of 20°C and above are normal for several months in much of Europe. We conclude that if temperature is the key environmental factor limiting transmission, then CHIKV, but not DENV is feasible in much of Europe.

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ASSESSING THE POTENTIAL RISK FACTORS ASSOCIATED WITH NODDING SYNDROME IN NORTHERN UGANDA

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Nodding Syndrome (NS) is a neurological disease of unknown etiology primarily affecting children between the ages of 5 and 15 in a few districts in northern Uganda. NS has been classified as a form of atonic epilepsy and symptoms include uncontrolled head nodding, stunted growth and intellectual disability. Not only does NS cause debilitating symptoms in those affected, but also provokes stigma and unrest throughout affected communities. Although the etiology is unknown, some studies show an association between NS and onchocerciasis, and propose that the vector carrying the causative agent of NS is the *Simulium* spp. black flies. This project aimed to support the hypothesis of *Simulium* spp. as the vector for NS by exploring the prevalence of these black flies in areas affected by NS, and through the creation of a spatial map of potential risk factors. This goal was achieved through two specific objectives. The two objectives of this project were: 1) to better understand and spatially map possible Nodding Syndrome risk factors through household assessments and surveys, and 2) to determine density and distribution through collection and identification of *Simulium* spp. black flies as well as screening of a subset for potential NS pathogens. Demographic and characteristic data was collected from area households both with and without the known presence of a NS case. Black flies were collected, classified, and screened for pathogens. The *Simulium* spp. densities, statistically significant data obtained from the households, and remotely sensed data was mapped atop NS case prevalence data in order to visualize possible patterns and associations of risk factors of the disease. It is our hope that this research will contribute to alleviating suffering in the communities affected by Nodding Syndrome over time by increasing knowledge on this disease and its hypothesized vector.

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ACHIEVING THE VISCERAL *LEISHMANIA*SIS ELIMINATION TARGET IN INDIA WITH EFFECTIVE VECTOR MONITORING

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Visceral leishmaniasis (VL) is a vector-borne neglected tropical disease of public health importance in Bihar and is transmitted by the bite of an infected *Phlebotomus argentipes* sand fly. Since the inception of the VL elimination programme in 1934, indoor residual spraying (IRS) has been conducted with dichlorodiphenyltrichloroethane (DDT) 50% wettable powder (WP). In 2015, in response to evidence showing a rapid decline in *Ph. argentipes* susceptibility, the elimination programme switched to pyrethroid class insecticide, alpha-cypermethrin 5% WP. Entomological monitoring is crucial to ensure insecticide efficacy during the transmission season. Surveys conducted to determine susceptibility status of F1 and field caught *Ph. argentipes* from Bihar showed 100% corrected mortality rates when exposed to 0.1% alpha-cypermethrin and 0.05% deltamethrin. Reduced corrected mortality rates were observed when field caught sand flies were exposed to 0.05% alpha-cypermethrin (87.5-100%) and 4% DDT (24.6-37.5%). To assess the intensity of DDT resistance, CDC bottle bioassays were conducted using F1 *Ph. argentipes*. After 45 minutes of exposure at the diagnostic dose (100µg/bottle) 30% of sand flies were killed and 69% at 10x the diagnostic dose. Mortality breaching the 98% WHO limit for susceptibility was only found at 10x the diagnostic dose after 75 minutes and 5x the diagnostic dose after 150 minutes, demonstrating the intensity of resistance. The efficacy of IRS was assessed by a two stage testing process treating tiles and then artificial walls made of three of the most common surfaces in Bihar (mud, brick and limewash), with either DDT or alpha-cypermethrin. Efficacy of DDT on F1 *Ph.argentipes* sand flies exposed for 30 minutes, was 13.45-21.97% on tiles treated at 1g/m^2, whilst walls treated with the same dose showed mortality of 35.01-67.50%. Observed mortality on alpha-cypermethrin treated walls was within the acceptable WHO range (81.61-90.91%). Monitoring entomological indicators across Bihar provides early indications of sub-optimal impact and could support the programme in achieving its 2017 elimination target.

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SANDFLY OCCURRENCE, DISTRIBUTION AND DIVERSITY IN *LEISHMANIA* ENDEMIC REGIONS IN KENYA

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Phlebotomine sandflies are the only proven vectors of visceral leishmaniasis (VL) but knowledge of their distribution and diversity in Kenya is partial. Accurate knowledge of this is fundamental to implementation of vector control strategies. We explored the occurrence, distribution and diversity of sandflies in leishmaniasis endemic areas in Kenya. Vector sampling was done from three Counties: Baringo, Nakuru and Marsabit. Leishmanaises hot spots were identified using health facility screening and treatment records. Trapping was done indoors and outdoors around termite mounds, vertisols, sleeping areas, animal sheds and burrows using CDC light traps and sticky papers. Morphological and molecular identification of vector species was done using taxonomic keys and sequencing of the mitochondrial cytochrome c oxidase subunit 1 (COI) gene. Dissected midguts of sandflies suspected to harbor promastigotes were cultured in NNN media overlaid with complete Schneider's media or blood agar. Vector density from each collection site was recorded. 14,000 sandflies were collected: Baringo (52.3%), Nakuru (8.6%), Marsabit (37.2%). Overall 40% were *Phlebotomus martini*. In Baringo, Marigat sub-county, *P. martini* was the only vector trapped while in East Pokot *P. duboscqi* (40%) and *P. martini* (30%) were the most prevalent. In Gilgil (Nakuru), *P. guggiesbergi* (60%) was prevalent, *P. saevus* (6%) and *P. sergenti* (5%) were also identified. In Marsabit, two main vectors were collected, *P. martini* and *P. orientalis*. Outdoor trapping yielded the highest number with *P. martini* , *P. orientalis* and *P. duboscqi* found both indoor and outdoor. 95% of the *P. orientalis* were from acacia dried swampy cracked soils areas while *P. duboscqi* was collected along the river bed. Presence of *P. duboscqi* in East Pokot, here identified for the first time, could indicate the presence of cutaneous leishmaniasis. *Leishmania*sis transmission could be occurring outdoors as many people slept outside. Vector control strategies should target both indoor and outdoor settings. Vector studies add to understanding dynamics of leishmaniases' transmission which is important for disease control.

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EVOLUTION OF *GLOSSINA FUSCIPES* S.L IN HUMAN AFRICAN TRYPANOSOMIASIS *FOCI* - EVIDENCE FOR CRYPTIC SPECIES

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Human African Trypanosomiasis (HAT) or sleeping sickness is a neglected parasitic disease endemic to rural sub Saharan Africa. Gambiense HAT which accounts for more than 95% of all HAT cases has been targeted for elimination by 2030 through the scale up of novel, and highly cost-effective, vector control tools such as 'tiny targets' in combination with drugs. However there are long standing gaps in our understanding of the heterogeneity of HAT transmission and the ecology of tsetse flies (genus *Glossina*). HAT foci have historically remained spatially stable despite the high mobility of both the host and the vector. We hypothesised that some of this spatial heterogeneity in HAT may be driven in part by vector population structure. Information on the evolutionary relationships within and among populations of *G. fuscipes* s.l that accounts for >90% of HAT transmission is limited. We carried out a preliminary study using both mitochondrial (cytochrome oxidase sub unit 1 (CO1), NADH dehydrogenase sub unit 2 (ND2) and 16S ribosomal (16S)) and nuclear (internal transcribed spacer 1 of ribosomal (ITS1)) DNA markers to examine the phylogenetic relationships within *G. fuscipes* s.l in HAT foci in Uganda and the Democratic Republic of Congo, with a particular emphasis on *G. f. fuscipes* and *G. f. quanzensis*. Our results suggest that there is marked interspecific divergence between these two sub-specific forms. Further, in areas where there is a single sub-species we have generated evidence of marked differentiation between sub-populations and even within sampling locations. The public health importance of these preliminary findings is vector diversity may be contributing to the epidemiological complexity of HAT transmission and its control.

1281

SPATIO-TEMPORAL ANALYSIS AND *TRYPANOSOMA CRUZI* (AGENT OF CHAGAS DISEASE) INFECTION PREVALENCE OF CITIZEN-COLLECTED TRIATOMINE VECTORS ACROSS THE SOUTHERN USA

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Due to increased reports of local transmission and widespread media and public interest in Chagas disease in the southern United States, defining the spatial and temporal occurrence of triatomine vectors and their infection with *Trypanosoma cruzi* is critical for public and veterinary health protective measures. Through a citizen science program and field collections from 2013 to 2015, we collected 2,812 kissing bugs from diverse ecological regions in Texas, as well as 66 bugs from 7 additional southern states. The majority of citizen-collected bugs were found in homes, kennels, patios, or other peridomestic settings. Using a combination of morphological and molecular identification, we identified 7 different species of *Triatoma*. Most commonly (97% of adults), triatomines were encountered between May and October. The two most common species, *T. gerstaeckeri* and *T. sanguisuga*, exhibited activity peaks in mid-summer and early fall, respectively. A point pattern analysis revealed unique geographic occurrences of the different *Triatoma* spp., suggesting that suitable habitat varies among the triatomine species. Using real-time PCR to detect *T. cruzi* DNA in bug hindguts, we found an overall *T. cruzi* infection prevalence of 63%. *T. cruzi* infection prevalence varied among triatomine species, ranging from 29% (95% CI: 19-39%) in *T. rubida* to 69% (95% CI: 65-73%) in *T. gerstaeckeri*. Parasite lineages revealed through strain typing were TcI (43%) and TcIV (57%). These results demonstrate wide-spread occurrence of triatomine bugs in Texas, with ubiquitous infection with *T. cruzi* infection of strain types TcI and/or TcIV. However, heterogeneity existed in triatomine species' spatial and temporal occurrence, and infection with different lineages of *T. cruzi*. Consideration of local temporal and spatial heterogeneity of *Triatoma* spp. occurring in Texas will allow targeting of vector control and medical/veterinary outreach initiatives to reduce human and animal vector contact.

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BARCODED LIVE ARTHROPOD SCREENS FOR HIGH THROUGHPUT DISCOVERY OF NOVEL VECTOR CONTROL AGENTS

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To accelerate the search for new vector control agents we have developed a high throughput screening method for phenotypic screens on live arthropods. This new method relies on DNA-barcoding to trace individual insects during experiments. To identify novel mosquitocidal agents, we mixed DNA-barcoded microspheres with a bloodmeal and

test compound prior to membrane feeding of *Anopheles stephensi* on 96-well plates. Each well contained a unique barcode and test specimen. Twenty-four hours post feeding we pooled dead mosquitoes and used PCR amplification and Luminex-based multiplex detection of barcode sequences to identify compounds with mosquitocidal activity. Similarly, the fraction of live mosquitoes was analyzed to assess sampling of every well. Plate feeding was very efficient, with over 90% of fed mosquitoes and minimal cross-feeding between different wells. The barcoding approach reliably detected positive control compounds that were spiked in different wells on the plate. Screening of a chemical library identified a number of compounds with potent adulticidal activity against *Anopheles*. Two of these compounds appeared to have excellent pharmacokinetic properties in Beagle dogs and showed plasma levels well above the IC90 for more than eighty days at well-tolerated doses. These compounds are promising candidates for development of mosquitocidal drugs for human or veterinary use. We explored other barcoded screening modalities and have generated proof of concept for repellent and attractant screens, which lead to an underrepresentation and overrepresentation of sample barcodes, respectively. Using this technique we can screen 96 different test specimens on a single container of mosquitoes, which exceeds the current throughput capacity substantially and will significantly contribute to discovery and optimization of novel vector control agents.

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A RANDOMIZED CONTROLLED TRIAL OF THE NEUROPSYCHOLOGICAL BENEFITS OF COMPUTERIZED COGNITIVE REHABILITATION TRAINING IN UGANDAN CHILDREN SURVIVING SEVERE MALARIA

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We have previously documented persisting neurocognitive deficits from cerebral malaria (CM) and severe malaria anemia (SMA). In this RCT, 150 Ugandan CM/SMA survivors (two years after illness) 5 to 12 yrs old and 150 non-malaria children from their households were randomly assigned to 3 treatment arms. One treatment arm was computerized cognitive rehabilitation training (CCRT) with 9 games for enhancing attention, working memory, and visual-spatial processing in which game difficulty increased with proficiency. The limited CCRT arm was the same only with training cycling through simpler levels of difficulty. Children in the passive control arm received no CCRT. Before and after 24 sessions of training over 8 weeks, and one year following training, children were evaluated with tests previously used to establish persisting neurocognitive deficits for CM/SMA. These were the Kaufman Assessment Battery for Children, 2nd ed. (KABC-2), computerized Tests of Variables of Attention (TOVA), computerized CogState cognitive tests, the Behavior Rating Inventory for Executive Function (BRIEF; caregiver rating), and the Achenbach Child Behavior Checklist (CBCL; caregiver rating). Malaria survivors receiving either full or limited CCRT showed significant improvements (compared to passive controls) on KABC-II Mental Processing Index (MPI; composite of all scales), visual-spatial processing (VSP), and the executive functioning (EF) test of conceptual reasoning; persisting to 1-yr follow-up only for VSP. BRIEF and CBCL behavior measures significantly improved, but not until 1-year post CCRT. Non-malaria children receiving CCRT benefited on KABC-II Story Completion (EF), not persisting to 1-yr follow-up. CogState maze chase (visual-motor tracking/attention), and maze learning improved, and these benefits continued at 1-yr follow-up. We present RCT evidence that CCRT is viable for evaluating and enhancing some domains of cognitive performance in brain-injured children in resource-limited settings. However, additional follow-up CCRT intervention components are needed for extending the long-term benefits for clinical populations.

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ASSESSING THE POTENTIAL TOXICITY HAZARD TO AQUATIC LIFE FROM IMMERSION OF INSECTICIDE-TREATED MOSQUITO NETS DURING FISHING AND WASHING

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The combination of efficacy and a favorable environmental and human health profile has made the pyrethroid insecticides a mainstay of malaria vector control. Pyrethroids are extremely toxic to fish and other aquatic life, but appropriate indoor usage is unlikely to contaminate lakes, rivers, or coastal environments. Long-lasting insecticidal nets (LLINs) were expected to mitigate the potential environmental impacts of bednets by eliminating the need for on-site (re)treatment and thus the possibility of concentrated insecticide dipping solutions ending up in local water bodies. However, LLINs have brought new concerns: enhanced durability makes these nets appealing for misuse as fishing gear. Furthermore, LLINs contain more insecticide than conventional treated nets, but local practices for washing nets - often in a nearby lake or stream - have not changed. We present a rigorous, quantitative assessment of the potential toxicity hazard to aquatic life from LLIN immersion during washing or fishing. Fourteen LLINs currently recommended by the WHO were included in our analysis. We aggregated existing data on insecticide release from nets, physicochemical properties of pyrethroids, and environmental breakdown pathways, as well as on pyrethroid toxicity. A model was built to simulate insecticide release and persistence in the environment following immersion of LLINs. Aggregated data were used to bracket concentrations and environmental transformations for a number of simplified, hypothetical scenarios. The results were compared to toxicity data to determine the potential threat to aquatic organisms. Although limitations in the currently available data precluded a full risk assessment, our results suggested that there is evidence to support concerns that immersion of LLINs could pose a threat to aquatic life, particularly in small water bodies or areas with limited circulation. Aquatic macroinvertebrates may be at greater risk than fish species. This is the first assessment to consider the potential ecotoxicological impacts from LLINs in such quantitative terms, including sorption, net-, and compound-specific interactions.

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EVALUATING THE IMPACT OF THE NATIONAL SCALE-UP OF MALARIA CONTROL INTERVENTIONS IN LIBERIA FROM 2004 TO 2013

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Beginning in 2004, after the civil war, significant investments were made to expand malaria control and prevention in Liberia. To assess these efforts, an impact evaluation was conducted using a pre and post design with a plausibility assessment. Trends in all-cause childhood mortality (ACCM) were analyzed against trends in coverage of malaria control interventions and contextual factors that affect child survival. Data from Demographic and Health Surveys, Malaria Indicator Surveys, and the health information system were used in the evaluation. Household coverage of at least one

insecticide-treated bednet (ITN) rose from 30% in 2007 to 55% in 2013. Increases were observed in ITN use among children under-five (26% to 38%), pregnant women (33% to 37%), and the general population (23% to 32%) from 2009 to 2013 (no previous data available). Coverage of intermittent preventive treatment in pregnancy (two or more doses of sulfadoxine-pyrimethamine), introduced in Liberia in 2005, rose to just under 50% by 2013. Care seeking for children with fever remained stable during the evaluation period (65% in 2007 and 69% in 2013), while diagnostic testing for malaria among children with fever rose from 24% in 2009 to 42% in 2013, and treatment with first-line antimalarials increased from 13% in 2007 to 40% in 2011. ACCM gradually declined during this same period from 109 (95% CI: 99-120) in 2007 to 94 (95% CI: 84-103) deaths per 1,000 live births in 2013; however, this decline was mainly due to a decrease in infant mortality from 71 (95% CI: 62-80) to 54 (95% CI: 46-61) deaths per 1,000 live births as child mortality (mortality between age 1 and 4 years) remained stable during this period (41 and 42 deaths per 1,000 live births in 2007 and 2013, respectively). The evaluation period occurred within an overall environment of improvement in the country post-civil war, where the healthcare system was being rebuilt, GDP was rising, and other improvements in maternal and child health were taking place. The gradual expansion of malaria control interventions may have partially contributed to the decrease in mortality, but other factors also likely contributed to the decline.

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THE RELEVANCE OF OUTDOOR RESTING AND SLEEPING FOR BED NET USE IN THE GAMBIA

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Despite the level of coverage of Long-Lasting Insecticide-treated Nets (LLIN) and Indoor Residual Spraying (IRS) has steadily increased, malaria persists in The Gambia. This persistent transmission offers new challenges for malaria elimination. In order to gain further understanding in the human-vector interaction and its effect on malaria control, a social science study assessed human activity, resting and sleeping behaviour during the evening and at night in rural Gambia. Using a sequential mixed-methods study design, quantitative survey data and the direct observation of bed net use and evening activities (n=201) were complemented with qualitative research. Out of 76.1% respondents who slept under a mosquito net, 57.5% were adequately protected from malaria by the nets. In addition to net availability, net use was affected by sleeping patterns inside and outside the house. Adolescents (57.2% male and 50.2% female) and adults (57.2% male and 51.2% female) often socialize, rest or sleep unprotected outside their houses during the early evenings (18.00-21.00). Of the respondents, 16.4% moved between different resting and sleeping spaces during the evening, potentially leading to higher exposure to malaria. Qualitative data showed that specific subgroups are unlikely to use their bed nets, such as farmers protecting crops, herding cattle, burning charcoal or hunting during the evening. These findings suggest that unprotected resting or sleeping and evening activities might contribute to on-going transmission.

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COST-EFFECTIVENESS OF SEASONAL MALARIA CHEMOPREVENTION IN UPPER WEST REGION OF GHANA

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In Ghana, malaria is endemic and perennial (with significant seasonal variations in the three Northern Regions), accounting for 33% of all deaths among children under-five years, with prevalence rates in children under-five years old ranges from 4% in Greater Accra to 51% in Upper West Region. Ghana adopted the WHO-recommended Seasonal Malaria Chemoprevention strategy with a trial in the Upper West Region in 2015. The objective of this study was to estimate the cost-effectiveness of SMC. Costs were analysed from the provider and societal perspectives and are reported in 2015 USD. Data on resource use (direct and indirect costs) of the SMC intervention were collected from intervention records and a survey in all districts and at the regional level. Additional number of malaria cases and deaths averted by the intervention were estimated based on prevalence data obtained from an SMC effectiveness study in the region. Incremental cost-effectiveness ratios (ICERs) were estimated for the districts and region. Sensitivity analyses were conducted to test the robustness of the ICERs. The total financial cost of the intervention was US$1,142,040.80. The total economic cost was estimated to be US$7.96 million and US$2.66 million from the societal and provider perspectives respectively. The additional number of cases averted additional deaths estimated to be averted by the intervention were 24,881 and 808 respectively. The economic cost per child dosed was US$67.35 from societal perspective and US$22.53 from the provider perspective. The economic cost per additional case averted was US$107.06 from the provider perspective and US$319.96 from the societal perspective. The economic cost per additional child death averted by the intervention was US$3,298.36 from the provider perspective and US$9,858.02 from the societal perspective. The financial cost per the SMC intervention delivered to a child under-five was US$9.66. The ICERs were sensitive to mortality rate used. The SMC intervention is economically beneficial in reducing morbidity and mortality in children under-five years and presents a viable approach to improving under-five health in Ghana.

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EXPANDING THE TOOLBOX: A SYSTEMATIC REVIEW LOOKING AT OLD AND NEW VECTOR CONTROL TOOLS

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To achieve the new global targets for malaria elimination, additional vector control tools (VCTs) are critical to supplement long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS). We conducted a systematic review and expert consultations to identify VCTs with existing or future potential to reduce malaria transmission, to assess their readiness for implementation and to identify gaps in the supporting evidence. In consultation with expert groups, a total of 22 malaria VCTs were identified *a priori*, including larval source management, topical and spatial repellents, attractive toxic baits and endectocide treatment of humans and livestock, among other interventions. Six electronic databases and grey literature sources were searched from 1 January 1980 to 28 September 2015 to identify systematic reviews, Phase I-IV studies and models that assessed

the effect of each VCT on epidemiological and/or entomological outcomes across all age groups in all malaria-endemic settings. Eligible studies were summarized qualitatively and quality and risk of bias assessments undertaken where relevant. Recommendations of the Preferred Reporting Items for Systematic Reviews group were followed. Operational readiness and potential for impact were additionally assessed through consultations with field experts and national malaria control program managers. We will present search results and compare the current availability and quality of evidence (for systematic reviews and Phase III studies) for each VCT, in addition to the findings of the expert consultations on the relative potential of existing and nascent malaria VCTs to contribute to malaria elimination. Identifying VCTs to supplement LLINs and IRS will be central to global malaria elimination and eradication efforts.

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COMMUNITY HEALTH WORKERS' PERCEPTIONS OF AND SATISFACTION WITH THEIR ROLE IN IMPLEMENTING A COMMUNITY CASE MANAGEMENT FOR MALARIA PROGRAM: IMPLICATIONS FOR FEASIBILITY AND SCALE-UP

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Community case management for malaria (CCMm) programs target prompt diagnosis and treatment of the disease in populations with inadequate access to formal health facilities. The World Health Organization recently launched the Rapid Access Expansion Programme to scale-up integrated community case management (iCCM), a strategy which addresses other childhood illnesses in addition to malaria. The feasibility and sustainability of many CCMm and iCCM programs depend largely on community health workers (CHWs) consistently providing high-quality services. We implemented a CCMm program which provides training and support (but no direct compensation) for established CHWs to provide free rapid diagnostic tests for malaria (mRDTs), along with results-conditional coupons redeemable for discounted antimalarials at retail shops. Assessing CHWs' perceptions of and satisfaction with their volunteer role is essential to maintaining high-quality performance, identifying opportunities for program improvement, and demonstrating the potential for replication and scale-up. We therefore surveyed participating CHWs to determine the intrinsic and extrinsic factors that motivate (or conversely, discourage) their sustained involvement in providing CCMm services. Following training, 274 CHWs out of 287 had acceptable performance and were provided with commodities to perform mRDTs. Over the first six months of the program, six CHWs discontinued participation or were not invited to continue participation based on performance. We implemented a structured questionnaire to assess CHWs' perceptions of, and satisfaction with, their CCMm role as well as any perceived externalities of participation on their other activities and responsibilities both within and outside the context of their CHW position. The questionnaire captured diverse aspects of CHWs' perceptions of their role with regards to internal motivation, effectiveness, sustainability, community trust, and logistics. Our findings have implications for the sustainability and scale-up potential of CCMm and iCCM, especially for models dependent on a volunteer workforce.

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DISEASE-SPECIFIC CYTOKINE PROFILES IN PEDIATRIC PATIENTS WITH MALARIAL, HIV, AND SYSTEMIC BACTERIAL INFECTIONS

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We present 680 cytokine profiles of blood drawn from well-characterized pediatric malaria patients in the high-disease-burden environment of Siaya, Kenya. High levels of co-infections were observed in this group, including HIV and bacteremia from non-Typhoidal Salmonella (NTS) and *Staphylococcus* sp. Cytokine profiles were placed into one of nine disease categories, including healthy controls, reflecting the bulk of seriously ill suspected malaria patients accepted into our study at the Siaya County Hospital. Distinct cytokine signatures were identified using LASSO, a model selection algorithm. Bootstrapping of the model selection procedure provided robustness to our answers against artifacts arising from the complexity of our data. Linear models using selected cytokines were able to identify comorbidities as the most important complexity impacting the cytokine profile. We were able to distinguish bacteremia from malaria with ROC areas under curve of 0.98, 0.85, and 0.88 for differentiating mono-infection with NTS, co-infection of NTS with malaria, and mono-infection with Staphylococcus bacteremia, from mono-infection with malaria, respectively. Uninfected controls could be distinguished from the malaria background with an AUC of 0.91. IL-7, IL-8, TNFα, and MIG were the most informative cytokines for distinguishing NTS bacteremia from malaria, while IL-10 and IL-7 were the most able to distinguish Staphylococcal bacteremia from malaria. Progression of malaria to SMA was indicated by high levels of IL-2R and low levels of IP-10, while malaria was distinghished from the healthy controls with IL-2R, IL-10, MIP1b, and RANTES. Additional significant correlations of cytokine profiles with death (IL-8), malnutrition (IL-8, IP-10, TNFα, and IL-15), respiratory distress (Eotaxin and IL-8), high fever (IL-6, IP-10, and IL-10), hemoglobin level (IL-2R, IL-6, and RANTES), age (IL-1b, IL-2R, and Eotaxin), and the reticulocyte production index (RANTES and TNFα), were observed.

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COMPARISON OF THE INCIDENCE OF ACUTE LEPTOSPIROSIS IN THE KILIMANJARO REGION OF TANZANIA BETWEEN 2007-08 AND 2012-14

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The sole report of annual leptospirosis incidence in continental Africa of 75-102 cases per 100,000 population is from a study performed in August 2007 through September 2008 in the Kilimanjaro Region of Tanzania. To evaluate the stability of this estimate over time, we estimated the incidence of acute leptospirosis in Kilimanjaro Region, northern Tanzania for the time period 2012-2014. Cases were identified among febrile patients at two sentinel hospitals in the Kilimanjaro Region. Leptospirosis was diagnosed by serum microscopic agglutination testing using a panel

of 20 serovars belonging to 17 separate serogroups. Serum was taken at enrolment and patients were asked to return 4-6 weeks later to provide convalescent serum. Confirmed cases required a 4-fold rise in titer and probable cases required a single titer of ≥800. Findings from a healthcare utilization survey were used to estimate multipliers to adjust for cases not seen at sentinel hospitals. Among 1,115 patients presenting with fever, 19 (1.7%) had confirmed or probable leptospirosis. Of cases, the predominant reactive serogroups were Australis 8 (42.1%), Sejroe 3 (15.8%), Grippotypphosa 2 (10.5%), Icterohaemorrhagiae 2 (10.5%), Pyrogenes 2 (10.5%), Djasiman 1 (5.3%), and Tarassovi 1 (5.3%). We estimated the annual incidence as 11-18 cases per 100,000 population. We estimated a much lower incidence of acute leptospirosis than previously, with a notable absence of cases due to the previously predominant serogroup Mini. Our findings support the value of multi-year surveillance to understand leptospirosis epidemiology.

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FINE-SCALE GPS TRACKING TO QUANTIFY HUMAN MOVEMENT PATTERNS AND EXPOSURE TO LEPTOSPIROSIS IN THE URBAN SLUM ENVIRONMENT

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Understanding fine-scale movement of individuals is critical for understanding the dynamics of environmentally transmitted diseases, such as leptospirosis, for which the mechanisms underlying proxy associations with environmental sources of contamination are unknown. We recruited male and female participants from an ongoing cohort study in an urban slum community in Brazil with high leptospirosis infection rates (6.3% and 3.4% per year, respectively). We conducted 24 hours of GPS tracking at 30 second intervals, which resulted in data with a fine temporal and spatial resolution. We validated the data with diaries and exit interviews. GPS data were cleaned with a velocity filter and analyzed to estimate activity spaces and time spent in proximity to the household and to transmission sources for leptospirosis. Among the 172 recruited cohort subjects, 130 agreed to participate and 100 wore the GPS for a full 24 hours. Both male and female participants spent the majority of their timepoints near their residence (male mean 81.2%, female mean 85.0% within 50 meters of the home, p = 0.32) and within the slum community (male mean 86.4%, female mean 88.3%, p = 0.58). However, males had a significantly larger activity space during the sampling period than did females (61034m2 vs 42101m2, p = 0.015). The activity space within the urban slum environment was characterized by high density of open sewers, flood-prone regions, and rat activity as ascertained by tracking board studies. In summary, we found that slum residents spend most of their time near their households, indicating that exposures to leptospirosis occur in the environment where they reside. The finding that males visited a larger area within the peridomestic environment may explain the high infection rates observed in this group. GPS tracking therefore is able to delineate fine-scale movement patterns within complex slum environments, provide useful insights into the mechanisms of environmental exposures, and identify opportunities for targeted prevention.

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POSTPARTUM INFECTION AT A UGANDAN REGIONAL REFERRAL HOSPITAL: MICROBIOLOGY AND ANTIMICROBIAL RESISTANCE PATTERNS

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The World Health Organization estimates that puerperal sepsis causes 10% of maternal deaths in Africa, but prospective studies on sepsis incidence, microbiology and outcomes are scant. We performed a prospective cohort study of 4,235 Ugandan women presenting to a regional referral hospital for delivery or postpartum care, measured vital signs after delivery, performed microbiologic evaluation of all febrile and hypothermic women, and followed them until 6 weeks postpartum by phone. Mean age was 24.9 years, 487 (12%) were HIV-1 infected, and 50% had cesarean delivery. Temperature was measured for 4179 (99%); 201 (4.8%) were febrile or hypothermic, and blood and urine samples were collected from 186 (93%). Of these, 58 (31%) had infection confirmed, 52 (90%) of whom were febrile. Five (8.6%) had malaria, 5 (8.6%) had bloodstream infection, 7 (12%) had pyelonephritis, 13 (22%) had catheter-associated urinary tract infection, and 43 (74%) had postpartum endometritis. Postpartum infection incidence did not differ by delivery mode or HIV status. Of 5 bloodstream infections, 3 were Gram-negative rods (GNRs, *S. typhi*, *Acinetobacter*, and *E. coli)*, of which 2 demonstrated extended-spectrum β-lactamase (ESBL) phenotype. Of 7 women with pyelonephritis, 5 associated organisms (71%) were GNRs, all of which (100%) were ESBL phenotype. Of 13 catheter-associated urinary tract infections, 8 organisms (62%) were GNRs (6 *Acinetobacter* spp. and 2 *E. coli*), 7 of which (88%) were ESBL phenotype. Maternal mortality incidence was 0.06% in-hospital and rose to 0.26% by 6 weeks postpartum. Combined stillbirth and neonatal mortality incidence was 4.7% in-hospital, rose to 5.9% by 6 weeks postpartum, and did not differ between women with or without postpartum infection (*P*=0.17 in-hospital, *P*=0.32 at 6 weeks). Here, we demonstrate infection is common among febrile Ugandan women hospitalized for delivery or postpartum care. The microbiology of urine and bloodstream infections is dominated by antibiotic-resistant Gram-negative rods. Increasing availability of microbiology testing to inform appropriate antibiotic use should be a high priority in this setting.

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EMERGING PATHOGENIC BACTERIUM *ELIZABETHKINGIA ANOPHELIS*: DIVERSE MOBILE GENETIC ELEMENTS ARE PRESENT ACROSS STRAINS AROUND THE WORLD

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Genus *Elizabethkingia* was separated from *Chyseobacterium* in 2005, with two member species, *E. meningoseptica*, a notorious pathogen causing meningitis, and *E. miricola*, an isolate obtained from condensation water of Space Station Mir. The third species, *E. anophelis* was originally isolated from the gut of *Anopheles* mosquitoes and described in 2011. In 2013, *E. anophelis* caused human infections were documented in Central Africa, and an outbreak in an intensive-care unit in Singapore was reported. In 2015, evidence came to light that *E. anophelis* infections could be transmitted from mother to infant. In 2016, an *E. anophelis* outbreak occurred in Wisconsin. The genome annotation revealed a large genetic capacity of the antibiotic resistance, defense against oxidative stress and TonB dependent transporters. Those features may contribute

to the virulence and pathogenesis. In this study, we reciprocally compared genomes of mosquito isolates and human isolates in different geographic locations including Central Africa, Singapore, Hong Kong, China and Wisconsin, in an attempt to recognize mobile DNA elements that may provide clues to identify genome signature that is related to pathogenesis. The comparison revealed the presence of variable discrete integrative conjugative elements (ICE) across the isolates. These ICEs contain genes that are involved in pathogenicity functions such as antibiotic resistance and virulence. The ICEs in mosquito isolates were degenerated with missing necessary Tra genes for mobility. Interestingly, a Type II CRISPR cas unit was identified in the pathogenic isolate from Central Africa. The genome comparison provided valuable information for further studies of pathogenesis, ecology and evolution of the species.

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FAILURE OF STRAIN-SPECIFIC IMMUNE INDUCTION TO GROUP A STREPTOCOCCUS MAY UNDERLIE THE EPIDEMIC OF STREPTOCOCCAL PYODERMA: OVERCOMING IMMUNE RESISTANCE THROUGH VACCINATION

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The epidemic of streptococcal pyoderma is responsible for Australia's Indigenous populations suffering the highest rates of rheumatic heart disease worldwide. The cause of the epidemic is poorly understood from an immunological perspective. There are in excess of 200 different strains of group A streptococcus (GAS) based on sequence differences in the M protein and it is known that antibodies to the serotypic amino-terminal segment of the protein can kill organisms *in vitro*. It is assumed that M protein sequence diversity is solely responsible for the prolonged period of time required to develop immunity, with immunity developing to common strains one at a time as a result of individual infections. We used four endemic pyoderma strains of GAS from patients in the Northern Territory to model the acquisition of natural immunity. Surprisingly, infection with one strain led to short-term protection only against a challenge infection with that particular strain. Immunological memory did not develop. Two sequential infections with the same strain were required to induce enduring strain-specific immunity. Sequential infections with different strains resulted in partial short-term immunity and only to the last strain to which the mice had been exposed. Mice exposed to multiple strains, either sequentially or simultaneously, did not develop antibodies to a conserved M protein vaccine peptide, J8, demonstrating that this epitope is cryptic to the immune system. However, in contrast to the lack of strain-specific immunity that follows infection, immunity following vaccination with J8 protects against multiple strains delivered sequentially or as a co-infection. Moreover, vaccine-mediated immunity was maintained following sequential heterologous infections. This study describes a major reason why immunity to GAS pyoderma is so slow to develop, but also shows that vaccination with a conserved peptide vaccine can prevent infections with multiple strains.

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HOUSEHOLD MODELLING OF YAWS DATA INDICATES THAT TARGETING TREATMENT USING CASE FINDING AND CONTACT TRACING MAY BE UNSUCCESSFUL AT ERADICATING THE DISEASE

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Yaws is a painful and disabling infectious disease that causes skin and bone lesions. It is most commonly seen in children in warm, humid tropical areas. Individuals with the disease can be effectively treated with a single dose of oral azithromycin. Yaws is known to be clustered, even within endemic regions, but the spatial epidemiology remains poorly understood. Previous eradication campaigns used either mass treatment with benzathine-penicillin or more targeted treatment of cases and their contacts, depending on the prevalence of clinical disease. As many individuals are latently infected without clinical evidence of disease, this often resulted in failure to adequately treat latently infected individuals, resulting in subsequent rebound in disease incidence and ultimately failure of the eradication programme. The new WHO strategy mandates an initial round of MDA followed either by further MDA or active case finding and treatment of cases and their contacts. Multiple rounds of MDA can be expensive and requires large amounts of antibiotics, which are not currently donated for yaws eradication. We employ a household model to study the transmission of the disease using data collected from a pre-Mass Drug Administration (MDA) survey conducted in the Solomon Islands. We used this model to assess whether targeting cases and their household contacts would be sufficient to interrupt transmission. Our data indicate that a limited number of rounds targeting cases and their household contacts would leave 75% of latently infected individuals untreated, leading to the need for either many more rounds of treatment or a broader treatment strategy to successfully break transmission.

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LONG-TERM EFFECT OF MASS DRUG ADMINISTRATION FOR SCABIES IN FIJI: EXPERIENCE FROM THE SHIFT TRIAL

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Control of scabies based on treatment of individual cases is difficult because of frequent re-infestation. We implemented a community intervention trial of mass drug administration (MDA) for scabies to ascertain the efficacy and safety of two alternative regimens (topical permethrin and oral ivermectin MDA), compared with standard care. We identified three isolated island communities in Fiji and randomly assigned one of the three treatment regimens: ivermectin MDA, permethrin MDA or standard care with permethrin. All participants were sought for re-examination at 12 months, and at 24 months via a 20% sample. The study enrolled 2051 people. At baseline, scabies prevalence was high in all arms (32.1%, 41.7% and 36.6% in the three arms respectively). After one year the prevalence of scabies, previously reported, fell to 1.9% in the ivermectin arm corresponding to a reduction in prevalence of 94%. Scabies prevalence was also reduced to a lesser extent in the two other arms. At two years, scabies prevalence in the ivermectin arm was 3.7%, compared to 13.4% and 15.4% in the other two arms. In conclusion, the effect of MDA, particularly with ivermectin, was long lasting, with very low prevalence maintained even after two years following administration.

The study was the first to compare MDA for scabies with the conventional approach of treating symptomatic cases and contacts, and the first to undertake two year follow up. This strategy is likely to be highly beneficial for communities where this disease is endemic.

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PLAGUE IN MADAGASCAR: LIMITING THE TRANSMISSION BY IMPROVING THE CONTROL OF *XENOPSYLLA CHEOPIS*, THE MAIN FLEA VECTOR OF *YERSINIA PESTIS*

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Madagascar is the second country most affected by plague worldwide, with around one thousand cases per year. The bubonic plague, resulting directly from infected fleas bite, is the more encountered plague form in Madagascar. Insecticide dusting is the method used to control rat fleas during epidemic season. In this study our two mains objectives are: evaluating the current status of flea population's susceptibility to insecticides and improving the methods allowing better control of fleas involved in plague transmission. Primarily, 12 insecticides, clustered in four families: organophosphate, carbamates, organochlorine and pyrethroid, were used to test the resistance level of *Xenopsylla cheopis*, the main plague vector. We found that *X. cheopis* from 30 out to 32 localities was found resistant to deltamethrin, a pyrethroid the first-line insecticide used to control plague during at least one decade. More, deltamethrin resistant fleas were resistant to nearly all tested insecticides, except dieldrin, an organochlorine. Besides, resistance level to each insecticide was different according to flea's origin, complicating the vector plague management. Thus, it becomes crucial to find more targeted approach to fight against rat fleas. One way which worth to be explored is the use of systemic insecticide, by incorporating insecticide in rodents baits. We assessed acute toxicity of fipronil, by contact and by the systemic way, on highly deltamethrin resistant fleas. No resistance to this compound was noticed at 0.05% when applied to fleas by contact, with 100% mortality. However, the toxicity against fleas was 90 fold higher when mixed to Rattus rattus and R. norvegicus baits. The use of systemic insecticide as a method for controlling vectors of *Y. pestis* has many benefits compared with insecticide dusting, by targeting rat fleas directly on their host, then reducing the cost and the amount of insecticide spilled in the environment.

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SOURCE OF HOST BLOOD AFFECTS LOCALIZATION OF THE BLOOD MEAL AND INFECTION PREVALENCE OF *YERSINIA PESTIS* IN THE FLEA VECTOR

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Flea-borne transmission of *Yersinia pestis,* the etiologic agent of plague, can occur during the first four days of infection by an unknown mechanism termed early-phase transmission (EPT). One week or later post-infection, *Y. pestis* is transmitted by the biofilm-dependent regurgitation mechanism. In laboratory studies of flea vector competence, infection rates and transmission efficiencies vary considerably between flea species as well as among conspecifics from different studies. One variable that may explain this variation is the species of animal blood used in the infectious blood meal. To investigate the effect of host blood source on flea vector competence, we determined the infection prevalence in groups of *Xenopsylla cheopis* rat fleas one day after they had fed on mouse, rat, or sheep blood containing equivalent concentrations of *Y. pestis*. In addition, we examined the flea digestive tract to determine the localization pattern of recently ingested blood. Consistent with previous studies, fleas fed on infected rodent blood had high infection rates (85-100%). In contrast, most fleas that fed on sheep blood cleared the infection (10-20% infection rate) within one day. Interestingly, 15-30% of fleas that fed on infected rat blood were observed to have blood in the esophagus (BIE), in addition to the midgut, within 24 hours after an infectious bloodmeal. In contrast, little to no BIE (≤1%) was observed in fleas that fed on sterile blood or fleas that fed on infected mouse or sheep blood. Upon feeding again, within three days of infection, a subset of fleas with BIE retained a combination of older blood and the developing mass of plague bacilli in the esophagus which appeared to obstruct passage of the most recent blood meal. Our results indicate that the source of host blood influences the likelihood that a flea will become persistently infected with *Y. pestis*. In addition, the presence of rat blood and bacteria in the flea foregut may impede feeding sufficiently to influence the efficiency of EPT and is suggestive of a regurgitative mechanism for this type of transmission.

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VECTOR COMPETENCY OF TICK-BORNE RELAPSING FEVER SPIROCHETES

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Tick-borne relapsing fever (RF) spirochetes are globally distributed pathogens that cause significant morbidity and mortality if left untreated. Most species are primarily transmitted by argasid ticks in the genus *Ornithodoros*. A defining characteristic between *Ornithodoros* species and RF spirochetes is vector specificity, where a given species of tick only transmits a specific species of spirochete. We have developed the *Borrelia turicatae-Ornithodoros* turicata model of RF spirochetes. The vector is distributed in the southern United States into Latin America. In the United States there is a western population of *O. turicata* ranging from California to Texas, a gap through Louisiana, Mississippi, and Alabama where the tick has not been identified, and an isolated eastern population in Florida. This eastern population has previously been designated a subspecies, *O. turicata americanus*. A current gap in knowledge is vector competency between western and eastern populations of *O. turicata* for geographic isolates of *B. turicatae*. In this study we established uninfected tick colonies of *O. turicata* that originated in Floirda, Texas, and Kansas. Vector competency and transmission studies were performed with the Oz (Ozona, Texas) and Florida canine *Borrelia* (Sumter County, Florida) isolates of *B. turicatae*. Furthermore, with salivary gland colonization essential for transmission of RF spirochetes, the tissues from each group of tick were assessed for infection by *B. turicatae* isolates. Our results indicate significant differences in the ability of Florida, Texas, and Kansas ticks to maintain and subsequently transmit geographically distinct *B. turicatae* isolates.

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RETROTRANSPOSON-TARGETED BLOODMEAL REMNANT IDENTIFICATION IDENTIFIES MEADOW VOLES AS THE MAIN HOST FOR SUBADULT DOG TICKS

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Martha's Vineyard, MA has continuously sustained endemic transmission of *Francisella tularensis* for over 15 years. Our study site comprises a stable natural focus that depends on dog ticks (*Dermacentor variabilis*). However, efforts to identify the *F. tularensis* reservoir have been hindered by low trap success and failure to detect evidence of infection from any sampled animals. It is likely that most infected hosts die rapidly of infection and are thus less likely to be trapped. We have previously reported on results of bloodmeal remnant identification analyses to determine which animals serve as the major host for subadult dog ticks in our site and thereby incriminate a potential reservoir. Assays described in the literature fail to amplify more than half of sampled ticks; we find them to be poorly sensitive, unreliable and difficult to reproduce. We report on an assay with greater sensitivity and reproducibility that will work with all ticks regardless

of extraction method. Retrotransposons integrate into genomes and replicate themselves; 40% of a mammalian genome can be made up of such "junk DNA", yielding more than a thousand copies of any particular one. In addition, retrotransposons have ancient origins and have coevolved with different families of mammals making it possible to design host-specific PCR primers. Accordingly, we designed real time retrotransposon PCR primers that can distinguish between the possible host species found on the island: mice, voles, rabbits, shrews, chipmunks/squirrels, deer, rats and raccoon/skunks. Archived dog tick DNA templates from 2006 were screened by real-time PCR, including samples that had previously failed to yield host bloodmeal remnant identification using existing protocols. Of the 137 ticks tested, all amplified with at least one set of primers. The majority of ticks, 75% (103) tested positive for vole DNA, 13% (18) for mouse, 10% (14) for deer, and 2 samples had multiple positives results. We conclude that voles are the primary host for immature dog ticks on Martha's Vineyard and likely critical hosts for the maintenance of *F. tularensis*.

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UPREGULATION OF SPHERICAL BODY PROTEIN 2 COPY 11 IN *BABESIA BOVIS* IS A SIGNATURE OF ATTENUATION

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Babesia bovis is the causative agent of bovine babesiosis, a tick-borne hemoparasitic disease that affects more than 500 million cattle annually worldwide. Currently, the only effective strategy to alleviate economic losses caused by this disease is the use of a live, attenuated vaccine which has some inherent risks. Better understanding of how attenuation is acquired and the identification of factors expressed in the vaccine strains that contribute to protective immunity, are essential for vaccine improvement. Our long-term goal is to understand the biological processes behind virulence loss and acquisition in *Babesia* so that a safe and effective subunit vaccine, incorporating all the necessary attenuation components can be developed. Our published work comparing genomes of three geographically distinct virulent parental and attenuated strain pairs illustrated no changes at the shared coding level among the phenotypic strains although all attenuated derivatives consist of significantly reduced genomic diversity. Our subsequent transcriptomic investigation of two of the strain pairs revealed that spherical body protein 2 truncated copy 11 (*sbp2t11*) transcript was differentially regulated. Thus, we hypothesized that *sbp2t11* is a *B. bovis* attenuation marker. Using additional virulent and attenuated strain pairs, we confirmed that *sbp2t11* is translated and that expression of SBP2t11 is significantly higher in the attenuated strains. Further analysis of SBP2t11 demonstrated proteolytic processing of the full length 30 kDa protein into a 17 KDa carboxyl terminal-derived fragment via a PEXEL-like domain, a cleave signal shared with *Plasmodium*, *Toxoplasma*, *Cryptosporidium* but not *Theileria*. To determine if upregulation of *sbp2t11* directly contributes to the attenuated phenotype, stable transfected virulent *B. bovis* over expressing *sbp2t11* was successfully generated. Ongoing *in vivo* experiments will determine if *sbp2t11* upregulation in virulent *B. bovis* recovers the attenuated phenotype.

1303

LARGE-SCALE DRUG SCREENING AGAINST *BABESIA DIVERGENS* PARASITE USING A FLUORESCENCE-BASED HIGH-THROUGHPUT SCREENING ASSAY

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Babesia divergens causes a serious infection in both humans and cattle in Europe. A severe *B. divergens* infection is a rapidly fatal disease showing clinical symptoms such as fever, malaise, hemolytic anemia, and end fatally with general organ failure 4–7 days after hemoglobinuria. Chloroquine was the initial pharmacologic agent thought to be effective against *B. divergens*. Diminazene aceturate, an antiprotozoal compound known to be effective in veterinary cases, failed to cure a patient with a severe *B. divergens* infection. Recently, antibabesial drugs commonly used in veterinary medicine have shown problems regarding parasitic resistance and toxicity to the host. Thus, the search for novel alternative compounds for the veterinary market is urgent. In this study, the validation of a fluorescence-based high-throughput screening (HTS) assay for determining the efficacies of large chemical libraries against *B. divergens* (bovine strain) in *in vitro* cultures is evaluated. Hematocrits (HCTs) of 2.5%, 5%, and 10% were used for the *in vitro* culture at 1% parasitemia without daily replacement of the medium. Linearity and HTS assay results revealed that the best HCTs were 5% and 10%. The obtained IC_{50} values of diminazene aceturate, either by fluorescence-based HTS assay with and without daily replacement of medium or by fluorescence- and microscopy-based methods, did not differ significantly at 5% HCT. Actinonin was the most effective drug against the *in vitro* growth of *B. divergens*, followed by diminazene aceturate and then chloroquine diphosphate, while moderate activity was observed with pyronaridine tetraphosphate- and luteolin-treated cultures. On the contrary, tetracycline hydrochloride and (-)-epigallocatechin-3-gallate from green tea exhibited poor activity as compared with diminazene aceturate (positive control drug). The data indicated that 5% HCT without daily replacement of the culture medium mixed with bovine serum *in vitro* using a fluorescence-based HTS assay creates the best conditions for large-scale drug screening against *B. divergens* that infect cattle.

1304

EVALUATION OF INHIBITORS OF *LEISHMANIA* PARASITOPHOROUS VACUOLE DEVELOPMENT

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Leishmania parasites are able to evade host immune responses during infection by residing within parasitophorous vacuoles (PVs), which are specialized phagocytic compartments formed within phagocytic immune cells during *Leishmania* infection. Our lab has previously shown that PVs contain molecules from both the secretory and endocytic pathways that are actively recruited by live parasites during infection. Disruption of this recruitment through the knockdown of secretory pathway vesicle fusion molecules such as Sec22b and Syntaxin-5 (Stx5) reduced the size of PVs that harbored *L. mexicana* parasites and inhibited parasite growth within Raw264.7 macrophages. In follow up studies we showed that Retro-2, a member of a novel class of small retrograde inhibitor molecules, specifically inhibits Stx5 localization, which results in reduced PV sizes and parasite numbers during *L. mexicana* infections. Moreover, Retro-2 reduced mouse foot pad lesions and parasite burden during *in vivo* infections of Balb/C mice. In addition, Retro-2 had a direct inhibitory effect on parasite replication in axenic culture. The purpose of this study

was to determine if secondary derivatives of Retro-2 are more effective at killing parasites and controlling parasite replication in axenic culture and during *in vitro* infections. We have found that the secondary derivative dihydroquinolinone 36 (DHQZ 36), kills L. amazonensis parasites with an IC50 of 10μM, which demonstrates that it is more potent at killing *Leishmania* parasites than the parent drug. In light of the fact that this class of drugs targets the secretory pathway, specifically Stx5 and in light of the fact that *Leishmania* parasites have been shown to have a limited number of secretory pathway SNARE genes, we evaluated the effect of DHQZ 36 on parasite secretion. We will show that prior to killing *Leishmania* parasites, DHQZ 36 limits secretion from by the parasite. This effect on parasite secretion by this new class of molecules has important implications for its function within macrophages where parasite secretion appears to play important roles in the parasite-induced evasion mechanisms.

1305

EVALUATING PKB/AKT AS THE TARGET OF MILTEFOSINE IN *LEISHMANIA* TREATMENT

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Miltefosine is an orally administered drug that is currently used to treat *Leishmania* infections. In light of the fact that some *Leishmania*s exhibit inherent resistance to Miltefosine and that there is increasing concern of the emergence miltefosine-resistant *Leishmania* strains, there is urgency to identify miltefosine's target and the mechanism of miltefosine resistance. Our previous studies had shown that *Leishmania* infection of macrophages induces sustained activation of PKB/AKT, a downstream kinase in the PI3K signaling pathway. In light of the fact that miltefosine was originally shown to target PKB/AKT in tumor cells we set out to test the hypothesis that PKB/AKT is the target of miltefosine in *Leishmania* infections. To evaluate whether PKB/AKT is the target of miltefosine, we have generated macrophages that express inducible shRNAs specific for AKT1 by transduction of a single lentivirus vector constructed to express oligos that target the AKT1 gene. Control cells expressing either the lentivirus alone or lentiviruses expressing PGK were generated as well. After infecting with *Leishmania* parasites, suppression of PKB/AKT levels was induced by adding doxycycline which induced shAKT1 production. Even prior to adding Miltefosine, reduction of PKB/AKT levels in cells resulted in death of 40% of parasites within infected cells. Remarkably, Miltefosine even at relatively high concentrations was unable to reduce the number of parasites further. To further assess PKB/AKT as a target for killing *Leishmania* parasites, we evaluated other specific inhibitors of PKB/AKT. Cells in which the AKT1 specific shRNA was induced were refractory to killing by the specific inhibitors of PKB/AKT. These parasites could be killed with paramomycin, whose mechanism of action is known not to include PKB/AKT signaling. Taken together, these results implicate PKB/AKT as the target of miltefosine. We are presently evaluating whether the capacity to induce activation of PKB/AKT by *Leishmania* parasites correlates with their relative resistance or susceptibility to miltefosine.

1306

THE COMPOSITION OF MICROVESICLES DERIVED FROM *LEISHMANIA DONOVANI* INFECTED MACROPHAGES PROVIDES PERSPECTIVES INTO THEIR BIOGENESIS AND CONTRIBUTIONS TO PARASITE PATHOGENESIS

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Extracellular microvesicles have emerged as important mediators of cell-to-cell communication and have been shown to contribute to the pathogenesis of microorganisms. To better understand the properties of extracellular vesicles produced by *Leishmania donovani* infected macrophages, we performed comparative proteomics of microvesicles derived from RAW 264.7 mouse macrophages uninfected or infected with *L. donovani*. We have obtained a preliminary profile of the host and parasite derived proteins in the microvesicles released from infected and uninfected macrophages. In addition to host cell derived molecules previously identified by others in exosome preparations, we have observed in microvesicle preparations obtained from infected cell cultures significant representation of the exocyst complex component 3 (Exoc3), which has been implicated as a mediator of the release of some microvesicles. In additional analyses we have compared the proteomic profiles obtained from these experiments with recently published studies of the composition of exosomes released by axenically cultured *L. donovani*. The putative 40S ribosomal protein S3a and RPL3 found in exosomes from axenically grown parasites were not found in the microvesicles from *Leishmania*-infected macrophages. Conversely, a putative condensin subunit 1, phosphatidylinositol 3-kinase, and signal recognition particle molecules were found in microvesicles from *Leishmania*-infected macrophages but were not found in exosomes from axenically grown parasites. To confirm the identification of *Leishmania* derived molecules, comparable preparations were obtained from infections with parasites that lack the centrin gene, making these parasites unable to mature into the intracellular amastigote form. Our results show a significant diminution of the parasite derived molecules from macrophages derived from centrin knockouts. Taken together, we will present a comprehensive molecular profile of the molecules released in extracellular microvesicles from *L. donovani*-infected macrophages. Insight in the mechanism of their biogenesis will be presented as well.

1307

CHARACTERIZATION OF THE TRYPANOSOMATID SECONDARY ALTERNATIVE OXIDASE - A NOVEL POTENTIAL DRUG TARGET

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Kinetoplastid parasites of the *Trypanosoma* and *Leishmania* genera cause widespread disease and death in much of the developing world. Current treatments are outdated, increasingly ineffective and associated with severe adverse effects, and new therapies are urgently needed. One of the limiting factors in the drug discovery pipeline is the identification of useful drug targets. The trypanosome alternative oxidase (TAO) has been well characterized as a drug target in *T. brucei*, but is absent from *T. cruzi* and *Leishmania* spp. Here we report evidence of a previously uninvestigated secondary alternative oxidase (AOX2) that is expressed in all three parasites, but importantly has no mammalian ortholog, making it an attractive drug target. Using reverse genetics we have shown that AOX2 is an essential protein in *L. major*, *T. cruzi* and bloodstream form *T. brucei*. By overexpressing AOX2 *in vivo* we have confirmed the subcellular localization of AOX2 to be mitochondrial, as it is for TAO in *T. brucei*. We are examining the effects of AOX2 overexpression/underexpression on cell growth and mitochondrial respiration in *T. brucei* and *T. cruzi* to determine the role of this protein in these parasites. We have established optimal conditions for recombinant expression of the *T. brucei*, *T. cruzi* and *L. major* AOX2 in *E. coli*. We have solubilized and purified all three AOX2s allowing enzyme activity studies. We are screening for selective inhibitors of these AOX2s using our in-house natural product-like library and a fragment library to identify lead compounds. Therefore we are genetically and chemically validating AOX2 in trypanosomatids.

1308

UNDERSTANDING THE ROLE OF *LEISHMANIA* RNA VIRUS-1 (LRV-1) IN THE PATHOGENESIS OF AMERICAN TEGUMENTARY *LEISHMANIA*SIS USING A HUMAN MACROPHAGE MODEL

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Leishmania RNA virus-1 (LRV-1) is a double stranded RNA virus primarily identified in the *Leishmania Viannia* complex endemic to Latin America. LRV-1 has been documented in 20-25% of *Leishmania Viannia* guyanensis and *L. V. braziliensis* strains, known to progress to mucocutaneous leishmaniasis, found in Brazil and Peru, and has been been correlated to increased levels of proinflammatory cytokines and chemokines. Our objective was to compare biomarker expression in human macrophages infected with LRV1-positive or negative strains of *Leishmania*. Human monocytes (U937) were transformed to macrophages over 72 hrs at 37 C. Promastigotes of LRV-1 positive (*L. V. guyanensis*, *L. V. braziliensis*) and LRV-1 negative (*L.V. braziliensis*, *L. tropica, L. infantum*) strains of *Leishmania* were inoculated into macrophage cultures, and culture supernatants were obtained at 24-, 48-, and 72-hrs. Proinflammatory markers measured by ELISA at 24-, 48-, and 72-hrs of incubation included IL-1β, IL-4, IL-5, IL-6, IL-12, TNF-α, CXCL10, CCL5, iNOS, and superoxide dismutase (SOD). Virulence factor transcript expression, including Heat Shock Protein 20 (HSP20), HSP70, HSP83, Mannose Phosphate Isomerase (MPI), Cysteine Proteinase B (CPB), zinc-metalloproteinase (GP63) was quantified in by real time RT-PCR. LRV-1 status did not affect expression of TNF-α, CXCL10, or IL-6, however, LRV-1 positive strains had increased CCL5 (p=0.022) and reduced IL-1 (p=0.023) expression at 24- and 48-hours, respectively. SOD expression was reduced in all macrophages infected with *Leishmania* spp. regardless of LRV-1 status. The LRV-1 positive *L. V. braziliensis* strain showed higher levels of HSP20, HSP83 and GP63 expression compared to the LRV-1 negative *L. V. braziliensis* strain with 41-, 14- and 92% increases, respectively. LRV-1 status remains a potential biomarker of disease severity in American tegumentary leishmaniasis. Our observation of varying cytokine, chemokine, and virulence factor expression by LRV1 status suggests that LRV-1 could potentially contribute to the mechanism by which *L. V. braziliensis*, in particular, leads to pathogenicity.

1308

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1309

INVESTIGATING VIRUS PERSISTENCE IN BODY FLUIDS OF EBOLA SURVIVORS IN SIERRA LEONE

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At the start of the West African Ebola epidemic, there was limited evidence on persistence and duration of Ebola virus (EBOV) and viral ribonucleic acid (RNA) in semen or other body fluids of Ebola Virus Disease (EVD) survivors. The Sierra Leone Ebola Virus Persistence Study (VPS) is an observational cohort that aims to assess the presence and duration of EBOV and viral RNA in semen and other body fluids of EVD survivors. A pilot study launched in May 2015, which enrolled 100 male EVD survivors in the Western area, collecting and testing semen biweekly until two consecutive qRT-PCR negative results were obtained. The main study launched in November 2015, enrolling 120 male and 120 female EVD survivors primarily from Western and Port Loko districts. Sweat, saliva, tears, urine, rectal swab, and as appropriate semen or vaginal swab, menstrual blood, and breast milk were collected. Virus isolation was attempted on qRT-PCR positive specimens. Participants from the pilot and main studies received qRT-PCR test results and risk reduction counseling. To date, the longest period of EBOV RNA detected in semen of pilot participants was 406 days post-onset of symptoms. Proportions of participants with qRT-PCR positive semen decreased with increasing time post-onset. Four semen specimens yielded EBOV isolates; the longest period of time post-onset that viable EBOV was detected was 157 days. To date, 84 women and 92 men have enrolled in the main study. For males and females tested at 6 to 19 months post-onset, all body fluids were qRT-PCR negative, with the exception of 15 men who had EBOV RNA detected in semen and a single male participant who had qRT-PCR positive urine detected to 292 days post onset, during which time his semen also tested positive. A female participant enrolled in the study on the day of discharge from an Ebola Treatment Unit had qRT-PCR positive vaginal swab specimens until day 35 post-onset. All other body fluids tested in this woman were negative. These preliminary descriptive results provide valuable information regarding EBOV persistence in EVD survivors long after recovery.

1310

MAPPING ANTIBODY EPITOPES ON THE EBOLA VIRUS ENVELOPE PROTEIN BY SHOTGUN MUTAGENESIS

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To characterize the detailed immune response to Ebola virus (EBOV), we applied high throughput epitope mapping to the EBOV envelope glycoprotein (GP). We used Shotgun Mutagenesis to create a comprehensive alanine scan library comprising 641 single mutations in GP individually arrayed in 384 well plates. GP variants were expressed in human cells and assayed for reactivity with monoclonal antibodies (MAbs) using high-throughput flow cytometry to identify GP residues required for the binding of each MAb. Cocktails of MAbs that target EBOV GP have great promise as therapeutics. However, for ZMapp, the most advanced cocktail, the detailed epitopes are not known. We epitope mapped the ZMapp and related ZMAb and MB-003 cocktails, resolving the amino acid epitopes for all six MAbs in these cocktails and for the standard reference MAb KZ52. We have also epitope mapped over 90 additional MAbs that recognize EBOV GP, including 6 MAbs obtained from a human survivor of Bundibugyo ebolavirus infection, and a MAb, cross-reactive with ebolavirus species, that binds to GP1 head and blocks the interaction of EBOV GP with its endosomal receptor Niemann-Pick C1. Identification of epitope residues for the ZMapp MAbs helps to: distinguish between MAbs that bind competitively in the same GP region but use different epitope residues, explain their reactivity against different EBOV species, predict viral evasion against these MAbs, and design new cocktails of MAbs that may offer improved functional complementarity. Epitope mapping is expanding our understanding of how the immune system recognizes EBOV GP. Correlating MAb epitopes with their neutralizing capabilities is being used to develop anti-EBOV therapeutics and vaccines.

1311

IDENTIFICATION OF HUMAN T CELL EPITOPES IN THE EBOLAVIRUS GLYCOPROTEIN FOLLOWING VACCINATION WITH CHAD3 EBO Z GP AND MVA BN

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Despite research into the immune response to Ebolavirus for several years, no human CD8+ T cell epitopes have been described following either natural infection or vaccination with any of the candidate vaccines. Here we present several novel 9 amino acid-long peptide epitopes in the Zaire Ebolavirus glycoprotein from humans vaccinated with the ChAd3-MVA regime. Primary studies of T cell immunogenicity were performed using IFNγ ELISPOT assays with ten pools of overlapping peptides 13-17 amino acids long on samples from 43 volunteers that had received a priming immunisation of ChAd3 EBO Z GP and a booster immunisation with MVA BN Filo between 3 and 10 weeks later. We then analysed seven pools in detail using individual 15mer peptides to select the most immunodominant sequences in a subset of volunteers. Overlapping 9mer peptides were then synthesised spanning the 18 dominant 15mers in these pools and assayed by ELISPOT in the same samples. The responses to epitopes were further categorised with intracellular cytokine staining to show large production of IFNγ and TNFa in the CD8+ cytotoxic T cell lineage. The epitopes described span the length of the GP protein and were found in both the GP1 and GP2 domains. We also performed HLA typing on these volunteers and demonstrate broad recognition of these epitopes on multiple HLA backgrounds, suggesting that this vaccine is likely to be immunogenic in genetically diverse populations. Analysis of the position of the epitopes within the 3-dimensional structure of the protein is ongoing and will be presented. The novel human T cell epitopes discovered could be utilised for future vaccine development, as well as in further understanding the immune response to the ChAd3-MVA vaccine and EBOV infection.

1312

THE SIERRA LEONE TRIAL TO INTRODUCE A VACCINE AGAINST EBOLA (STRIVE)

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In response to the 2014-16 Ebola epidemic, clinical development of candidate Ebola vaccines was accelerated. By late 2014, Phase 1 studies of candidate vaccines started, and multiple organizations began planning phase 2/3 studies with collaborators in the most heavily Ebola-affected countries. The US Centers for Disease Control and Prevention sponsored a phase 2/3 vaccine trial In Sierra Leone, in collaboration with the College of Medicine and Allied Health Sciences, University of Sierra Leone and the Ministry of Health and Sanitation. STRIVE was designed as an individually randomized trial for phased introduction of a single 2 x 107 pfu/mL dose of candidate rVSVΔG-ZEBOV-GP vaccine in healthcare and frontline Ebola response workers, while simultaneously evaluating vaccine safety and efficacy. No placebo was used. Participants were randomized to immediate (≤7 days) or delayed (18-24 weeks) vaccination and followed for 6 months after vaccination for serious adverse events (SAE) and Ebola virus disease (EVD). Reactogenicity data were collected through a safety sub-study of the first ~400 participants (200 vaccinated, 200 unvaccinated). An immunogenicity sub-study of ~500 participants assessed IgG levels at baseline, 28 days, 6 months, and 9-12 months after vaccination using a glycoprotein Elisa assay. Enrollment began on April 9th, and vaccination ended December 12th 2015 with ~8,650 participants enrolled and ~8,000 vaccinated. As of 1 April 2016, preliminary data from ongoing safety follow up indicates no vaccine-related deaths or other vaccine-related SAEs; 48 participants were evaluated for EVD and had negative test results. Systemic symptoms more commonly reported in vaccinated safety sub-study participants included headache, fever/feverishness, fatigue, muscle pain and joint pain; few were graded as severe. Ebola response measures successfully interrupted transmission, so vaccine efficacy could not be assessed. STRIVE provides the largest SAE database on this vaccine and will yield critical immunogenicity data to support a vaccine licensure application. Preliminary immunogenicity data will also be presented.

1313

SAFETY, IMMUNOGENICITY, AND EFFICACY OF THE MERCK RVSVΔG-ZEBOV-GP EBOLA VACCINE

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The 2013-2016 Ebola outbreak has caused over 28,000 cases and 11,000 deaths. Merck & Co., Inc. is working with private and public partners to develop an Ebola vaccine that has demonstrated efficacy during this outbreak. The vaccine is a live recombinant vesicular stomatitis virus (VSV) with complete substitution of the VSV-G envelope glycoprotein (GP) with

Zaire ebolavirus GP. Phase 1-3 clinical trials have been conducted to assess safety, immunogenicity, and/or efficacy of rVSVΔG-ZEBOV-GP in humans. One intramuscular dose of $2x10^7$ plaque forming units is well-tolerated when administered to healthy adults. Injection site reactions following vaccination are typically mild or moderate and self-limited. There is a predictable period of generally mild reactogenicity, including fever and a flu-like syndrome typically lasting 1-3 days. Joint pain is a common part of the early flu-like syndrome. In a small proportion of subjects (<5% in most studies), joint swelling (arthritis) may develop in the weeks following vaccination. Arthritis is generally mild to moderate in severity and is likely mediated by direct viral infection of joint tissues; the vast majority of arthritis events resolve spontaneously, though persistent and recurrent symptoms have also been reported. Anti-GP antibodies are detectable by ELISA by 14 days postvaccination in 95% of vaccinees; to date, 100% seroconversion has been observed by 28 days. Durability of the anti-GP response response has also been demonstrated for at least 6 months. A ring vaccination trial in Guinea randomized 7,651 subjects in 90 clusters to receive immediate or delayed vaccination. Interim analysis identified no cases of Ebola virus disease with symptom onset at least 10 days after randomization in the immediate vaccination group, whereas in the delayed vaccination group there were 16 cases of Ebola virus disease (vaccine efficacy 100%, 95% CI: 74.7, 100.0; p=0.0036). No new cases of Ebola virus disease were diagnosed in vaccinees from the immediate or delayed groups from day 6 postvaccination. In this presentation we will provide the current status of the rVSVΔG-ZEBOV-GP development program.

1314

PHASE 1 EVALUATION OF A LIVE ATTENUATED HUMAN PARAINFLUENZA VIRUS TYPE 3 VECTORED VACCINE CANDIDATE EXPRESSING EBOLAVIRUS ZAIRE GLYCOPROTEIN

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The 2013 outbreak of Ebola Virus Disease in West Africa brought into sharp focus the urgent need for safe and effective medical countermeasures. The primary objectives of this open label vaccine clinical trial were to determine the safety, tolerability and immunogenicity of a 2-dose regimen of a live, recombinant parainfluenza virus type 3 expressing the Ebola virus (Zaire) glycoprotein (HPIV3-EbovZ-GP) as a vaccine candidate in healthy adults. Thirty subjects were enrolled sequentially into 2 cohorts of 10 and 20 subjects, respectively. The investigational new drug (IND)-approved protocol plan was for both cohorts to receive 2 doses of the vaccine candidate intranasally 4 to 8 weeks apart as follows: Cohort 1 to receive 10^6 plaque forming units (PFU) of HPIV3-EbovZ-GP vaccine and Cohort 2 to receive 10^7 PFU. During protocol implementation, two doses of 10^6 PFU of HPIV3-EbovZ-GP vaccine were administered to Cohort 1 subjects 4 weeks apart. The vaccine was well tolerated and infectious (7/10 subjects had detectable virus by rRT-PCR with a mean peak titer 3.8 $\log_{10}$ genomic equivalents/mL and 4/10 with vaccine virus on culture.) The viral shedding period was longer than expected with a mean of 7.9 days after vaccination. Little shedding was detected after the second dose. Cohort 2 received one of two planned doses of 10^7 PFU of HPIV3-EbovZ-GP vaccine. Vaccine virus infectiousness in Cohort 2 was similar to Cohort 1 but shorter in duration, with a mean of 3.7 days of shedding. In both Cohorts, the vaccine was well tolerated; the majority of symptoms mild. Asymptomatic ALT elevations were noted in 5 volunteers in Cohort 2 after vaccination: 3 mild elevations, 2 moderate (68-184 U/L). ALT elevations were associated with viral shedding, all had resolved by day 28. The study was halted due to these elevations of ALTs and the volunteers in Cohort 2 were not given the second dose. Expression of Ebola virus GP was stable in the virus shed by volunteers. Little to no detectable neutralizing antibody was induced in the subjects. We conclude that the HPIV3-EbovZ-GP vaccine virus is more infectious but less immunogenic than anticipated with longer viral shedding periods.

1315

SEROPREVALENCE OF FILOVIRUS INFECTION IN VILLAGES WITH NO HISTORY OF OUTBREAK IN THE DEMOCRATIC REPUBLIC OF CONGO

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The Democratic Republic of Congo (DRC) has experienced the most Ebola Virus Disease (EVD) outbreaks on record. While evidence is limited, previous studies suggest that there may be a significant number of cases of Ebola and other viral hemorrhagic fevers (VHFs) that go unreported because they are non-progressing or asymptomatic. In 2007, a population-based survey was conducted to assess human exposure to monkeypox in healthy, rural populations in the Kole and Lomela health zones within the Kasai Oriental province of DRC. Fourteen villages were randomly selected and all healthy individuals ≥1 year of age were eligible. Among the 5,687 individuals eligible for enrollment, 4,574 were enrolled in the original study population, of whom a subset (n=810) were randomly selected for serologic assessment of antibody response to Ebola (EBOV) and Marburg (MARV) viruses. In this preliminary study, nearly all subjects (>99%) were from Lomela health zone. Overall, 7% of subjects tested positive for EBOV in either neutralizing assay (confirmed with titration assay), viral matrix protein (VP40) ELISA or nucleoprotein (NP) ELISA, while 2% tested positive for MARV in either neutralizing assay (confirmed with titration assay) or nucleoprotein (NP) ELISA. Prevalence of filovirus antibody varied slightly by age; specifically 1-4 year olds had the highest prevalence for both EBOV and MARV (11% and 3%, respectively). Additionally, seropositivity was significantly associated with gender; EBOV seropositivity was higher in males than females (5% and 9%, respectively), while MARV seropositivity was higher in females than males (3% and 1%, respectively). While analyses are preliminary, we found evidence of infection in vulnerable subgroups of the population in non-outbreak locations in the DRC. Such sero-surveillance studies are of paramount importance as they may provide key information about asymptomatic or non-progressing infections that can better prepare health care workers and policy makers for future outbreaks.

1316

IMMUNOASSAYS FOR CHARACTERIZING AND EVALUATING VACCINE CANDIDATES THAT TARGET PRE-ERYTHROCYTIC STAGES OF *PLASMODIUM VIVAX* AND *P. FALCIPARUM*

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Evaluating pre-erythrocytic (PE) vaccine candidates is challenging due to the biological complexity of *Plasmodium* parasites and their host interactions. In particular, identifying and characterizing new PE vaccine candidates has been hampered by the inefficiency of functional assays to assess targets in the PE stages of *P. vivax* and *P. falciparum*. To overcome this obstacle, we developed novel functional assays to immunologically assess potential PE targets of *Plasmodium* sporozoites and early liver stages. The functional assays recapitulate the pivotal period of sporozoite transition from mosquito to human by physical modification of the *in vitro* culture microenvironment and exposure to biological stimulatory factors. In this study, liver-stage development was assessed by sporozoite inoculation into an *in vitro* human liver model platform where high content image analysis was used to quantify parasite invasion and initial development in primary human hepatocytes. As proof of concept for assessing PE vaccine candidates, inhibition of liver-stage development assays (ILSDA) targeted the *P. vivax* and *P. falciparum* circumsporozoite (CSP) protein with species-specific, anti-CSP monoclonal antibodies. The modified ILSDA was sensitive and efficient, showing blocking of early PE stages of both *P. vivax* and *P. falciparum* in a concentration-dependent manner. Further ILSDA experiments were conducted with a second target antigen, which showed nanomolar activity with 80% inhibition of liver-stage development.
To refine functional analysis of PE targets in early infection phases, we analyzed sporozoite migration in real-time in a 'live' motility assay and a hepatocyte cell traversal assay, and also by high-content imaging. Finally, micro-pillar arrays were designed for real-time study of sporozoite migration and mechanical flexibility in a structured microenvironment mimicking *in vivo* conditions. Together, these novel functional assays simulate key development and transition phases that enable us to evaluate potential PE vaccine candidates and analyze complex *Plasmodium* sporozoite phenotypes.

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GAMETOCYTE-SPECIFIC IMMUNITY PROVIDES A RATIONALE FOR NOVEL TRANSMISSION BLOCKING INTERVENTIONS IN *PLASMODIUM FALCIPARUM*

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Drugs and vaccines targeting *Plasmodium falciparum* transmission stages have recently gained prominence as necessary tools for malaria elimination. Though most current transmission-blocking approaches focus on mosquito stages, targeting gametocytes - the form developing in the human host - provides a more convenient endpoint for validation, and has tremendous potential to reduce global transmission of malaria. Antibodies recognizing immature (stage I-IV) gametocytes could confer protection by 1) inhibiting binding interactions between specific host receptors and adhesins on the surface of infected red blood cells (iRBCs), 2) increasing killing by effector cells, and/or 3) inducing uptake by other immune cells. Hypothesizing that early-stage gametocytes are targets of host antibody responses, we performed the first systematic characterization of immune responses recognizing these stages. Utilizing a gametocyte-enriched protein array, we identified a subset of exported parasite antigens whose reactivity correlates with exposure and/or reduced parasite burden. We next characterized recognition of the gametocyte-iRBC (giRBC) surface in a cohort of Malawian sera by flow cytometry. A subset of sera recognize both giRBCs and asexual-iRBCs (aiRBCs) while others uniquely recognize giRBCs. The strength and prevalence of both aiRBC and giRBC surface recognition increase with age, though this increase occurs more slowly for gametocytes. Immunofluorescence microscopy confirms that early (stage I-IIA) gametocytes are recognized more than later gametocytes, and Western blots using giRBC and aiRBC membranes provide evidence for both shared aiRBC-giRBC and unique giRBC antigens. Candidate antigens have been identified by mass spectrometry and their surface expression is being validated through various methodologies. We are also investigating various mechanisms of antibody-mediated protection, including opsonization for phagocytosis, and inhibition of binding to host receptors. Our study suggests a new paradigm for transmission stage immunity and provides a rational basis for novel transmission-blocking therapeutics.

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REPEATED MALARIA INFECTIONS ACCELERATES BIOLOGICAL AGEING IN CHILDREN IN DISEASE ENDEMIC AREA

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Accelerated ageing and reduced lifespan mediated through faster telomere shortening has recently been shown in birds chronically infected with malaria parasites. Furthermore, we have found that single malaria infection accelerates telomere degradation for up to three months after cured infection in human. Here, we have analyzed whether multiple malaria episodes accelerate telomere attrition in disease endemic area. Children living in Nyamisati village in the Rufiji river delta, coastal Tanzania were followed with passive case detection and repeated cross-sectional surveys between 1993 and 2010. Parasite prevalence in children declined from 90% in 1993 to 10% in 2010. Telomere length was analysed in peripheral blood by real time quantitative PCR in repeated cross-sectional surveys 1993-2010. Our preliminary findings show that telomere shortening was more pronounced in the children during the 1990s when transmission was moderate to high, compare to between 1999 and 2010

when transmission had declined. Children those were malaria positive in surveys have shorter telomere length and antimalarial antibodies levels were negatively correlated with telomere length, irrespective of age. These findings suggest that repeated malaria infections accelerate telomere shortening and might contribute to biological ageing in human. These results further urge the need for upscaling efforts to eliminate malaria.

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ATYPICAL ACTIVATION OF HUMAN PRIMARY DENDRITIC CELLS BY *PLASMODIUM FALCIPARUM*

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Malaria is characterized by high levels of inflammation and while an early inflammatory response is important for parasite clearance, excessive and persistent inflammation can contribute to severe forms of the disease. At the same time, *P. falciparum* infections fail to induce sterile immunity. Reports about the role of dendritic cells (DCs) in the immune response to *P. falciparum* and how they contribute to the activation of $CD4^+$ T cells during blood stage have been contradictory. To analyze this critical part of the malaria immune response we enriched primary human DCs from peripheral blood of naïve donors and co-incubated them with *P. falciparum*-infected red blood cells *in vitro*. Although DCs up-regulated surface expression of HLA-DR, co-stimulatory markers, and secretion of chemokines, they did not secrete significant amounts of inflammatory cytokines. Surprisingly, these parasite-activated DCs were able to activate and polarize naïve autologous $CD4^+$ T cells into Th1-like cells secreting high levels of IFNγ and TNF. A re-stimulation with autologous *P. falciparum*-activated DCs specifically increased proliferation and cytokine secretion of the primed $CD4^+$ T cells, indicating that the DCs were able to induce an antigen-specific response. We further analyzed the activation phenotype of the two major DC subsets, myeloid and plasmacytoid DCs, upon stimulation with *P. falciparum*. Co-culture of both subsets was essential to up-regulate parasite-induced chemokine secretion. Although plasmacytoid DCs were activated by the parasite through TLR9 and secreted IFNα, they were dispensable for $CD4^+$ T cell activation. To further address whether this phenotype might involve activation molecules other than MHC class II we analyzed CD1-restricted T cell activation. Preliminary results indicate that a proportion of $CD4^+$ T cells that expand in co-cultures recognize lipids presented by CD1. Our findings might contribute to a better understanding of the mechanisms involved in the initiation of the adaptive immune response against *P. falciparum*.

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ATYPICAL MEMORY B CELLS AND CIRCULATING MARGINAL ZONE-LIKE B CELLS CHANGES ASSOCIATED TO MALARIA CHRONIC EXPOSURE

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Malaria exposure affects circulating B and T cell populations, inducing increased frequency of "atypical" memory B cells (MBCs) and reduced proportion of circulating marginal zone (MZ)-like B cells. Although the role of antibody responses in reducing clinical symptoms is well known, little is known about the role of atypical MBC and MZ-like B cells against malaria infection. We characterized the status and function of B cell subpopulations in a malaria-exposed and unexposed populations and tested the hypothesis that impaired immune response was associated with anergic stage of B cells related to Pf exposure. We selected 45 adults from high malaria transmission area in Papua Nueva Guinea and classified them as high, medium and low exposure based on responses to 8 *Plasmodium falciparum* and *P. vivax* antigens. Peripheral blood mononuclear cells were assayed by flow cytometry to identify expression of activation-, inhibition-, lineage- and survival-associated markers. In exposed individuals, active atypical MBCs (aaMBCs) had high frequency of IgG, PD1, CD95, CCR3 and CD71 and low proportion of CD62L expression. The expression of PD1, CD95 and CD71 on aaMBCs was associated with level of exposure. As a result of chronic antigen exposure, aaMBCs have dual expression of both of CD40-CD95, leading aaMBC to an anergic state and at the same time preventing cell death. We found higher IgG- and PD1-expressing peripheral MZ-like B cells in malaria exposed compared to non-exposed adults. Conversely, TACI expression was greatly reduced in exposed individuals. Our findings suggest that in chronically exposed adults, the expression of PD1, CCR3 and CD95 on aaMBCs could be the result of immune homeostatic mechanisim for mantaining B cell development and function while simultaneously inhibiting hyper-reactive B cells. Thus, keeping B-cell activation threshold high enough to control but impaired enough to tolerate chronic infection. Increased IgG- and PD1- and decreased TACI-expressing MZ-like B cells confirm the role of germinal center-independent responses in chronically exposed individuals, being a potential target for reversion in anti-malarial therapies.

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KENYAN CHILDREN AND ADULTS WITH ACUTE UNCOMPLICATED MALARIA HAVE DYSFUNCTIONAL MEMORY B CELL RECALL RESPONSES TO POLYCLONAL STIMULATION

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The development of acquired immunity to *Plasmodium falciparum* (Pf) is not fully understood. It takes years of repeated exposure to Pf before immunity to clinical disease develops, implying that B cell memory is impaired and incomplete. B cells are a heterogeneous cell population, consisting of subtypes differentiated by their surface markers (naïve B cells $CD19^+CD21^+CD27^-$, classical memory B cells (MBC) $CD19^+CD21^+CD27^+$, activated B cells $CD19^+CD21^-CD27^+$, and atypical MBC $CD19^+CD21^-CD27^-$). ELISPOT assays were used to measure immunoglobulin (Ig) G secretion in peripheral blood mononuclear cells (PBMC) from Kenyan children aged 1-10 years at presentation of acute uncomplicated malaria and six weeks following treatment. Quantities of antibody secreting cells (ASC) were greatly reduced in children with active malaria, and restored 6 weeks following treatment (average numbers of ASC per 5000 plated PBMC were 6.67 and 52.67, respectively, p=0.0039). We also found that PBMC from an adult with acute malaria showed a similar outcome (4 ASC per 5000 PBMC during acute malaria versus 28 ASC six weeks following treatment). This suggests that there is a deficiency in the MBC recall response during acute illness, regardless of patient age. Flow cytometry was performed on PBMC in order to compare B cell subtype frequencies. Children with acute malaria and at 6 weeks follow-up had very similar frequencies of circulating classical MBC (average frequencies 14.49% and 17.56%, respectively, p=0.0419), which indicates the MBC were present in circulation at the time of acute malaria, though not functioning similarly. Interestingly, activated B cells were not increased at the time of acute malaria (average frequencies 4.98% and 3.42%, respectively, p=0.2663), while the acute cases showed some increase in proportions of atypical MBC during acute malaria versus recovery (average frequencies were 26.53% and 12.3%, respectively, p=0.0007). Future experiments will focus on determining if B cells or T cells play key roles in the lack of IgG secretion during acute malaria.

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CYNOMOLGI MALARIA IN RHESUS MACAQUES INDUCES PHENOTYPIC AND FUNCTIONAL CHANGES IN NEUTROPHILS

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The innate immune system likely plays a key role in *Plasmodium vivax* infection, but studies focusing on its impact have been limited. Neutrophils are the most abundant innate immune subset in blood and serve as a primary defense against microorganisms via phagocytosis, as well as the production and release of inflammatory mediators that amplify immune responses. However, excessive neutrophilic responses can lead to tissue damage and impact subsequent adaptive immune responses negatively. Thus, more detailed study of neutrophilic responses during malaria are warranted. In the context of *P. vivax* infection, previous studies have reported significant neutrophil activation, although more studies are needed to dissect out their diverse and dynamic functions. Here, the rhesus macaque – *P. cynomolgi* model was used as a model for vivax malaria to assess functional changes in neutrophils during infection. Five rhesus were infected with *P. cynomolgi* and their neutrophil function assessed during acute infection using flow cytometry-based assays. Neutrophils became activated based on expression of surface markers such as CD63 during infection, demonstrating a role for this cellular subset during *P. cynomolgi* infection. Additionally, neutrophil caspase-1 activity, measured by the fluorescent substrate FLICA, increased and correlated with an increase in IL-1β in the plasma. By contrast, neutrophils were impaired in both phagocytic ability and reactive oxygen species production during acute infection. Changes in neutrophil function correlated with parasitemia. Following these pilot data, our group is now examining the role of the various circulating neutrophil subsets (e.g., bands, segmented, and hypersegmented) to determine if a relationship exists between the functional changes observed during cynomolgi malaria and the abundance of such subsets. Indeed, humans with vivax malaria display changes in the frequency of neutrophil subsets in the blood during infection, which emphasize the relevance of our *P. cynomolgi* model. Overall, this model will be useful for better understanding neutrophil dynamics and potential functions during malaria.

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SPECTRUM-MALARIA: A USER-FRIENDLY PROJECTION TOOL FOR HEALTH IMPACT ASSESSMENT AND STRATEGIC PLANNING FOR MALARIA PROGRAMS IN SUB-SAHARAN AFRICA

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The Spectrum suite of policy planning models is used by over 120 countries to support estimation of burdens, trends, service needs and program impact. We developed the Spectrum-Malaria module, that projects impact of malaria interventions on case incidence and deaths in 0-4 year, 5-14 year and 15+ year olds, and falciparum infection prevalence (PfPR) among children 2-9 years, based on user-specified targets for people sleeping under insecticide-treated nets (ITNs), people protected by indoor residual spraying (IRS), children 6-59 months old receiving 3 courses of seasonal malaria chemoprophylaxis, and uncomplicated and severe cases effectively managed. Intervention effectiveness was estimated by generalized linear statistical models that emulate impact drivers as simulated by the dynamic OpenMalaria model. ITN and IRS effectiveness were validated on child health outcomes in 3 ITN trials. Spectrum projects impacts at province level starting from 2015 case, death and coverage levels, PfPR and seasonality estimated by the Malaria Atlas Project and World Health Organization. Pilots for Democratic Republic of the Congo (DRC) and Zambia, Nigeria and Senegal show that intervention scale-up reduces malaria burdens in the three age groups by similar proportions, but most cases and deaths are averted in under-5s. Proportional burden reductions are larger in lower-endemic settings, but numbers of cases and deaths averted for a given coverage increase are larger in higher-endemic settings, within and across countries. For DRC, given high ITN coverage but low effective case management coverage in 2015, case management is the intervention for which scale-up could have most additional impact by 2030 but programmatic inputs and resources to achieve this remain to be assessed by linking to the Spectrum costing module OneHealth Tool. In initial pilots, users appreciated the tool's alignment with monitoring indicators also as used in performance frameworks for program target setting and impact evaluation, and its graphical interface embedded in Spectrum's demographic platform for relatively quick comparison of policy scenarios.

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ASSESSING METHODS FOR ESTIMATING HOUSEHOLD BITING PROPENSITIES, SEASONALITY AND NOISE IN COUNTS OF MALARIA VECTORS

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Heterogeneity in malaria transmission varies with the intensity of transmission and it does not follow a Pareto rule. The distributions instead follow power laws across households or seasons in that the variance S and mean m are related by $S=am^b$. Understanding what drives these power laws and assessing the likely benefits of targeting requires having some quantitative understanding of heterogeneity and its underlying causes. These include seasonality, all the factors that make some households more attractive or easier to enter than others, environmental noise, and measurement error. The study focuses on mosquito counts data from an entomological surveillance conducted between October 2011 and March 2015 for 330 households at three study sites in Uganda and a simulation study investigating pseudo-data with known properties. We evaluate the performance of several statistical methods for partitioning the variance in mosquito biting into household biting propensities, seasonality, and environmental and measurement noise. We consider specific probability models that are capable of handling excess zeros while modeling non-zero counts properly. Seasonal adjustment of the time series data is performed using a range of temporal smoothing techniques, including a Gaussian smoothing kernel for sampling days and several Bayesian prior distributions for the temporally structured random effects. Using a range of model selection criteria, a zero-inflated negative binomial model was found to be robust and well-suited in modeling the mosquito counts across various simulated scenarios and real settings. The choice of the temporal smoothing technique differed slightly for each dataset. The information on household-level biting heterogeneity permits interventions to be targeted towards the locations of households with high malaria risk within them. Once transmission in an area has decreased but is maintained in hotspots of malaria transmission, such targeted interventions are likely to become increasingly important tools in malaria elimination efforts.

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SYSTEMS METABOLIC MODELING REVEALS DIFFERENTIAL NETWORKS PERTURBED AT PRIMARY INFECTION AND RELAPSE, IMPLICATING POTENTIAL BIOMARKERS FOR ACUTE AND CHRONIC MALARIA

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We applied Flux Balance Analysis (FBA) to model stage-specific metabolism of Non-Human Primate (NHP) model animals infected with *Plasmodium cynomolgi* or *P. coatneyi.* We derived genome-scale metabolic models (GEMs) for peripheral blood (PB) and bone marrow (BM), using transcriptomics data as constraints for metabolic fluxes. By bridging transcriptome and *in silico* metabolomics/fluxomics data, we identified key pathways that were perturbed during each stage of the parasite infection, highlighting key host metabolic modules in different tissues responding to parasite invasion. We further interrogated species-specific mechanisms by comparing GEMs constructed for *P. cynomolgi* and *P. coatneyi.* Focusing on purine metabolic pathway discovered by GEMs, we developed Generalized Mass Action (GMA) models to simulate kinetics of purine metabolism in PB and BM in *P. coatneyi* or *P. cynomolgi* infection. Notably, we found non-linear relationships between gene expression and corresponding fluxes. Tissue-specific comparisons showed that RNA metabolism is more active and more tightly regulated in BM compared to PB at primary infection, which is common for both parasites. Importantly, we observed positive correlation between increased fluxes toward hypoxanthine/uric acid and higher parasitemia in *P. coatneyi* infection, whereas in *P.cynomolgi* infection, the same fluxes were shown to be correlated with severity of disease. Strikingly, fluxes toward hypoxanthine and inosine were only shown to be constantly up-regulated across chronic infection in *P. coatneyi* but not in *P. cynomolgi* infection. Furthermore, this work derived a comprehensive map of temporal differential fluxes by longitudinal comparison in both *P. coatneyi* and *P. cynomolgi* infection, providing a resource for characterizing dynamics of purine metabolic pathways perturbed by malarial pathogens. These identified common and distinct fluxes and metabolites provide a paradigm to understand convergent and divergent molecular mechanism of host response to infections by two malaria species. This study showcases the application of metabolic modeling in biomarker discovery.

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JOINT MODELING OF *PLASMODIUM FALCIPARUM* AND *P. VIVAX* INFECTIONS USING A BIVARIATE POISSON LOGNORMAL MODEL

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We utilized a bivariate Poisson lognormal model (BPLM) to estimate a covariate-adjusted association between *Plasmodium falciparum* and *P. vivax* infections and malaria clinical episodes. These two parasites are commonly seen as coinfections in Papua New Guinea (PNG). It is unclear whether they are positively associated with one another, or if one parasite suppresses the other. This was the primary motivation for fitting a BPLM, because it permits estimation of negative correlation, unlike most other multivariate Poisson models. We first simulated data similar to a cohort study that was conducted in PNG and compared two available methods for estimating the parameters of a BPLM. One method was a Bayesian model fit using MCMC methods and the other used adaptive Gaussian quadrature (AGQ) to estimate the model. We then estimated the association between two measures of burden from the PNG data using BPLMs: 1) the count of clinical episodes caused by *P. falciparum* and *P. vivax* parasites and 2) the count of genetically unique *P. falciparum* and *P. vivax* infections over an interval of observation. Our findings suggest that when the means of the two variables are large and exhibit overdispersion, it is possible to get estimates with low bias and correctly estimate the standard errors using either available method. However, when the means and variances are small, the MCMC method tends to produce biased estimates with slightly inflated standard errors and the AGQ method produces slightly biased estimates with extremely large standard errors. When the BPLM was fit to the PNG data, there was a moderate positive association between *P. falciparum* and *P. vivax* infections (correlation from BPLM 0.4, 95% CI [0.1, 0.8]), while adjusting for use of an insecticide treated bednet and age. Although there were higher rates of *P. vivax* infections (15.3 per child per year) in these children compared to *P. falciparum* (5.4 per child per year), there were more clinical episodes caused by *P. falciparum* (1.9 per child per year) than those caused by *P. vivax* (1.6 per child per year) over the entire cohort. We found no indication that *P. vivax* is protective against *P. falciparum* infections.

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PHARMACOKINETICS AND ACCUMULATION OF PIPERAQUINE WHEN USED FOR INTERMITTENT PREVENTIVE TREATMENT IN PREGNANCY (IPTP)

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While pharmacokinetic (PK) studies of dihydroartemisinin-piperaquine (DP) suggest that dose adjustment may not be necessary for treatment of malaria illness in pregnancy, similar data are needed for its use as intermittent preventive treatment in pregnancy (IPTp). We evaluated the PK and accumulation of piperaquine (PQ) when used as IPTp-DP in the context of a randomized controlled trial in Kenya. Among 371 HIV-negative pregnant women, 6, 57, 127, 121, and 60 received 1, 2, 3, 4, and 5 or more full 3-day treatment courses of IPTp, respectively. Plasma samples were collected at each antenatal care visit, following a breakthrough symptomatic malaria infection, and at delivery. PQ PK properties were evaluated using nonlinear mixed-effects modelling. PQ PK was described adequately by a 3-compartment disposition model with a flexible absorption model. Predicted median trough plasma concentrations accumulated (152%) during monthly IPTp; 10.7, 14.4, 15.7, 16.1, and 16.3 ng/mL following 1, 2, 3, 4, and 5 treatment courses, respectively. Simulations using the final PK model indicated much lower steady-state trough plasma concentrations of PQ after 5 treatment courses of IPTp at intervals of 45 (7.90 ng/mL) and 60 days (4.22 ng/mL) compared to monthly administration (16.3 ng/mL). Fifty pregnant women presented with breakthrough malaria infections at a median (IQR) observed PQ concentration of 4.94 ng/mL (2.80-8.65 ng/mL); no malaria occurred in women with a trough concentration above 34 ng/mL. No increases in adverse events were seen with increasing courses of IPTp-DP. Approximately monthly dosing of IPTp-DP resulted in PQ accumulation, though less than that reported among non-pregnant adults in Thailand (336%), likely due to the effect of pregnancy on PK properties. In the context of previously reported high efficacy, tolerability and safety, these data suggest that the standard DP dose regimen for *P. falciparum* is likely adequate and safe for monthly IPTp in a high malaria transmission area, with an advantage over bi-monthly IPTp. These are the first data on PK and accumulation of DP used for IPTp. Final PK modeling results will be presented.

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BROTHERS, SISTERS, AUNTS AND UNCLES: TRANSMISSION OF RELATED PARASITES IN POLYGENOMIC INFECTIONS OF *PLASMODIUM FALCIPARUM*

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Genomic analysis of natural *Plsmodium falciparum* populations can give us key insights into changes in population biology as malaria transmission is reduced following intensive interventions. Such data is valuable both as a direct assessment of transmission and in modeling the impact of interventions. There has been a strong correlation between declining genetic diversity and transmission intensity, suggesting that genetic diversity metrics could serve as proxies for declining transmission rates. Most studies have focused on the genetic diversity found within monogenomic infections, or those infections composed of a single parasite type. This is limiting and not representative of many transmission settings, since the proportion of multiple strain infections, or polygenomic infections, tends to be high. Polygenomic infections are largely assumed to be the result of superinfection, or infection by multiple mosquito bites, which would imply that the genetic diversity within polygenomic infections are directly linked to transmission intensity. However, the mosquito may influence the genetic diversity of parasites in subsequent infections, particularly if multiple strains are co-transmitted, or introduced simultaneously with a single mosquito bite. We analyzed the genetic relatedness of parasites within 32 polygenomic infections collected from Senegal and found that these infections are most likely the result of co-transmission. We also simulated the co-transmission process and found that the genetic diversity within polygenomic infections is influenced most strongly by the complexity of infection, or the number of unique parasite types, within the initial human host, and the number of oocysts that form within the mosquito midgut. Our results suggest that the genetic relatedness within polygenomic infections is a reflection of both the overall transmission intensity and the dynamics within the mosquito vector. We anticipate that polygenomic infections could greatly aid our understanding of transmission dynamics within malaria endemic regions, since it could be used to derive information from both the human and mosquito hosts.

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VECTOR "VACCINATION": OPTIMIZATION OF NON-MENDELIAN-BASED GENE DRIVES FOR MOSQUITO POPULATION REPLACEMENT

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As the efforts towards malaria control and elimination expand across socio-geographical strata, the penetration, accessibility, and correspondingly success rates of established interventions vary. Difficult to reach and/or dangerous locations render implementation of interventions requiring sustained complex logistical coordination and robust infrastructure hard, if at all feasible. Recently, advances in the CRISPR/Cas9-mediated constructs, along other genetic modification technologies, have allowed for gene drives altering mosquito populations at scale. Homing endonucleases, TALENs and more recently CRISPR constructs, for instance, could be used to express anti-falciparum antibodies in target mosquito species. We implemented such a gene drive, replacing wildtype populations with mosquitoes resistant to Pl. falciparum within the EMOD modeling framework. We studied four distinct use cases in Tanzania, Nigeria, DRC, and Somalia - each characterized by distinct climates, disease prevalence and mosquito densities, etc. -- representing a realistic range of mosquito habitats and seasonality intensity. We investigated the optimal parametrization of genetic constructs - e. g. in terms of fitness penalty tolerance, infection modification and population replacement rates - along with gene drive logistics - e.g. mosquito release numbers, schedules, etc. We demonstrate feasible parameter ranges, where infection modification gene drives can replace wildtype mosquito populations in each of the four use casses. We caution that the resulting parasite prevalence and hence the success of a gene drive depends significantly on the infection modification rate and provide the respective thresholds for successful genetic constructs. The robustness of parasite prevalence reduction under different gene drive strategies in all use cases was evaluated with respect to malaria re-importation and mosquito species heterogeneity.

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PENTOSE PHOSPHATE PATHWAY INHIBITION ELEVATES OXIDATIVE STRESS AND IMPEDES FECUNDITY IN *ANOPHELES GAMBIAE*

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Blood digestion in hematophagous insects is associated with elevated reactive oxygen species (ROS) resulting from pro-oxidant heme ingestion. Mosquito capacity for defense against oxidative stress is limited and an overabundance of ROS can lead to reduced fecundity and death. Reducing power from internal sources is essential for oxidative stress defense which can impact insecticide sensitivity and defense against pathogens. The primary system used to alleviate oxidative stress is the pentose phosphate pathway (PPP). The major role of PPP is the regeneration of NADPH by reducing NADP+, and 6AN is a competitive inhibitor of G6DPH, the rate-limiting enzyme of PPP. PQ is an exogenous stress inducer, and PPP inhibition results in the accumulation of endogenous stress. We examine the dynamics of oxidative stress by induction by paraquat (PQ), inhibition of the PPP by 6-aminonicotinamide (6AN) and alleviation of oxidative stress by lycopene by oral feeding followed by egg counts and biochemical assessment of females. We hypothesis that PQ and 6AN will induce oxidative stress and result in reduced fecundity. Lycopene should rescue this phenotype by scavenging ROS. Both PQ and 6AN feeding increased oxidative stress levels and decreased fecundity. Co-feeding with lycopene attenuated these adverse effects. 6AN when fed with PQ results in a normal egg number possibly due to inactivation of NADPH production which is required for PQ toxicity. Lycopene also improves 6AN reduction in egg number suggesting that lycopene can alleviate ROS species induced by reducing NADPH production. 6AN reduced NADPH production resulting in a high NADP+:NADPH ratios indicating that the PPP is inhibited by 6AN in our model system. GSSG:GSH ratio also was increased by both 6AN feeding and PQ indicating both of these compounds result in increased oxidative stress. These antioxidants and pro-oxidants can provide a manipulatable link between mosquitoes and egg production capacity. This knowledge can be used to design novel and effective vector control strategies which may influence insecticide sensitivity, infection susceptibility, fecundity and longevity.

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INVESTIGATING *ANOPHELES FUNESTUS* SUSCEPTIBILITY AND IMMUNE RESPONSE TO *PLASMODIUM FALCIPARUM* INFECTION

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Anopheles funestus is a major vector of malaria in Africa. However, because it is difficult to colonize, research on this mosquito species has lagged behind other vectors, particularly the understanding of its susceptibility and interactions with the *Plasmodium* parasite. In order to fill this important knowledge gap, experimental infections were conducted from March to June 2015. 3-5 day old *An. funestus* F_1 mosquitoes derived from wild-caught females from Cameroon were fed with infected blood taken from gametocyte carriers using an artificial glass-parafilm feeding system. Feeding rate was recorded, and fed mosquitoes were dissected at day 7 for oocysts count. Comparative and parallel experiments were performed with the known *Plasmodium*-susceptible, *An. coluzzii* Ngousso laboratory strain. Microarrays analysis was performed to assess the molecular basis of *An. funestus* immune response to *P. falciparum* invasion.The results revealed that *An. funestus* displays a similar level of susceptibility to *Plasmodium* infection compared to *An. coluzzii*. The prevalence of infection in fed *An. funestus* mosquitoes was 38.52% (range: 6.25-100%) and the median oocyst number was 12.5 (range: 1-139). In parallel, the prevalence in *An. coluzzii* was 39.92% (range: 6.85-97.5%), while the median oocyst number was 32.1 (range: 1-351). Genome-wide microarray-based transcription analysis showed that *An. funestus* innate immune system is activated during midgut invasion. A total of 222 genes were found to be differentially expressed between infected and non-infected mosquitoes including several known immune response genes such as C-type Lectine, APL1 family genes, LRIM1, Serine protease, Serine collagenase and niemann-pick type c. However, genes such as TEP1 were not over-expressed in contrast to *An. gambiae* suggesting possible differences between both species. The high susceptibility of *An. funestus* to *P. falciparum* and its widespread distribution across Africa highlight the need to also tackle this vector for significant malaria vector control program.

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ELUCIDATING THE ROLE OF LIPOGENIC AND LIPOLYTIC PATHWAYS IN MOSQUITO REPRODUCTION AND *PLASMODIUM FALCIPARUM* TRANSMISSION

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Female *Anopheles* mosquitoes undergo a number of blood feeding cycles on a vertebrate host in order to produce multiple egg batches, and these obligatory steps in the mosquito life cycle are exploited by *Plasmodium* parasites for their own transmission. Blood feeding is therefore a key step for both mosquito reproduction and parasite transmission. Indeed these two processes are temporally and physiologically coupled and can be exploited to impact malaria dynamics in endemic areas. Previous studies revealed a correlation between blood meal digestion and major changes in transcriptional profiles of metabolic genes involved in lipid biosynthesis, transport, and breakdown, suggesting the occurrence of de novo lipid synthesis triggered by blood feeding followed by lipid mobilization. Here, we aim to elucidate the specific role of blood meal-derived lipids (and/or of lipids synthesized de novo after a blood meal) in *Anopheles* reproduction and parasite development in mosquito stages. To address this, we performed targeted depletion of key lipogenic and lipolytic enzymes in the main African malaria vector using RNA interference (RNAi) and assessed their impact on oogenesis and *P. falciparum* infection. Strikingly, knockdown of acetyl-CoA carboxylase (ACC), one of the rate-limiting enzymes in de novo fatty acid synthesis (lipogenesis), reduced egg development and *P. falciparum* infection in *An. gambiae*. On the other hand, inhibition of triglyceride (TAG)-lipase, involved in lipolytic breakdown of TAGs to yield free fatty acids and diacylglycerol (DAG), had opposing effects on egg development and *Plasmodium* infection: depletion of TAG-lipase significantly impaired the number of eggs developed but resulted in a significant increase in oocyst size without any apparent impact on the number of oocysts per midgut. The latter results suggest occurrence of possible scavenging of host TAGs by malaria parasites to meet developmental needs within the *Anopheles* vector. While further characterization is underway, these data provide the first direct evidence of the requirement of host lipids by human malaria parasites for successful transmission.

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DISRUPTING STEROID HORMONE SIGNALLING IN ADULT *ANOPHELES GAMBIAE* FEMALES BLOCKS *PLASMODIUM* DEVELOPMENT AND OFFERS ALTERNATIVE TARGETS FOR MOSQUITO CONTROL

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Human malaria is a major public health burden in tropical and subtropical countries and is transmitted exclusively by female *Anopheles* spp. mosquitoes. Malaria control strategies based upon the deployment of pyrethroid-impregnated long lasting insecticide treated nets (LLINs) are threatened by the continued spread and intensification of insecticide resistance. This represents a major obstacle to malaria elimination and as such new means of protection against the mosquito vector are desperately needed. Here we report that treatment with non-steroidal ecdysone receptor agonist dibenzoylhydrazines (DBHs) such as methoxyfenozide impact a number of parameters key to the vectorial capacity of the principal malaria vector *Anopheles gambiae*. Topical application of methoxyfenozide causes extensive apoptosis in the primary ovarian follicles of treated females, significantly reducing egg production while also impacting lifespan, oviposition and - in virgin females - mating refractoriness. Importantly, application of methoxyfenozide prior to females receiving an infectious *Plasmodium falciparum* blood meal triggered up to an 87% reduction in oocyst prevalence 7 days after blood feeding, suggesting that female susceptibility to infection is mediated in part via ecdysone signalling. This work provides critical insights into vector/parasite interactions and - in the face of the potential collapse of existing vector control methods - sets forth the case for the use of DBH compounds in malaria control strategies.

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THERE AND BACK AGAIN: A MOSQUITO SPERM'S JOURNEY FROM INSEMINATION TO FERTILIZATION

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Interfering with mosquito reproduction to control vector populations holds significant promise. Most investigative effort to develop novel control targets has focused on females, yet male contributions to reproduction are often overlooked. In particular, sperm biology and sperm's movement through the female reproductive tract are poorly understood, but studying sperm may provide various opportunities to interrupt reproduction. During insemination, sperm are deposited in a semen-receiving organ, where they display hyperactivated motility. They quickly localize to ducts leading to long-term storage organs called spermathecae. Within minutes, they travel up these ducts and are maintained by the female for her entire life. Ultimately, they are carefully released for fertilization as eggs are laid. Completion of this journey requires the precise coordination of motility, interactions with the ejaculate, nourishment by the female, and possibly modifications to sperm that make them fertilization competent. These

processes have been superficially examined microscopically, but very little is known about how sperm function on the molecular level. We discuss what is known of mosquito sperm's path through the female, highlighting areas for future exploration and discussing possible molecular targets that could be exploited by vector control strategies. We also provide unprecedented footage of mosquito sperm motility inside the female reproductive tract that will aid our understanding of how sperm function *in vivo*.

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SICPIN, A MULTIFUNCTIONAL IMMUNOMODULATORY SALIVARY PROTEIN FROM THE BLACK FLY *SIMULIUM NIGRIMANUM*

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Hematophagy is key to blood feeding arthropods reproductive success and an important link in pathogen transmission cycles. Salivary gland homogenates from blackflies have been shown to contain immunomodulatory activity on murine splenocytes. However, the molecule(s) responsible for this salivary activity remains elusive thus far. Here, we report the first immunosuppressive protein from blackfly salivary glands. Sicpin (*Simulium* cell proliferation inhibitor) was produced in *E. coli* and purified using size exclusion and ion exchange chromatography. Sicpin inhibited cell proliferation in a dose-response manner independently of the mitogen utilized (ConA, LPS, CD3/CD28 and Pokeweed). LPS or ConA stimulated cells had a significant lower proliferation rates ($P<0.001$) in the presence of Sicpin (IC50=0.5μM) with 10uM completely abrogating cell proliferation. Flow cytometry analysis showed that Sicpin inhibits proliferation of CD19+ B-cells and CD4+/CD8+ T-cells; also inhibiting antigen-specific cell proliferation without inducing apoptosis in resting or mitogen-induced splenocytes. The production IFN-α, IL4, IL5, IL6 and IL10 by splenocytes stimulated by ConA or LPS was dose-dependently reduced by Sicpin. Additionally, carrageenan-induced paw-edema model showed that the intensity of edema significantly decreases in the presence of Sicpin. The molecular mechanism of Sicpin on cell proliferation inhibition is currently under investigation; however, initial binding experiments using SPR analysis showed a direct binding to soluble CD4 receptor with a calculated KD of 17.77 nM. Direct binding of Sicpin to CD4 could inhibit the subsequent TCR ligation-induced T cell signaling at the earliest steps including tyrosine phosphorylation of the receptors, downstream effector proteins, and lipid raft reorganization. The immune suppressive and anti-inflammatory properties of Sicpin should be explored as a strategy to modulate immune responses in infection and tumor proliferation as well as its involvement in parasite transmission.

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A LOOK AT TWO FACTORS THAT MODULATE *AEDES AEGYPTI* MOSQUITO VECTOR COMPETENCE FOR DENGUE VIRUS

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Dengue virus (DENV) is a single stranded, RNA virus principally transmitted by the *Aedes aegypti* mosquito. While there is currently no vaccine or treatment available for those infected with the virus, DENV transmission can be prevented via vector control strategies. However, both biological and physical methods that have been employed thus far have had minimal success in curtailing the virus; and without a thorough understanding of how the mosquito modulates DENV infection; we may never be able to achieve this goal. Studies have shown that interactions between the mosquito's immune system, the pathogen, and the mosquito's endogenous midgut microbiota are critical determinants of the outcomes of transmission. Viral replication in the midgut results in the activation of a signaling cascade that turns on the mosquito's immune response. Thus far, we have isolated two key restriction factors, DVRF1 and DVRF2, which are downstream effectors of the JAK-STAT immune signaling pathway that have anti-dengue activity. But very little is known about how these specific effector molecules mediate this anti-pathogenic effect. The natural microbiota of mosquitoes is also a great influence on the mosquito's biology. Interactions between the mosquito microbiota and the virus also modulate vector competence for DENV infection via mechanisms such as immune response activation, anti-viral molecule production and resource competition. We have started the process of screening several mosquito-gut associated fungus for their effects on DENV susceptibility, from which we hope to characterize their mechanisms for infection modulation. Studying theses two important factors that modulate DENV infection is a step in the right direction toward developing alternative strategies for viral transmission control.

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CHIKUNGUNYA FEVER IN CLINICALLY DIAGNOSED PATIENTS: COMPARATIVE STUDY BETWEEN LABORATORY CONFIRMED VERSUS NEGATIVE CASES DURING THE 2015 OUTBREAK IN YUCATAN, MEXICO

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In the second half of 2015, chikungunya and dengue outbreaks took place simultaneously in the state of Yucatan, Mexico. This coexistence of both outbreaks posed a challenge to differential clinical diagnosis. During the outbreak, only a subsample of chikungunya dengue cases were confirmed by laboratory standard methods. This study was undertaken to identify signs and symptoms useful for clinically discriminate chikungunya from other endemic infections in early febrile stage. In this comparative, cross sectional study, we analyzed the data from the chikungunya surveillance cases at the main public general hospital in the state of Yucatan, including for our analyses only those whose blood samples were referred for its confirmation by the epidemiologic reference laboratory in the period between August and December of 2015. We compared the clinical manifestations of confirmed cases versus discarded cases using a logistic regression model. We included 181 of which 152 tested positive for Chikungunya virus, finding that pruritus is a suggestive symptom of an acute infection caused by CHIKV. Osteoarticular manifestations did not differ significantly, between confirmed or discarded cases, but pruritus was twice as common among chikungunya confirmed cases. Pruritus was a suggestive symptom of an acute infection caused by CHIKV. In 2015, Yucatan Mexico experienced a simultaneous occurrence of chikungunya and dengue outbreak. Clinical differentiation between CHIKV and dengue represented a diagnostic challenge, after statistical analyses, we can conclude that pruritus was an early suggestive symptom of an acute infection caused by chikungunya.

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EVOLUTIONARY INFLUENCES ON THE REDUCTION IN ENZOOTIC CIRCULATION AND HUMAN INCIDENCE OF WESTERN EQUINE ENCEPHALITIS

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Understanding the evolutionary and ecological circumstances in which arboviruses emerge into naïve geographical areas is critical for the development of targeted maintenance and prevention strategies. This

need was highlighted by the recent emergence of chikungunya and Zika viruses in the Americas. In order to develop a complete understanding of the ways in which viruses emerge, the factors surrounding a reduction in virus activity (submergence) must also be studied, and Western equine encephalitis virus (WEEV) provides a unique opportunity to study this. WEEV caused several epizootic events in the early 20th century that account for the death of thousands humans and equids. However, the last human case in North America occurred in 1994 even though virus can still be detected in mosquito pools, albeit at reduced levels. Previously, we identified six nonsynonymous mutations that were phylogenetically significant and have a phenotypic effect on WEEV's enzootic hosts. Competitive fitness assays show contemporary mutations have a competitive advantage in both *Culex* tarsalis and house sparrows, but have no effect on virulence in the Syrian golden hamster. These data suggest mutations have accumulated by positive selection only enhance the ability to transmit between its enzootic hosts and vector. We also hypothesize the mutations that confer mammalian virulence were purified out of the population by negative selection due to a reduction in selective pressure on those residues. Overall, the evolutionary profile of WEEV over the 20th century trends away from disease in mammals and toward its enzootic cycle. Several factors could account for this including vaccination and drastic reduction of the US equine population, the use of screens on windows and doors, and/or changes in irrigation practices. In summary, the submergence of WEEV presents a case study where its reduction was likely precipitated by an ecological shift critical for the virus' maintenance of the mutations that connote virulence in mammals and subsequently compensated by increasing its adaptability to its enzootic hosts.

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THE BURDEN OF CHRONIC CHIKUNGUNYA DISEASE AND QUALITY OF LIFE IN CURAÇAO

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The burden of chronic chikungunya disease and quality of life in Curaçao Curaçao, an island in the southern Caribbean Sea, was affected by a major chikungunya (CHIK) epidemic in 2014 resulting in an estimated 25.000-30.000 cases of CHIK at the end of the outbreak (January 2015). After the epidemic culminated, CHIK remained a public health problem given the chronic phase of the disease which can include joint pain, arthritis, fatigue and depression for up to five years. However, studies on the chronic phase of CHIK remain scarce, especially in the Americas. The aim of this study was to estimate the burden of the CHIK outbreak in Curaçao in terms of duration of disease, symptoms and impact on quality of life 3-16 months after diagnosis. Following the CHIK epidemic of 2014-2015 on Curaçao, a comprehensive cross-sectional survey was performed in June and July 2015. A total of 411 adult participants were contacted and invited to join the study, of which 339 consented (response rate= 82.5%). Interviews took place 92-460 days after disease onset. Of those interviewed, 306 individuals had a laboratory confirmed CHIK virus infection. Symptoms of the chronic disease course were evaluated, and quality of life was assessed using the RAND-36 score. We will present a comparison of the fully recovered and the still affected population of chikungunya patients. The mean age of the participants was 52 years (range: 18-94 years). Preliminary results show that the degree in which subjects were affected by chronic chikungunya disease differs: 37.2% were defined as fully recovered, while the remaining 62.8% were defined as still being mildly affected (35.7%) or highly affected (27.1%). Of the total population, only 21.4% reported to be fully recovered from CHIK within one month. We will give a detailed description of the clinical spectrum of chronic chikungunya disease and will show the impact on the quality of life aspects reported by the studied population. We believe that this comprehensive study will provide important insight in the disease course of chronic chikungunya in the Americas and its impact on its population.

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CHIKUNGUNYA EPIDEMIC IN CARABOBO STATE, VENEZUELA 2014: A STUDY ON EPIDEMIOLOGICAL DEVELOPMENT, CLINICAL MANIFESTATIONS AND RISK FACTORS

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Chikungunya (CHIK) was a relatively uncommon and poorly documented illness. However, in the last decade this re-emerging viral vector-borne disease caused an increasing number of outbreaks in the tropical and subtropical regions of Africa and Asia. At the end of 2013, CHIK reached the Americas spreading rapidly through most countries. By mid 2014, Venezuela was hit by a devastating CHIK epidemic that swept the country with an estimated attack rate of 60%. Carabobo State, one of the first Venezuelan regions to be affected, reported its first autochthonous case in June 2014. We aimed to characterize the epidemic, clinical manifestations and risk factors associated with CHIK transmission in Carabobo State. Epidemiological and clinical data of patients attending health centers was obtained from the surveillance system of the Regional Ministry of Health. Between June-December 2014, data from 613 patients were included, of which 167 laboratory confirmed (103 (61.7%) positive). Univariate and multivariate analysis of laboratory-confirmed and suspected cases were performed. We detected an epidemic peak in week 34, 74 days (10.6 weeks) after the first reported case. The mean of the epidemic curve was 14.3±3.7 weeks. A two week lag was observed between the time of symptom onset and that of case notification. In laboratory confirmed patients, rash alone (OR=3.39, p=0.018) and the combination of fever, rash and arthralgia (OR=2.39, p=0.066) were associated with CHIK. Housewives and domestic workers had 79% lower risk of being CHIK positive (p=0.050). Similar findings were obtained when comparing the study group of suspected and laboratory-confirmed CHIK cases showing a relatively accurate clinical diagnosis from physicians. In addition, crowding (≥1.5 people/bedroom), a marker for lower socio-economic status, was positively associated with acquiring CHIK (OR=1.75, p=0.059). Our findings may add to the current diagnosis guidelines and give insights about CHIK associated risk factors in Venezuela. Additionally, by improving the time response of case notification, earlier preventive measures may be put in place to reduce CHIK transmission.

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SEASONAL PREVALENCE OF ALPHAVIRUSES AND FLAVIVIRUSES IN CHILDREN IN WESTERN KENYA

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Arboviruses present a significant threat in many regions of the world, continuing to spread through explosive expansion to previously unaffected areas. Many elements may influence the dynamics of exposure through environmental, behavioral, and biological factors, as well as the related spectrum of disease. This study aims to describe the prevalence of alphaviruses, such as chikungunya virus (CHIKV) and o'nyong n'yong

virus (ONNV), and flaviviruses, such as dengue virus (DENV) and West Nile virus (WNV), in western Kenya over time. Serum samples were taken from healthy afebrile children in two inland communities, Chulaimbo and Kisumu, at enrollment and during a 3-month follow up visit. Enrollment took place in March-May of 2014 for Kisumu, and October-December 2014 for Chulaimbo. Questionnaires on health history, socioeconomic status, home environment, and mosquito exposure were collected during each visit to determine risk for arbovirus transmission. Sera were tested using indirect IgG ELISAs using CHIKV and DENV antigens to identify previous exposure to alphaviruses or flaviviruses (cross-reactivity within each viral genus is common). Of 748 children, 8% (CI95 6-10%) were seropositive for CHIKV indicating previous exposure to alphavirus, and 11% (CI95 9-13%) were seropositive for DENV indicating previous exposure to a flavivirus. At follow-up, 30% (CI95 25-36%) and 36% (CI95 32-39%) of participants were seropositive for alphaviruses and flaviviruses, respectively. Flaviviruses seropositivity was significantly higher in Chulaimbo ($p = 0.01$) at follow-up in January-March 2015. Comparatively, prevalence at the time of the follow-up visit differed significantly between villages for both alphaviruses ($p = 0.0004$) and flaviviruses ($p < 0.0001$). These data indicate suggest an event, such as flooding with an increase in local mosquito populations increased exposure. Because alphavirus infections increased prior to June and flavivirus infections prior to January, their exposure may also correlate with seasonal variation. Additional ecological, social, and demographic risk factors will be discussed.

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RISK FACTORS FOR CHIKUNGUNYA PATIENT HOSPITALIZATION — PUERTO RICO, 2014

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The Sentinel Enhanced Dengue Surveillance System (SEDSS) is an acute febrile illness (AFI) surveillance and research platform that determines the etiology and clinical outcome in febrile patients presenting to two hospitals in Puerto Rico. Chikungunya emerged in the Caribbean in late 2013, and diagnostic testing was incorporated into SEDSS in March 2014. The objectives were to estimate the proportion of chikungunya virus (CHIKV) infection in patients presenting with AFI, estimate the incidence and identify risk factors for chikungunya patient hospitalization. Demographic and clinical information were collected at presentation. Medical records were reviewed to collect information about clinical manifestations and outcomes. Of 3,035 patients enrolled in SEDSS during May-December 2014, 1,469 (48%) had confirmed CHIKV infection by RT-PCR. In total, 157 (10.7%) patients with evidence of CHIKV infection were hospitalized, 6 (0.4%) were admitted to the intensive care unit, and 2 (0.1%) died. Median age among hospitalized and non-hospitalized patients was 10 years (range: 0 to 93) and 26 years (range: 0 to 97), respectively (p-value=0.00). Rate of hospitalization was highest in infants (67%) and the elderly (17%). Neither the presence of co-morbid conditions nor day of presentation for care post-illness onset were associated with patient hospitalization. Clinical and laboratory findings associated with hospitalization (relative risk >1.5 or p-value= 0.00) included white blood cells, hematocrit, platelet count, pale or cold skin, skin rash, bruises, cyanosis, seizures, and irritability. Additional analyses will adjust for age in identification of risk factors for chikungunya patient hospitalization. The most common atypical manifestations among hospitalized patients were cardiac arrhythmia (7%), encephalitis (4%), and vesiculobullous skin lesions (3%). Fatal cases were associated with exacerbation of underlying chronic medical conditions. Although chikungunya is a self limiting illness, some patients - particularly infants and the elderly - may develop severe manifestations and merit closer monitoring.

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PROTEIN SPECIFICITY OF ANTIBODY RESPONSES TO SOUTH AMERICAN ALPHAVIRUS INFECTIONS USING A NOVEL MULTIPLEXED ASSAY

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Arboviruses are a leading cause of emerging and re-emerging diseases around the world. Members of the Alphavirus, Flavivirus, and Bunyavirus genera are primarily responsible for causing disease in humans, with infections ranging from asymptomatic to mild symptomatic, and can sometimes turn severe. Because many arboviral infections cause mild, undifferentiated symptoms, illnesses are often undiagnosed or misdiagnosed, especially in Dengue-endemic regions, often leading to improper estimations of disease incidence rates. In addition, diagnostic testing may be attempted post-acute phase after viral clearance, often limiting detection of past infection to serological-based assays only. Unfortunately, commercially available serological diagnostics are not readily available for many such diseases, and antibody cross-reactivity with related, non-etiologic agents may occur, leading to misdiagnosis. To gain a better understanding of disease prevalence, particularly in resource-limited areas, a detection platform with high specificity is needed to cover a wide range of endemic and emerging diseases. Towards this goal, we have developed a multiplexed alphavirus protein microarray to perform serological-based assays to identify specific viral exposures. The protein microarray contains three purified, recombinant structural proteins from multiple arthrogenic or encephalitic alphaviruses, including Chikungunya virus (CHIKV), Mayaro virus (MAYV), and Venezuelan Equine Encephalitis virus (VEEV). To detect specific antibody binding to alphaviral antigens, convalescent sera from patients in South America with PCR-confirmed alphavirus exposures were tested for antibody binding to antigens in the protein microarrays. In particular, IgG in early convalescent sera from patients with MAYV, VEEV or CHIKV infections were tested for specific antigen binding. We determined that by using purified alphavirus proteins, we were able to detect IgG binding to one or more specific viral antigens, with minimal cross-reactivity occurring with viral antigens with high levels of sequence homology.

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ALTERING BLOOD BRAIN BARRIER PERMEABILITY: HOW ROUTE OF INFECTION, CYTOKINE INDUCTION AND HEPARAN SULFATE BINDING CONTRIBUTE DURING ENCEPHALITIC ALPHAVIRUS INFECTIONS

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Alphaviruses are arthropod-borne, enveloped viruses that contain a single-stranded, positive-sense RNA genome. Alphaviruses are generally categorized into two categories based on geographic location and disease manifestations: old world alphaviruses mainly cause febrile/arthritogenic disease while new world alphaviruses can cause encephalitis. Encephalitic

alphaviruses have a range of morbidity and mortality in humans with the most virulent causing ~40% mortality, while all can cause permanent neurological sequelae. There are currently no licensed vaccines or antiviral therapies, therefore it is important to understand how the encephalitic viruses enter the central nervous system (CNS) and alter the blood brain barrier (BBB) so that therapeutic strategies can be designed to target these events. Our initial hypothesis, based on previous studies, was that an initial early opening of the BBB occurs, presumably due to cytokine induction, allowing the virus to gain entry into the CNS, and then a later opening of BBB occurs due to viral replication within the CNS. Our goal is to determine if route of exposure (subcutaneous vs aerosol) and the ability to bind heparan sulfate (HS) alters entry into the CNS and permeability of the BBB. Using fluorescently labeled molecules of different molecular weights, our data suggest that there is an initial opening of the BBB for lower molecular weight molecules, likely due to cytokine induction, but it may not be large enough for the alphaviruses to enter into the CNS. Additionally, the opening of the BBB to larger particles, of similar size to a virion, does not occur until late in infection. Interestingly, route of infection can play a role in the ability of certain encephalitic alphavirus to cause leakage of the BBB to small molecules, but not for all the encephalitic alphaviruses and this may be greatly influenced by the ability to naturally bind HS. Taken together, our data suggest that encephalitic alphaviruses do not alter the permeability of the BBB to gain entry into the CNS, however route of infection, innate immune responses and bind HS binding impact the ability each virus to induce BBB permeability.

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COMPREHENSIVE MUTAGENESIS OF DENGUE VIRUS ENVELOPE PROTEINS TO MAP ANTIBODY EPITOPES AND IDENTIFY RESIDES ESSENTIAL FOR FUNCTION

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To characterize the immune response to dengue virus (DENV) infection, we have developed a high-throughput strategy that enables the rapid identification of both linear and conformational epitopes on DENV prM/E envelope proteins from all four DENV serotypes. For each DENV serotype (1-4), we used Shotgun Mutagenesis technology to create a comprehensive library of single mutations in DENV prM/E, 3,380 mutations in total. Each library of individual mutant expression plasmids was arrayed into 384 well plates and transfected into human cells to achieve native protein expression and folding. The immunoreactivity of MAbs to the prM/E variant in each individual well was quantified by high-throughput flow cytometry, resulting in approximately 200 MAb epitopes. The epitopes obtained have been correlated with their abilities to protect against DENV infection. We have also produced DENV virions from all four mutation libraries using a previously developed DENV reporter virus particle (RVP) system, allowing us to screen each individual DENV Env variant protein for DENV particle budding and infectivity. For DENV3, analyses of budding and infectivity, along with the MAb binding studies, identified residues whose mutation eliminated virus infectivity, but did not impact E protein expression, antigenicity, virion assembly, or particle budding. We identified variants that showed increased DENV virion budding, up to 5-fold above wild-type, indicating the ability to engineer highly expressed, non-infectious DENV variants that can be used for vaccine design. Our research has identified neutralizing epitopes in DENV prM/E and specific sites that are critical for DENV infectivity, providing new targets and opportunities for vaccine development.

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THE CLINICAL OVERLAP OF SEVERE DENGUE CATEGORIES

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The WHO (2009) classification has the following three categories of severe dengue i) dengue shock / respiratory distress with fluid accumulation (vascular leakage), ii) severe bleeding, and iii) severe organ manifestation. The prospective multicentre DENCO study provides one of the largest datasets of hospitalised dengue patients from 7 Countries in Asia and Latin America (N=1734). All patients were followed daily throughout the evolution of their illness by trained physicians using a single comprehensive case report form. Here we analyse the frequency and overlap between these categories in 271 confirmed severe dengue patients. The overall proportion and categories of severe disease did not differ significantly between Asia and Latin America, but between age groups. Severe dengue occurred in 17.3% of children (< 15 years) compared to 12.9% of adults (≥ 15 years). Within the severe children, 94.0% were diagnosed with vascular leakage and 12.0% with severe bleeding, whereas in severe adults 81.6% had vascular leakage and 19.5% severe bleeding. The trajectories of the platelet counts between patients with severe bleeding and severe vascular leakage diverged at day of illness 3 with significantly lower platelet counts in patients with severe bleeding on days 5 and 6. Severe vascular leakage occurred in 244 patients (90% of all severe patients), of whom 213 (87%) did not experience severe bleeding or severe organ dysfunction, 210 were diagnosed with clinical shock, 79 with fluid accumulation with respiratory distress, and 45 with both clinical shock and fluid accumulation with respiratory distress over the course of the illness. Severe bleeding and severe organ dysfunction accounted for 39 and 28 cases respectively, of whom 12 (31%; severe bleeding) and 14 (50%; severe organ dysfunction) did not overlap with the other categories. Thus, the majority of the vascular leakage cases and 30-50% of the cases with severe bleeding or severe organ manifestations were classified as severe in only one category, highlighting the usefulness of these categories and their potential as research endpoints.

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A PHASE 1 EVALUATION OF THE SAFETY AND IMMUNOGENICITY OF RDEN3Δ30 AS A DENGUE 3 HUMAN CHALLENGE STRAIN

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As human experimental medicine models become important in the testing of candidate dengue vaccines, we developed a Dengue 3 model. DENV-3 Sleman/78, isolated from central Java, and was associated with a clinical illness milder than from other circulating DEN3 strains. To attempt to further attenuate the strain for possible use as a candidate DENV-3 vaccine, 30 nucleotides were removed from the 3′ untranslated region and the virus was designated rDEN3Δ30. During pre-clinical testing of this virus in rhesus macaques, rDEN3Δ30 was indistinguishable from the DEN3 Slemen/78 wild type parent virus; there was no difference in mean peak titer of virus or number of days of viremia. For this reason, rDEN3Δ30 was evaluated as a potential DENV-3 challenge virus in a dengue human infection model. We describe the clinical manifestations and viremia associated with this DENV strain in healthy human subjects, and its future role as part of DENV challenge studies.14 subjects were enrolled;10 subjects received 103 PFU of DENV3 vaccine and 4 received

placebo. Viremia and safety labs were measured at Days 2,4,6,8,10,12 and 16. Subjects were followed for evidence of illness or fever alternating days (QOD) in clinic or by phone. The most common side effects headache and fatigue were the same in rDEN3Δ30 recipients and placebos. 80% of rDEN3Δ30 recipients developed a transient Dengue-like rash and 100% had rDEN3Δ30 recovered from the blood; no subject had fever. The major lab findings in vaccines were mild thrombocytopenia (n=2) and one mild Neutropenia. No SAEs were reported. This was first time rDEN3Δ30 was administered to healthy human volunteers. No volunteer developed fever or dengue like illness. Overall, the strain appeared well-tolerated with the exception of mild- moderate transient rash in 80% of vaccines. The virus was recovered from 100% of treated subjects. The high incidence of viremia and rash induced by this virus supports its use in dengue human infections studies. Previous studies have demonstrated the LATV formulation prevents against infection with DEN2 challenge. The results of this phase 1 study will provide a foundation for future challenge studies.

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ANALYSIS OF THE CURRENT MAJOR DENGUE OUTBREAK IN ARGENTINA IN AN AREA WITH PERMANENT CONTROL ACTIVITIES AGAINST *AEDES AEGYPTI* SINCE 2009

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The city of Tartagal (Salta Province) is located in the northeast of Argentina, 100 km north of the Tropic of Capricorn and 50 km south of Bolivia. It has a population of 69,225 inhabitants and 18,052 households. Mundo Sano has a Surveillance and Vector Control Program for *Aedes aegypti* in place since October 2009 in collaboration with the Municipality of Tartagal with the objective of diminishing the incidence of dengue cases in the locality. Until epidemiological week (Epi week) 14 of 2016, the quantity of dengue infected people registered in Argentina reached 55,431 (2,909 from Salta), with circulation of both DEN1 and DEN4 serotypes. In Tartagal, the number of infected people until the same Epi Week was 106. The last major epidemic in Argentina occurred in during 2008/2009, where Tartagal presented 665 cases, including the first death by severe dengue reported in in the country. The actions included in the program for integrated control of *Aedes aegypti* and the eco-epidemiology of dengue in Tartagal are the following: a) Focal Cycles (during the Summer Season), b) Entomological monitoring (throughout the entire year), c) evaluation of the gonadotrophic activity through the use of ovitraps (throughout the entire year), d) environmental manipulation to remove breeding sites (previous to the Summer Season), e) organization and development of focal blocking activities (in coordination with the J.D. Perón Hospital from the city of Tartagal), e) capture of adults for the detection of viral infection and f) evaluation of insecticide resistance in *Ae. aegypti* populations in the city. The objective of the present study is to show the importance of a permanent Surveillance and Vector Control Program, with planned activities, continued and uninterrupted, in order to reduce the abundance of *Ae. aegypti* through the control of larval stages and their breeding sites, especially during outbreaks of dengue and other arboviruses transmitted by *Ae. aegypti*.

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DISSECTING ANTIBODY RESPONSE INDUCED BY CHIMERIC YELLOW FEVER-DENGUE, LIVE-ATTENUATED, TETRAVALENT DENGUE VACCINE (CYD-TDV) TO UNDERSTAND VACCINE EFFICACY IN NAÏVE AND DENGUE EXPOSED INDIVIDUALS

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Dengue vaccine development is complicated by the presence of 4 virus serotypes. Sanofi Pasteur has developed a chimeric yellow fever-dengue, live-attenuated, tetravalent dengue vaccine (CYD-TDV) that is approved for use in children >9 years of age in several countries. In two large scale phase III efficacy trials, CYD-TDV was efficacious at reducing laboratory-confirmed dengue cases. Efficacy varied by serotype, in addition to being higher in DENV exposed than in DENV-naïve participants. While these results are encouraging, they highlight the complexity of human immune response to vaccination, which is often not balanced across the 4 serotypes and is influenced by prior immune status of vaccinees. Our study compare the properties of DENV-specific antibodies in naïve and DENV exposed individuals who received three doses of CYD-TDV. Our results, which demonstrate differences in the quality of neutralizing antibodies depending on virus serotype and pre-vaccination immune status, provide better understanding of the efficacy data from dengue vaccine trials. Samples from DENV naïve subjects at baseline were analyzed, and DENV neutralizing antibodies induced by CYD-TDV were measured. There was considerable variability in the levels of neutralizing antibodies to the different serotypes, where the mean levels to serotype 2 and 4 were higher than 1 and 3. Further analysis showed that the majority of these antibodies were cross-reactive (CR) with the exception being DENV4 which was mostly type-specific (TS) antibodies. Samples from pre-immune vaccinees, at one month post the final dose were similarly analyzed. Data shows that the neutralizing antibody titers are higher compared to the naïve recipients. The majority of these neutralizing antibodies are CR, with the highest titers to DENV1, 2 and 3. In contrast to the other serotypes DENV4 neutralizing antibodies in pre-immune individuals were at similar levels as the naïve vaccinees and mostly CR. Our depletion studies showed that CYD-TDV boosts CR antibodies in pre-immune individuals, while maintaining the proportion of TS antibodies the subject developed after natural DENV infection.

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SAFETY AND IMMUNOGENICITY OF AN AS03$_B$-ADJUVANTED DENGUE PURIFIED INACTIVATED VACCINE ADMINISTERED ON THREE SCHEDULES TO HEALTHY U.S. ADULTS

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The number of vaccine doses and their intervals influence a vaccine's immunogenicity. We evaluated the safety and immunogenicity of a candidate AS03$_B$-adjuvanted tetravalent dengue purified inactivated vaccine (DPIV) administered intramuscularly in a 0.5mL volume on 3 schedules to healthy, adult subjects 20-49 years of age in a phase 1/2, randomized, observer-blind study (NCT02421367). One hundred forty subjects were randomized to receive either 2 doses of DPIV (1µg per serotype) 1 month apart (N=35) or 3 months apart (N=70), or 3 doses of DPIV at 0, 1 and 6 months (N=35). Primary study objectives were i) to evaluate the safety and reactogenicity of DPIV+AS03$_B$ from Day 0 to Day 28 following each dose, ii) to demonstrate the added value of a third, booster dose at Month 6, based on humoral immunogenicity, and iii) to demonstrate the benefit of a longer interval between doses. Humoral immunogenicity was measured using a microneutralization (MN50) assay. The primary immunogenicity endpoints were MN50 titers to each DENV serotype for sera collected prior to Dose 1 and 28 days after the second and third dose. Primary reactogenicity and safety endpoints included the occurrence, intensity, and relationship to vaccination of solicited injection site and general adverse events (AEs) for Days 0-6 after each dose and for unsolicited AEs for Days 0-27 after each dose. Grade 2 and Grade 3 laboratory abnormalities were determined at Days 0 and 7 after each dose. Occurrence of potential immune-mediated diseases (pIMDs), medically

attended AEs, and serious adverse events (SAEs) were reported from Day 0 through Day 28 after the last dose (Month 7 Visit). The results generated in this ongoing clinical trial and their clinical implication will be presented.

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STOCHASTIC SPREAD OF WOLBACHIA THROUGH *AEDES AEGYPTI* POPULATIONS IN SPATIALLY HETEROGENEOUS LANDSCAPES

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Infection with Wolbachia bacteria suppresses *Aedes aegypti* populations and reduces their competence as a vector for dengue. Because Wolbachia-infected mosquitoes have a reproductive advantage over their wild type counterparts, widespread introduction of Wolbachia into wild *Ae. aegypti* populations is considered an efficient, long term control measure for dengue. However, the success of this strategy depends on whether Wolbachia can spread spatially through the mosquito population from a small number of initial releases. In particular, variations in habitat may slow or halt the spread. Using a two-dimensional, stochastic metapopulation model which incorporates the full dynamics of the mosquito life cycle, we investigate how spatial heterogeneities in habitat affect the likelihood and speed of Wolbachia spread. We generate clustered landscapes containing both good and bad habitat. Landscapes are classified according to the proportion of good habitat they contain and how clustered together good habitat is. We also consider landscapes in which good and bad habitat are randomly interspersed. For each landscape we simulate the release of Wolbachia mosquitoes multiple times. Overall we find that for random landscapes the speed of spread is independent of the amount of good habitat. For clustered landscapes, the speed of spread is high when the amount of good habitat is either very low or very high, but decreases for intermediate values. This reduction in speed is more prominent for highly clustered landscapes. However, the likelihood and speed of spread also depends on habitat quality in the release patch; in highly clustered landscapes with a high proportion of good landscape, released Wolbachia-infected mosquitoes will fail to invade if they are released in an island of low quality habitat. These results highlight the importance of understanding and accounting for habitat diversity when modelling and planning for large scale Wolbachia releases as a dengue control measure.

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EXPLORING THE ROLE OF ASTHMA IN DENGUE PATIENTS

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Dengue is a self-limited, systemic viral infection transmitted by mosquitoes that has a wide spectrum of clinical presentations, ranging from undifferentiated fever to severe dengue. Severe dengue can lead to serious complications and death, but if identified early morbidity and mortality can be reduced. Since epidemiologic studies had associated asthma with severe dengue, our study aims to describe demographic characteristics and clinical manifestations of laboratory confirmed dengue cases with past medical history of asthma. Data was collected from patients enrolled in the Sentinel Enhanced Dengue Surveillance System (SEDSS) established in St. Luke's Episcopal Hospitals in Ponce and Guayama, Puerto Rico from May 7, 2012 to May 6, 2015. We will compare asthmatic cases with acute, intermittent and persistent disease to determine their risk for severe dengue. SEDSS collects clinical and demographic data and specimens for testing with RT-PCR and immunodiagnostic methods as appropriate for 21 pathogens that cause acute febrile illness, including DENV. Of 1,691 enrolled patients with history of asthma, 169 had laboratory confirmed dengue. half (50.9%) of which were male ;and median age was 14.0 years (range: 1 - 73). One hundred thirty nine (77.5%) were patients under 19 years. Seventy nine cases (46.7%) were admitted to the hospital, of which 55.7% were between 10-19 years. One case was transferred to another institution (0.6%) and no deaths were reported. The most common symptoms upon presentation were headache (148, 88.1%), fever (126, 76.4%), muscle pain (114, 68.7%), facial flush (100, 59%) and rash (81, 50.3%). Other co-morbidities of asthmatic cases were diabetes (14, 8.3% and hypertension (13, 7.7%). Patients with a history of asthma and laboratory confirmed dengue had similar symptoms as dengue cases described in the medical literature. Admission rates were high for this group, therefore further analysis is being conducted to characterize and compare asthma severity among patients enrolled in SEDSS who developed severe dengue during their clinical course.

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ESTIMATION OF THE MAGNITUDE OF DENGUE INCIDENCE UNDERREPORTING THROUGH A MODELLING WITH DISMOD II SOFTWARE

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National surveillance systems have as a main goal to provide information on imminent threats to public health and to help in the monitoring of priority diseases. However, it is not uncommon to use figures coming from surveillance systems as proxies of real incidence rates. Surveillance data usually underestimates the real incidence, either because some patients might not look for care, or because symptoms may lead to misdiagnosis, as well as other organizational reasons influencing quality of report. In the specific case of dengue surveillance, the underreporting is linked to the high frequency of mild cases and the difficulty for some physicians to recognize the disease. The magnitude of the underreporting is a matter of concern, since the adequate gauge of the economic and sanitary burden of this disease, as well as the solid assessment of control measures, require robust data. Consequently, several approaches have been used to correct this issue and to obtain a better proxy of real dengue incidence. We used an IPM (incidence, prevalence, mortality) model to adjust dengue incidence estimates in order to have a better perspective of dengue epidemiology in Mexico. We used data correspondent to Yucatan, an endemic Mexican State located at the east of the country. To obtain our model, we used the DISMOD II software, developed by WHO in collaboration with Erasmus University at Rotterdam, in Netherlands. The inputs were dengue seroprevalence data of 2015, and official incidence and dengue specific mortality of the period 2010-2014. We assumed that all people infected by dengue virus stay seropositive for the rest of their life. Our results show that the real magnitude of dengue incidence is 6 times higher than the officially reported, reaching a rate of 1330 cases per 100,000 inhabitants. As an additional positive feature, this model allows to associate specific levels of incidence with predicted seroprevalence levels. We conclude that the use of DISMOD II and the IPM models in general, are useful to answer questions related to the internal consistency of epidemiology variables or to solve the lack of some parameter in order to understand dengue epidemiology.

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CHANGING CLIMATE AND TRAVEL ACTIVITY MIGHT EXACERBATE DENGUE TRANSMISSION IN TAIWAN

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Southern Taiwan has been a hotspot of Dengue Fever (DF) transmission since 1998. The incidence of dengue fever in Taiwan shows strong seasonality. Mosquito ecology and the transmission of dengue fever are influenced by multiple environmental factors, especially for climate

variations. Thus, interannual variability in climatic conditions could be important drivers for annual outbreaks. Taiwan has experienced tremendous dengue outbreaks in 2014 and 2015. Whether the sharp increase of dengue cases was due to recently climate changes or other factors should be investigated carefully. This study explored the spatial patterns of dengue outbreaks in Tainan and Kaohsiung City in Southern Taiwan throughout 1998 to 2015. Multiple climatic indices generated from weather stations and satellite remote sensing images at these two study regions were used to develop models to evaluate the impacts of changing climate on dengue transmission. Two strategies have been applied in the analysis. (1) Distributed lag non-linear model (DLNM) has been used to capture the lag effects of local climatic parameters. (2) Regional El Niño Southern Oscillation (ENSO) and Indian Ocean Dipole (IOD) effects have been evaluated by wavelet analysis. Travel statistics has been acquired to analyze the increasing patterns and their countries or origin. The Inter-annual variability of dengue outbreaks is obvious and the large-scale outbreaks might be related to a 4-year interval, however, the periodicity has been reduced after 2006. The results of DLNM have highlighted the important short effects of temperature and rainfall. However, ENSO and IOD have demonstrated different coherency patterns in the whole study period and partially explained the significant outbreaks in 2014 and 2015. Non-climatic factors, including the gas pipeline explosion in 2014 and increasing trends of tourists from endemic regions might play certain roles. Our study has revealed that dengue transmission might become more complicated due to the interaction between climate changes and human activity.

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SEROTYPE-SPECIFIC CHARACTERISTICS OF THE NEUTRALIZING ANTIBODY RESPONSE TO THE SANOFI PASTEUR DENGUE VACCINE IN PHASE III EFFICACY TRIALS

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Two Phase III efficacy trials (NCT01373281 and NCT01374516) of Sanofi Pasteur's tetravalent dengue vaccine (CYD-TDV) were conducted in dengue endemic areas of Asia-Pacific and Latin America, with subjects between the ages of 2 and 14 and between the ages of 9 and 16, respectively. The vaccine was administered in 3 doses: baseline, month 6, and month 12. The primary per-protocol analysis of vaccine efficacy was assessed for 12 months from 28 days after the third dose with hospital phase safety outcomes followed for 4 years beginning in month 25. The goal of this study is to assess characteristics of the anti-dengue neutralizing antibody (nAb) response generated in subjects in the vaccine efficacy studies outlined above. We employed a bead-based virus-depletion approach combined with a flow cytometry-based neutralization assay using U937 DC-SIGN, a known receptor for dengue virus attachment, cells to qualitatively assess whether the serum nAbs to each of the 4 dengue serotypes from these subjects were homotypic and/or heterotypic (cross-reactive). Employment of this method on post-dose 3 (PD3) samples from a clinical trial in a non-dengue-endemic region (NCT01134263) demonstrated that nAb responses to DENV1, DENV2, and DENV3 were primarily heterotypic while the responses to DENV4 were primarily homotypic. In endemic populations, vaccination has triggered a stronger and broadly cross-reactive neutralizing Ab response. Additional analysis of dengue-endemic sera from PD3 CYD-vaccinated or placebo subjects that subsequently developed a dengue case requiring hospitalization during the monitoring phase for serotype-specific homotypic and heterotypic nAbs. These nAb profiles of these samples were compared with age- and center-matched controls that did not acquire a hospitalized dengue case to determine whether the homotypic and heterotypic profile of the dengue-specific antibody responses in CYD-TDV-vaccinated and placebo-vaccinated individuals affects the likelihood of an individual acquiring a hospitalized/severe case of dengue.

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USE OF A BIOLAYER INTERFEROMETRY-BASED ASSAY TO DETERMINE ANTIBODY AFFINITY TO DENV FOLLOWING IMMUNIZATION WITH THE SANOFI PASTEUR DENGUE VACCINE IN PHASE II AND PHASE III CLINICAL TRIALS

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The goal of this study was to measure the affinity of the Sanofi Pasteur dengue vaccine-induced antibodies to each of the four serotypes, to help assess the role in protection of the quality of the antibodies induced by vaccination. A biolayer interferometry-based assay was developed using Octet RED384 (ForteBio) to determine dengue-specific antibody affinity and concentration. The method was developed and optimized using sera from naturally-infected dengue-experienced donors. An initial proof of concept study analyzed sera from adults in a phase II trial (NCT00740155) in a dengue non-endemic area which compared affinity changes after the first and second doses of Sanofi Pasteur's tetravalent dengue vaccine (CYD-TDV). In a second step, we used sera from the CYD14 and CYD15 phase III clinical efficacy trials (NCT01373281 and NCT01374516, respectively). The trials were conducted in dengue endemic regions in children between 2 and 14 years of age (CYD14, in Asia-Pacific), and 9 and 16 years of age (CYD15, in Latin America). Vaccine efficacy was assessed during an initial 25 month active phase, after which a 4-year follow-up safety study is still ongoing, called long-term follow-up (LTFU) hospital phase. Post-dose 3 sera samples from the active phase were selected from subjects that developed a confirmed dengue case that required hospitalization during the LTFU surveillance phase along with age and site-matched controls who did not have a confirmed dengue case. The difference in antibody concentration and affinity for vaccinated individuals versus placebo-treated subjects was assessed, in addition to comparing the antibody levels and binding strength between hospitalized and non-hospitalized subjects, and <9 and ≥9 year old age groups. This investigation could contribute to determining the role of antibody quality, including affinity, for protection from dengue virus infection.

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ENHANCED DENGUE SENTINEL SURVEILLANCE IN METROPOLITAN SRI LANKA: 2012 TO 2015

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Dengue poses significant disease burden in Sri Lanka. Geographic spread, incidence and severity has increased since the first reported dengue hemorrhagic fever (DHF) epidemic in 1989. Nationwide routine disease surveillance established two decades ago is based on clinical diagnosis, with infrequent laboratory confirmation. To obtain robust disease burden data, a laboratory based enhanced sentinel surveillance was established in metropolitan Colombo. Here we present study design and results of three years. Three tertiary government hospitals and 3 outpatient clinics were selected. Following informed consent patients presenting

with acute undifferentiated fever were enrolled. Blood samples were collected and tested for dengue-specific PCR, NS1, and IgM-ELISA at first presentation. Sub-set of samples were sent to Duke-NUS Singapore for quality assurance, virus isolation and serotyping. Total of 5,436 patients were enrolled from April 2012 to March 2015 with 2,058 (37.5%) as outpatients and 3,389(62.3%) as inpatients. Mean age was 20.4 years (range 1moth to 90years). Mean duration of illness at first presentation was 4 days. For inpatients and outpatients, 2,851(78.5%) and 471 (22.9%) had laboratory-confirmed dengue respectively. Mean duration of hospitalization was 4 days. Proportion of DHF in lab-confirmed hospitalized dengue cases was 20.8% and 5(0.26%) died. Serotypes 1 (86.5%) and 4 (13.5%) were the only viruses detected. Clinicians' diagnosis of dengue at the time of first presentation had a sensitivity of 95.7% and specificity of 46.1%. Dengue infection was responsible for high proportion of febrile illnesses during the study period, with co-circulation of serotypes 1 and 4. One fourth of hospitalized dengue cases in Colombo developed DHF, but the case fatality rate was low. Clinicians' judgement was associated with good sensitivity, but to enhance specificity laboratory confirmation is important.

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GENETIC VARIABILITY OF DENGUE VIRUS TYPE 2 AND CLINICAL OUTCOME DURING THE 2009-2010 EPIDEMIC OF DENGUE IN COLOMBIA

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The pathogenesis of the severe outcome in dengue is the result of multiple factors attributed to both, the host and the virus. The aim of this study was to determine the serotype associated with severity and the variation within NS4B and E genes among strains of DENV-2 isolated from patients with different outcomes in Colombia. Severe cases were defined according to a compound outcome (hypotension or bleeding) in the baseline or follow-up. The serotype was determined by RT-PCR. Phylogenetic reconstruction was performed by the Maximum Likelihood method. Single nucleotide polymorphisms (SNPs) were identified using MEGA v6.06. One hundred ninety eight patients were evaluated at baseline and follow-up. Serotype distribution was heterogeneous across outcomes with DENV-2 being predominant in complicated patients (OR 6.06, 95% CI: 2.10, 17.5). The type of infection (primary vs. secondary) was not associated with the presence of the compound outcome (OR 1.58, 95% CI 0.83, 3.00). In 54 DENV-2 sequences three distinct lineages within the Asian-American genotype were identified. Neither lineages nor NS4B or E polymorphisms were associated with clinical outcome; they rather were associated with the place of residence. In summary, the DENV-2 serotype was associated with the development of severe forms of the disease but no SNP in NS4B or E genes was identified as associated with severe outcomes.

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A DENGUE VIRUS TYPE 2-SPECIFIC MONOCLONAL ANTIBODY BINDS TO THE DENGUE VIRUS-COMPLEX-REACTIVE ANTIGENIC SITE ON ENVELOPE PROTEIN DOMAIN 3

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Dengue disease is caused by four phylogenetically and serologically-related dengue viruses (DENV) throughout the tropics and subtropics worldwide. The envelope (E) protein is the major component of the viral surface and is structurally subdivided into three domains ED1, ED2, and ED3. The majority of antibodies target ED2, and ED3 elicits potent neutralizing antibodies. Two major DENV-2 antigenic sites were previously mapped to ED3: the DENV-type specific and the DENV-complex reactive antigenic sites, which are composed of a limited subset of residues that are required for monoclonal antibody (mAb) binding. In the present study, binding to recombinant ED3 mutants and neutralization of DENV-2 strain New Guinea C mutants demonstrated that the amino acid side-chains K307, V308, K310, I312, P332, L387, L389, and N390 are functionally critical for DENV-2-type-specific mAb 9A3D-8. Surprisingly, the binding footprint of mAb 9A3D-8 is predicted to overlap primarily with the DENV-complex-reactive antigenic site on ED3. This unique binding site enabled mAb 9A3D-8 to neutralize virus infectivity at relatively low occupancy of virions compared to other mouse mAbs. Monoclonal antibody 9A3D-8 is a unique DENV-2-type-specific mAb due to its virus species specificity and its high neutralization potency, the DENV-complex reactive site for physical binding, and exhibits increased occupancy efficiency. This is a new DENV-2 type-specific antigenic site on ED3.

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PERFORMANCE OF A RAPID TEST FOR THE DETECTION OF DENGUE DURING THE OUTBREAK OF ZIKA VIRUS IN COLOMBIA

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Diagnosis of Zika virus (ZIKV) infection is done by detection of viral RNA (real time PCR) as serological tests have shown cross-reactivity with other genetically related viruses such as dengue (DENV). The aim of this study was to evaluate the performance of SD BIOLINE Dengue test for the diagnosis of DENV and to determine cross-reactivity with ZIKV in febrile patients. We evaluated 60 serum samples from patients with history of fever (less than or equal to 5 days of duration) for the detection of dengue NS1 antigen, IgM, and IgG antibodies. Thirty samples were randomly selected from participants of a dengue passive-facilitated surveillance study conducted in Piedecuesta, Colombia, before the introduction of ZIKV in the country (August to December 2014). The samples were positive for

dengue using RT-PCR and negative for ZIKV (real time RT-PCR, CDC). The Laboratory of the National Health Institute of Colombia provided a second set of 30 samples collected after the introduction of the ZIKV in the country (September of 2015), which were confirmed as positive for this virus (real time RT-PCR, CDC) and negative for DENV (real time RT-PCR, CDC). All 60 samples were tested for dengue NS1 antigen, IgM, and IgG (SD BIOLINE dengue DUO [NS1/IgM/IgG]) by the same operator and in a single batch. Two trained observers independently interpreted the results. We estimated sensitivity and specificity (95% confidence interval; 95%CI) of the NS1 antigen, IgM, and IgG. The two observers fully agreed on the interpretation of all the tests. Twenty out of 30 samples of confirmed cases of DENV were positive for NS1, that is, a sensitivity of 66.7% (95%CI: 47.2 - 82.7). There were no false positive results of the NS1 (100% specificity). Sensitivity of IgM and IgG was the same (3.3%, 95%CI: 0.1 - 17.2) and specificities were 93.3% (95% CI: 77.9 - 99.2) and 86.7% (95% CI: 69.3 - 96.2), respectively. In this study, the rapid test SD BIOLINE showed cross-reactivity for IgM and IgG antibodies but not for NS1. Further studies will test the reproducibility of our findings and control for variables such as viral serotype, duration of disease, type of infection and host genetics.

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EARLY CLINICAL INDICATORS OF DEVELOPING SEVERE DENGUE IDENTIFIED FROM A PROSPECTIVE ACUTE FEBRILE ILLNESS STUDY IN PUERTO RICO

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Because dengue is a dynamic disease characterized by progression in some to a life-threatening disease, early identification of at-risk patients could enable timelier follow-up and initiation of supportive care. To identify early clinical features associated with severe dengue, data from a prospective AFI study conducted in Puerto Rico during May 7, 2012-May 6, 2015 was analyzed. Febrile patients presenting to the emergency department were enrolled and followed through their illness. Blood and nasopharyngeal specimens were collected and tested by RT-PCR and immunodiagnostic methods for dengue viruses 1-4 and 16 other pathogens. Dengue patients who were not severe at enrollment but later developed severe dengue (Cases) were compared with dengue patients who never developed severe dengue (Controls). Of 684 laboratory-positive dengue patients with complete follow-up, 174 (25%) met criteria for severe dengue, 90 (52%) at enrollment and 84 (48%) later in their clinical course. Cases and controls were similar with regard to age, but cases were more likely to be female (62%, p = 0.003). At enrollment, cases were more likely to have anorexia (91% vs. 76%, p = 0.01), nausea (80% vs. 63%, p = 0.01), and leukopenia (87% vs. 72%, p = <0.01). Controls were more likely to present with rash (51% vs. 38%, p = 0.05) and hemoconcentration (37% vs. 17%, p = <0.01). After controlling for age and sex in logistic regression analysis, cases were more likely to have nausea at enrollment (OR = 2.70, 95% CI: 1.28-4.90) and leukopenia (OR = 2.67, 95% CI: 1.34-6.58), while controls were more likely to have rash (OR = 0.47, 95% CI: 0.28-0.80) and hemoconcentration (OR = 0.39, 95% CI: 0.19-0.78). Cases were more likely to have history of asthma (OR = 2.33, 95% CI: 1.12-3.78). Enrolling febrile patients at initial presentation enabled an unbiased determination of early clinical predictors of severe dengue. These data suggest that nausea and leukopenia may be predictors of developing severe dengue. Clinicians should be aware that patients with asthma or those presenting with nausea are at increased risk for developing severe dengue after initial presentation.

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DECODING THE SANOFI PASTEUR DENGUE VACCINE INFECTIVITY AND IMMUNOGENICITY USING THE HUMAN *IN VITRO* MIMIC® SYSTEM

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Sanofi Pasteur's licensed tetravalent dengue vaccine generates equivalent neutralizing titers against all 4 serotypes and pooled phase III clinical data in subjects over 9 years of age demonstrated conclusive, but differential levels of efficacy against the serotypes. To better understand the efficacy trial results, we studied the infectivity of the phase III lots using the innate arm of the MIMIC® system. The MIMIC system's peripheral tissue construct was adapted to assess DC viral infectivity and viral progeny levels in the supernatants for each of the 4 serotypes from the CYD vaccine as well as DC activation and cytokine profiles. The hierarchy of response for infectivity and viral progeny as measured by RT-PCR and plaque assay, respectively, for CYD vaccines in MIMIC was CYD4>CYD3>CYD1>CYD2. Previous published data and current experiments show that *in vitro* infectivity studies in IL-4 and GM-CSF derived mDCs do not show any differences between CYD serotypes, which could be due to the high level of DC-SIGN expression on the cytokine-derived mDCs. We also tested whether the difference in infectivity was due to interference between vaccine serotypes by evaluating them individually as monovalents. We show that no competitive inference was detected among the CYD serotypes in the MIMIC system and showed the same infectivity hierarchy for the monovalent lots. We assessed the immune profile induced by the CYD dengue vaccine and were able to detect up-regulation of CD86, and secretion of CXCL10/ IP-10 which have been reported as protective innate signatures in dengue infections. We also show that the pro-inflammatory cytokines such as Macrophage Inhibitory Factor (MIF) and IL-8 are secreted at markedly lower levels after infection with the dengue vaccine than by parental DENV controls. Further studies have been initiated to investigate how *in vitro* infectivity in the MIM aligns with clinical results in endemic populations following vaccination. These analyses demonstrate that the CYD dengue vaccine induces a protective innate immune signature and that the MIMIC system is a valuable preclinical tool for future vaccine candidate evaluations.

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CLINICAL IMPACT OF DENGUE AND RESPIRATORY VIRUS CO-INFECTION IN A PASSIVE SURVEILLANCE, IN THE PERUVIAN AMAZON, PERU

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Dengue virus is an important cause of morbidity and mortality in developing countries. In the Peruvian Amazon where dengue is highly endemic, respiratory viruses also have significant public health impact, especially in the cities of Iquitos and Yurimaguas. In some periods, both viruses co-circulate resulting in co-infections whose clinical characteristics remain poorly characterized. Clinic-based passive febrile surveillance established by NAMRU-6 in both cities provided the opportunity to analyze these viral co-infections. From 2010-2014, patients with acute undifferentiated febrile illness and/or influenza like-illness who sought medical evaluation in one of the thirteen hospitals or primary health

care facilities, supplied clinical data and paired blood samples and/or an oropharyngeal swab. Acute samples were tested for dengue or respiratory virus by cell culture or PCR, while acute and convalescent blood samples were tested by ELISA for dengue IgM. Of 7,150 febrile cases, 2,145 (30%), 597(8.3%), and 15 (0.2%) had laboratory evidence of dengue, respiratory virus, and co-infection, respectively. Most of the dengue infections (1616 cases, 75%), were due to serotype 2. Of the fifteen co-infections, 8 (53%) were due to Influenza B, 3 (20%) to Influenza A/H1N1pdm09, 2 (13.3%) to Influenza A/H3N2, and 2 were unidentified subtypes of Influenza A. Eleven cases (73%) were detected between February and June 2014. Rhinorrhea, cough, and shortness of breath were associated with co-infection in contrast to dengue alone ($p < 0.05$, Pearson Chi square test), while hospitalization rate (26.6 vs. 25.3%) and shock (0 vs. 0.1%) were similar in both groups ($p>0.05$). There were no fatal cases. Co-infections reported here, did not display enhanced severity compared to DENV-2 infections. Considering that asymptomatic/non-febrile cases are reported for both types of infections were not included, and despite seem to be a temporal correlation there was not a correlation spatial circulation at fine-scale foci (house). A cohort study with geo-spatial analysis would be important for continuing this work.

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ROLE OF SKIN MAST CELLS IN DENGUE VIRUS INFECTION

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Dengue virus (DENV) causes the most common vector-borne viral disease in humans living in the tropics. Transmission of DENV occurs when a mosquito vector takes a blood meal from a DENV infected host. The DENV-containing saliva is deposited in the skin of the host during probing. Human skin contains many types of immune cells, including mast cells. Here, we show that mast cells are a target of DENV in human skin and that DENV infection of skin mast cells induces degranulation. Additionally, DENV infection of primary human skin mast cells results in altered cytokine and growth factor expression profiles. Importantly, we also demonstrate for the first time that DENV localizes within secretory granules in infected skin mast cells. In addition, DENV within extracellular granules was infectious *in vitro* and *in vivo*, trafficking through lymph to draining lymph nodes in mice. We demonstrate an important role for human skin mast cells in DENV infection and identify a novel mechanism for systemic spread of DENV infection from the initial peripheral mosquito injection site. Together, these findings demonstrate a critical previously unrecognized role for skin mast cells in the infection and propagation of DENV in humans.

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DENGUE VIREMIA IN KENYAN CHILDREN WITH ACUTE FEBRILE ILLNESS

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Dengue virus (DENV) remains the most prevalent arboviral infection worldwide, causing an estimated 400 million infections per year. By mathematical modeling, 16% of DENV infections occur in Africa. However due to lack of routine surveillance programs, the burden of DENV infection in many African countries is largely unknown. As a part of an ongoing study on arboviral infection in Kenyan children, we collected blood samples from subjects 1 to 17 years of age who presented with fever of unclear etiology to one of four centers located either in western (Kisumu and Chulaimbo) or coastal Kenya (Ukunda and Msambweni). We tested the samples for the presence of DENV RNA by RT-PCR. DENV RNA positive samples were then serotyped by PCR. Testing is ongoing, however, preliminary results have identified DENV viremia more frequently in subjects with acute febrile illness in western vs. coastal Kenya (9.2% positive [75 of 814 subjects] vs. 0.9% [4 of 435 subjects], respectively, $p<0.001$). In western Kenya, all four serotypes were identified; 51 samples had serotype 1 (DENV-1), two had DENV-2, thirteen had DENV-3, and two had DENV-4. There were also subjects who had dual infection with two DENV serotypes: one subject with DENV-1+3, three with DENV-1+4, and one with DENV-2+3. Only DENV-1 was identified in samples from coastal Kenya. To investigate the phylogeny of the DENV strains, we performed exploratory next-generation sequence (NGS) on a limited subset of the samples. DENV-1 sequences were over-represented from blood samples of seven subjects from western Kenya (five from Chulaimbo, two from Kisumu) and mapped to a strain from Thailand (accession AF180818) with 98.5-99.4% homology. Further sequencing experiments will be important for developing a better understanding of the phylogeny of DENV strains currently circulating in Kenya. Together, our preliminary results suggest that DENV may be an important cause of acute febrile illness in Kenyan children, but the incidence and disease burden may differ by geographic location.

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DEFINING THE CLINICAL MANIFESTATIONS OF ZIKA AND DENGUE PATIENTS ATTENDED IN RIBEIRÃO PRETO, BRAZIL

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Zika is an emergent arthropod-borne disease that is circulating in Brazil since 2015. Since last year, we suspected that zika virus (ZIKV) was circulating in Ribeirão Preto (RP) at the same time of dengue virus (DENV). Up to this moment, little is known about the clinical aspects of this disease. Hence, the present study aimed to investigate the clinical presentation of Zika in patients with a probable diagnosis of Zika or Dengue referred to a tertiary hospital of RP. We conducted a retrospective analysis of the 162 patients attended from January to March 2016. Of these, 43 had positive results for ZIKV by RT-PCR in blood, 44 had dengue confirmed by detection of NS1 antigen and/or ELISA for IgM antibodies against DENV and 75 had other febrile illnesses. Rash was found in all Zika patients, predominantly macular or maculopapular and one had petechial rash; 57% had a malar rash. The rash usually appeared in the first day of symptoms. Among dengue patients, 75% and 37.5% had exanthematic and malar rash, respectively. Zika and dengue presented with malaise in 81.8% and 80%; myalgia in 63.0% and 78.3%, respectively. Arthralgia was more frequent in zika than in dengue (82.6% and 55.7%, respectively) although in both groups, about 20% of the patients with arthralgia had periarticular swelling or arthritis. Fever was present in 69.2% of dengue but was not common in Zika (37.9%). Conjunctival injection was reported in 59.1% of Zika and only in 28.6% of dengue patients. Less common symptoms in Zika patients were headache (52.2%), retro-orbital pain (53.3%), nausea (18.2%) or vomiting (9.1%), diarrhea (13.6%), and bleeding (4.0%). Upper respiratory tract symptoms were observed only in dengue patients (16.7%). Characterization of disease presentation is important for diagnosis to differentiate between other arboviral diseases that could occur simultaneously in the same area, especially in epidemic situation where laboratory testing become impracticable. Although there were some distinction between Zika and dengue, our data show the clinical hurdles to differentiate these diseases and justify the need for developing a fast and specific laboratory test for Zika.

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BINDING OF HUMAN MONOCLONAL ANTIBODIES TO DENGUE VIRUS WITH DIFFERENT MATURATION STATUS: A COMPARATIVE ANALYSIS

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The four serotypes of dengue virus (DENV) cause the most important arboviral disease in humans. Envelope (E) protein is the major target of neutralizing (NT) antibody. The ectodomain of E protein consists of 3 domains (DI, DII and DIII). Previous studies have shown that monoclonal antibodies (mAbs) recognizing DIII are more potent neutralizing (NT) than those recognizing fusion-loop (FL) of DII. During the maturation process, the precursor membrane (prM) protein on immature particles is inefficiently cleaved by furin, resulting in a mixture of mature, immature and partially immature virions in the culture supernatants. We studied the relationships between epitope accessibility, binding avidity and NT potency of mAbs on DENV virions produced from two cell lines with differential maturation status. To generate immature, mixed and mature virions from 293T and BHK cells, DENV1 were inoculated in the presence or absence of ammonia chloride, and furin over-expression, respectively. A virion-capture ELISA were carried out to examine the relative prM content in various particles with differential maturation status, and the binding of human anti-FL and anti-DIII mAbs. Maximum binding (Bmax) and dissociation constant (Kd) were determined (GraphPad Prism 6). NT potency, accessibility and avidity were assessed by 1/FRNT50, Bmax and 1/Kd, respectively. Regardless the sources of DENV particles, anti-DIII mAbs showed significantly lower Kd to mature virions than anti-FL mAbs, suggesting the higher binding avidity on the infectious virions may contribute to stronger NT activities of anti-DIII mAbs compared to anti-FL mAbs. Some anti-FL mAbs showed different Kd to mixed virions derived from 293T and BHK cells, which can be attributed to differential maturation status of virions from the two sources. The results on DENV virions are generally in agreement with our previous study using DENV virus-like particles and have implication for immunogen design to induce more potent NT antibodies against DENV.

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SUPERENSEMBLE FORECASTS OF DENGUE OUTBREAKS

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Dengue is a mosquito-borne viral disease prevalent in the tropics and subtropics, with an estimated 2.5 billion people at risk of transmission. In many areas with endemic dengue, disease transmission is seasonal but prone to high inter-annual variability with occasional severe epidemics. Predicting and preparing for periods of higher than average transmission is a significant public health challenge. Recent work has demonstrated that accurate forecasts of the timing and severity of disease outbreaks can be generated using a framework combining a dynamical model of disease transmission and data assimilation methods. However, because no model perfectly represents transmission dynamics in the real world, infectious disease forecasts made by a single model are prone to error due to this model misspecification. In weather and climate forecasting, this problem has been addressed by combining forecasts from multiple competing models in a superensemble. The intent is that some of the biases inherent in the different models will offset so that the superensemble produces more accurate predictions than those generated by any individual model. Here, we develop three distinct forecasting systems for dengue outbreaks in San Juan, Puerto Rico and then use Bayesian averaging methods to combine the predictions from these systems and create a superensemble forecasts. We demonstrate that on average, this approach leads to more accurate forecasts than those made from any of the individual forecasting approaches.

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LESSONS LEARNED FROM THE LARGEST AND MOST SEVERE EPIDEMIC OF DENGUE VIRUS SEROTYPE 2 (DENV-2) IN TAIWAN, 2015

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Most of dengue outbreaks in Taiwan in each year start from imported cases coming from South East Asia, except for the four over-wintering years (1987-88, 2001-02, 2009-10, 2014-15). Among all indigenous dengue cases, DENV-1 was the most common in the years before 2000, 2007, and 2014 whereas DENV-3 was isolated more frequently in 2005-06 and 2009-10 and DENV-2 was highly prevalent in 2001-03, 2011, 2013, and 2015. Therefore, DENV-2 had lower occurrence for recent 11 years until 2015. The epidemic started from dengue cluster cases occurring in the flea market of Tainan in May, 2015 and spread to Kaohsiung in July. Retrospective big data analyses identified that age groups of 19-34 and 35-49 years in Tainan played a major role of initial spreading since June 18 till July in Tainan. At the end of August, Advisory Committee was appointed by the Mayor. Health education began to target at these age groups and geographical information system (GIS) was implemented to daily evaluate emerging cases and predicting cases in future weeks, using the smallest neighborhood area (Li). By September, DENV-2 has become the dominant serotype in Kaohsiung till April of 2016, even though DENV-1 was predominant serotype from 2014 to August, 2015. Viral sequence and phylogenetic analyses of the E region found that the causing agent was the DENV-2 came from Indonesia Cosmopolitan genotype that was different from the DENV-2 in 2001-02 arisen from the Philippines Cosmopolitan genotype and the DENV-2 Asian 2 genotype in 1981 imported from the Philippines. By November, Tainan City government successfully controlled the epidemic before winter season. In conclusion, this is the first time that open-data resources and timely big data analyses were applied to be integrated with epidemiological analysis in Tainan. Most of severe dengue cases were elderly with chronic illness. Our valuable experiences indicate that web-based epidemiological information was very helpful for local residents and government officials at different levels and agencies to have rapid communication and contain the epidemic much earlier. More experiences will be shared in this meeting.

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WHAT NOW? CIRCULATION OF ZIKA, DENGUE AND CHIKUNGUNYA VIRUSES IN A CITY FROM BRAZIL

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Dengue (DENV) is undeniably a public health problem that cannot be put aside. Nor its importance can be lessened due to Zika virus (ZIKV) or any other arboviral disease. Brazil presented one of the worst outbreaks in 2015, with 1,6 million cases officially reported. There has also been an increase in disease severity and number of deaths. But *Aedes aegypti* mosquitos are not transmitting only dengue in Brazil. Chikungunya and Zika viruses are spread all over the country, including Araraquara, central portion of the State of São Paulo. The idea was to establish a potential collaboration between the Municipal Department of Health and a

research institution of the city to search for arbovirus in humans. People presenting dengue-like illness were directed to a particular Health Unity, where a trained person of our team was collecting blood and performing epidemiological surveys. We collected 362 serum samples and tested them for the presence of ZIKV, CHIKV and the four DENV serotypes by RT-PCR. DENV-1 was detected in 60 patients. DENV-4, as well as CHIKV, was detected in one patient. Eight patients were infected with ZIKV. Symptoms such as fever, arthralgia, myalgia, and rash were common. No microcephaly cases were reported in the city. The circulation of four different viruses within the urban space indicates that vector control and prevention strategies have to be reevaluated. The collaboration between two different public institutions provided epidemiological information that had never been evaluated until that point and may be an opportunity to detect virus introductions when they occur with a real possibility of avoiding viral spread.

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POTENTIAL IMPACT OF DENGUE VACCINE IMPLEMENTATION ON SURVEILLANCE AND DIAGNOSIS - INSIGHTS FROM SEROLOGICAL PROFILES OF FEBRILE CASES IN PHASE III DENGVAXIA® EFFICACY TRIALS

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Dengue surveillance is widely based on detecting IgM/IgG dengue antibodies in one post-infection sample. We previously communicated results showing that CYD-TDV vaccination induces false positive cases detected by IgM/IgG ELISA. In a post-hoc analysis of a subset of individuals from two PhIII efficacy studies (CYD14/CYD15), we describe IgM/IgG serological profile of febrile sera samples in 145 virologically confirmed dengue cases (VCD) and of 2646 febrile sera from non-confirmed dengue episodes (non-VCD) according to their dengue baseline status. This allows us to further assess the impact of dengue vaccination on serological detection of probable dengue cases IgM profile of 145 VCD cases shows that 95.9% (95%CI: 91.2-98.5) were IgM positive regardless of baseline dengue status or study group. Among 1825 febrile non-VCD episodes in seropositives, a lower but similar proportion were IgM positive in both groups (22% [19.3-24.0] in vaccine; 21% [18.0- 24.5] in control). On the other hand, among 821 non-VCD in seronegatives, a statistical difference is observed with 33% (28.7-37.0) IgM positives in vaccine and 15% (11.4-19.8) in controls, highlighting, in seronegatives, the previously reported vaccine-induced IgM positive samples. IgG profile in VCD cases indicates no difference between vaccine & control groups (100% for both in seropositives & in seronegatives 100% [89.4-100] vaccine *vs*. 89% [70.8-97.5] control). Among non-VCD episodes in seropositives, a trend for higher rate of IgG positive samples in vaccine is observed (97% [95.5-97.6] *vs*. 88% [85.6-90.8] for control). In seronegatives, a significant difference is observed (77% [73.2; 80.6] vaccine *vs*. 14% [10.2; 18.3] control; 5.5-fold difference). This highlights the impact of CYD-TDV vaccination on IgG detection in febrile non-VCD episodes. In conclusion, Dengue vaccination impacts IgM and IgG ELISA detection of probable cases in seronegative individuals. This presents a challenge for IgM/IgG ELISA based surveillance in countries where Dengue vaccine is implemented. New practical, dengue specific diagnostic algorithms are needed. * confirmed by PCRs or NS1-antigen ELISA.

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SUSCEPTIBILITY OF MEDICALLY IMPORTANT *CULEX* SPECIES MOSQUITOES TO JAPANESE ENCEPHALITIS VIRUS

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Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus that is considered an important human and animal pathogen. Whilst transmission of JEV is mainly achieved by *Culex tritaeniorhychus* in endemic countries, it has been demonstrated that the virus is capable of infecting multiple mosquito species, which can subsequently become competent vectors for disease transmission. Previously, our group has demonstrated *Cx. quinquefasciatus* in the United States is a competent species for JEV. However, susceptibility of other medically important *Culex* species mosquitoes in North America remains undetermined. Based on the importance in the transmission of arboviruses in North America, susceptibility of three American *Culex* species mosquitoes to JEV was determined through oral infection. *Cx. pipiens* was chosen based on its importance in the transmission of West Nile virus (WNV) and Saint Louis encephalitis virus. *Cx. restuans* and *Cx. tarsalis* were tested because of their role as competent vectors for WNV and Western equine encephalitis virus, respectively. Infection and dissemination were observed at 7 and 14 days post infection in all three species, indicating that multiple medically important *Culex* species mosquitoes are susceptible to JEV. As observed with WNV, which rapidly established itself in the United States by utilizing multiple species of mosquitoes as vectors, JEV is a significant public health threat to the United States as it also possesses the capacity of infecting multiple species of mosquitoes. In the event of its introduction, establishment of enzootic transmission can take place by infecting multiple species of mosquitoes.

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DECREASED ZIKA VIRUS REPLICATION IN MOSQUITO CELLS CO-INFECTED WITH NHUMIRIM VIRUS

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Nhumirim virus (NHUV) is a flavivirus isolated from Brazil with an apparent insect-specific host restrictive phenotype. Previous studies in *Aedes albopictus* cells (C6/36) have demonstrated the ability of NHUV to restrict West Nile virus (WNV) growth more than a million fold, Saint Louis encephalitis virus (15,000-fold) and Japanese encephalitis virus (80-fold). Similar viral growth reduction was demonstrated for WNV/NHUV co-infection in alternative *Ae. albopictus* cells (C7-10). *Culex quinquefasciatus* and *Cx. pipiens* mosquitoes were intrathoracically inoculated with WNV or NHUV/WNV and transmission assessed. A decreased proportion of WNV transmitting Cx. *quinquefasciatus* mosquitoes was observed in NHUV/WNV mosquitoes at 7 and 9 days post-inoculation (dpi) compared to WNV-only, suggesting NHUV could act as a potential transmission barrier for other medically important flaviviruses. Currently, there are no approved vaccines or prophylaxis treatments for human Zika virus (ZIKV) infections so reduction in exposure rates to ZIKV infected mosquitoes is the principal means available to reduce human disease. To asses whether ZIKV replication is affected by pre- or concurrent NHUV infection, C6/36

cells were concurrently inoculated with NHUM (MOI 5) and ZIKV (MOI 0.1) or similarly inoculated with NHUV at 5, 3, or 1 day(s) prior to ZIKV inoculation and titers determined by plaque assay. ZIKV-only cultures achieved significantly higher titers at 1-7 dpi than dually inoculated cells. Mean peak titer of ZIKV-only cultures was 10.5 log10 (PFU/ml) while peak titers for pre- or concurrently inoculated NHUV/ZIKV cultures ranged from 3.4 - 5.5 log10 (PFU/ml), resulting in an approximate 100,000-fold reduction. No effects on timing of NHUV infection compared to ZIKV inoculation were observed. These *in vitro* results suggest NHUV could serve as a possible ZIKV transmission barrier, thus potentially modulating Zika vector competence and force of transmission in geographic areas in which NHUV and similar flaviviruses exist. Dual infection *in vivo* studies in prospective western hemisphere ZIKV vectors are being planned to address this potential.

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AVAILABILITY OF ZIKA VIRUS INFORMATION ON OBSTETRIC PRACTICE WEBSITES AND SOCIAL MEDIA ACCOUNTS IN THE UNITED STATES

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Provider to patient communication, whether domestically or internationally, is critical during a public health emergency. Understanding health care providers' utilization of the Internet for dissemination of health information is useful for emergency public health messaging strategies. In early 2016, the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists advised health care providers to communicate the risks of Zika virus (ZIKV) infection and prevention methods to their patients. This study's objective was to estimate the proportion of obstetric practice websites in the U.S. providing information on ZIKV within two weeks following initial release of interim guidance for care of obstetric patients. Out of 1,004 obstetric practice websites examined, only 244 (24.3%) posted information pertaining to ZIKV on their websites or website-linked social media accounts. Among those posting on ZIKV, information was more often found on their practice-sponsored social media accounts (74.2%; p=0.006) or elsewhere on their website (45.9%; p=0.35) compared to the homepage (17.2%). Practices affiliated with non-academic hospital systems and academic-hospital systems were significantly more likely to post ZIKV information (31.3%, odds ratio [OR] 2.71, 95% confidence interval [CI] 1.90-3.87; 51.3%; OR 6.29, 95% CI: 3.99-9.91, respectively) compared to obstetric practices (14.4%). 84.8% of the content posted mentioned international travel advisories and 62.3% provided information on the use of insect repellent. Although there is growing use of the Internet and social media to provide patients with health information, ZIKV information was not readily available on most obstetric care practice websites within two weeks following the release of national guidance on care of obstetric patients. Ensuring that providers around the world have the information they need to confidently utilize their practice websites and social media accounts for provision of urgent health information could keep patients as informed as possible during an evolving public health emergency.

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ZIKA AND OTHER MOSQUITO-BORNE VIRUS DETECTION AND DIFFERENTIATION USING A MULTIPLEXED, BEAD BASED RT-PCR ASSAY

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Since May 2015, South and Central America have experienced an epidemic outbreak of Zika Virus. Several travel related cases have already been identified in the United States. Zika infection during pregnancy has been implicated in the development of microcephaly in the developing fetus and is thought to be responsible for an increased incidence of Guillain-Barre syndrome. The expanding footprint of the disease, along with the devastating neurological effects associated with Zika Virus warrant rapid and early detection of Zika Virus during the critical viremic phase. In areas with co-circulating mosquito borne illnesses, viruses must not only be detected, but differentiated in order to provide accurate results. An RT-PCR based multiplex microsphere assay was developed to detect and differentiate Zika Virus, Chikungunya Virus, Dengue Virus (Serotypes 1-4), West Nile Virus, and Yellow Fever Virus. Assay performance was established using representative virus strains and clinical samples. The assay demonstrates required analytical sensitivity and is able to detect and differentiate each virus. The multiplex RT-PCR assay eliminates the need for sequential testing and complicated patient care algorithms. The multiplex format allows for simultaneous identification of viruses among a group of viruses that are difficult to distinguish due to simultaneous circulation of the viruses and strong similarities in the associated symptoms.

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ARBOVIRUS IMMUNOHISTOCHEMISTRY: CHARACTERIZING CROSS-REACTIVITIES OF DIFFERENT IMMUNOHISTOCHEMISTRY ASSAYS

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Dengue (DENV), Zika (ZIKV), yellow fever (YFV), chikungunya (CHIKV), West Nile (WNV) and Japanese encephalitis (JEV) viruses are mosquito-borne arboviruses. Several other viruses share the same *Aedes* vectors, overlap in their endemic areas, have recently re-emerged globally, and pose a major threat to public health. While RT-PCR in general is the most specific and sensitive test for these arboviruses in pathology specimens, immunohistochemistry (IHC) has value in demonstrating the presence of viral antigens in tissue and can provide insight into pathogenesis. Because serological cross-reactivity is well documented, particularly for flaviviruses, it is imperative to evaluate the level of cross-reactivity of arbovirus antibodies (Ab) used in immunohistochemical assays. In a diagnostic reference laboratory, we tested six different arbovirus Ab against cell controls, made with cells infected with different flaviviruses, and RT-PCR confirmed clinical specimens to characterize cross-reactivities. IHC assays were performed on 4µm sections of FFPE tissue using a polymer-based indirect immunoalkaline phosphatase detection system with colorimetric detection of antibody/polymer complex with Fast Red Chromogen. The JEV showed cross-reaction with all flavivirus-infected tissue tested. WNV and ZIKV assays had minimal cross reactivities with only one other arbovirus (CHIKV and DENV respectively), and YFV and DENV assays had intermediate cross-reactivities with 2-3 other arbovirus (YFV cross-reacts ZIKV and DENV, and DENV cross-reacts WNV, ZIKV and JEV). The observed assay cross-reactivity are directly related to genetic similarities among the viruses. Importantly however, different viruses have characteristic tissue

and cellular tropism by IHC which contributes to its diagnostic utility. These cross-reactivity data provide insight to the strengths and limitations of IHC assays for certain arboviruses in a diagnostic reference laboratory.

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CHARACTERIZATION OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME DURING THE ZIKA EPIDEMIC IN VENEZUELA

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Guillain-Barré syndrome (GBS) is an acute or subacute autoimmune inflammatory demyelinating polyradiculoneuropathy. It is the most common cause of flaccid paralysis and can be life threatening. GBS is characterized by a rapid-onset acute symmetrical muscle weakness, habitually ascending, affecting 1:100,000 people. In most cases GBS has been preceded in the last 6 weeks by gastroenteritis or a respiratory tract infection. During the zika virus epidemic that affects Venezuela since December 2015, a massive and rapid increase in the number of GBS patients presenting to the emergency department of the main referral hospital (CHET) of Valencia city, Venezuela has been reported. Typically, one GBS patient per month is recorded at CHET however, during the zika epidemic around 45 cases were admitted during the months of January and February 2016. We aim to characterize the clinical presentation of GBS patients and the possible association with a previous or current zika virus infection. A study is ongoing to collect clinical, laboratory and paraclinical tests data of confirmed GBS patients after informed consent along with a blood sample to perform differential diagnosis between zika, chikungunya and dengue virus infection, as these three arboviruses currently co-circulate. Preliminary results of 12 patients indicate a mean age of 56 years (range 37-83 years) with a predominance of male patients (67%). A short time (average= 6.5 days, range 1-15 days) is described between the onset of symptoms compatible with Zika infection and the beginning of neurological symptoms. Most patients rapidly progressed to life threatening disease within 24-48h. Five patients were admitted to intensive care unit of which three died (mortality=25%) despite treatment with plasmapheresis and/or immunoglobulin. A detailed description of the clinical spectrum, possible risk factors and serological diagnosis of arboviruses will be presented on the totality of patients included in the study.

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VIREMIA AND CLINICAL PRESENTATION AMONG NICARAGUAN PATIENTS WITH ZIKA VIRUS AND DENGUE VIRUS INFECTIONS

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The first autochthonous cases of Zika virus (ZIKV) were reported in Nicaragua in January 2016. ZIKV now co-circulates with dengue virus (DENV) and chikungunya virus (CHIKV) throughout the country. Although the duration of viremia in Zika fever is reportedly shorter than the duration observed in DENV infections, little quantitative viremia data has been published. In the current study, we tested acute-phase serum from sequential patients with a suspected arbovirus infection. Serum was collected as part of a national surveillance system in Nicaragua. 346 samples were tested using a single-reaction multiplex real-time RT-PCR for ZIKV, CHIKV and DENV (the ZCD assay), and viremia in ZIKV- and DENV-positive samples was quantitated. Overall, 263 (76.0%) serum samples were positive for one or more pathogens. 75 patients (28.5%) tested positive for ZIKV (47 mono-infections, 28 co-infections). 109 (41.4%) patients were positive for DENV (54 mono-infections, 55 co-infections). Identified co-infections included all combinations of the 3 viruses: ZIKV-CHIKV (n=16), ZIKV-DENV (n=6), DENV-CHIKV (n=43), and ZIKV-CHIKV-DENV (n=6). The mean duration of symptoms was similar for ZIKV-positive (3.4 days, SD 1.1) and DENV-positive patients (3.4 days, SD 1.3; p=0.81). Quantitated viremia in ZIKV-positive samples (mean 4.7 log10 copies/mL serum, SD 1.0) was significantly lower than DENV-positive samples (5.8 log10 copies/mL serum, SD 1.8; p<0.01). The distribution in viremia also differed significantly (p<0.01 by Kruskal-Wallis test), and only 39/75 (52.0%) ZIKV-positive samples had quantifiable viremia compared to 94/109 (86.2%) DENV-positive samples. For both viruses, viremia was significantly lower in co-infections than mono-infected samples. Finally, an analysis of clinical signs and symptoms in relation to viremia at presentation will be presented. Results from this study have important implications for ZIKV diagnosis in the acute phase and expand upon the available literature regarding viremia in ZIKV infected patients.

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EFFECTS OF TEMPERATURE ON ZIKA, DENGUE AND CHIKUNGUNYA TRANSMISSION BY *AEDES AEGYPTI* AND *AE. ALBOPICTUS*

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The geographic distribution of vector-borne diseases is shaped by many ecological and evolutionary factors, including the response of vectors and pathogens to environmental drivers. Mosquito-transmitted diseases such as Zika, dengue, and chikungunya are intimately linked with environmental temperature and humidity because of mosquito and pathogen physiological responses, including growth, development, survival,

reproduction, and behavior. Current models often inaccurately predict that warmer temperatures will tend to increase mosquito transmission even as temperatures warm above 30°C. In contrast, models that include more physiologically accurate, nonlinear thermal responses of the mosquito and pathogen vital rates that drive transmission predict intermediate optimal temperatures. Here, we develop a model of arbovirus transmission (particularly dengue, chikungunya, and Zika viruses) by *Aedes aegypti* and *Ae. albopictus* mosquitoes that includes physiologically accurate, nonlinear mosquito and parasite thermal responses. *Ae. aegypti* and *Ae. albopictus* development rates, longevity, fecundity, and biting rates, as well as dengue virus vector competence and extrinsic incubation rates have hump-shaped responses to temperature with intermediate optima. As a result, dengue, chikungunya, and Zika virus transmission are optimal at intermediate temperatures (27-29°C) and decline steeply above 32-36°C and below 15-17°C). The model predictions are consistent with field data from the Americas on the number of human dengue, Zika, and chikungunya cases across space and time. These intermediate optimal temperatures are robust to uncertainty in trait thermal responses. We quantify sources of uncertainty in transmission across temperatures and make prescriptions for future experimental work to resolve this uncertainty. Together, the results imply that much of tropical, sub-tropical, and temperate North, Central, and South America and the Caribbean are suitable for seasonal or year-round transmission.

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GUILLAIN-BARRÉ SYNDROME RISK AMONG INDIVIDUALS INFECTED WITH ZIKA VIRUS

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As of early April, 2016, local Zika virus (ZIKV) transmission had been confirmed in 33 countries in the Americas where transmission had never previously been reported, and 9 of those countries had reported notable increases in the number of cases of the neurological disorder Guillain Barré Syndrome (GBS). These increases were spatio-temporally correlated with reports of Zika cases and ZIKV infection has been confirmed in some of the GBS cases. A potential connection between ZIKV infection and GBS was first noted during an outbreak of Zika in French Polynesia. It was later shown that all forty-two reported GBS cases in French Polynesia had evidence of previous ZIKV infection, compared to only approximately half of non-GBS controls. Estimated GBS risk in French Polynesia was approximately 2.4 cases per 10,000 ZIKV infections, more than 10 times the expected baseline risk. We built an inference framework to combine data on ZIKV infections, Zika cases, and GBS cases from locations with previous outbreaks (Yap and French Polynesia) with real-time Zika and GBS case data from the ongoing outbreak in the Americas to estimate the risk of GBS that may be associated with ZIKV infection. These estimates indicated that ZIKV-associated GBS risk in the ongoing outbreak may be similar to the risk estimated in French Polynesia, though current point estimates are slightly lower. Sensitivity analyses highlighted how integrating data from previous, better described outbreaks with current estimates can help improve confidence in estimating current risks. These methods and the estimates they produce are of paramount importance for response and preparedness planning in locations experiencing Zika outbreaks .

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RELATIVE FITNESS OF ZIKA VIRUS LINEAGES IN MOSQUITOES AND CELLS

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Zika virus has undergone a dramatic range expansion in recent years, including a dramatic outbreak that is currently ongoing in South America. Interestingly, it is likely that ZIKV, for the first time in its evolutionary history, is replicating extensively in human beings. In addition, a hallmark of arbovirus introductions into new ecological niches has been increased fitness in local vector populations. This has been clearly observed with WNV and CHIKV as they have colonized new regions. It seems likely that this may also occur as ZIKV spreads within the Americas. Therefore, we assessed the relative fitness of Asian lineage ZIKV from the new world compared to West African (Senegal 41525) and East African (Uganda MR766) lineage viruses. Briefly viruses were mixed 1:1 and allowed to compete in several test systems including: Mexican *Ae. aegypti* mosquitoes, US *Ae. albopictus* mosquitoes, US Cx. *quinquefasciatus* mosquitoes, BHK-21 cells, and human neuroblastoma, dorsal root ganglion and CRL-1973 (pluripotent testicular) cells. After an appropriate period of competition, virus was harvested from mosquitoes and relevant tissue cultures and the proportion of each competitor determined by analysis of sequence chromatograms (i.e. "quantitative sequencing.) Results of these competition studies, and their implications for virus adaptation, will be discussed.

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EVALUATING THE EFFECTS OF TEMPERATURE VARIATION ON ARBOVIRUSES

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Emerging and re-emerging mosquito-borne diseases represent a substantial global health burden. Viruses like Chikungunya, Zika and Dengue are all transmitted by the *Aedes aegypti* and *Ae. albopictus* mosquitoes. The U.S. is home to both mosquito vectors with *Ae. aegypti* constrained to highly urban environments in southern coastal states and A. albopictus distributed throughout urban, suburban, and rural areas in 26 states. This study investigates the effects of temperature on Chikungunya virus (CHIKV) and Zika virus (ZIKV) growth dynamics in mosquito tissue culture cells derived from both mosquito hosts. Aag2 (*Ae. aegypti*), C6/36 (*Ae. albopictus*) and U4.4 (*Ae. albopictus*) mosquito larval cell lines were inoculated with attenuated CHIKV (vaccine strain 181/25) and ZIKV (MEX 1-44). Samples maintained at six constant temperatures (16°C, 24°C, 28°C, 30°C, 32°C and 34°C) were collected at different time points for att. CHIKV and ZIKV. Viral titer was calculated as plaque forming units (PFUs) per milliliter through standard plaque assays on Vero cells. As expected from the literature, Aag2, C6/36 and U4.4 cell lines had differential growth responses to temperature. Cell lines grew slower at the lowest temperature and displayed slower viral replication. At the higher temperature conditions, virus growth was reduced, but to differential effect between the cell lines. These data suggest that there may be differences in viral growth kinetics at different temperatures in the two vector hosts (*Ae. aegypti* and *Ae. albopictus*) and future work will investigate these interactions *in vivo*.

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ZIKA VIRUS INFECTIONS: PAYING ATTENTION TO ATYPICAL PRESENTATIONS

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Zika disease has reemerged recently and its most common clinical manifestations are still being described. Low-grade fever, pruritic rash, conjunctivitis, arthralgia, myalgia and other minor constitutional symptoms are reported more often. Brazil has been experiencing an important Zika outbreak since May 2015, and since the beginning of this year a great number of patients was attended in our teaching hospital due to a Zika-like disease. Interestingly, patients sought medical attention primarily because the presence of a rash and not because they were feeling ill. Most patients presented with the symptoms described above and had an uneventful course; there was not a single case of microcephaly, but an increased number of Guillain-Barré Syndrome was admitted to our ICUs. Additionally, we report here three Zika confirmed cases of patients (2 males and a female) who had an atypical disease presentation. One of the patients presented with an orchiepididymitis about five weeks after an acute Zika presentation. Real-time RT-PCR was positive for Zika virus in blood and urine in both occasions. The patient recovered completely with standard treatment and remains asymptomatic. The other patient presented with muscle pain and Zika classical symptoms, but his creatine phosphokinase level (CPK) was initially 13,500 µg/L. Patient was treated for rhabdomyolysis, CPK levels reached normal levels in a week and he recovered without any renal sequelae. Finally, a young woman was referred to our hospital due to an extensive petechial rash and arthritis on knees and ankles. Lab results were all normal and prednisone was prescribed to the patient. Five days later, she was able to walk without pain and the petechial rash had faded. Real-time RT-PCR was also positive for Zika virus in blood and urine for both patients. Although all three patients recovered completely, if they were not promptly diagnosed and treated, they could have had a complicated course of the disease. Thus, although the great majority of patients will recover from Zika, we must pay attention to details of disease presentation to detect the atypical findings of this disease.

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MODEL-BASED PROJECTIONS OF ZIKA VIRUS INFECTIONS IN CHILDBEARING WOMEN IN THE AMERICAS

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Zika virus is a mosquito-borne pathogen that is rapidly spreading across the Americas. Due to a probable association between Zika virus infection and a congenital neurological disorder called microcephaly, the epidemic trajectory of this viral infection poses a significant concern for the nearly 15 million children born in the Americas each year. The potential magnitude of the ongoing Zika epidemic is exceedingly difficult to gauge based on existing data, due to a number of uncertainties that cloud the relationship between observed cases and true infections. As an alternative to methods that depend on unreliable case data, we developed and applied a new method that leverages highly spatially resolved data about drivers of Zika transmission to project that 1-2 million infections in childbearing women and approximately 100 million infections across all demographic strata could occur before the first wave of the epidemic concludes. Our projection is largely consistent with annual, region-wide estimates of 53.8 (40.0–71.8) million infections by dengue virus, which has many similarities to Zika. Based on independent estimates of microcephaly rates, our results suggest that the current epidemic has the potential to negatively impact tens of thousands of pregnancies. Uncertainties in these projections and up-to-date comparisons against case reports will be discussed.

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EVALUATING STRAIN SPECIFICITY OF THE ZIKA VIRUS NEUTRALIZING ANTIBODY RESPONSE

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Zika virus (ZIKV) is a mosquito-borne flavivirus that has emerged as a significant global health problem. Recent outbreaks of ZIKV infection in French Polynesia and Brazil have been associated with more severe manifestations, including microcephaly and intrauterine growth retardation in fetuses and infants born to women infected with the virus while pregnant. There are two lineages of ZIKV, African and Asian, that share ≥ 95% amino acid identity. The spread of ZIKV to the Americas has been attributed to the Asian lineage. No vaccines are available for use in humans, and little is known regarding the ability of neutralizing antibodies elicited against one lineage to protect against another. The primary target of neutralizing antibodies is the envelope (E) protein, of which 180 copies comprise the ZIKV virion surface. To facilitate the study of ZIKV antibody responses, we generated pseudo-infectious ZIKV reporter virus particles (RVPs) by co-transfection of a DNA-launched West Nile virus sub-genomic replicon that expresses GFP with a second plasmid encoding the ZIKV structural genes (capsid, pre-membrane, and E). ZIKV RVPs representing both African and Asian strains were used to assess neutralizing antibody responses in a panel of ZIKV-confirmed convalescent human serum samples collected 3-12 weeks post onset of symptoms. Our results demonstrated minimal strain-specific differences in neutralizing antibody responses. These findings were confirmed using a flow cytometry-based infectious Zika virus assay; comparisons of antibody titers obtained using ZIKV RVPs and fully infectious virus revealed excellent agreement. These findings suggest that vaccination with a single ZIKV strain may elicit cross-protective neutralizing antibody responses against both lineages. Furthermore, our studies establish ZIKV RVPs as a high-throughput and quantitative alternative to the use of fully infectious virus for assessing ZIKV-specific antibody responses.

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DURATION OF INTESTINAL IMMUNITY FOLLOWING ADMINISTRATION OF INACTIVATED POLIO VACCINE (IPV) IN INDIAN CHILDREN PRIMED WITH ORAL POLIO VACCINE (OPV)

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As per "The Polio Eradication and Endgame Strategic Plan 2013-2018", IPV has been introduced in all OPV using countries since the last quarter of 2015. Few studies have demonstrated boosting of short term mucosal immunity after IPV administration in children already primed with OPV, but no study has evaluated the duration of intestinal immunity after IPV administration. The aim of the study was to compare intestinal immunity to poliovirus, in OPV immunized children, 6 months and 12 months after a single supplemental dose of IPV to children who did not receive a supplementary IPV dose, measured by shedding of Sabin types 1 and 3 poliovirus in stool samples collected 7 days after a "challenge" dose

of type 1 and 3 bivalent OPV (bOPV). It was a single centre, open-label randomized controlled trial (CTRI/2014/09/004979) conducted in Vellore, India, with 3 groups enrolling a total of 900 children aged 12-59 months (300 each in control, IPV-6 month, and IPV-12 month arms). Blood samples were collected at recruitment from the control group and 28 days after IPV administration in the IPV-6 and IPV-12 groups, to evaluate anti-poliovirus neutralizing antibodies against all three poliovirus serotypes (PV1, PV2, PV3). Shedding of Sabin poliovirus 1 and 3 were determined by one-step multiplex real-time PCR. The geometric mean titres (GMT) of neutralizing antibodies against PV1, PV2, and PV3 respectively were: control arm (103.14, 186.64, 53.01), IPV-6 arm (737.34, 847.68, 839.55), IPV-12 arm (833.08, 910.61, 851.06). The proportion shedding Sabin1 poliovirus 7 days after challenge in the three arms were: control (22.3%,66/296), IPV-6 (15.8%,45/284), IPV-12 (17.8%,53/297). For Sabin3, the proportion shedding were: control (25%,74/296), IPV-6 (15.1%,43/284), IPV-12 (13.8%,41/297). There was a significant reduction in shedding of Sabin3 in the IPV-6 (p=0.004) and IPV-12 (p=<0.001) groups compared to controls. For Sabin1, shedding was significantly less in the IPV-6 (p=0.048) but not in the IPV-12 (p=0.17) group compared to controls. Thus, the study demonstrated effective long term intestinal immunity after IPV administration in OPV primed children.

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EVALUATION OF A MEASLES ROUTINE IMMUNIZATION PROGRAM IN THE DEMOCRATIC REPUBLIC OF CONGO

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Estimates of population-immunity to vaccine preventable diseases (VPDs) are useful to assess the performance of immunization programs, identify susceptible groups and at-risk populations. A comparison of seroprevalence and coverage data can be useful in quantifying the impact immunization programs have on reducing vaccine-preventable diseases such as measles. In collaboration with the 2013-14 Demographics and Health Survey (DHS) conducted in the Democratic Republic of the Congo (DRC), we evaluated the seroprevalence of IgG antibodies to measles using a multiplex format (M2) from dried blood spots from children 6 - 59 months of age and compared these results to 2013 administrative vaccination coverage data provided by the DRC Expanded Programme on Immunization (EPI) to evaluate the DRC Routine Immunization (RI) program. The lowest seropositivity rates were seen in Kasai Occidental (53.6%), Kasai-Oriental (51.9%), Katanga (51.4%), and Maniema (51.9%) provinces. Average measles vaccination coverage rates were 92%, 91%, 93.3%, 88% respectively. Of the 516 health zones in DRC, 71 reported vaccination coverage rates above 100%. Our findings suggest that gaps in measles immunity exist throughout the country and administrative coverage rates may be overestimated. Vaccine effectiveness and vaccination coverage rates should be thoroughly assessed to understand the drivers of immunity gaps that should be addressed to improve the RI system.

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DETECTION OF HUMAN ENTEROVIRUS 71 FROM AN OUTBREAK OF HAND FOOT AND MOUTH DISEASE IN BANJARMASIN, INDONESIA

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Enterovirus 71 (EV71), a single-stranded RNA virus of the Picornavirus family, is a common cause of Hand, Foot and Mouth Disease (HFMD). The infection usually manifests with fever, rash, blister and in severe cases may proceed to encephalitis. EV71 epidemics have occurred in the Asia-Pacific region, including Taiwan, mainland China, Hong Kong, Malaysia, Vietnam, Singapore, and Thailand for the past decade. We identified EV71 virus in 9 specimens from children presenting with fever and HFMD in Banjarmasin, South Kalimantan (n=13) in early 2016. Viral RNA was isolated from nasal swab, followed by cDNA synthesis using random primers. Specimens were tested by conventional PCR using enterovirus genus-level primers, followed by specific primers to determine the strain using DNA sequencing. Sequencing analysis demonstrated 98-100% similarity with the Malaysian strain and was shown to belong to subgenotype B5. Phylogenetic analysis of the VP1 gene suggests that the EV71 strain causing the outbreak in Banjarmasin could have originated from Malaysia. In parallel, virus was isolated in Green Monkey Kidney Epithelial Cells (Vero 81) which displayed severe cytophathic effects (n=7) after 2 passages. We report the finding of EV71 as a causative agent of HFMD outbreak in Banjarmasin. To our knowledge, this is the first detection and isolation of EV71 in Indonesia.

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DYNAMIC MODEL OF ROTAVIRUS TRANSMISSION WITH IMPACT OF TEMPERATURE

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Although rotavirus exhibits seasonality, water quality risk assessments do not consider temperature. Additionally, prior rotavirus transmission models have not previously considered the water as a driver of transmission. We conducted a meta-analysis to estimate the effect of temperature on rotavirus decay rate separately for monophasic and biphasic decay. We then used these estimates in a rotavirus transmission model that explicitly modelled the water reservoir. The model was seeded by allowing water to flow into the water reservoir from an upstream community. We assessed the critical transmissibility from water to humans necessary to seed the outbreak and assessed how this might vary by temperature. Temperature was significantly associated with decay rates for monophasic decay, with 8.77°C increasing in temperature related to 1 log increase in rotavirus decay rate ($p = 0.0003$). For biphasic decay, temperature had a marginally significant effect on the first phase of decay with 3.37°C being associated with a 1 log increase in rotavirus decay rate ($p = 0.0735$). Temperature did not appear to effect the second phase of decay. In our transmission model, we found that a rotavirus outbreak was inevitable as long as pathogen existed in water source regardless of the transmission rate from water to humans, because of the combination of high shedding rates and low infectious dose for rotavirus. Temperature altered the time period before peak of infected arrived, with higher temperatures leading to slower outbreaks. These results show a mechanism by which temperature may affect risk of rotavirus and suggest that the water may be an effective conduit of disease between communities.

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FIRST LABORATORY CONFIRMATION OF AN OUTBREAK OF RIFT VALLEY FEVER VIRUS IN 50 YEARS IN KABALE DISTRICT, SOUTHWESTERN UGANDA

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On March 10, 2016, the Uganda Virus Research Institute/Centers for Disease Control (UVRI/CDC) Viral Hemorrhagic Fever (VHF) laboratory was notified of 2 suspect VHF cases from Kabale district, South Western Uganda. Both cases were confirmed as RVF by RT-PCR and IgM serology. Within 24 hours a team from UVRI, the Uganda MOH, and CDC-Uganda traveled to Kabale to carry out epidemiological and ecological investigations. Both cases presented with febrile illness and reported fever, vomiting, fatigue, abdominal pain, headache, epistaxis, and melena. The initial case was a butcher who worked in the central Kabale abattoir. The second case was a student who resided approx. 12Km south from central Kabale. The two cases were not epidemiologically linked. There were a total of 8 suspect cases and 2 probable deaths identified. The team performed an initial investigation to determine the extent of the outbreak. Samples from 21 family member and community members of the confirmed and probable cases were collected, along with 86 livestock specimens from the same locations. One suspect human case was positive for RVF by IgG, but negative for IgM and RT-PCR, and classified as a convalescent confirmed case. No additional human cases were confirmed from the samples collected. 9% of livestock specimens tested positive for RVF by IgG, and one caprine from the village of one of the confirmed cases also tested positive by RT-PCR. An expanded district-wide human and livestock serosurvey was initiated following these results to determine how widespread RVF transmission is in the region. A total of 657 human and 1052 livestock samples were collected and are currently being tested. Extensive outbreaks of RVF have occurred elsewhere in East Africa, notably in 1997-8 and 2006-7. This RVF outbreak in Kabale represents the first reported laboratory confirmed human cases in Uganda since 1968. It also represents the 11th independent VHF outbreak confirmation in Uganda since the beginning of enhanced VHF surveillance in 2011.

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A RETROSPECTIVE COHORT STUDY OF SEROPREVALENCE OF EBOLA AND MARBURG VIRUSES IN HUMANS FROM TWO DIFFERENT ECOLOGICAL ZONES IN UGANDA

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Filoviruses cause high morbidity and mortality and pose a threat to human and animal populations. Uganda has experienced eight filovirus outbreaks in the past 15 years; five caused by Ebola virus and three by Marburg virus. The aim of this study was to determine if people living in and around bat inhabited mines in medium-high mountainous areas in Western Uganda might have increased exposure to filovirus infection compared to those in wooded savannah in Central Uganda. A retrospective cohort study was conducted. The exposed groups were miners and their family members; and communities within 50km from Kitaka mine in Ibanda district, Western Uganda. The control group was located in Central Uganda with no mining activity. A risk factor questionnaire was administered and blood samples collected from 740 people. Blood samples were tested for the presence IgG against Sudan Ebolavirus and Marburg virus at the Uganda Virus Research Institute. The exposed group comprised 60% (444/740) and controls were 40% (296/740). Filovirus seroprevalence was 3.2% (24/740) overall; Sudan ebolavirus 2.4% (18/740) and Marburg virus 0.8% (6/740). Although not statistically significant, the exposed group had 2.5 times the risk of being infected with filovirus compared to the control group; RR=2.5(95%CI, 0.96 - 6.7) whereas miners or their family members were 2.2 times as likely to be infected compared to other occupations (RR=2.2, 0.98 - 4.7). Other risk factors include going into mines or caves inhabited by fruit bats (RR=2.5, 1.12 - 5.66), residing in a village that had a previous outbreak of filovirus (RR=2.7, 1.24 - 6.04) and having had contact with a suspect case of filovirus infection (RR=4.5, 1.66 - 12.56). This sero-survey in Uganda indicates there may be an underestimate of filovirus infections occurring, thus more outbreaks going undetected. Health facilities need to increase their level of suspicion for Uganda viral hemorrhagic fever (VHF) as a possible cause of acute febrile illness. The Uganda VHF surveillance program has initiated enhanced febrile illness surveillance strategies to detect and respond to potential sub-clinical filovirus infections.

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THE POTENTIAL ECONOMIC IMPACT OF THE ZIKA VIRUS

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The sudden rise of Zika cases is unnerving. This situation has forced the World Health Organization (WHO) to declare the epidemic of microcephaly cases in regions affected by Zika virus a matter of public health emergency of international concern. Beyond the silent suffering among those directly affected by the Zika virus, there are many concerns about the negative impact that the Zika outbreak will have on the economy of countries affected by Zika. One concern is the potential negative impact of the Zika virus on the tourism industry. Though currently there are no travel restrictions imposed by the WHO, there have been anecdotal reports about international airlines already cancelling or rescheduling flights for passengers that are traveling to the region that are pregnant or may become pregnant. Moreover, evidence is emerging on the impact that *Aedes aegypti* diseases have on tourism revenues. Added to the potential significant losses associated with tourism, the possible decline on foreign direct investment due to the Zika outbreak is a major concern. Investments in outbreak control and surveillance infrastructure may also be impacted by the recent Zika outbreak. The loss of productivity due to the Zika outbreak is an even greater concern. At a macro level, the Zika outbreak could have other long-term repercussions. There are several challenges that affected communities in the Americas face to contain the spread of the virus. In the current systematic review we will explore these challenges and delve deep into the potential economic impact of the Zika virus. Evidence of the economic potential of the Zika virus is critical to informing policy decisions and securing financial support for future Zika prevention and control strategies.

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THE EVOLUTION AND DIVERSITY OF HUMAN METAPNEUMOVIRUS IN PERU

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Human metapneumovirus (HMPV) causes substantial morbidity in the very young, elderly and immunosuppressed, yet there is limited knowledge

of the diversity and epidemiology of this virus in Peru and other tropical countries. Therefore, we examined the evolution and spatial patterns of HMPV in Peru through phylogenetic analysis of 61 whole-genome sequences of HMPV collected in three regions of Peru; the largest genomic dataset from any tropical country to date. 61 HMPV PCR positive respiratory specimens archived from an influenza-like-illness sentinel and active surveillance study in Lima (temperate capital), Piura (northern coastal desert) and Loreto (tropical Amazon) from 2008-2012 underwent high-throughput whole genome sequencing using Illumina and Ion Torrent platforms. A 375 F-gene sequence dataset was constructed that included Peruvian and other global background sequences available from GenBank. A Maximum Likelihood tree, with 100 bootstrap replicates, was inferred by the RAxML package using a GTR + gamma nucleotide substitution model. Extensive genetic diversity of HMPV was identified in Peru, including the A2, B1 and B2 subgroups (A1 was not identified). Within a single year, the genetic diversity of HMPV identified in Peru represented nearly the entire global diversity of HMPV, owing primarily to multiple independent viral introductions into Peru each year. Possible multi-year persistence of HMPV was observed in Loreto and Piura, although low background sampling from other countries and locations in Peru complicates conclusions about local persistence. The high diversity observed in more isolated tropical locales such as Loreto and Piura is attributable to both viral introductions from other countries as well as gene flow within Peru. There is evidence of substantial HMPV viral traffic within Peru and between Peru and other global regions. Significant HMPV diversity exists even in more isolated regions of Peru. These findings underscore the rapid and extensive diffusion of respiratory viruses in tropical countries, which may have implications for the effectiveness of a HMPV vaccine across diverse global regions.

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EVALUATION OF THE BIOJECT NEEDLE FREE VACCINE DELIVERY DEVICE FOR VACCINATING RATS WITH RIFT VALLEY FEVER VACCINE CANDIDATES

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Rift Valley Fever virus (RVFV) is a major public health and agricultural concern in Africa and the neighboring region. The only potential approach for preventing epidemics of RVFV is to develop and deliver an effective vaccine for livestock and humans. The aim of this study was to evaluate a Bioject needle free vaccine delivery device for potential use to vaccinate animals. In this study as preliminary assessment the Bioject device were conducted in laboratory Wistar rats, using the device with and without a spacer, suggesting a route of delivery to be intradermal and intramuscular respectively. Two doses of the RVF MP-12NSm-del vaccine of 1 x 10^3 and 1 x 10^5 plaque forming units (PFU) were used. Blood samples were collected on day -1 before being vaccinated and at days 7, 11, 15, and 25 post-vaccination (PV), and tested for IgG antibodies by ELISA, and using 80% reduction in the MP-12 virus dose as the endpoint for determining the neutralizing antibody (NA) titers. Most all animals vaccinated with the RVF MP-12NSm-del vaccine with or without a spacer developed detectable NA by day 7 PV and persisted at or above the titers on day 7 through 25 days PV or the duration of the experiment, with titers ranging from 1:10 to 1:1280. In contrast, the ELISA optical density (OD) values were below IgG antibody positive levels on day 7 PV and not until day 11 PV that positive OD values started to become detectable, with the OD values being higher for the animals that were vaccinated without the spacer. In contrast to the animals vaccinated with the Bioject device, the NA titers and the ELISA OD values were lower for the animals vaccinated with 1 x 10^5 PFU of the RVF MP-12NSm-del and 1 x 10^5 PFU of the RVF MP-12 vaccines using a needle, thus suggesting that the Bioject needle free delivery device may be a more convenient and effective method of vaccinating animals with RVF vaccines. Finally, these preliminary data are very exciting and promising in regard to our goal of utilizing a needle free delivery method for vaccinating animals with RVF vaccines in Africa. Acknowledgement/Disclaimer: This work was made possible by the generous support of the American people through the United States Agency for International Development (USAID) *DISCLAIMER The author's views expressed in this publication do not necessarily reflect the views of the United States Agency for International Development or the United States Government.*

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CHARACTERIZATION AND IMAGING OF THE PRIMATE MODEL FOR NIPAH VIRUS INFECTION

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Nipah virus (NiV) is a zoonotic pathogen endemic to parts of Indonesia and the Asian subcontinent, particularly Bangladesh. Infection in humans can lead to severe respiratory or neurologic disease and death. Mechanisms of NiV-related disease and discriminators between respiratory or neurologic disease are unknown. Here, we focused on expanding the understanding of NiV infection in African Green Monkeys (AGM) by quantifying multiple parameters of the immune response to NiV infection. We also used Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) to assess disease progression following intratracheal (IT) and aerosol administration of virus. Animals developed a primarily respiratory disease, with those infected by the IT route developing pulmonary lesions with significant edema and consolidation. Animals infected by small particle aerosol developed a more diffuse disease. Two animals developed changes in the brain vasculature with suggestion of slightly engorged cortical veins late in the disease process, of unknown clinical significance. Survival times post-challenge were equal in the two groups (~8 days). Five of 6 animals developed a profound thrombocytopenia, manifested by severe subcutaneous hemorrhage at necropsy. Assessment of leukocytes revealed evidence of lymphopenia and neutrophilia, but with apparent expansion of activated CD8+ T cell populations in two of the aerosol exposed animals. These findings correlated with increases in serum cytokine levels indicating a proinflammatory response and Th1 differentiation of T cell populations. Populations of immune cells in the lungs were largely unremarkable except for elevated monocyte populations in the aerosol group relative to the IT inoculated group. These data demonstrate that IT and small particle aerosol inoculation of AGM results in a rapidly progressing respiratory disease largely devoid of neurological indications. These studies support previous work demonstrating a significant role for endothelial cell dysfunction in disease. It was evident that the rate of disease progression limited development of an effective immune response.

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SEROEPIDEMIOLOGICAL STUDIES FOR INFECTIONS BY VECTOR-BORNE AND ZOONOTIC PATHOGENS AMONG U.S. MILITARY PERSONNEL

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Vector-borne and zoonotic pathogens have long detracted from operational readiness of U.S. forces stateside and deployed around the world. Notable historical examples include the impact of malaria and dengue during World War II, hantavirus infections during the Korean War, and more recently, a 2003 outbreak of *Plasmodium falciparum* among marines deployed to Liberia. Military populations present a challenge for public health surveillance, as they are highly mobile and often deploy to austere settings in remote and, at times, unstable regions of the world, which limits available diagnostic and treatment options. Vector-borne and zoonotic infections are often associated with acute undifferentiated febrile

illness and thus are difficult to distinguish clinically, further exacerbating challenges for diagnosis and control. As a result, the burden of vector-borne diseases among U.S. military personnel remains poorly defined. To address this gap, we initiated seroepidemiological studies among U.S. military personnel, capitalizing on serum samples available through the Department of Defense Serum Repository (DoDSR). The DoDSR has been utilized to measure infections among DoD personnel to a diverse set of pathogens, including *Rickettsia* spp. in South Korea, Coxiella burnetii in Iraq, and *Plasmodium falciparum* in Liberia. Recently initiated studies will address infections by vector-borne and zoonotic pathogens among DoD personnel deployed to West Africa and to measure the incidence of infections by emerging viral pathogens, including dengue virus, chikungunya virus, and Zika virus, in the Caribbean. Results from these analyses, in conjunction with associated febrile illness data reported through electronic surveillance systems, can be used to inform force health protection measures and prioritize the development of diagnostics and medical countermeasures.

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DETERMINATION OF HEPATITIS B VIRUS (HBV) INFECTION IN FAMILY MEMBERS OF HBSAG CARRIERS: SEARCH STRATEGY OF CARRIERS FOR A ELIMINATION PLAN OF HBV

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Huanta was a city with a high endemic of hepatitis B virus (HBV). However, now a HBV elimination plan HBV is feasible because the immunization in people under the age of 20 that started in 1994 have had a good impact. The aim of our study is to determine the prevalence of hepatitis b virus (HBV) infection in family members of HBsAg carriers as a search strategy of carriers for an HBV elemination plans. This cross-sectional study included the family members (n=40) of 15 HbsAg (+) patients at Huanta's Hospital. Demographic data, vaccination status, relationship with the patient and risk factors were reviewed by a questionnaire. Blood samples were taken to determine HBV and hepatitis D virus (HDV) markers. Data were analyzed using t-test and chi-square. The protocol of this study was approved by the Ethics Committee of the Institute of Tropical Medicine of the National University of San Marcos. The 5.5% of the family members have an acute infection and 22.2% were chronically infected. All of them were over the age of 23. Family members that have or had HBV infection were significantly older, consumed significantly more alcohol and traveled significantly more to endemic zones than those who never had the infection (p=0.00, p=0.04 and p=0.02 respectively). None of the family members were infected with the HDV. The main limitation of this study is that it is only a pilot study before establishing a global search strategy of HBsAg carriers. In conclusion, the HBV carriers search in families found a high prevalence of HBV and would help to identify chronic carriers that can be treated and contribute to a HBV elimination plan Key-words: Hepatitis B, intrafamiliar, carriers.

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IS IT EBOLA OR IS IT A VACCINE REACTION? EVALUATION OF SUSPECTED EBOLA CASES IN A VACCINE TRIAL DURING AN EBOLA EPIDEMIC: SIERRA LEONE TRIAL TO INTRODUCE A VACCINE AGAINST EBOLA (STRIVE)

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STRIVE is a phase 2/3 trial of rVSV-ZEBOV (Merck) candidate Ebola vaccine among healthcare and frontline response workers in Sierra Leone. The early symptoms of Ebola virus disease (EVD) typically include fever, headache, fatigue, and muscle/joint pain, similar to immediate vaccine reactions. Rapidly distinguishing EVD from vaccine reactions was a key component of STRIVE. Isolation and treatment were essential for true EVD, but referring participants with vaccine reactions to Ebola Holding Units (EHU) could increase the risk of Ebola exposure. In consultation with national response authorities, we developed a modified algorithm for management of EVD-like illness following vaccination. The national EVD case definition was temperature > 38.0oC and > 3 of the following 11 symptoms: headache, loss of appetite, fatigue, muscle/joint pain, diarrhea, unusual bleeding, difficulty breathing, nausea/vomiting, abdominal pain, difficulty swallowing, hiccups. The case definition was modified for participants vaccinated within the past 48 hours to require that one of the three symptoms be EVD-specific (diarrhea, unusual bleeding, difficulty breathing, nausea/vomiting, abdominal pain, difficulty swallowing, hiccups). Those vaccinated participants who did not meet the modified case definition could remain home and be followed for up to 24 hours if improving rather than referral to an EHU unless they reported direct, unprotected Ebola exposure or breach in the use of personal protective equipment in the prior 21 days. Participants referred to an EHU were tested by PCR for Ebola virus. To implement the modified algorithm, we trained EHU staff and Ebola hotline telephone operators to ask about participation in STRIVE and on post-vaccination symptoms and the modified algorithm. As of April 5, 2016, 48 STRIVE participants had been evaluated for suspect EVD; all were negative. The most common diagnosis was malaria, reported in approximately half. STRIVE was able to develop and implement a modified Ebola case definition to evaluate suspected EVD cases and prevent unnecessary admissions to EHUs during an Ebola outbreak.

1399

DEFINING A MULTIVALENT VACCINE AGAINST HEMORRHAGIC FEVER VIRUSES BASED ON INSECT CELL EXPRESSED RECOMBINANT SUBUNITS

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We have previously developed a preclinical Ebola vaccine candidate based on soluble recombinant Ebola virus (EBOV) glycoproteins (GP) and matrix proteins (VP24 and VP40) produced using the Drosophila S2 cell expression system combined with antigen-specific immunoaffinity chromatography purification. The immunogenicity and efficacy of this candidate has successfully been evaluated in mice, guinea pigs and macaque models. The lead candidate, which is protective in non-human primates, is undergoing additional pre-clinical development with a focus on defining correlates of protection. To broaden the efficacy profile of the core vaccine, GP subunits of Sudan virus (SUDV), Marburgvirus (MARV), and Lassa virus (LASV) have been expressed and purified using the same production platform. Having achieved a similar level of purity for the additional subunits, we started immunogenicity and preliminary efficacy testing in rodent models. As expected, GP subunits of the additional filoviruses show a similar

immunogenicity profile as EBOV GP with SUDV GP showing greater cross-reactivity with EBOV GP than MARV GP. With the use of clinically relevant adjuvants, potent antigen-specific IgG titers were observed after two or three immunizations of Swiss Wester (outbred) mice. Antigen balancing studies using the three filovirus GP proteins allowed the selection of candidate formulations that consistently achieve balanced humoral immunity to all three viruses. Current work focuses primarily on incorporation of the LASV GP to achieve a broadly effective formulation targeting all major hemorrhagic fever viruses with epidemic potential in sub-saharan Africa.

1400

DENGUE, ZIKA AND CHIKUNGUNYA CO-INFECTIONS AMONG ACUTE FEBRILE ILLNES PATIENTS IN SALVADOR, BRAZIL

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Chikungunya (CHIKV) and Zika viruses (ZIKV) have recently emerged in tropical countries of the western hemisphere, causing large epidemics in settings where dengue virus (DENV) transmission is endemic. Since all of these RNA arboviruses transmitted to humans by the same *Aedes spp*. mosquitoes, co-infections may occur regularly during outbreaks. However, as the manifestations in the initial stages of illness asued by thee viruses aresimilar and laboratory diagnosis are not widely available, detection of co-infections is uncommon. We investigated the frequency of DENV, CHIKV and ZIKV co-infections among acute febrile illness outpatients during a period of high arboviral transmission in Salvador, Brazil. RT-PCRs specific for DENV, CHIKV and ZIKV, as reported previously, were performed on acute-phase serum samples of 180 acute febrile illness patients who visited an Emergency Center in Salvador, Brazil between September 2014 and October 2015. An arboviral infection was detected in 46 (25.5%) of the 180 tested samples. Arboviral co-infections were detected in 5 samples (2.8% of the 180 tested samples and 10.9% of the 46 arboviral positive samples). DENV was detected in 16 (8.9%), CHIKV in 18 (10.0%), and ZIKV in 7 (3.9%) of the samples. DENV and CHIKV co-infection was detected in 4 (2.2%) samples, while DENV and ZIKV co-infection was detected in 1 (0.6%) sample. Among the samples that were solely positive for DENV, four were type 1, six were type 3, and five were type 4. All four samples that tested positive for DENV and CHIKV were DENV type 4, while the sample positive for DENV and ZIKV, wasDENV type 3. All five co-infected patients had fever, headache, retro-orbital pain, myalgia, arthralgia, prostration and rash, and recovered completely. In conclusion, our study indicates that arboviral co-infections are not a rare event in settings where DENV, CHIKV and ZIKV co-circulate. Apparently, co-infections do not change disease presentation and disease course, but further studies with larger number of patients are warranted to confirm this observation.

1401

KNOCK DOWN RESISTANCE (KDR) GENE IN *ANOPHELES COLUZZII* AND *AN. GAMBIAE* THAT SURVIVED THE DIAGNOSTIC CONCENTRATION OF PYRETHROIDS AND DDT IN TWO ECO-EPIDEMIOLOGICAL ZONES (GUINEA SAVANNAH AND COASTAL MANGROVE) OF NIGERIA

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The scale-up of long-lasting insecticidal nets (LLINs) has contributed significantly to the reduction of malaria morbidity and mortality in Nigeria. However, insecticide resistance remains a challenge. Here, we report susceptibility status to insecticides and the frequency of the kdr alleles in *Anopheles coluzzii* and *An. gambiae*. Susceptibility tests were carried out on *An. gambiae* s.l. mosquitoes from larval collections, with deltamethrin and DDT using standard WHO procedures. Additionally, adult mosquitoes were sampled inside houses using human-baited CDC Light Trap collections between May and September 2015 and were identified using morphological keys. These samples were subjected to polymerase chain reaction (PCR) assays for species identification and detection of *An. coluzzii* and *An. gambiae*. The kdr genotypes were determined both in *An. gambiae* s.l. collected indoors and those that survived insecticide exposure using allele-specific PCR tests. PCR results show that *An. coluzzii* and *An. gambiae* occurred in sympatry at both sites. However, *An. gambiae* predominated, representing 71.2% and 84.4% of the 500 *An. gambiae* s.l. tested in Nasarawa and Lagos, respectively. There was no detection of *An. coluzzii* + *An. gambiae* bands in any specimen suggesting the absence of hybrid state. The kdr diagnostic PCR showed the presence of the kdr-west mutation in 3.3% of samples collected indoors at Nasarawa, but in 27.0% of samples that survived deltamethrin exposure. In Lagos, kdr-west was present in 10.0% of samples collected indoors versus 28.8% in those that survived deltamethrin exposure. The difference between both sets of samples was statistically significant ($p<0.0001$) with a higher kdr frequency on samples that survived the diagnostic dosages than those collected indoors. More homozygotes were found among samples that had kdr, while none of *An. coluzzii* in both sites was positive for the kdr mutation. Overall, kdr frequencies were within the range recorded earlier in Southwestern Nigeria between 2002-2005. Further investigation is needed to learn the operational implication of the frequency of kdr genotype observed.

1402

INTERCEPTOR G2: A NOVEL LN FOR MALARIA CONTROL AND BEYOND

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The utility of bed nets to combat the scourge of malaria has been undeniably successful. However, a negative consequence of the

widespread use of long-lasting insecticidal nets or LNs, has been the accompaniment of selection which further exacerbates well-known resistance issues to neuro-toxic chemistries (like pyrethroids) for mosquitoes. The technical difficulties of utilizing other insecticidal active ingredients with alternative modes of action (beyond pyrethroids) has been a limiting factor for LN development, largely owed to mitigation needs for safety to sleepers (like pregnant mothers and children) that would use them and the physical-chemical nature of the insecticides' opportunity to be incorporated into LNs—most notably solubility of insecticides is challenging to overcome in order to insure they adhere to both the wash-resistance and efficacy performance profile recommended by WHOPES. Interceptor G2 achieves this difficult balance of needs. Interceptor G2 is a novel net unique among LNs, because it is truly the first net which includes two discrete adulticides, each with unique modes of action with both an excito-repellent component (alpha-cypermethrin) and a physiological insecticide (chlorfenapyr) that work in a concerted way to provide improved protection to LN users. This unique combination can provide significantly better efficacy to resistant mosquitoes. Field testing results from Benin, Burkina Faso and Tanzania have unequivocally demonstrated significantly higher efficacy to resistant mosquito strains (40-60% increased mortality to resistant strains). This net, developed by BASF through a partnership with IVCC holds great promise as a remarkable LN that can complement any area-wide efforts to protect malaria transmission unlike any other LN currently in the market, exploiting mosquito resistance mechanisms against themselves and affording improved protection to its users.

1403

WHO SUSCEPTIBILITY TEST VS. CDC BOTTLE BIOASSAY: COMPARISON OF THE CURRENT METHODOLOGIES FOR CONDUCTING INSECTICIDE RESISTANCE MONITORING

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Malaria incidence has dropped by 37% among populations at risk between 2000 and 2015 and death rates have decreased by 60% globally. Vector control interventions, namely insecticide treated nets and indoor residual spraying, have proven to be the largest contributors to the reduction in malaria incidence over the past 15 years. The extensive use of these insecticide based vector control techniques have selected for resistance in the *Anopheles* mosquitoes, the principal vectors of the malaria parasite. Numerous studies have demonstrated the presence of insecticide resistant mosquito populations throughout Sub-Saharan Africa. The World Health Organization (WHO) susceptibility test and the Centers for Disease Control and Prevention bottle assay are used to detect insecticide resistance within mosquito populations. To determine if the two methods are comparable, both assays were conducted on six laboratory reared insecticide resistant mosquito strains from three different *Anopheles* species: *An. gambiae* (RSP, ZAN/U and TORORO), *An. coluzzi* (AKDR, AKRON), and *An. arabiensis* (SENN). The six strains were tested against five compounds from three of the four classes of insecticides recommended by WHO: organochlorides (dieldrin and DDT), carbamates (bendiocarb) and pyrethroids (permethrin and deltamethrin). Results indicate definite differences in 24 hour mortality and knockdown rates between the two test methods with the CDC bottle assay often yielding significantly higher mortality. Significant variability, between methods as well as test reps, was seen across all mosquito strains when testing for organochloride (DDT) resistance. Both tests use the same standard for determining resistance: 98% to 100% mortality indicates susceptibility, 90% to 97% mortality suggests the possibility of resistance with additional tests needed, and <90% mortality confirms insecticide resistance. These test methods are important instruments for insecticide resistance surveillance systems and inconsistency between the two can lead to different insecticide resistance classifications and subsequent vector control program actions.

1404

CAN CHICKEN FEATHERS BE USED TO PRODUCE EFFECTIVE, RE-USABLE, DURABLE AND LOW-COST MOSQUITO NETS?

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Treated mosquito nets have dramatically reduced indoor malaria transmission. However, they are not readily accessible and affordable. Among challenges of existing nets include easily torn-out and fail to inhibit blood feeding after few years of use. Here we study possibilities of using chicken feathers, a waste by-product, to produce low cost, durable, reusable, effective, and community affordable mosquito nets that adheres to WHO standards. Initial stages prior to making the nets involved laboratory tests similar to WHO cone test (i.e., regeneration time, wash-resistance, and efficacy) against pure feathers, and on fabrics material made from chicken feathers. The tests were performed on *Aedes aegypti* using permethrin. The preliminary results indicate that pure feathers and made fabric material can absorb and retain insecticide. Pure feathers had 100% knockdown and mortality effect, and made fabric had 80-100% knockdown and mosquito mortality. These results were read after 3 consecutive washes (i.e., 48, 72, and 96 hrs). The promising findings from initial stages indicate that there are possibilities of using chicken feathers to potentially produce effective, re-usable, durable, and affordable mosquito nets. Such nets will be subjected to semi-field WHO cone test using malaria vectors with different insecticide before comparing them against commercialized mosquito nets. Although initial thought of the study is based on mosquito carrying malaria parasite, the same net can also be effective against mosquitoes carrying Zika virus.

1405

TRANSCRIPTOME ANALYSIS OF GENES ASSOCIATED WITH DELTAMETHRIN RESISTANCE IN *ANOPHELES ALBIMANUS*

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Malaria remains one of the most important and debilitating diseases in the tropical world. One of the greatest emerging threats to malaria prevention and control is the development of insecticide resistance in the mosquitoes that transmit malaria. In the Americas, as malaria programs begin to shift their focus to regional malaria elimination, insecticide-based vector control strategies will intensify. Decades of unmanaged insecticide use and routine exposure to agrochemicals have left many populations of malaria vectors in the Americas resistant to multiple classes of insecticides, including pyrethroids, which are most cost-effective class of public health insecticides currently available. Comparatively little is known about the molecular basis of this resistance. Diagnostic tools are urgently needed to understand how malaria vector control interventions could be compromised by insecticide resistance. Applying a genomics approach utilizing advanced molecular detection tools, this project aims to comprehensively characterize mechanisms of deltamethrin (a pyrethroid insecticide) resistance in one of the most important malaria vectors in the Americas, *Anopheles albimanus*. *An. albimanus* were collected from Tumbes, Peru in 2015 and phenotyped as deltamethrin-resistant or susceptible using the CDC bottle bioassay. Whole non-ribosomal RNA from field-collected resistant, field-collected non-exposed, and a susceptible laboratory strain of *An. albimanus* are being analyzed using Illumina-Hiseq sequencing for comparison of gene expression profiles. Preliminary data will be presented, as well as a discussion of how these data will be used to develop mechanism-specific assays.

1406

INSECTICIDE RESISTANCE PROFILE OF *ANOPHELES GAMBIAE SENSU LATO* IN AREAS WITH AND WITHOUT INDOOR RESIDUAL SPRAYING IN MALI, WEST AFRICA

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In Mali, long lasting insecticide-treated nets (LLINs) are at the frontline of malaria vector control tools. Since 2008, US President Malaria Initiative (PMI) is supporting the implementation of an Indoor Residual Spraying (IRS) in three districts (Koulikoro, Baroueli, and Bla) in addition of the LLINs. Insecticide used for IRS has been changed from pyrethroid to carbamate and then to organophosphate because of the development of insecticide resistance by malaria vectors. The objective of this study is to determine the insecticide resistance profile of *Anopheles gambiae* s.l. in areas where LLINs together with IRS (Koulikoro district) are being implemented compared to areas with LLINs alone (Banamba & Kati districts). WHO bioassay tests were performed on F0 and/or F1 progeny of *An. gambiae* s.l. from larvae and/or from female adults, respectively, to assess their phenotypic resistance. The Taqman method was used to determine the different resistance mechanisms underlying the phenotypic resistance. A very strong phenotypic resistance was observed in all investigated localities in both areas. The 24 mortality rates were 6%, 29%, 29% and 30% (N=100) respectively in Koula, Karadie (in IRS area), and in NGalamadibi and Dangassa (non IRS area). Both West (L1014F) and East (1014S) kdr resistance mechanisms were observed in all localities. The frequency of the West form (43.54%; N = 182) was 2.5-fold higher than that of the East form (17.22%; N = 206) in LLINs+IRS areas compared to LLINs areas. Glutathione S transferase genes "GSTe2" (L119) and the Ace gene (N645I) were observed only in IRS+LLINs areas. This study showed that metabolic resistance mechanisms were encountered in area where IRS is associated to LLINs and absent in nearby area where LLINs are being implemented.

1407

EVALUATING HETEROGENEITY IN INSECTICIDE SUSCEPTIBILITY FOR IMPROVED RESISTANCE MANAGEMENT STRATEGIES TO AID MALARIA ELIMINATION

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Southern Mozambique is currently designing and piloting activities to eliminate malaria by 2020. Insecticidal vector control measures are an important component of the elimination strategy. However, insecticide resistance in malaria vectors is a critical threat to malaria control and elimination programs. As such the longitudinal monitoring of insecticide susceptibility is crucial to select appropriate vector control tools, but also to inform insecticide resistance management plans and generate the essential biological data needed for mathematical modeling aimed at designing novel resistance management plans. Here we show detailed insecticide resistance data for the major malaria vectors (*Anopheles funestus* and *An. arabiensis*) in Manhiça and Magude districts, obtained by WHO tube and CDC bottle bioassays. We studied spatial heterogeneity in insecticide susceptibility on different spatial scales at district, village and neighborhood level, aimed at identifying the barriers to the spread of resistance that will affect insecticide resistance management strategies.

1408

INSECTICIDE RESISTANCE IN *ANOPHELES GAMBIAE* AND *AN. FUNESTUS* IN TWO RURAL SITES IN TANZANIA

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Over the last decade, considerable reductions in global malaria burden have been achieved by scaling-up key vector control strategies across endemic areas. However, long-term effectiveness of both long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) is currently under threat from widespread emergence of insecticide resistance, especially resistance to pyrethroids. To characterize levels of insecticide resistance across Tanzania, CDC bottle bioassays were undertaken in two rural sites: Muleba (Northwest, Kagera region) and Muheza (Northeast, Tanga region). Insecticides tested were pyrethroids permethrin and alphacypermethrin. *Anopheles gambiae* and *An. funestus* were collected through resting indoor catches (Muleba) and larval collections (Muheza). Kisumu (susceptible *An. gambiae* strain) were used as a comparison where available. Resistance frequency was tested by exposing mosquitoes to the diagnostic dose of each insecticide and resistance intensity by using a range of doses. In Muheza, mortality in *An. gambiae* after 30 minutes exposure was 73% for 21.5µg/ml of permethrin and 70% for 12.5µg/ml of alphacypermethrin. All insecticides produced 100% mortality in Kisumu. In Muleba, only 42% of *An. gambiae* died after exposure to permethrin (21.5µg/ml), as well as 430µg/ml (20x the diagnostic dose) producing only 79% mortality and 645µg/ml (30x the diagnostic dose) 94% mortality. 56% of An. *funestus* died after exposure to 21.5µg/ml of permethrin. These results suggest that pyrethroid resistance is present in *An. gambiae* and An. *funestus* in both locations, and at particularly high levels in Muleba. Research into pyrethroid resistance, as well as resistance to other insecticide classes, is ongoing in Muheza. This research is vital in determining the appropriate vector control strategies to continue the decrease in malaria prevalence in these locations.

1409

KDR MUTATIONS CONFER FITNESS COST AND COMPETITIVE DISADVANTAGE IN FIELD POPULATIONS OF *AEDES AEGYPTI*

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Vector control strategies for *Aedes aegypti* are being threatened by the evolution of insecticide resistance. Point mutations in the *para*-orthologous sodium channel gene confer resistance to pyrethroid insecticides, named *kdr* for "knock-down resistance." While these mutations increase survival in the presence of insecticide, they also carry a fitness cost which could allow populations to recover susceptibility in the absence of insecticides. Additionally, resistant individuals could be inferior competitors to susceptible ones when subjected to density dependent competition. To investigate the fitness cost and competitive ability of *kdr* individuals, we conducted experiments with two field populations of *Ae aegypti:* a susceptible population with 1% *kdr* frequency of I1016 and zero C1534 mutations, and a resistant population with 100% frequency of C1534 and 73% frequency of I1016. First instar larvae from each population were placed in separate 1L buckets in two density treatments: 50 larvae or 500 larvae. A third population consisted of a 50/50 mix of individuals from each original population to test competitive ability. After all mosquitoes emerged, a subset of adults were bloodfed and eggs per female were enumerated to estimate fecundity. All populations laid fewer eggs per female in the high density treatment than the low (ANOVA,

F=5.6, p=0.031), though both the susceptible and mixture populations produced 4.3 times more eggs per female than the resistant population after controlling for density (GLM, F=9.68, p=0.0008), indicating a significant fitness cost to the *kdr* mutations. CDC bottle bioassays were also conducted on each treatment with the diagnostic dose of permethrin. The resistant population performed significantly worse in the high density treatment than the low, with a 93% knock-down rate at the diagnostic time in the high density compared to 52% in the low density (t-test, t=-2.6, p=0.05). These results suggest that the resistance phenotype can be altered by ecological interactions in the larval stage. Future control strategies could exploit the fitness and energetic cost of *kdr* to regain susceptibility into populations.

1410

DYNAMIC OF MALARIA VECTORS SUSCEPTIBILITY TO PYRETHROIDS AND MECHANISMS OF RESISTANCE IN SENEGAL

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Malaria vector control in Senegal rests on long-lasting insectidal nets (LLINs) and indoor residual spraying (IRS). Since 2007, IRS was implemented in selected districts, with pyrethroids until 2010, and then with carbamates. LLINs are distributed nationwide, with a universal coverage strategy since 2010. To monitor vector sensitivity to insecticides, sentinel sites were established to reflect the epidemiological strata of Senegal and the use of IRS. Annual monitoring was carried out at sentinel sites from 2008-2013 using World Health Organization (WHO) insecticide-impregnated papers. Tests were performed on an F1 generation aged 2 to 5 days, collected from wild *Anopheles gambiae s.l.*, with 25 female subjects in each of four tests, and a control of 25 females. Tests were interpreted according to the following criteria: mortality of 98-100% was considered sensitive, 80-97% considered suspected resistance, and less than 80% resistant. Sensitivity to the pyrethroids, deltamethrin and permethrin was assessed in 2 IRS districts (Velingara and Nioro) and 2 control district (non IRS). " The vector susceptibility to pyrethroids increased in IRS districts after the shift to carbamates (2011), even though universal coverage of LLINs started the same year (2010-11). " The same tendency is not observed in non IRS districts. " Increase in resistance to pyrethroids not convincingly seen with introduction of universal coverage of LLINs. " The vectors are susceptible to carbamates and organophophates in both IRS and non-IRS districts, but resistant to organochlorines in both IRS and non-IRS districts. The presence of Kdr-east is preliminarily detected in Nioro and this allelic frequency seems to show a fixation of this gene in field Anophelines. Additional analyses are underway to search for other mechanisms of resistance, other than the mutation of the target involving the Kdr gene. Preliminary evidence indicated the presence of the metabolic resistance among vector populations from several localities in the country.

1411

SPATIO-TEMPORAL EVOLUTION OF RESISTANCE TO DELTAMETHRIN AND KDR MUTATIONS IN *AEDES AEGYPTI* POPULATIONS IN FRENCH GUIANA: A WORRYING SITUATION FOR VECTOR CONTROL

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Aedes aegypti is vector of dengue, chikungunya and zika viruses in urban area of French Guiana, a French territory in South America. Deltamethrin remains the sole insecticide molecules authorized for adult control in the European Union to which French Guiana belongs. Since 2009, resistance to deltamethrin has been monitored in several populations of *Ae. aegypti* from French Guiana, by using WHO test kit at a diagnostic dose of 0.06%. In complement, mutations located at the position 1016 and 1534 of the sodium voltage-gated channel gene were monitored in some of these populations by Taqman Allelic Discrimination Assays. These mutations were already linked to pyrethroid resistance in *Ae. aegypti* populations from Latin America. A high resistance level was observed even before 2010, year from which deltamethrin has been outdoor sprayed. Our study also demonstrated a spatial and temporal heterogeneity of both mortalities at the diagnostic dose (from 1% to 92%) and resistant allele frequencies (from 14 to 98% of I1016 and from to 31 to 100% of C1534). Those frequencies have increased from 2009 to 2015. These results highlight a worrying situation for vector control efficacy and public health concern in French Guiana with no other insecticide yet authorized. Alternative control strategies will be discussed regarding these results.

1412

ONE YEAR OF COMMUNITY LED LARVICIDING :BIOKO ISLAND

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Background Larviciding has historically recorded success in vector control, known to be effective in urban setting where breeding sites are generally and easily assessable. This study is aimed accessing acceptability and implementation of a community led larviciding in a rural setting. Methods Community Agents (ACPs) were identified and recruited in 13 communities with the help of the community leaders; trained and provided materials. At baseline , the entomology team and the ACP identified and characterized existing habitats; type of habitat, existence of larvae and the stages of larvae. Weekly, the ACPs were expected to visit and treat all habitats that the owners consented and identify and treat new ones. The leader of the ACPs kept a register of attendance. The entomology team visits the community on the same day of the week but at a later time to monitor the activities of the ACP and recorded; if the each habitat has been treated, habitats are categorized as being old or new, the stages of larvae and updated the ACP's attendances register. Periodically, the ACPs were given a feedback on their activities at a community meeting. Result: At baseline there were 1100 habitats in the 13 communities, about 64.0% of the habitats were in only 2 communities, there were 92 ACPs. About 83.2% of the habitats were household water containers, 4.6% car tracks, and the drainage system being 4.5%. In all 2.9% of the habitats were *Anopheles* positive and 38.5% were positive for another culicine mosquitoes. Weekly an average of 1376 habitats were to be treated, 25(1.9%) were new, 82(6.0%) were not treated because the owners rejected treatment. The weekly average of habitats treated by ACPs was 76.0 %(std 7.8%), the average attendances to treatment activities is 82.0%(std 9.2%) Conclusion: Larviciding requires 100% treatment of all known habitats to be successful. The degree of refusal to accept larviciding

and the non-attainment of the 100% coverage by the ACPs suggest community led larviciding needs a closer look at regards community entry and how the ACPs were chosen.

1413

INDOOR RESIDUAL SPRAYING FOR MALARIA CONTROL USING BENDIOCARB REDUCES *KDR* L1014S HOMOZYGOTE FREQUENCY IN *ANOPHELES GAMBIAE* S.S.

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Resistance of malaria vectors against pyrethroid insecticides has been attributed to selection pressure from long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS), and agricultural chemicals. The use of different classes of insecticides in combination or by rotation has been recommended for resistance management. The aim of this study was to evaluate the role of using carbamate insecticides for IRS in the management of resistance against pyrethroids used in LLINs. *Anopheles gambiae* s.s. were collected from 33 different sites in nine districts of Uganda, three of which were under bendiocarb spraying. The *kdr* L1014S homozygote (RR) frequency (*kdr* homozygosity) was used as the outcome variable to test the effects of various factors using a logistic regression model. Spray status with bendiocarb, annual rainfall, altitude, collection type (larvae or adults), long-term LLIN use estimated from old nets found hanging, LLINs distributed in the previous five years, household use of agricultural pesticides, and intensity of malaria transmission (prevalence in children 2-9 years old) were entered as explanatory variables. Spray status, collection type and annual rainfall had statistically significant effects. *A. gambiae* s.s. collected from areas sprayed with bendiocarb had significantly lower *kdr* homozygosity than those collected from non-sprayed areas. Mosquitoes collected as adults from indoor collections had significantly higher frequency of *kdr* homozygotes than mosquitoes collected as larvae, possibly indicating selective sampling of resistant adults following exposure to insecticides inside houses. Sites with high rainfall had significantly lower *kdr* homozygosity. The results indicate that bendiocarb spraying may potentially increase susceptibility of *A. gambiae* s.s. to pyrethroids by reducing *kdr* resistant genotypes. Although bendiocarb spraying did not result in elimination of the *kdr* resistant genotypes, the analysis indicated that IRS with carbamates, or possibly also organophosphates, could have a role in pyrethroid resistance management.

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ENGINEERED *ANOPHELES GAMBIAE* IMMUNITY TO *PLASMODIUM* INFECTION

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Impairing sporogonic development of *Plasmodium* using the transgenic manipulation of its mosquito vector has been achieved in different malaria-transmitting species. We have previously generated immune-enhanced *Anopheles stephensi* mosquitoes with greater resistance to *Plasmodium* and microbial infection through transgenic over-expression of the IMD pathway-controlled Rel2 transcription factor, as reported previously. Despite the relevance of *Anopheles gambiae* (A. *gambiae*) as the major human malaria vector in sub-Saharan Africa, it has not been extensively used as a vector model for transgenic research because of being technically more cumbersome to transform. In the present study, we have successfully developed a genetically modified immune-enhanced A. *gambiae* line, by over-expression of the FBN9 gene, hence overcoming previous technical challenges. Engineered anti-*Plasmodium* activity of the IMD pathway has been further explored by investigating the potential of the Rel2-regulated anti-*Plasmodium* immune factor FBN9 (fibrinogen immunolectin 9) to confer resistance to *Plasmodium*. We used the fat body-specific blood meal-inducible Vitellogenin 1 promoter to drive transgene expression of this anti-*Plasmodium* factor. The promoter, FBN9 gene and the Trypsin 1 terminator were ligated into an entry vector containing the DsRed marker. Newly laid eggs from female A. *gambiae* mosquitoes (G3 strain) were injected and larvae screened for transient fluorescence. Transient mosquitoes were outcrossed with wildtype ones and, following blood feeding, the offspring was screened for transgenics. FBN9-transgenic mosquitoes showed increased resistance to *Plasmodium*, by reduction of both infection prevalence and intensity at the oocyst stage. The temporal expression pattern of the recombinant FBN9, the antibacterial response of the immune-enhanced transgenic mosquitoes and the impact of this genetic modification on mosquito fitness have been analysed.

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DISPERSAL AND THE SPREAD OF A DENGUE-SUPPRESSING BACTERIUM IN THE DENGUE VECTOR *AEDES AEGYPTI*

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Wolbachia is a promising tool for arbovirus control, with its potential to suppress virus transmission and to establish and spread through wild mosquito populations under the right conditions. *Aedes aegypti* infected with the *w*Mel strain of *Wolbachia* were released into two suburbs of Cairns, Australia. At each site, *Wolbachia* spread was spatially heterogeneous, and slower than initially expected. Also, the invasion appeared to stall at the boundary of a major road, suggesting this to be a strong barrier to mosquito dispersal. Conversely, a rapid influx of uninfected mosquitoes to the centre of one of the sites was observed suggesting long distance dispersal of *Ae. aegypti* in Cairns. To test this further, we investigated spatial genetic structure among 161 field-caught *Ae. aegypti* from the same area using ddRADseq. We observed little genetic structuring across the range of our study site (4 km^2) and found a weak barrier effect of roads. These findings support our hypothesis that long-range dispersal is common in *Ae. aegypti* in Cairns. A highly leptokurtic distribution of dispersal distances can lead to slower *Wolbachia* spread and the potential reinvasion of infected regions in seasonally dynamic populations, these findings thus inform future releases of *Wolbachia.*

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IDENTIFICATION OF MIDGUT ACTIVE CIS-REGULATORY SEQUENCES TO EVALUATE THE IMPACT OF NON-CODING VARIATION ON *AEDES AEGYPTI* SUSCEPTIBILITY TO DENGUE VIRUS INFECTION

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The basal level of expression of immunity genes is correlated with *Aedes aegypti* strain susceptibility to Dengue virus, as reported previously. The basal level of expression is determined in large part by the set of cis-regulatory sequences that are active in midgut cells. A portion of the variation in the basal level of gene expression in the midgut is potentialy related to variations in cis-regulatory sequences. Therefore, in order to have a genomic template cis-regulatory sites to analyse the impact of non-coding variations on strain susceptibility, we set out to identify and characterize cis-regulatory sequences active in the non-stimulated midgut of *Ae. aegypti*. Since open chromatin is a hallmark of cis-regulatory function we carried out open chromatin profiling on pools of disected midguts from 3 to 5 day old female mosquitoes. Genomic libraries were constructed with DNA samples enriched for cis-regulatory fragments.

These genomic libraries were then sequenced by NGS in an Illumina GAx II instrument. More than ten million non-redundant, uniquely mapping sequence tags were used to map enriched peaks corresponding to cis-regulatory sequences. Analysis of these sequence tags by MACS and DFilter identified more than 30 thousand cis-regulatory sequences. Characterization of these cis-regulatory sequences allowed identification of motifs and cis-regulatory modules (CRMs) for the binding of a diversity of transcription factors. This set of cis-regulatory sequences, motifs and CRMs will be useful to assess the potential impact of non-coding variation on *Aedes aegypti* susceptibility to Dengue virus infection.

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MOLECULAR CHARACTERIZATION OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY SPECIFIC VARIANTS IN AMHARA REGION, ETHIOPIA

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Glucose 6-phosphate dehydrogenase deficiency (G6PDd) is an X-linked hereditary genetic defect, affects an estimated 400 million people worldwide. Severe clinical manifestation associated with G6PDd (e.g., chronic hemolytic anemia) depends on the type of G6PD molecular variants and exposure to hemolytic triggers (e.g., antimalarial like Primaquine). However, scarce studies on G6PDd renders the use of Primaquine for effective therapeutic treatment of malaria. This study was undertaken to determine the availability and characterize selected molecular variants of G6PDd specific genes among selected populations in malaria endemic area of Ethiopia. Using cross sectional study design a total of 156 dried blood samples were randomly selected from 360 stored samples of national malaria indicator survey of 2011 starting from July 30/2014 to January 30/2015. Polymerase chain reaction and restricted fragment length polymorphism technique was applied to characterize G6PDd variants as G6PD*A, G6PD*A- and/or G6PD*Mediterranean. Binary logistic regression was applied to see association (P<0.05 is significant) among different parameters. Of 156 studied dried blood spot samples, 10(6.4%) had G6PD genotype available. G6PD*A (100%) was the only genotype characterized, while neither G6PD*A- nor G6PD*Mediterranean genotypes were detected. There was no statistical significant difference between G6PDd and other socio demographic and risk related variables (P>0.05). In conclusion, G6PD*A variant was the only G6PDd genotype detected in this study. G6PD*A variant has almost (90%) the same enzymatic activities with the wild type. Therefore; this result supports the safe use of primaquine, especially the single low dose for transmission interruption of *Plasmodium falciparum* gametocyte and radical cure of *P. vivax*, as a part of malaria elimination toolkit, among selected populations in malaria endemic areas of Amhara region.

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UNIDIRECTIONAL HYBRIDIZATION AND REPRODUCTIVE BARRIERS BETWEEN TWO BIOTYPES OF *CULEX PIPIENS* COMPLEX

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Understanding the processes of reproductive behavior in mosquitos is crucial for improving mating competitiveness and mating specificity for sterile insect release program. *Culex pipiens* form pipiens and form molestus, two biotypes for *Cx. pipiens* complex, are vectors for West Nile Virus, St. Louis encephalitis virus, and lymphatic filariases. Hybridization of these biotypes is shown to occur in nature, even though f. pipiens mate above ground in larges spaces (eurygamy) and f. molestus preferentially in small spaces (stenogamy) like subways and sewage tunnels. The hybridization between two biotypes may allow gene flow of biotype-specific characteristics that are crucial in the disease transmission cycle. In the present study, we examined the mating behaviors, insemination rates, fecundity and fertility in F1 hybrids between *Culex pipiens* form pipiens and f. molestus in stenogamy conditions (cage 27.5cm x 17cm x 20cm). The F1 hybrid crosses along with parent backcrosses were also accessed for mating success. Despite the considerably high insemination rates from hybrid males to females and likewise in backcross lines to parent females, the fertility and fecundity rates from the respective females were varied among different crosses. This observation could suggest the asymmetric allele introgression in the hybrid zone. We also document a failure of heterospecific males to produce fertile eggs in f. pipiens females, which may be due to gametic incompatibilities and may serve as an additional barrier to gene exchange.

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SMALL INSERTION AND DELETION MUTATIONS IN *ANOPHELES COLUZZII* AND *AN. GAMBIAE*

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Whole genome resequencing experiments now routinely leverage large data sets to explore genomic variation in organisms from diverse taxa, including arthropod vectors of disease. In these vectors, resequencing has the potential to detect cryptic populations, uncover signals of insecticide resistance, and monitor the progress of control campaigns, along with other contributions to disease eradication. However, these experiments often focus wholly on single nucleotide polymorphisms (SNPs), excluding small insertions and deletions (indels) as well as large structural variants. While current short-read technology makes examination of the latter fraught with technical artifacts, routinely including indels in the analysis of resequencing data is a way to increase the power of these experiments as well as detect patterns that cannot be uncovered using SNPs alone. We reanalyzed previously published short read data from 38 samples of *Anopheles gambiae* and *An. coluzzii*, focusing on variants longer than one base pair. We find that similar numbers of base pairs are involved in indel variants as in SNPs in this data set, suggesting that indels are indeed an important category of variation in these malaria vectors. We also find that pipelines commonly used for the detection and quality control of SNPs can easily be adapted for indels, and that indels analyzed this way show similar population genomic trends to SNPs, suggesting their reliability. Finally, we examine patterns of frameshifts in these malaria vectors, identifying genes whose expression may be radically altered in a way SNP data cannot easily detect.

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MOLECULAR AND MORPHOLOGICAL CHARACTERIZATION OF *ANOPHELES MELAS* POPULATIONS IN ENDEMIC AND NON-ENDEMIC LYMPHATIC FILARIASIS COMMUNITIES IN COASTAL GHANA

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Anopheles melas, known to be an efficient vector of lymphatic filariasis occurs along the coastal part of Ghana, especially in estuarine areas. This study was aimed at seeking explanation to why there is different patterns of lymphatic filariasis distribution along coastal Ghana. The hypothesis was that the eastern *An. melas* populations could be different from those occurring to the west of Accra at both morphological and molecular levels. Two sites representing communities to the east of Accra in the Ga

Adangme District and two communities in the Ahanta West District were selected for the study. The mosquitoes were molecularly identified as *An. melas*. Deoxyribonucleic acid (DNA) of each identified *An. melas* was then used as the template for COI analysis. Polymerase chain reaction products obtained were purified, sequenced and analyzed using BioEdit and MEGA V6 software for construction of phylogenetic tree.In-silico restriction enzyme digest was done to determine restriction site differences between the two *An. melas* populations and Similarity index determined using Sørensen's formula. The study found no significant differences between the sequences of the two *An. melas* populations (Z-test of neutrality = 0.33). Results of the phylogenetic analysis though not significant, revealed a geographic relationship only between two eastern populations clustering together, with one population branching off on a different node. Analysis of the in-silico showed eight mutational differences with QS value of 0.99. The restriction site analysis however revealed 16 unique site differences between them. The mean numbers (n, median and range) of cibarial teeth were 14.54 (n = 13, 15, 11 = 18) and 14.1 (n=13, 14, 11-19) for western (Azizanya) and eastern (Asemko) respectively, which were not statistically different (t=1.53, P = 0.14). In conclusion the two *An. melas* populations could be said to be similar in all aspects, however restriction enzyme differences could be potential markers for distinguishing the two populations.

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POPULATION STRUCTURE OF *ANOPHELES FUNESTUS* IN SOUTHERN AFRICA

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Malaria control and eradication faces many challenges; among these is *Anopheles funestus*, one of three major malaria vectors in sub-Saharan Africa. *An. funestus* poses a significant threat because of its expansive distribution and high rates of insecticide resistance. However, relatively little is known about the population structure and dynamics of *An. funestus* compared to other major malaria vectors such as *An. gambiae* and *An. arabiensis*. In this study, individual samples (N=44) from geographically distant sites in Zambia, Democratic Republic of the Congo, and Tanzania were subject to whole genome sequencing for determining the degree of population structure of *An. funestus* in Southern Africa, and for the development of genome-wide markers suitable for population genetic studies at the spatial scale of this region. A reliable set of single nucleotide polymorphism markers will allow for high-throughput and cost-effective population genomic analyses at the spatial scale required by this study. Preliminary assessment suggests that more gene flow than expected exists between populations from Zambia and DRC, however a more detailed analysis is required. Robust estimate of gene flow between populations, especially related to insecticide resistance genes, could be used to assess efficacy of vector control. Moreover, association of whole-genome-based genetic clusters in relation to our discovery of sympatric *An. funestus* mitochondrial Clade I and Clade II in northern Zambia could illuminate if mitochondrial clades are relevant to mating structure within the *An. funestus* complex. Additional structure within the complex, if related to ecological or behavioral traits, would have implications for vector control strategies.

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GENERATION OF *AEDES* GENE KNOCKOUTS TO CHARACTERIZE LIGHT-DRIVEN PHOTORECEPTOR RESPONSES

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Daily shedding and rebuilding of the photoreceptor's photosensitive rhabdomeric membranes is common in invertebrate species. *Aedes aegypti* shows a robust response and loses all Aaop1 rhodopsin from the rhabdomeric membranes during the shedding process at dawn. We seek to characterize these cellular processes and determine how modulation of visual capabilities during this daily cycle impacts mosquito vision and behavioral responses. The shedding process at dawn is a light-triggered event. The rhodopsin is moved to cytoplasmic vesicles and degraded during the daytime. However, the rhodopsin is capable of being rapidly moved back to the rhabdomeric membranes if dark conditions are restored prior to degradation. During the daytime period, vesicles containing newly synthesized Aaop1 rhodopsin accumulate within the cytoplasm. At dusk, these vesicles rapidly deposit newly synthesized Aaop1 into the rhabdomere. These results show that light is a negative regulator of rhodopsin maturation and document the extensive management of rhodopsin content during the daily light-dark cycle in *Aedes* mosquitoes. We propose that these events give the mosquito exceptional visual capabilities in the low light environments of dawn and dusk without triggering light-induced damage to photoreceptors upon exposure to brighter daylight. We are testing this proposal by creating germ-line mutations in the Aaop1 rhodopsin gene using CRISPR-CAS9 technology. We also will create mutations in the two arrestin genes coding for adapter proteins responsible for initiation of the membrane shedding process. These three mutant strains will be examined for rhodopsin movement, retinal degeneration, and behavioral responses to determine the importance of proper rhodopsin management to *Aedes* fitness.

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USE OF THE OXFORD NANOPORE MINION MKI FOR SIMULTANEOUS VECTOR AND PATHOGEN IDENTIFICATION

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Vector-borne disease surveillance in remote locations is difficult at best. The vast majority of sequencing and antibody detection equipment on the market is bulky, delicate, and expensive. The MinION is a pocket-sized DNA sequencer that has previously been used in the field to track the Ebola outbreak in West Africa. The MinION has the potential to greatly expand vector surveillance capability in the US military. To this end, the Navy Entomology Center of Excellence, the USDA Center for Medical, Agricultural, and Veterinary Entomology, and Naval Medical Research Unit 3 (Cairo) are developing a protocol for simultaneous vector and pathogen identification using the MinION. Whole DNA is extracted from vectors using standard kits and prepared for sequencing using the simplest available protocol. The prepared libraries are sequenced using the MinION and locally BLASTed against a database of vector sequences for identification. A test run consisting of 5 mosquito species combined into a single library shows that a sufficient number of high quality 2D reads are produced to allow genus-level identifications within just a few hours. Next steps include expanding the reference database to include pathogen sequences, protocol testing on laboratory-infected mosquitoes, and further simplification of the protocol for field expediency.

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HUMAN-DISEASE CAUSING ARBOVIRUS PREVALENCE IN KENYAN MOSQUITOES

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Arboviruses comprise some of the most important emerging pathogens due to their geographic spread and increasing impact on vulnerable human populations. Despite this significant global health burden, the transmission, epidemiology, and incidence of arboviruses remains poorly defined, particularly in sub-Saharan Africa. In Kenya, the continued population growth and associated urbanization are conducive to proliferation of mosquito vectors and arboviral transmission; thus the characterization of arboviral circulation in this region is imperative to better inform human risk assessments and vector control practices. We used a variety of trap types and capture methods to collect *Aedes* and *Anopheles* species mosquitoes, at varying stages of the life cycle and during different seasons, at four sites in Kenya: Msambweni and Ukunda on the coast, and Chulaimbo and Kisumu in the west. Mosquitoes were then sorted by species, sex, trap type and date of capture, and grouped into 391 pools of ~25 individuals. Tissue was mechanically lysed and total RNA was extracted. Using a multiplex real-time reverse transcriptase PCR assay, mosquitoes were tested for dengue (DENV) and chikungunya (CHIKV) viruses, as well as for the five *Plasmodium* species known to cause human disease. CHIKV was detected in 14 of 290 (4.8%) of *Aedes* spp. pools. Of these, 3 were from the western sites, caught between March and May 2014, and 11 were from the coastal sites caught between July and December 2014 in ovitraps, human-landing catches and BG sentinel traps. Interestingly, 8 of these CHIKV positive pools were male mosquitoes bred in the laboratory from ovi- and larval traps, suggesting transovarial transmission of these viruses. DENV was detected in 1 pool (0.3%) from the coastal sites from September 2014. Of the 101 *Anopheles* pools tested for the five *Plasmodium* spp., 1 pool (1.2%) tested positive for *falciparum falciparum*. These data suggest a considerable prevalence of CHIKV in Kenyan mosquitoes, and that viral distribution varies both geographically and temporally. These data contribute to arboviral surveillance in Kenya, and suggest that the prevalence of CHIKV is underestimated.

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ECOCLIMATIC DRIVERS OF SPATIO-TEMPORAL HOT SPOTS OF *AEDES ALBOPICTUS* ABUNDANCE IN A SOUTH EUROPEAN URBAN AREA

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The stable colonization of several south European urban areas by *Aedes albopictus* represents an increasing public health threat due to the species competence in transmitting Dengue, Chikungunya and Zika arboviruses, whose expanding worldwide distribution is increasing the risk of an infected traveller to reach Europe. In fact, a Chikungunya outbreak has already occurred in northern Italy in 2007 and cases of autochthonous Dengue transmission have been recently reported from France and Croatia. Despite in the absence of vaccines the only way to prevent the risk of outbreaks of these diseases in Europe is mosquito control, this is rarely efficiently carried out by public administrations due to lack of appropriate resources to cover the large areas colonized by the species. It has been proposed that a more cost-effective method to prevent arbovirus outbreaks could be the focal treatment of hot-spot of highest mosquito densities. The aim of this work was to identify eco-climatic drivers of higher *Ae. albopictus* abundance on the basis of data from seasonal-round monitoring carried out in 2012-2013 across and beyond the urban area of Rome. A fine scale (300 m radius) spatio-temporal dataset was built within each sampling site and exploited to analyse the effect of climatic (Land Surface Temperature, Daily Rainfall, Growing Degree Days), environmental (Land Cover as retrieved from digital multispectral aerial imagery) and demographic (human population density) variables on *Ae. albopictus* spatial abundance and temporal dynamics. Generalized additive mixed models highlighted a strong positive relationship between mosquito abundance and anthropic surfaces and population density and identified climatic drivers of the seasonal population dynamics. These results provide useful indications to prioritize public mosquito control measures in temperate urban areas in space and time for a more feasible and cost-efficient prevention of the risk arbovirus transmission in Europe.

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OUTDOOR EARLY BITING BEHAVIOR AND INSECTICIDE RESISTANCE IN *ANOPHELES ARABIENSIS* MIGHT CHALLENGE MALARIA ELIMINATION IN SOUTHERN PROVINCE OF ZAMBIA

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In Zambia, long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are the principal malaria vector control interventions. The use of these interventions depends on vector susceptibility to insecticides and indoor biting and resting behavior. However, there is limited information on the behavior of malaria vectors and their susceptibility to insecticides in Southern Province, an area targeted for malaria elimination. This study assessed vector behavior and susceptibility to insecticides commonly used in malaria vector control strategies. Indoor host seeking mosquitoes were collected during April and May 2015 to determine mosquito biting behavior. Species identification by PCR and insecticide susceptibility tests were conducted on 0.05% deltamethrin, 0.1% bendiocarb, 4% DDT and 0.25% pirimiphos-methyl following the WHO standard protocol. Metabolic resistance were determined in populations of *An. gambiae* s.l and *An. funestus* s.l. by using a synergist piperonyl butoxide (PBO). A total of 5,507 adult *Anopheles* mosquitoes were collected from April to May 2015. *An. gambiae* s.l constituted 66.7% (n = 3675) and 33.3% (n = 1832) were *An. funestus* s.l. *An. arabiensis*, *An.* quadriannulatus and *An. funestus* s.s. were identified. *An. arabiensis* was more frequently observed biting humans outdoors (0.567) than indoors (0.443) while *An. funestus* was observed biting indoors (0.532) more than outdoors (0.468). *An. arabiensis* was resistant to deltamethrin with mortality rates of 90-95% while resistance to deltamethrin (14-42%) and bendiocarb (41-56%) was detected in *An. funestus* s.s. Both species of mosquitoes were 100% susceptible to DDT and pirimiphos-methyl. Pre-exposure of *An. arabiensis* and *An. funestus* s.s. to PBO nullified both pyrethroid and carbamate resistance in populations of mosquitoes tested. Outdoor early biting of *An. arabiensis* may hinder malaria elimination efforts by extending residual transmission of malaria, while the detection of pyrethroid and carbamate resistance mediated by oxidases in vector populations might compromise the protective efficacy of ITNs and IRS using these ingredients.

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MODELLING POPULATION DYNAMICS OF THE VECTOR *CULEX PIPIENS* IN THE ATLANTA URBAN ENVIRONMENT

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Members of the *Culex pipiens* complex play a critical role in the spillover of urban abroviruses such as West Nile Virus or St. Louis Encephalitis. Mechanistically understanding the drivers of mosquito population

dynamics at larval stages is critical for better informing predictive models and vector management strategies. Despite this recognized need, there is a paucity of empirically fitted mathematical models explaining variable demographic parameters within the vector's main habitat in the USA: urban roadside catch basins. Here, we show results of a series of interlinked experimental and observational studies performed in the city of Atlanta, GA, to quantify the key life history parameters of *Culex pipiens quinquefasciatus* needed to develop a stage-structured population model predicting catch basin productivity. Parameters needed for such a model included survivorship and time to emergence under different nutrient and detritus levels as well as female fecundity on emergence. Larval experiments under controlled temperature conditions showed that in low nutrient environments, survivorship linearly increases with leaf litter presence (Generalized Linear Model, GLM, -4.2765 ± 0.363; $p < 0.001$). As nutrient availability increases, leaf litter has a positive and quadratic effect on survivorship and a negative effect on time to emergence (GLM, 19.3848 ± 0.9385; $p < 0.001$). The non-linear interaction between nutrients and leaf litter was statistically significant and indicative of an additive relationship between both trophic conditions. Ongoing work is incorporating these results into a stage-structured matrix projection model that will be used to predict the population dynamics of *Cx. pipiens quinquefasciatus* in catch basins. Mechanistic characterization of population dynamics of *Cx. pipiens quinquefasciatus* in catch basins can lead to an improved understanding of mosquito productivity in urban areas and the identification of more effective targets for vector management.

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FLIGHT APTITUDE OF FREE-FLYING MOSQUITOES AS A MEASURE OF LONG DISTANCE MIGRATION BEHAVIOR

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Malaria kills over 500,000 people every year in sub-Saharan Africa alone. During the dry season in the Sahel, surface water required for larval sites disappears, halting mosquito reproduction and bringing malaria transmission almost to a standstill. Recent studies have suggested that both *Anopheles gambiae* s.s and *An. arabiensis* (but not *An. coluzzii*) persist in this region by long-distance, wind-assisted migrations, migrating from locations where breeding occurs year round. Direct evidence of long-distance migrating malaria vectors to date is scant. In other insect taxa, in sub-Saharan Africa and elsewhere, windborne long-distance migration occurs seasonally and facilitates exploitation of renewed temporal resources. Our aim here was to measure flight behavior in free-flying, wild mosquitoes, and evaluate if flight propensity exhibits seasonal variation, in accordance with expected movement to- and from the Sahel. We have adapted an assay originally developed for the study of migratory flights in aphids, to measure flight behavior in a group of 100 mosquitoes of predetermined sex, physiology and origin, housed within a 200x30x30 cm vertical flight chamber. The assay involves the measurement of the total displacement of the mosquitoes, over an 18-hours experiment. Mosquito resting positions were captured by a series of digital photographs taken at intervals of 30 minutes, and displacement was calculated by indexing 'arrivals' and 'departures'. Initial laboratory studies revealed a typical circadian rhythm in flight and sugar-feeding patterns. The assay is currently used with field mosquitoes in Mali. Preliminary results suggest that flight propensity was elevated a few weeks after the first rains (June 2015), consistent with our results using a tethered mosquito flight assay. Comprehensive analysis of these experiments will be presented.

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SPATIAL DISTRIBUTIONS OF *ANOPHELES* SPECIES IN RELATION TO MALARIA INCIDENCE AT 70 LOCALITIES IN THE HIGHLY ENDEMIC NORTHWEST AND SOUTH PACIFIC COAST REGIONS OF COLOMBIA

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A proper identification of malaria vectors is essential for any attempt to control this disease. Between 40 and 47 *Anopheles* species have been recorded in Colombia, and 8 species complexes have been revealed in the last decade. An update of *Anopheles* species distribution and its relationship with malaria is required, particularly for newly identified members of species complexes. A cross-sectional entomological study was conducted at 70 localities in the highest malaria transmission areas in Colombia. In each locality, immature and adult mosquitoes were collected. All specimens were determined using morphological characters and Cytochrome *c* Oxidase I sequence gene. To detect natural *Plasmodium* infections, enzyme-linked immunosorbent assay and nested PCR analysis were used. *Anopheles* species distribution was spatially associated with malaria prevalence. A total of 1,736 larvae and 12,052 adult mosquitoes were determined. Thirteen *Anopheles* species were identified. COI sequence analysis suggested 4 new lineages for *An. albimanus* (*An. albimanus* B), *An. pseudopunctipennis* s.l., *An. neivai* (*An. neivai nr. neivai* 4), and *An. apicimacula*. Two members of species complexes were identified as *An. nuneztovari* C and *An. albitarsis* I. Another 7 species were confirmed. Four mosquitoes were infected with *Plasmodium* species: *An. albimanus* B (n=1) and *An. nuneztovari* C (n=3). In Northwest of Colombia, *An. nuneztovari* C, *An. albimanus,* and *An. darlingi* were present in the municipalities with API>35 cases/1,000 inhabitants. In the north of South Pacific coast, with a similar API, *An. nuneztovari* C were widely distributed inland, and the main species in coastal regions were *An. albimanus* B and *An. neivai* s.l. In the south of South Pacific coast, 3 *Anopheles* species were found in municipalities with API=15-88 cases/1,000 inhabitants: *An. albimanus* B, *An. calderoni* and *An. neiva* s.l. In conclusion, in the highest malaria areas, 13 *Anopheles* species and 4 new lineages were found. A DNA barcode analysis allowed the taxonomic identification, particularly for species complexes, and to improve the understanding of their relation with malaria transmission.

1430

STORM DRAINS AS LARVAL DEVELOPMENT AND ADULT RESTING SITES FOR *AEDES AEGYPTI* AND *ALBOPICTUS* IN SALVADOR, BRAZIL

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Brazil reports the larger number of dengue cases in the world (1.6 million in 2015), and simultaneous transmission of dengue, chikungunya and Zika viruses was firstly documented in 2015. Dengue control in Brazil is based on the search for breeding sites in an area, followed by their elimination or treatment. The failure to identify so-called cryptic locations may hinder

the finding of breeding sites, which can be important in diverse areas and circumstances. We studied the importance of storm drains as *Aedes* larval development and adult resting sites in four neighbourhoods, representing different socio economic, infrastructure and topographic conditions, of Salvador, Brazil. A total of 122 storm drains identified in the four study sites were surveyed twice during a 3-month period (total of 241 inspections), and in 49% of the inspections we observed the presence of accumulated water. Adults and larvae of *Ae. aegypti* were captured in two of the four sites, and adults and larvae of *Ae. albopictus* were captured in one of these two. A total of 468 specimens were collected, 148 *Ae. aegypti* (38 adults, 110 larvae), 79 *Ae. albopictus* (48 adults, 31 larvae), and 241 non-*Aedes* (mainly *Culex spp.)* mosquitoes (42 adults, 199 larvae). The presence of *Aedes* mosquitoes was independently associated with the presence of non-*Aedes* mosquitos and with lower accumulated rainfall during the preceding week. We demonstrated that in Salvador, an epicentre of the recent Zika virus outbreak, storm drains often accumulate water and serve both as larval development sites and as adult resting areas for *Ae. aegypti* and *Ae. albopictus*. These potential key environments for *Aedes* reproduction are located in public areas and are often overlooked by vector control campaigns. Targeting alternative breeding sites for surveillance and control needs to be incorporated into vector control programs in Salvador and other urban areas. Targeted efforts to control *Aedes* mosquitoes in these sites need to be developed and applied. In the long term, we advocate for a better design of storm drains that restrict the accumulation of water – though they still may serve as important adult resting sites.

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COMPLEX INTERACTIONS BETWEEN TEMPERATURE AND DIET IN MOSQUITOES REVEAL NEW INSIGHTS INTO MALARIA TRANSMISSION UNDER PROJECTED CLIMATE CHANGE SCENARIOS

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There is great concern as to how global climate change may affect vector-borne diseases. Numerous studies demonstrate a link between mean temperature and mosquito survival; however, in the field, temperature fluctuates dynamically throughout the day. Furthermore, temperature has been shown to significantly affect mosquito blood feeding behavior. Here, we observed the effect of several temperature regimes on daily mosquito survival. Mosquitoes were divided into six temperature groups: 27°C, 30°C, 34°C, as well as three treatments of the same mean, but allowed to fluctuate a total of 10°C over the course of the day. Females were then further allocated to one of four dietary regimes: 1) water feeding only, 2) sugar feeding only, 3) water feeding with the provision of a human blood meal every three days, or 4) sugar feeding with a blood meal every three days. Across all temperature treatments, blood feeding significantly improved survivorship compared to those maintained exclusively on sugar or water. Females imbibing both blood and sugar experienced the greatest increased survivorship; when compared to those feeding on blood and water, it is clear that sugar consumption provided an additional source of energy. As temperatures increase, the time to complete development of the malaria parasite within the mosquito decreases; these data show that in hotter temperatures, the daily survival rate of *Anopheles stephensi* females would be sufficient to effectively transmit malaria parasites. These results suggest a complex relationship between diet and temperature; not only are blood meals the source of disease transmission, but they also increase vector survival. It is crucial that these intricacies be taken into account when determining the best control programs for individual countries in the face of global climate change.

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INTERROGATING THE ROLE OF STEROID HORMONES IN THE REPRODUCTIVE ECOLOGY OF *ANOPHELES GAMBIAE* MOSQUITOES

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Human malaria is a major public health burden in tropical and subtropical countries and is transmitted exclusively by female *Anopheles* mosquitoes. Malaria control strategies aimed at inducing sexual sterility in natural vector populations are an attractive alternative due to increasing levels of insecticide resistance within medically important anophelines. However, the development of these strategies is hampered by a profound lack of knowledge regarding the most basic elements of *Anopheles* mating ecology. Recently, our group has demonstrated that the suite of mating induced changes in *An. gambiae* females is largely mediated by male transference of the steroid hormone 20-hydroxyecdysone (20E) during copulation. We have also demonstrated that precopulatory female choice is likely predicated upon the differential ability of males to synthesize 20E in their male accessory glands (MAGs). Females accept matings from males that not only have double the titers of 20E relative to their unsuccessful rivals, but also have distinctly different chemical contact cue profiles. In order to investigate this relationship further, we created a line of transgenic *An. gambiae* males that expresses a MAG specific 20E-targeting oxidase that inactivates the hormone. Here we show that this transgenic line of males is deficient in 20E synthesis, as males transfered ~ 70% less 20E to females than control males. Moreover, mating assays revealed that these transgenic males exhibit reduced mating success, with females refusing ejaculate transfer from these males even after forming a mating pair. Through GC/MS analysis of transgenic males, we have also tested the relationship between male 20E titers and chemical contact cue profiles. Taken together, these results provide compelling evidence for the first time that *An. gambiae* females exhibit both pre- and pericopulatory mechanisms of choice, with male 20E being a key factor, a critical insight into the mating ecology of a major disease vector.

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APPLICATION OF BAYESIAN MAXIMUM ENTROPY TO ESTIMATE THE ASSOCIATION BETWEEN ADULT *AEDES AEGYPTI* DENSITY AND SIX-MONTH RISK OF DENGUE VIRUS SEROCONVERSION

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Efforts to characterize *Aedes aegypti* indicators of abundance have not consistently identified associations with increased risk of dengue virus (DENV) seroconversion. This is partly the result of cross-sectional measures of mosquito density in which no mosquitoes are observed when low levels of infestation may truly be present. We created cross-sectional entomological monitoring indicators by incorporating the spatial distribution of adult mosquitoes to estimate the association between mosquito density and DENV seroconversion. Categorical density variables were generated based on the presence of any adult *Ae. aegypti* in an adjacent household as well as households within 30, 50 and 100 meters, respectively. Continuous density was calculated as adult mosquitoes per square meter, per resident reported and per household room surveyed; these measures were also analyzed as categorical variables (comparing ≥0.01 to <0.01). The spatial and temporal covariance of these continuous

measures were then modeled and mosquito density was estimated using the Bayesian Maximum Entropy (BME) geostatistical framework. Spatially-modified densities were used to estimate the six-month risk of DENV seroconversion using log binomial models. Construction of density variables by inclusion of adjacent households resulted in a weak association (risk ratio: 1.10 (95% CI: 0.99, 1.23), but measures within 30, 50 and 100 meters did not demonstrate an increased seroconversion risk. Adult *Ae. aegypti* per household area (RR: 1.01; 95% CI: 0.86, 1.18) and density predictions generated using BME (RR: 1.03; 95% CI: 0.91, 1.16) were not associated with risk. The spatial covariance model suggests that spatial correlation among entomological data occurs at a very fine scale, within approximately 25 meters. The lack of association with DENV seroconversion suggests that the inability of cross-sectional entomological measures of mosquito density to identify individuals at an elevated risk of DENV is not improved by incorporating measurements at various spatial scales.

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QUANTUM DOT LABELLING OF *AEDES ALBOPICTUS* BACTERIA: A NEW METHOD TO STUDY MOSQUITO DISPERSAL BEHAVIORS

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Aedes mosquito transmits important human diseases such as dengue and Zika. Bacterial microbiota-mosquito holobiont plays an important role in various aspects of mosquito life history and vector competence. The life table study using water from natural habitats but depleted with bacteria by filtering or antibiotics showed very high larval mortality in *Aedes albopictus,* demonstrating important role of bacteria in *Ae. albopictus* larval development in nature. Using Miseq pyrosequencing of the 16S rRNA gene V4 hyper-variable region, mosquito bacterial microbiota was examined at different developmental stages from major types of larval habitats. Despite of highly diverse bacterial microbiomes in aquatic habitats and mosquito larvae, *Wolbachia, Aromonas, Novisprillum* and several other genera were the dominant bacteria in adult mosquitoes. We applied the knowledge on the dominant and cultured bacteria in adult mosquitoes to determine whether bacteria can be used as a new labeling method to study mosquito dispersal behaviors. To prove the principle of this method, mannose-modified fluorescent carbon quantum dots (Man-CQDs) were synthesized and used to label *Escherichia coli*. *Aedes albopictus* fed with Man-CQDs labeled *E. coli* showed a constant fluorescence. Larval life table study found that Man-CQDs had low or no toxicity to the mosquitoes. We are currently testing this labeling method with the dominant and cultured bacteria found in natural adult mosquitoes, and conducting field experiments to determine mosquito dispersal behaviors. Mosquito fluorescence labeling through Man-CQDs labeled bacteria may provide a potential new method to explore the function of bacteria in mosquitoes and to study mosquito behaviors.

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MODELING THE IMPACTS OF CO-CIRCULATING HEMOPARASITES IN MOSQUITOES ON WEST NILE VIRUS TRANSMISSION

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Polyparasitism, or the simultaneous infection with two or more parasites in a single host, is a widespread phenomenon that may influence infectious disease dynamics. Because of the abundance of parasitic coinfections in nature, blood-feeding arthropods are often exposed to multiple parasites during a single blood meal. *Culex* mosquitoes, the main vectors of West Nile virus (WNV), may ingest a variety of viral, protozoan, and macro-parasitic hosts found among avian and mammalian bloodmeal hosts. However, the downstream transmission consequences of mosquitoes ingesting these organisms are unknown. SIR-based mathematical models were used to explore outcomes where WNV-hemoparasite co-ingestion altered vector survival, vector competence, the extrinsic incubation period, or vector feeding ecology. We conducted a sensitivity analysis to highlight the parameters with the greatest effect on the reproductive number of WNV. Results highlight the potential for population-level impacts of within-host interactions and identify mechanisms capable of driving fine-scale transmission of WNV.

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MIDGUT COMMENSALS REGULATE INFECTION BY ZIKA AND SINDBIS VIRUSES IN *AEDES AEGYPTI*

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In recent years, mosquito-borne viruses such as Dengue (DENV), Chikungunya (CHIKV), and Zika (ZIKV) have become globally disseminated and are a significant cause of human morbidity and mortality. In order for transmission to occur, viruses must first infect the mosquito midgut and subsequently pass into the hemolymph where they can circulate to infect other tissues. Numerous studies have demonstrated that the mosquito midgut is an important barrier that bloodmeal-acquired viruses must overcome. Therefore, understanding the mechanisms underlying successful infection of the midgut is crucial. The mosquito microbiome plays an important role in shaping the midgut environment and has been previously shown to regulate susceptibility to infection by different arboviruses. To contribute to this body of knowledge, we have tested whether reducing midgut commensal bacteria affects *Aedes aegypti* infection by both Zika virus (ZIKV) and Sindbis virus (SINV). Our preliminary data suggests that depletion of commensals by antibiotics during both of these viral infections results in a decrease in viral transcript levels. We are validating these results by assaying virus at the protein level by western blot and determining localization by confocal microscopy. Specifically, we are interested in exploring the mechanism behind this phenotype. 16S sequencing and CFU plating will be used to define the bacterial signals that elicit infection-permissive responses from the intestinal epithelium. Toll and Imd NF-κB signaling pathways are important for regulation of the gut microbiome. Bacterial products bind to cell surface receptors and activate signaling in the intestinal epithelium. Therefore, we are using RNA-seq to characterize the differences between antibiotic and sugarfed *Ae. aegypti* in activation of these pathways during viral infection. Results from these studies will lead to mechanistic insights that may yield novel strategies to block disease transmission.

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VECTORBASE: THE USE OF THIS DATABASE FOR NEW ANALYSES, DESCRIPTIONS AND HYPOTHESIS TESTING

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VectorBase is a NIAID/NIH-funded bioinformatics resource center for invertebrate vectors of human pathogens. This database has the genomes of vectors of medical importance such as *Anopheles gambiae*, *Aedes aegypti*, *Culex quinquefasciatus*, others in the groups Diptera, Hemiptera, Phthiraptera, Acari and the snail *Biomphalaria glabrata*, the intermediate host of *Schistosoma mansoni*. In the last year the number of genomes hosted has increased to 40, with new additions including *Aedes albopictus* and non-vector but useful key species for comparative genomics of traits of interest such as *Sarcoptes scabiei var. canis*, *Stomoxys calcitrans* and *Cimex lectularius*. In addition to genomes, transcriptomes and proteomes, VectorBase also hosts lab and field collected metadata, genetic variation (*e.g.,* SNPs), expression (microarrays and RNAseq) and insecticide-resistance phenotypes. We will demo how the freely available VectorBase

data can be visualized, browsed and queried, creating the possibility of new analyses, descriptions and hypotheses testing. Thesis or publications using this resource, are kindly ask to reference the paper or papers were the data was originally published and VectorBase most recent paper, as explained in the website under the "Help" navigation tab. We will also demo how to export or download big or small data sets, both for simple and complex queries. Analyses of these data can be performed with the site tools, which include Galaxy, a web-based platform for data intensive biomedical research, or any other external tool. Follow this link for the latest data, tool and resources updates called releases, www.vectorbase.org/releases, send questions or comments to info@vectorbase.org, and visit the site YouTube channel for video tutorials in this link, https://goo.gl/mChdGh.

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ECOLOGY OF LA CROSSE VIRUS (LACV) VECTORS ALONG FOREST-TO-FIELD ECOTONES IN WESTERN NORTH CAROLINA

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La Crosse Encephalitis (LACE) is a pediatric disease with a recent emergence in the number of reported cases in Appalachia. This increase may be due to improved reporting and/or a greater exposure to La Crosse virus (LACv) vectors. The LACv is historically transmitted by the sylvan eastern tree-hole mosquito (*Aedes* triseriatus). However, recently invasive species (*Ae. albopictus* and Ae. japonicus), likely secondary peri-domestic vectors known to co-occur with Ae. triseriatus, complicate the understanding of LACv ecology. The goal of this study was to determine the effect of landscape structure (i.e., forest-to-field ecotones) and artificial container introduction (i.e., tires) on the distribution and abundance of the LACv in western NC. We hypothesized that 1) Canopy-associated environmental variables determine LACv vectors' distribution and clustering along these ecotones; and that 2) Tire introduction increases local (habitat-specific) and overall (across ecotone) abundance of LACv vectors. We ran 2 parallel transects per site (6 sites total), each 200-meters in length, 15 ovitraps per transect; we also deployed traps for gravid (BG Sentinels and Landing-Biting) and resting (Nasci aspirator) mosquitoes. We incorporated 9 tires in each experimental plot: 2 sites received treatment in the field, 2 sites in the forest, and 2 sites served as control. Preliminary results suggest habitat preferences with *Ae. albopictus* more abundant in the field habitats, and Ae. japonicus as well as Ae. triseriatus more common in the forest and edge habitats. The artificial container introduction appeared to increase the abundance of all species, particularly in their "preferred" habitats; however, it did not result in altered oviposition patterns along the ecotone.

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EVALUATION OF KNOWLEDGE AND PRACTICES OF RESIDENTS FOR THE PREVENTION OF MOSQUITO-BORNE VIRUSES IN NEW ORLEANS, LOUISIANA

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To understand local transmission potential for the emergence of arboviral epidemics including Zika, dengue and chikungunya, the abundance of competent vector populations and residential sources should be evaluated. This study assessed the knowledge, attitudes and practices of New Orleans residents regarding mosquitoes and arboviruses and identified frequent breeding habitats on residential properties. Residents indicated frequent mosquito exposure including mosquitoes being a problem in the yard (63.2%), being bitten by mosquitoes frequently (45.9%) and spending time outside in evening daily (37.8%). Central air conditioning was common (70.5%) however, 30.0% reported opening windows frequently and sometimes finding mosquitoes inside the house (54.5%). Property inspections in November and December 2015 yielded an average of 1.4 water-holding containers per residence and a House Index of 31.8. Of the 115 containers surveyed 36.5% were positive for mosquito larvae and 13.9% for pupae. The most common mosquito species was *Aedes aegypti* (85.9%); far less common were Culex quinquefasciatus (11.3%) and *Ae. albopictus* (3.3%). Additional container surveys and questionnaires are planned for May-July 2016, and adult mosquito surveillance will be conducted using BG Sentinel traps. Large urban populations of *Aedes aegypti* and *Ae. albopictus* are present in New Orleans, Louisiana and the potential of introduction of Zika virus by a viremic individual is of great concern. It is essential to identify, educate, and eliminate residential mosquito breeding locations for *Ae. aegypti* on a community-wide level, and the results from these surveys will be used to produce tailored educational outreach materials. The long-term control of arboviral diseases is only possible through an integrated public health approach, rapid case identification, and sustainable vector control strategies.

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VECTORIAL CAPACITY OF *AEDES ALBOPICTUS* ACROSS THE UNITED STATES

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There is accumulating evidence that predicting vector-borne disease transmission is fraught with complexity. Recent work in a variety of transmission systems suggest that climate patterns have important direct impacts on vector-borne disease and define the potential environmental ranges of vector-borne pathogens. However, the realized distribution and extent of vector-borne disease transmission will also depend upon a variety of non-climatic factors, such as genotypic differences in local vector and pathogen populations, as well as socioeconomic and demographic factors that define variation in human exposure. The proposed study will investigate the invasive *Aedes albopictus* (Asian tiger mosquito) - arbovirus transmission system. *Ae. albopictus* is highly abundant, has a large and expanding distribution within the U.S., is a highly competent vector for dengue, chikungunya, and potentially Zika viruses, and has been linked to explosive arbovirus outbreaks in temperate zones.The goal of this project is to identify which environmental and genetic factors contribute to variation in vectorial capacity. To do this we first empirically quantified how fitness and transmission potential vary across the U.S. distribution of *Ae. albopictus* by running large-scale, common garden transplant experiments under semi-field conditions across a latitudinal cline. Using life table analysis, we compared the fitness differences in sympatric vs. allopatric populations to determine if populations are adapted to local environmental conditions and to generate age-specific estimates of key mosquito life history traits that drive transmission (e.g. larval development rates, longevity, fecundity, and biting rates). From this study, we generate age-dependent models of vectorial capacity to predict how lifetime transmission potential varies across latitude and populations of *Ae. albopictus* in the United States.

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DETECTION OF MAMMALIAN ANTIBODIES AGAINST ROSS RIVER VIRUS IN MOSQUITO BLOOD MEALS AND POTENTIAL FOR ARBOVIRUS SURVEILLANCE

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Mosquito-borne alphaviruses are the causative agents of several debilitating diseases that have been associated with large, cross continental outbreaks, as demonstrated recently by chikungunya virus. Ross River virus (RRV) is an alphavirus endemic to Australia and the Pacific which is the agent of a debilitating disease with symptoms including fever,

arthritic joint pain and rash. RRV is characterized by a broad association with a variety of mosquito vectors and vertebrate hosts. A number of these hosts are native Australian marsupials, including kangaroos, wallabies and koalas. The complex ecology of the virus present large challenges for disease surveillance, epidemiology and control. We are developing a novel xenodiagnostic assay strategy to determine the seroprevalence of RRV antibodies among vertebrate host populations. The strategy avoids animal ethics dilemmas by harnessing the natural behavior of resident mosquito populations to sample blood from a wide variety of vertebrate hosts. We demonstrate the ability to detect RRV IgG from within mosquitoes that originate from any vertebrate host species. We are utilizing a population of koalas with a seroprevalence for RRV IgG of 75% and a colony of flying foxes (Pteropus spp.) in a suburb of Brisbane. This work will provide insights and strategies for improved epidemiology of RRV and potentially other mosquito-borne diseases.

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TARGETED XENOMONITORING FOR LYMPHATIC FILARIASIS IN HIGH RISK COMMUNITIES AS PART OF POST-MASS DRUG ADMINISTRATION AND ENDGAME SURVEILLANCE IN MALAWI

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Malawi is on track for the elimination of lymphatic filariasis (LF), with more than five rounds of annual mass drug administration (MDA) and successful transmission assessment surveys (TAS) to indicate transmission has been interrupted. Now there is a need to implement post-MDA surveillance strategies, including xenomonitoring to provide further evidence of elimination, especially in high risk communities identified in baseline prevalence surveys. The Neglected Tropical Disease (NTD) laboratory in Blantyre provides essential support to the National LF Elimination Programme, and in 2010-2011 collected and analysed >12,000 mosquitoes from across the country during the initial stages of the MDA programme. Relatively high rates of LF infections by RT-PCR (8%) were found, and the majority of infections were in *Anopheles funestus* from Chikwawa District in the high risk Southern Region of the country. Co-incidentally high levels of pyrethroid insecticide resistance were also reported in this species, which has implication for the effectiveness of additional vector control interventions, especially long-lasting insecticidal nets (LLINs). The aim of this study therefore was to conduct a follow-up post-MDA assessment in the three high risk villages where high mosquito infection rates were found in the initial MDA stages. In addition, an assessment of five highly endemic villages where >10 morbidity cases have been reported during recent mapping activities in Chikwawa and Nsanje will be conducted. The work will specifically focus on collecting mosquitoes using pyrethrum spray catches (PSCs) and window traps over a three month period across 8 high risk villages from >20 individual trapping sites. More than 7000 mosquitoes are expected to be processed, including species identification, examination for *Wuchereria bancrofti* microfilaria infections using RT-PCR and insecticide resistance standard laboratory protocols. This study will help to establish a targeted xenomonitoring protocol in high risk areas and provide information to the LF programme as part of its post-MDA and endgame surveillance strategy.

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TROPICAL DISEASE IN LATE 18TH SURINAM: THE CASE OF CAPT. JOHN STEDMAN, 1772-1777

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Historians of tropical medicine have largely ignored John Gabriel Stedman's The Narrative of a Five Years Expedition against the Revolted Negroes of Surinam (1796). Contemporaries commandeered his writings as a cruelly vivid indictment of slavery in Surinam. Although a mercenary on the payroll of Dutch planters, Stedman himself condemned the brutally that he witnessed daily—observations often redacted from early editions. Stedman's five-year tale of life in Surinam represents far more than a graphic indictment of slavery. Rather, it provides a vivid window into late 18th century tropical medicine in South America. Drawing on Stedman's own first-hand observations, this project will examine his daily encounters with tropical disease, insect vectors, and medical therapy within the context of late 18th century colonial medicine in the Americas.

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DIFFERENCES IN PRELACTEAL FEEDING ON THE ISLAND OF HISPANIOLA: THE DOMINICAN REPUBLIC AND HAITI

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Despite sharing the island of Hispaniola, the Dominican Republic (DR) has significantly lower rates of exclusive breastfeeding (EBF) than Haiti in the first six-months of life. Prelacteal feeding (PLF), the use of non-breastmilk feeds in the first three days of life and/or before breastmilk comes in, is common in the DR and is known to undermine EBF. Whether PLF is more common in the DR than Haiti has not been examined in recent data, nor while controlling for other factors that influence PLF (e.g., caesarean sections [C-section]). This study aimed to determine (i) whether PLF differs between the DR and Haiti, and (ii) whether such differences persist after controlling for potential confounding variables. This study used data from the most recent Demographic and Health Surveys from the DR (2013) and Haiti (2012). PLF was found to be much higher in the DR (62.5%) than Haiti (20.3%). Infant formula and other non-breast milks were the most common PLF choices in the DR, but were rarely used in Haiti. In contrast, Haitians more often administered sugar water to newborns than Dominicans. In bivariate analysis, the prevalence of PLF increased as a function of increasing household wealth in the DR, but was unrelated to wealth quintiles in Haiti. In a final multivariate model, being Dominican substantially increased the odds of PLF despite controlling for multiple other variables. Having had a C-section and not having put the child to the breast within one hour after delivery also significantly and independently increased the odds of PLF. Further investigation is warranted to identify what other factors contribute to the significantly higher PLF rates amongst Dominicans versus Haitians. In addition, intervention studies are required to determine approaches to reduce PLF, which may increase EBF rates in the DR and elsewhere.

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POOLING KNOWLEDGE AND EXPERIENCE TO IMPROVE CLINICAL RESEARCH STANDARDS IN LOW- AND MIDDLE-INCOME COUNTRIES: THE EXPERIENCE OF THE SWITCHING THE POLES NETWORK (2008-2016)

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The Switching The Poles Clinical Research Network, started in 2008, brings together 13 research institutions from Belgium, Benin, Burkina Faso, Cambodia, Cuba, the Democratic Republic of Congo, Ethiopia, India, Indonesia, Nepal, Peru, The Gambia and Vietnam. It aims at strengthening partners' capacity to set-up, conduct and lead non-commercial clinical research programs that address the priority health needs of these regions and comply with appropriate ethical and Good Clinical (Laboratory) Practice (GC(L)P) standards. The Network adopted an approach based on practical thematic working groups, that favour the involvement of young researchers and traditionally 'neglected profiles' (*e.g.* data managers, laboratory staff), with the potential of bringing a direct benefit to research projects. The main groups include GCP, GCLP, clinical data management (DM) and clinical monitoring in resource-constrained settings, and informed consent in vulnerable communities. We developed a theoretical and practical approach to teaching GCP and GCLP; a set of standardised DM procedures; and an e-platform (admitnetwork.org) for consultation and peer advice among clinical data managers, who are traditionally quite isolated in small non-commercial research groups. We also started the field coaching of clinical monitors, facilitated South-South collaboration in different aspects of clinical research and took public positioning on research ethics issues, *e.g.* the double ethical review in externally-sponsored trials and the approach to informed consent in socially vulnerable populations. The inclusion of partners from three continents, with different linguistic and cultural features, resulted in cross-fertilization and enrichment, while the small size of the network favored interpersonal collaboration, and it could make some achievements sustainable also in absence of prolonged external funding. Our experience shows that small but multi-cultural networks are flexible, can rapidly adapt to address the partners' needs, and provide an excellent platform for supporting young researchers and promoting South-South collaboration.

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TELEPATHOLOGY FOR RAPID TURNAROUND TIME IN MALIGNANCY DIAGNOSIS IN LOW-MIDDLE INCOME SETTINGS

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Delivering cancer care in low-resource settings is dependent on developing efficient and accurate pathology systems. In this study, we analyzed the efficacy of implementing a telepathology system to remotely provide cancer diagnostics to Butaro District Hospital in rural Rwanda. Our system consisted of static images obtained by histotechnologists using a standard protocol, uploaded to ipath-network.com, and reviewed by a team of pathologists with various areas of expertise in common malignancies. Over the 9-month implementation of telepatholgy, we divided the study into three segments—training, technical workflow, and testing segment. In this presentation, we will breakdown the efficacy of the telepathology system in Butaro District Hospital for oncology cases. For the three implementation phases over the 9-month study period, we will present the turn-around time, from procedure date to result, as well as the volume of cases triaged for pathologist review that were unable to be diagnosed through telepathology. Over the three implementation phases, the turn-around time of cases drastically decreased, allowing clinicians to receive results and initiate more accurate and timely treatment for cancer patients. Simultaneously, the percentage of cases triaged for pathologist review that could not be properly diagnosed through telepathology significantly decreased through improvements in technical imaging, communication, and workflow management.

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EVALUATION OF A HANDHELD MOLECULAR ASSAY AS A RAPID CLOUD BASED POINT OF CARE ASSAY FOR THE FIELD DETECTION OF RESPIRATORY VIRUSES IN KENYA

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Influenza and respiratory syncytial viruses (RSV) are important causes of respiratory morbidity and mortality. Polymerase chain reaction (PCR) is the most reliable diagnostic test, but requires advanced laboratory facilities. Point of care (POC) rapid tests for influenza characteristically have low-moderate sensitivity, varying substantially with age and the time of testing related to illness onset. Rapid and accurate detection of respiratory pathogens in less resourced, often rural settings is key for effective public health interventions. The Biomeme real-time PCR mini thermocycler with iPhone offers several advantages to traditional PCR, including temperature-stable reagents, simplified protocols allowing for use at POC with limited laboratory experience, and instant communication of results. We evaluated the performance of this thermocycler against traditional Center for Disease Control and Prevention (CDC) real-time PCR assays. A total of 119 stored nasal and oral pharyngeal samples were identified, and RNA extracted and tested using both assays. CDC assays detected 35 Influenza-A, 11 Influenza-B, 45 RSV and 28 influenza/RSV-negative specimens. For Influenza A, Biomeme detected 30/35 positives compared with CDC assay, for a sensitivity, specificity and agreement of 86 (95% confidence interval (ci) 74,97), 96 (95% ci 90,100) and 81% (Kappa= 81(95% ci 67,95)) respectively. For Influenza B, Biomeme detected 7/11 positives compared with CDC assay, for a sensitivity, specificity and agreement of 64 (95% ci 35,92), 96 (95% ci 90,100) and 66% (Kappa=66 (95% ci 38,93)) respectively. For RSV, Biomeme detected 37/45 positives compared with CDC assay, for a sensitivity, specificity and agreement of 82 (95% ci 71,93), 100 and 78% (kappa=78(95% ci 64,92)) respectively. Generally, there was good test agreement between Biomeme and CDC assays. Biomeme has potential as an accurate alternative POC diagnostics in sub-Saharan Africa, allowing detection of Influenza and other respiratory pathogens in medical facilities with limited laboratory capacity.

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IDENTIFYING AVENUES IN THE MANAGEMENT OF FEBRILE ILLNESS BY EXAMINING COMMUNITY HEALTH SEEKING PATTERNS

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Malaria remains a major public health problem in Kenya. Early appropriate diagnosis and treatment can prevent severe illness. This depends on the recognition of the symptoms and signs and on treatment actions taken. We describe health seeking behavior for febrile illness in 3 rural malaria endemic areas prior to implementation of a large cluster randomized study. A population based household survey was conducted in western Kenya in a random sample of households. 2,065 participants who reported a malaria-like illness in the past four weeks were enrolled. 21% of respondents used drugs that were available at home as a first action, 53.5% visited drug shops and 24.6% went to a health facility. 44% of participants had a malaria test for the illness, and 82.2% of tests were positive by self-report. Adults (OR 1.29 95%CI: 1.08-1.55), those less educated (OR 1.29 95%CI: 1.08-1.55) and those not employed were more likely to go to drug shops as a first action. More educated participants were more likely to be tested (OR 1.42, 95%CI: 1.22-1.65), but less likely to have a positive test. Overall, 76.4% reported taking an Artemisinin Combination Therapy (ACT), including 53.3% of malaria-negative participants, and 68.6% of participants with no test. 60% of those who took an ACT purchased it from a shop. The odds of taking an ACT did not differ based on whether the participant had a malaria test or whether the test was positive or negative, but the odds of taking an ACT was three-times higher if they purchased drugs in a shop (OR 3.2, 95%CI: 2.6-4.0). 42.9% of those who took action for their illness also took a second follow up action, usually visiting a health facility (72%). Those who initially took drugs available at home and from drug shops were more likely to take a second action (34.74%, 56.21% respectively) as compared to those who had initially visited health facilities (8.7%). Most ACTs are obtained from the private retail sector but targeting of ACTs to those with a confirmed malaria infection is inadequate. This is underscored by the large proportion of people who do not recover after seeking treatment in the retail sector and go on to attend a health facility.

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EXPERIENCES AND CHALLENGES OPERATING AN EBOLA VIRUS DISEASE DIAGNOSTIC LABORATORY IN RURAL LIBERIA

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In August 2014, the World Health Organization declared the Ebola Virus Disease (EVD) outbreak in the West African nations of Guinea, Liberia, and Sierra Leone a public health emergency of international concern. As part of the international response to the outbreak in Liberia, laboratories were opened and dedicated to testing specimens for EVD infection across the nation. These laboratories served to provide rapid and accurate information to assist epidemiologists and other public health workers in controlling the spread of the outbreak by testing specimens from both living and deceased patients thought to be infected with the virus. In February 2015, the Academic Consortium Combating Ebola in Liberia (ACCEL), in coordination with the United States Centers for Disease Control and Prevention and the Liberia Ministry of Health and Social Welfare, began performing EVD testing in Tappita, Liberia. Since that time, the laboratory has processed and tested over 9,000 specimens and continues to be one of four enduring EVD laboratories in the nation. In addition to providing rapid molecular diagnostic capability for epidemiological investigations, the Tappita EVD Laboratory also provides rRT-PCR testing for the semen of male EVD survivors in support of Liberia's Men's Health Screening Program. Although testing for highly pathogenic agents presents inherent challenges, operating in rural Liberia offers unique challenges including further issues with logistics management, workforce development, sustainability, infrastructure improvement, and the implementation of new technologies. This requires both a knowledgeable and adaptable organization. Herein, we present our experiences running one of the largest EVD laboratories in Liberia and the challenges encountered.

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THE COSTS AND IMPACT OF COMMUNITY HEALTH SERVICES IN MALAWI AND SIERRA LEONE

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In Malawi and Sierra Leone, community health workers (CHWs) play a critical role in extending access to health services and addressing priority issues ranging from Ebola prevention to malaria case management. Despite evidence on the benefits of community health services (CHS), there is limited information on the required financing for effective, integrated CHW programs, and, consequently, programs frequently lack long-term financing plans and are under-funded. In February and March 2015, MSH, through funding from UNICEF, piloted a methodology and tool to calculate the costs and the estimated return on investment (i.e. lives saved) of national CHS packages in Malawi and Sierra Leone. Using an "ingredients-based" approach, MSH staff collected actual service and financial data through semi-structured questionnaires administered to 48 CHWs and 22 supervisors in four districts and program managers at all levels of the health system. Following data entry into the tool, MSH health economists conducted cost and impact analyses of the current CHS packages and projections of utilization scenarios up to ten years. Based on preliminary study findings in Sierra Leone, the total recurrent cost per CHW averaged $767.25 and the recurrent cost per live saved was $3,176. The main cost-drivers of CHW program were program management followed by CHW supervision and equipment and medicines. A comprehensive understanding of the costs and impact of CHS packages provides evidence for policy makers and planners to advocate for future funding and allocate financial and human resources based on cost and impact projections. However, to be cost-effective and affordable, CHW programs must be well-utilized and key bottlenecks such as stock-outs of medicines, human resource shortages, and inadequate CHW financial incentives must be addressed. This methodology and tool can be adapted for use in other countries for investment case advocacy, service package planning, resource allocation, and cost-effectiveness and financial gap analyses.

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TRENDS IN SOCIOECONOMIC-RELATED HEALTH INEQUALITY IN RURAL WESTERN KENYA: DATA FROM REPEATED HOUSEHOLD MALARIA SURVEYS 2006-2013

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Socio-economic disparity is well recognized as a barrier to achieving health-related international development goals. Socio-economic data are not always analysed or fully utilised for guiding decisions or monitoring the impact of health interventions and programs. In malaria-endemic western Kenya, we examined the trends in malaria parasitemia, malaria medication usage, and care-seeking behaviour at the household level by socio-economic status. We analysed data from annual malaria cross-sectional surveys from 2006 to 2013 based on systematic, cluster, and stratified sampling of 7,253 households in rural western Kenya. Data collected included socioeconomic status (SES), demographics, malaria parasitemia by microscopy, medication usage and care-seeking behaviour. A composite SES score was created from multiple correspondence analyses of household assets, and households were classified as poor (i.e., lowest three quintiles) or less-poor (i.e., highest two quintiles). The gap in the odds of malaria between poor and less-poor (for all ages) was significant in 2007 (OR=1.86, 95% CI: 1.1–3.1, p=0.016) but not in 2013 (OR=1.2, 95% CI: 0.9–1.6, p=0.331). Overall, the declining equity gap in the odds of malaria from 2006–2013 formed a polynomial curve (R^2=0.99; trend p<0.001). Amongst children aged <5 years, the trend in the odds of malaria gap between poor and less-poor was not significant over the study period (p=0.688). The trends in the inequalities in medication usage (p=0.876) and care-seeking behaviour (p=0.181) were not statistically significant over the study period. In western Kenya, substantial inequalities in health indicators, such as malaria parasitemia prevalence, medication usage and care-seeking behaviour, continue to exist. However, the health inequality gap in malaria parasitemia prevalence has decreased over time. These findings provide evidence that targeted malaria prevention and control efforts can help reduce health inequalities among the poorest households in western Kenya.

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ASSESSING URBANIZATION TRENDS FOR PUBLIC HEALTH: MODELLING NIGHTTIME LIGHTS IMAGERY IN AFRICA: 2000 - 2013

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The growth of urban centers and the transition of rural settlements to urban environments has a broad range of public health implications. Sub-Saharan Africa currently has the world's highest urban growth rate of any continent at roughly 4.2% annually and better understanding the spatiotemporal evolution of this process is key to many geospatial disease modelling and burden estimation efforts. Nighttime lights imagery (NTL) captured by National Oceanic and Atmospheric Administration's satellites offer a unique viewpoint for studying urban trends. These data, available as annual composites from 1992-2013 at 1 km resolution, provide a means for spatiotemporal analysis on a global basis. However, inter- and intra-annual differences between satellites make the raw imagery unsuitable for temporal analysis. The objective of this study was to generate a time series of annual inter-calibrated NTL images (2000-2013) to describe patterns of urbanization in Africa and provide input for studies on the relationship between urban land cover and electrification on malaria transmission. Processing included a regression based procedure for inter-calibration of images from different satellite/years. This method used a 1999 image as a reference and values in all other images were adjusted to match its data range. Subsequently, a weighted 5-year moving average was used to reduce annual variability. Low-light thresholding was also used to remove 'overglow', an exaggeration of brightness in urban peripheries. Urban agglomerations were identified using a region grouping function to detect contiguous lighted pixels. Urban cluster sizes were grouped into 6 categories on a log scale (1-100K km^2) and trends in total area assessed temporally. The maximum size and frequency of agglomerations increased in the 10K–100K and 100–1K km^2 categories for densely and sparsely populated countries, respectively. The processed NTL time series will be made openly available to global health researchers as well as the broader scientific community.

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THE ACT CONSORTIUM AND THE GLOBAL HEALTH NETWORK: COLLABORATING TO PROVIDE AN ONLINE, OPEN-ACCESS, COMPREHENSIVE PHARMACOVIGILANCE RESOURCE FOR THOSE WORKING IN TROPICAL INFECTIOUS DISEASES AND GLOBAL HEALTH

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Drug safety signals may remain undetected in resource-poor settings due to a lack of infrastructure for surveillance, under-developed regulatory oversight and poor access to guidance on research methods. Online resources are available but may be unaffordable. Moreover some websites lack maintenance, or provide guidelines and regulations without support for implementation. Few facilitate interaction about the successes and challenges in assessing harm. More tools, discussion and learning opportunities would advance drug safety research in these areas. The ACT Consortium (ACTc) took a comprehensive approach to antimalarial pharmacovigilance (PV); trials on the effects of repeated exposures of artemisinin-based combination therapies (ACTs), and interactions between ACTs and antiretrovirals; the participatory design of adverse event data collection tools; qualitative exploration of influences on participant safety data reports; and a web-based Drug Safety Repository (www.actconsortium.org). Sharing these experiences and resources should benefit others interested in drug safety in tropical infectious diseases and global health, particularly those struggling to access relevant information. As such, ACTc researchers have collaborated with the online open-access science park, The Global Health Network, TGHN (www.tghn.org), to develop a dedicated space for this field. Aside from creating a comprehensive PV resource of relevant information within TGHN, www.globalpharmacovigilance.org brings useful, high quality, up-to-date external resources together in one place. In addition there are original articles on pertinent PV topics, interviews with experts, and fora for discussing drug safety research in the real world. Links are provided to education and training providers, while new free eLearning courses are being developed in-house. The website coordinators make periodic contact with its user group to explore experiences and needs. By engaging

the website community, this contribution to global drug safety will develop iteratively to improve the practice of safety evaluations in resource-poor settings.

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EVALUATION OF CAPACITY BUILDING FOR LEADERSHIP AND GOVERNANCE IN ORDER TO STRENGTHEN HEALTH SYSTEMS IN DEVELOPING COUNTRIES

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In many countries, teaching the topic of leadership is not part of the medical curriculum, however with the recent Ebola outbreak, it clearly showed how a lack of leadership can be a threat to an entire health system. A training course in leadership was taught to 24 medical doctors from eight sub-Saharan countries. The aim of the project was to evaluate the leadership training course and it is application in the context of health systems strengthening in developing countries. The evaluation study was designed using a qualitative methodology whereby individual interviews with all the participants and trainers from the leadership training course were conducted. Focus group discussions were organised in four countries. Questions from the individual interviews were designed following the Kirkpatrick Model for evaluating training programmes, which include, the reaction to the training; learning uptake; behaviour change; and results of the training. The themes generated from the interviews which were highlighted as important to effective leading and governing of health systems in developing countries were, enthusiasm; being a better leader; need for a change; communication; teamwork; personal development; process of implementation of activities; responsibility and governance. During the focus group discussions the themes discussed were non-governmental organizations and representation at the ministry level. The presenter will explore these themes further and demonstrate subsequent changes following the capacity building initiative. The discussion will include positive reaction from all the trained participants, which has enabled them to keep track of their progress through their actions. Training also determined the essential skills required for a leader in healthcare and how participants are able to apply the knowledge gained during the training to their work setting. Additional factors to improve healthcare services by increasing collaboration with Governments and the MOH in order to increase sustainability of healthcare services were addressed.

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HEALTH CARE WORKER MOTIVATION ONE YEAR AFTER THE EBOLA OUTBREAK IN LIBERIA

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Staff motivation is an often overlooked ingredient of quality health services. After a crisis like Ebola, particular attention should be paid to helping health care workers recover. During the Ebola Virus Disease (EVD) outbreak in Liberia, Redemption Hospital, the only free secondary care facility in the city, became the physical and emotional epicentre of the disease. Twenty health care workers became infected and twelve died. The hospital ceased providing most services and was transformed into a holding unit for suspected Ebola cases. In January 2015, Redemption Hospital resumed comprehensive health services with the support of the International Rescue Committee (IRC). Initially it lacked the systems to maintain proper IPC, physical infrastructure for safe waste disposal, personal protective gear, and a sufficient number of skilled staff. Staff morale had been destroyed by the trauma of the outbreak; many did not return and those that did expressed fear and distress. From the outset, the IRC prioritized the mental and physical safety of staff, in addition to focusing on quality services. A year after the resumption of health services, the IRC assessed perceptions of change and factors affecting motivation for staff at Redemption. The qualitative findings revealed that staff expressed an improved sense of safety coming to work, increased confidence in their ability to deliver quality care to patients, and improved sense of pride and value as individuals. A quantitative survey verified these findings: the most important motivating factors reported by staff included commitment to the job (94%), smooth working relationship among staff (86%), and availability of PPE (83%). The least significant factors were monthly salary (27%) and transportation to work (31%). While monetary incentives are important, these findings show that they are not the primary motivator for health care workers at Redemption Hospital, a year after it resumed full services after being closed due to Ebola.

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ESTIMATING THE POTENTIAL DEMAND OF A DENGUE VACCINE TO INFORM VACCINE INTRODUCTION IN THE YUCANTAN PENINSULA: CASE STUDY FOR MEXICO

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Dengue has become a disease of growing importance in Mexico with disease prevalence in endemic areas as high as 80%. In 2015, Sanofi Pasteur's Dengvaxia® became the first dengue vaccine to be licensed for use in Mexico in the 9-45 year olds. As governments at the national and state levels discuss and plan strategies in response to dengue fever and the industry develops and prepares to scale up the production of vaccines, there is a need for estimates of the demand for dengue vaccine and for insights on where the introduction of the vaccine would have strong social and economic impact. In this perspective, strategic demand forecasts can be used to accelerate vaccine access by providing stakeholders with vital information on supply, potential demand, and vaccine costs of vaccine introduction scenarios. Demand estimates will be presented to accelerate vaccine access in the Yucatan peninsula. We will estimate the potential demand, costs, and impact of introducing a dengue vaccine in the Yucatan peninsula based on key stakeholder preferences for 35-year analytic horizon. The Yucatan Peninsula is formed by three states (Yucatan, Campeche and Quintana Roo) in Mexico where dengue fever is on the increase with 2,117 and 2,990 confirmed cases, 8,459 and 31,559 probable cases and 729 and 785 hospitalized cases reported in 2014 and 2015, respectively. We developed an Excel-based model to estimate the potential demand in the Yucatan peninsula from the public and private healthcare perspectives. Introduction scenarios are developed along with model algorithms to model the 35-year analytic horizon based on stakeholder interviews. Model assumptions are derived from government, funders and industry stakeholder interviews and from administrative and surveillance data produced by the Federal Government of Mexico.

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ESTIMATING THE POTENTIAL DEMAND FOR DENGUE VACCINES IN HONDURAS AND PARAGUAY: PRELIMINARY FINDINGS

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Honduras and Paraguay, both Latin American countries with a national GDP per capita below $US31 billion, continue to report growing incidence of and morbidity attributed to dengue fever. The increasing burden of dengue in these countries and the recent approval of the first Dengue vaccine, Dengvaxia®, in neighboring Latin American countries

has highlighted the need for country-specific, equitable dengue vaccine introduction strategies. Currently, there are no studies that quantify the demand and supply of the dengue vaccine to inform the value of vaccine introduction in Honduras and Paraguay. Strategic demand forecasts are a decision-making tool that can evaluate the temporal demand for vaccination, estimate the costs associated with vaccine implementation strategies, and approximate the funding requirements for the vaccine according to different introduction scenarios. This study aims to generate new evidence on the potential demand for two dengue vaccine candidates. We adopt an existing strategic demand forecast model to assess the potential demand for the two vaccine candidates and estimate the implementation costs and health impact of this demand in Honduras and Paraguay. Preliminary findings about the potential demand for dengue vaccines in Honduras and Paraguay will be presented based on extensive stakeholder consultations and a number of vaccine introduction scenarios. Results will rest on country- and state-specific sociodemographic characteristics, dengue epidemiology, price, supply constraints, and timing of licensure. Understanding the potential demand for and associated impact of a dengue vaccine can help develop a viable vaccine introduction strategy, which can significantly accelerate vaccine introduction and decrease the time it takes for countries to begin vaccination following licensure.

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A THRESHOLD ANALYSIS OF THE COST-EFFECTIVENESS OF A DENGUE VACCINE PROGRAM IN YUCATÁN, MEXICO

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The past few months have been pivotal in the effort to prevent and alleviate the burden of dengue fever worldwide. Mexico, Brazil, the Philippines, El Salvador and Paraguay have approved the first dengue vaccine - CYD-TDV, developed by Sanofi Pasteur, paving the way for vaccination campaigns in other endemic countries. The Philippines began its first public, school-based dengue immunization program in selected high-risk areas. Several other dengue vaccine candidates are currently in clinical development. Yucatán is one of Mexico's state that is most challenged with the burden of dengue with an annual incidence rate of 70.89 per 100,000 person-years in 2015, compared to the national average of 22.04 per 100,000 person-years. The cost of introducing the dengue vaccine in this region is likely to be significant. It is important to examine the level of cost per unit of outcome below which this new vaccine might be described as cost-effective to inform vaccine introduction policy. We use a decision tree model, embedded in a strategic demand forecast model, to estimate the incremental cost-effectiveness of using the new dengue vaccine program compared with the status quo, over 5-, 10-, and 15-, 20- and 30-year periods from a government perspective. Standard acceptability curves will be constructed to represent uncertainty around the incremental cost-effectiveness ratio decision rule, and to make cost-effectiveness results comparable to opportunity costs resulting from other health care strategies. Initial results about the cost-effectiveness threshold of a dengue vaccine program in the Yucatán region will be presented and analytic issues will be discussed. The results of the threshold analysis will highlight the importance of threshold values in dengue vaccine introduction decisions.

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TREATMENT AND REFERRAL OF SICK CHILDREN PRESENTING WITH ILLNESSES AT PRIVATE HEALTH CARE FACILITIES IN UGANDA

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Objectives: The main objective of this study was to assess treatment and referral practices for sick children seen at private health care facilities in order to explore ways of improving quality of care in this sector. Methods: A survey was conducted within 57 geographical areas (parishes) from August to October 2014 in Mukono district, central Uganda. Data was collected using a structured questionnaire supplemented by focus group discussions and key informant interviews with community members and private providers. Results: A total of 241 private health facilities were surveyed; 170 (70.5%) were registered drug shops, 59 (24.5%) private clinics and 12 (5.0%) pharmacies. The majority of facilities were selling artemesinin-based-combination therapy, (>96%), Amoxicillin (>90%), Zinc tablets (>77%) and oral rehydration salts, (>76%) all important in treating malaria, pneumonia and diarrhoea among children. Few drug shop (7.1%) and some private clinics (33.9%) had guidelines on integrated management of childhood illnesses. Similarly, only a few drug shop vendors (17.6%) and staff at private clinics (15.3%) knew that amoxicillin was the first-line treatment for pneumonia. Overall, 104/241 (43.2%) of the private health facilities reported that they had referred sick children to higher levels of care in the two weeks prior to the survey. The main constraints to follow referral advice by caretakers were: not appreciating the importance of referral, gender-related decision making and negotiations at household level, poor quality of care at referral facilities, inadequate finances at household level; while the perception that referral leads to loss of prestige and profit was a constraint at facility level, Conclusion: In conclusion, the results show that treatment and referral of sick children at private health facilities faces many challenges. Thus interventions to address constraints to referral of sick children are urgently needed.

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THE CARTER CENTER INTERNATIONAL HEALTH PROGRAM REVIEWS—A UNIQUE MODEL TO ASSESS PROGRAM PROGRESS, CHALLENGES AND IMPROVE PERFORMANCE

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The Carter Center has provided assistance to national programs to interrupt transmission of Guinea worm disease (dracunculiasis) since 1986. The collaborative effort of The Carter Center, ministries of health, WHO, CDC, UNICEF and other partners has reduced cases from an estimated 3.5 million in 1986 to 22 in 2015. The assistance provided by The Carter Center included development of operating procedures and monthly monitoring and reporting of program indicators. These requirements emphasized the need for all components of the programs to be accountable, and programs to be accountable to each other and to partner organizations and donors. In order to keep all staff informed of the status of the national eradication campaign, it became necessary to hold national Guinea Worm Eradication Program (GWEP) reviews, as well as an international review for national programs to report on the status of eradication efforts to partners and donors. This unique forum allows

partners to convene to peer review program progress, discuss challenges and make recommendations focused on improving performance and achieving the goal of eradication. Since its inauguration in Atlanta, GA in 1986, the program review has become the model used to measure program progress and inform programmatic decisions by both The Carter Center and national GWEPs. By 1996 the review had expanded to over 150 participants from 20 countries. In 2006 the review included representation from 21 countries, after the establishment of a separate program in Southern Sudan.

Due to its impact on successful program implementation, the program review model has been adopted by other Carter Center health programs. In 2016, the Center hosted 5 program reviews at its headquarters. While the review has evolved over the past 30 years, it remains an integral part of programming that has informed the Carter Center GWEP as it has helped stop transmission of Guinea worm disease in 17 countries in Africa and Asia. With 4 endemic countries (Chad, Ethiopia, Mali, South Sudan) remaining, The Carter Center will continue to coordinate review meetings at the national and international levels until eradication is achieved.

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LAND COVER MAPPING FOR CONTINENTAL AFRICA

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Land cover type influences transmission of a number of diseases, including vector-borne diseases such as malaria. However, high spatial resolution land cover data through time are lacking for continental Africa, hindering the ability to model and test hypotheses. The objective of this study was to develop a high spatial resolution (30 meter) land cover dataset for continental Africa for the years 2000 and 2015. To generate gold standard model data, high resolution satellite imagery was visually inspected and used to identify (7212 sample points) Landsat pixels that were entirely made up of 1 of 7 classes (water, impervious surface, high biomass, low biomass, rock, sand and bare soil). For model validation purposes, 80% of points from each class were used as training data, with 20% withheld as a validation dataset. Cloud free Landsat 7 and 8 annual composites for 2000 and 2015 were generated. Spectral bands from the Landsat image were then extracted for each of the training and validation points and a random forest model using the full dataset was used to classify the 2000 and 2015 Landsat images into each of the 7 classes. In addition to the Landsat spectral bands, spectral indices such as normalized difference vegetation index (NDVI) and normalized difference water index (NDWI) were used as covariates in the model. Additionally, calibrated night time light imageries from the National Oceanic and Atmospheric Administration (NOAA) were included as a covariate. Using the validation dataset, classification accuracy including omission error and commission error were computed for each land cover class. Model results showed that overall accuracy of classification was over 90 percent. This high resolution land cover product developed for the continental Africa will be available for public use and can potentially enhance the ability to test models and hypotheses.

1462

USING TREATMENT SEEKING DATA TO DEFINE HEALTH CATCHMENT AREA MODELS: EVIDENCE FROM ZAMBIA

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While routine health facility outpatient data are a vital source for tracking numbers of clinical disease cases in space and time, they are an imperfect measure of disease incidence in communities. Two main difficulties arise when trying to estimate community level incidence from cases reported at the health facility level. First, health records are only representative of those individuals who sought treatment. Thus, the number of cases captured and recorded via health facilities is likely to be an underestimate of the actual number of cases. Second, as information on the location of residence of cases is often lacking, catchment boundaries and populations are often uncertain. A better understanding of the drivers of treatment seeking, as well as the spatial distribution of the patients attending a health facility can help better estimate true incidence rates. Using data from eight rounds of parasite censuses amongst a population of over 300,000 in Southern Province, Zambia, where information on health facility choice and residence location of those seeking treatment for fever was collected, we define a probabilistic model that encodes the decision process of an individual when seeking for treatment and choosing a health facility to attend. Our model factors travel time (based on travel distance and maximum speed allowed by the terrain) as well as the types of health facilities in close proximity (Hospital, Health Center or Health Post). Results demonstrate a negative relationship between travel time to the closest health facility and the decision to seek treatment. Results also demonstrate that individuals are sometimes willing to undergo longer travel times to receive treatment at a specific type of health facility, rather than going to the closest facility available. The model allows for overlapping weighted catchment areas to be defined for each health facility depending on its type, travel time and location of other facilities. This catchment area model will be used in future geospatial modeling work to develop high resolution estimates of the incidence of malaria infection across Zambia.

1463

A CROSS-SECTIONAL SURVEY OF PERCEPTIONS RELATED TO SYMPTOMS OF MALARIA, CURABLE REPRODUCTIVE TRACT INFECTIONS AND ASSOCIATED TREATMENTS AMONG PREGNANT WOMEN AT HEALTH FACILITIES IN TANZANIA

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Malaria and curable sexually transmitted/reproductive tract infections (STIs/RTIs) in pregnancy are unacceptably high in sub-Saharan Africa due, in part, to poor coverage of antenatal interventions. Investigating the perceptions about these infections and related treatments among pregnant women may help to identify key barriers and facilitators to care-seeking and care provision. A cross-sectional survey of 397 pregnant women was conducted in rural Tanzania to examine perceptions of risk related to symptoms of malaria infection and curable STIs/RTIs, and associated treatments. Overall, 52% of pregnant women reported having a febrile episode in the last four weeks, of whom 79% received

antimalarial treamtent, this despite only 46% of them being diagnosed with malaria. Fever during pregnancy was considered somewhat, very, or extremely harmful by 11%, 25%, and 34% of pregnant women, respectively, whereas 7%, 7%, and 10% believed fever to be not at all harmful, slightly harmful, or somewhat harmful, respectively. Over 20% of participants did not know if malaria treatment was harmful. In the previous four weeks, 53%; 41%; 13% and 9% of pregnant women reported experiencing symptoms of curable STIs/RTIs - lower abdominal pain, genital or vaginal itchiness, vaginal discharge with fishy smell, and genital or vaginal ulcers - respectively. Only 24%, 27%, 33%, and 26% of these women received treatment for their STIs/RTIs symptoms, respectively. The public health implications of these results are evident. Although between 65-70% of pregnant women recognise the potential harm of malaria infection and curable STIs/RTIs in pregnancy, 20-25% of women do not know, or do not believe, that these infections may be harmful to their pregnancies. Malaria treatment is given too commonly without diagnosis, and only one-quarter to one-third of pregnant women with symptoms of curable STIs/RTIs are treated.

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CURABLE REPRODUCTIVE TRACT INFECTIONS: A CROSS-SECTIONAL SURVEY OF PERCEPTIONS RELATED TO SYMPTOMS AND ASSOCIATED TREATMENTS AMONG HEALTH-CARE PROVIDERS AT HEALTH FACILITIES IN TANZANIA

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A cross-sectional survey was conducted among 131 health-care providers in rural Tanzania to examine the knowledge and availability of treatment for syndromes related to curable sexually transmitted and reproductive tract infections (STIs/RTIs) in pregnancy: (1) lower abdominal pain (gonorrhoea and chlamydia), (2) vaginal discharge (bacterial vaginosis, trichomoniasis and yeast infection), (3) genital or vaginal ulcers (syphilis, gonorrhoea, chlamydia, and chancroid), and (4) genital or vaginal itchiness (yeast infection). Perceptions of harm attributable to these syndromes, and to treatment, were recorded. Nine of ten providers believed lower abdominal pain, vaginal discharge, genital or vaginal ulcers were extremely harmful to mothers (89%, 93%, and 95%, respectively); three-quarters (78%) responded similarly about genital or vaginal itchiness. Comparable proportions of providers said syndromes 1-3 were extemely harmful to unborn babies (88%, 94%, and 90%, respectively); three-quarters (76%) considered symdrome 4 to be extremely harmful. Nearly one-third of providers reported that the treatment of lower abdominal pain, vaginal discharge, genital or vaginal ulcers was harmful to mothers (32%, 30%, and 32%, respectively); whereas one in six (16%) providers said treatment of genital or vaginal itchiness was harmful to mothers. Similar proportions of providers reported syndromes 1-3 would be extremely harmful to unborn babies (31%, 35%, and 33%, respectively); one in five (19%) providers believed that treatment of syndrome 4 was harmful to unborn babies. Treatment for these four syndromes was available in 59%, 65%, 46%, and 47% of facilities, respectively, but only one-quarter of 397 pregnant women at the same facilities who reported having an STI/RTI syndrome in the previous four weeks received treatment. These findings suggest that reducing the burden of curable STIs/RTIs during pregnancy will, in part, require investment in retraining to reduce the occasions when some providers may withhold treatment of curable STIs/RTIs out of concern that treatment may be harmful to mothers or unborn babies.

1465

MAPPING MEASLES IMMUNITY GAPS AT THE SUBPROVINCIAL LEVEL IN THE DEMOCRATIC REPUBLIC OF THE CONGO (DRC) USING 2013-2014 DEMOGRAPHIC AND HEALTH SURVEY (DHS) DATA

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Disease surveillance in the Democratic Republic of Congo (DRC) is logistically challenging due to years of debilitating civil war, insufficient funding and poor infrastructure. Under resource-limited conditions, it is crucial to identify high-priority regions within the country where vaccination efforts should take precedence. We mapped measles immunity gaps throughout the country by geographic survey cluster using data obtained from the 2013-14 DRC Demographics and Health Survey (DHS) with ArcGIS 10.2 software. To estimate measles antibody seroprevalence within areas that were not surveyed during the DHS, we produced a smoothed, interpolated prediction surface to visualize possible differences in measles immunity at the subprovincial level. "Hotspot" spatial clusters of low measles immunity within the country were identified through a Kulldorff spatial scan statistics analysis. Both the interpolated surface map and the spatial scan analysis identified southern Kasai province and western Lualaba province as the most significant hotspots of low measles immunity within the DRC. This study demonstrates that the use of geostatistical mapping methods can be a useful tool for the DRC Expanded Program on Immunization to identify specific areas at the subprovincial level that should be of the highest priority for future measles catch-up campaigns, and offers a novel alternative strategy compared to previous efforts which have treated heterogeneous populations within large administrative areas with the same treatment.

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EBOLA VACCINATION KNOWLEDGE, ATTITUDES, AND BEHAVIOR AMONG HIGH-RISK HEALTH CARE AND FRONT LINE WORKERS, DECEMBER 2014 - JANUARY 2015

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The Centers for Disease Control and Prevention's (CDC) sponsored a phase 2/3 clinical trial of the candidate rVSV-ZEBOV vaccine that was conducted with the College of Medicine and Allied Health Sciences (COMAHS), University of Sierra Leone and the Ministry of Health and Sanitation (MoHS). CDC and MoHS approved the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) with provisos that 1) communications around the vaccine and trial, including rumor control, were carefully managed and 2) clinical trial activities not impede or conflict with any outbreak response activities. Formative communications research was conducted In December 2014 - January 2015, focusing on health care and frontline workers and the general public to ascertain their understanding and acceptance of an experimental Ebola vaccine. The research was a mixed-methods approach consisting of 1) in-depth interviews with 31 public health official and decision-makers, 2) 35 focus group discussions (FGD) with a total of 316 participants from the target populations,

and 3) a survey of 146 health care and frontline Ebola workers. The findings of the formative research were used to inform a field based communications strategy that focused on three objectives: 1) to build trust in the community by proactively countering potential inaccurate negative perceptions that could impact both the success of the trial and larger response efforts; 2) providing culturally understandable information about the vaccine and STRIVE to potential participants so they could make informed decisions about participation in the trial; 3) to ensure communications supported human subjects protection throughout the trial. We will present the formative research results as well as how that research was applied to the communications strategies and materials for STRIVE. The success of the communication strategy was demonstrated both by the support STRIVE received from the community and by the absence of any sustained negative public concern about the study. This success contributed to the enrollment and vaccination of ~8,000 high-risk health care and frontline Ebola response workers.

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OUTBREAK-RELATED ANXIETY AND PUBLIC POLICY: THE CASE OF EBOLA VIRUS DISEASE AND POLICY PREFERENCES

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Public health officials rely on state-citizen communication and public cooperation to maximize success of emergency preparedness and response endeavors. The role of the public's emotions, particularly fear and anxiety, in behavior and political support during an outbreak is under-investigated yet may yield useful insights for infectious disease policymaking. Data from a nationally representative survey of 1,425 Americans conducted in December 2014 were analyzed using multiple ordered logistic regression models to determine whether fear-based claims about the 2014 West Africa Ebola outbreak, as opposed to claims appealing to morality and human rights, will increase support for the Obama administration's proposed $6.2B appropriations to fund disease control measures. Additional analyses were performed to determine whether fear-based claims have the additional effect of increased support for more exclusionary policies, such as quarantine, isolation, deportation, flight bans, and the destruction of personal property. Respondents' self-rating of both higher anxiety and sadness was positively associated with support for emergency Ebola appropriations. Identification as Republican and conservative was negatively associated with support for Ebola appropriations. For respondents who considered the likelihood of an Ebola outbreak in the next 12 months to be high, there was a positive association with support for appropriations. Respondent belief that Ebola is dangerous was positively associated with support for appropriations. Support for a 21-day quarantine for health workers returning from West Africa was negatively associated with support for appropriations. Support for Obama's executive order suspending deportation orders for undocumented immigrants was positively associated with support for appropriations.

1468

EBOLA SURVIVOR NETWORKS IN WEST AFRICA: A STRUCTURED APPROACH TO ESTABLISHING EBOLA SURVIVOR SUPPORT NETWORKS AS AN EFFECTIVE COMMUNITY ENGAGEMENT STRATEGY TO HELP FIGHT FUTURE EBOLA EPIDEMICS

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West Africa was disproportionately affected by recent Ebola outbreak. Meaningful engagement of Ebola survivors is increasingly important in the prevention, care and support of Ebola patients in future Ebola epidemics. Engaging with Ebola survivors may speed the translation of discoveries into improved health outcomes. Ebola survivor support networks provide a non-traditional route for authentic engagement of Ebola survivors, patients and communities. As a follow-up to our clinical trial of plasmapheresis of convalescent plasma to treat Ebola victims in West Africa, Clinical Research Management in 2015 began testing new approaches for community engagement which led to the establishment of Ebola Survivor Support Networks in Liberia, Sierra Leone and Guinea. This structured program facilitated project-specific input from governments, communities, academic research institutions and Ebola survivor stakeholders. Peer-to-peer approach was used to recruit, train and organize survivors into networks. The networks were registered as legal entities by respective governments. Basic demographic data of the survivors was systematically collected and stored and a registry of Ebola created for Guinea, Liberia and Sierra Leone. The networks set up offices to support operations. Developers prepared networks to engage with stakeholders and facilitated regular in-person and virtual meetings. A total of six (6) Ebola Survivor Networks were registered. The networks opened national offices in Liberia, Guinea and Sierra Leone. A total of 2800 Ebola survivors were recruited into the Networks and one registry of Ebola survivors created in each country. The Networks engaged 15 research community stakeholders. Participating researchers, reported that partnership with Networks was valuable and that the Networks helped to determine project feasibility and enhanced research implementation. Stakeholders found the Networks to be an acceptable method of engagement. A tool kit was developed to replicate this model and to disseminate this approach.

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THE IMPACT OF CLUSTERING OF UNVACCINATED INDIVIDUALS ON RISK OF OUTBREAKS

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The foundation of efforts to control and eliminate vaccine-preventable diseases like measles rely on estimates of the effective reproduction number (R) and critical vaccination threshold (Vc). Commonly calculated as R = R0*(proportion susceptible), we assume evenly-mixed populations. However, in real populations this assumption fails, and thus true outbreak risk is likely underestimated. We developed a novel methodology to produce an R that captures heterogeneity through scaling the R estimate by the relative probability of susceptible individuals being in contact with one another. We used data available through Demographics and Health Surveys (DHS), which are conducted every 3-5 years in over 90 countries (dhsprogram.com). We developed methods to estimate the clustering of susceptibles that accounts for the clustered sample structure of these data. Applying these methods to Zambia and Tanzania to examine the impact of clustering and its effects on the 2009-10 outbreak in Zambia, we found Tanzania to have a relative level of clustering of 1.37 times that of Zambia (95% CI = 1.04-1.89). We found a ratio 0.96 comparing the estimated R of Tanzania and Zambia. Thus, while Tanzania experienced greater clustering, they counter with higher overall vaccination, resulting in comparable outbreak potential to Zambia. While measles attack rates in Tanzania were relatively constant (mean (SD): 9.3(10.5) per 100,000), in Zambia they were highly variable (mean (SD): 51.2(81.8) per 100,000). This contrast might be partially the consequence of the vaccination and clustering levels, whereby Tanzania experienced more frequent, smaller outbreaks, possibly from higher clustering, while Zambia had a large, population-wide outbreak from lower vaccination coverage and a build-up of susceptibles during non-epidemic years. Our novel approach accurately quantifies the increasing potential for measles outbreaks with increasing clustering of unvaccinated individuals, and our model provides an accessible method to estimate this outbreak potential.

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FAMILY PLANNING IN THE DEMOCRATIC REPUBLIC OF CONGO: UNWANTED PREGNANCY AND ASSOCIATED SOCIODEMOGRAPHIC CHARACTERISTICS

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Unintended or mistimed conceptions, collectively referred to as unwanted pregnancies, are associated with adverse outcomes for both the mother, as they may not be in optimal health for childbearing, and infant, as prenatal care may be delayed. As factors such as educational attainment and socioeconomic status may impact knowledge and attitudes regarding family planning practices, a clear understanding of both the determinants and effects of unmet contraceptive needs is indispensable in low resource settings such as in the Democratic Republic of Congo (DRC). Using 2013 Demographics and Health Survey (DHS) cross-sectional data, we assessed associations between sociodemographic characteristics and select health outcomes with family planning history and attitudes for 18,716 female respondents 15-49 years of age. Of 1164 women reporting an unwanted pregnancy, 75% were not using contraception of any kind, citing breastfeeding (25%), postpartum amenhorrhea (20%), and unknown source for contraceptive attainment (17%) as the most common reasons for nonuse. Unwanted pregnancy was positively associated with maternal age, birth order, and number of children under 5 years of age, while inversely associated with maternal education. Interestingly, head of household sex was also associated with desire for pregnancy, and 706 respondents reported a female head of household. In these preliminary analyses of DRC-DHS nationally representative data, we identified associations between sociodemographic variables and pregnancy intention. Shedding light on the family planning landscape can help to inform public health policy, and programming and, if assessed over time, may indicate changing societal attitudes regarding planning practices. Additionally, unintended and unwanted childbearing can have negative health, social and psychological consequences in children; therefore it is of great importance to assess relationships between pregnancy intention and child health indicators. Such investigations may identify vulnerable subgroups of the population to whom family planning and other public health services may be targeted.

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THE GLOBAL HEALTH EXCHANGE FELLOWSHIP: A PILOT PROGRAM

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The Global Health Exchange Fellowship was a six month pilot project aimed at making global health real through experiential learning for UK and Kenyan trainees in General Practice/Family Medicine and Public Health. The multi-professional and multi-cultural team had two consecutive placements in areas of deprivation, in a low income and high income country. The first was within a rural Maasai community in Kenya, and next was an inner city area in the UK. Using Qualitative research methods, a health needs analysis was carried out in each community. Challenges to health, including socio-economic determinants, were identified and organised into themes by the fellows. These themes were prioritised by the communities using an innovative voting methodology developed by the fellows. Findings were presented to the local health authorities with the aim of informing resource allocation to improve health and reduce inequalities. and fed back to the communities. The Capability Approach was incorporated to encourage community ownership of solutions. Access to healthcare was voted as the number one priority in the rural Maasai community while Education was the top priority in inner city UK. Surprisingly there were a number of similarities in the results from both communities. For instance, Gender Inequality and Culture gave us significant concern as healthcare professionals, however these themes received the fewest votes in the "Very Important" category in Kenya (a low income country) and in the UK (a high income country). The Fellowship was a true exchange between a diverse team of healthcare professionals in terms of knowledge, location, culture and experience. Through their participation, the fellows experienced remarkable personal and professional development. We learned that the challenges to health facing deprived communities globally are complex but similar, and require context specific solutions which take into account social determinants like culture and poverty. This calls for improved interdisciplinary collaboration to improve health and reduce inequalities.

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FACILITATING TRAVEL READINESS IN A GLOBAL ORGANIZATION: SUCCESS OF A PILOT

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Our developmental organization has approximately 18000 employees in 180 different countries globally and is known for a high number of staff members traveling away from their duty-stations, known as mission travel. Staff based in Washington DC have access to a full service travel clinic, used by all our staff, however staff based out of other locations have less access, although are covered under our insurance. In 2015, a travel pilot was launched based out of Johannesburg and Pretoria, South Africa to assess the impact of having similar access to travel medicine preventive care. South Africa was chosen as an appropriate location for the pilot because of the size of the offices as well as the fact that most of the travel taking place is to Sub-Saharan Africa where there are a number of tropical risks not present in South Africa. Data was analyzed from the health risk survey performed in 2014 to assess both knowledge as well as staff habits with respect to pre-trip travel vaccination as well as utilization of malaria prophylaxis. An active intervention was staged over 4 months, with an onsite doctor, education campaigns and travel kits being provided. At the end of 4 months, clinical data was analyzed and staff were surveyed for change in behavior. Significant change was seen in malaria prophylaxis usage as well as increased vaccination. Staff satisfaction was increased greatly as well. This pilot served to demonstrate the value of an active intervention campaign in a high-risk traveling population. Although the staff had coverage for care under their insurance, ease of access helped to facilitate greater coverage and change in behavior. With one on one consultation providing significant value in persuading staff as to the usage of malaria prophylaxis.

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REDUCING HEALTH DISPARITIES IN REFUGEES FROM SUB-SAHARAN AFRICA ENTERING THE UNITED STATES FOR RESETTLEMENT: RETROSPECTIVE REVIEW

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During 2014 there were an estimated 60,000,000 refugees globally. 18,000,000 or 30% of this population was in Sub-Sahara Africa (SSA).

Approximately 75,000 or 0.42% from Sub-Sahara Africa were resettled in the United States. Peer reviewed medical literature and evidence based research for the past two decades described the exposure of refugees to the detrimental effects of pathogenic parasites from countries of origin or while in refugee camps. The aim of the Study is to contribute to a reduction of health disparities that may challenge the effective implementation of interventions and strategies to reduce or eliminate asymptomatic and reactivated diseases. Misdiagnosis of endemic diseases in Sub-Saharan refugees arriving to settle in the United States was also included. We examined peer reviewed medical literature and evidence based research from 2002-2015 using: National Vital Statistics System (NVSS), MEDLINE, PubMed, Cochrane Library, and Science Direct. Data on prevalence of asymptomatic or reactivated pathogens as well as clinical misdiagnosis amongst refugees entering the United States to settle was included in the search. Five medical conditions were selected: Latent TB, Malaria, Schistosomiasis, Strongyloidiasis and Oral health. The criteria applied were: Eosinophil count, regional diagnosis disease, geographical analysis, mapping, screening and surveillance. Although the population of Sub-Saharan refugees entering the United States is small (0.42% or approximately 75,000) findings of the Study indicate that hospital departments are concerned with the economic burden of treating refugees and immigrants. Hospitals may lack health care professionals with sufficient training and skills to treat refugees with tropical or endemic disease. Medical schools must include differential diagnosis in their syllabi that train students to: diagnose, treat and manage the health of the growing foreign born population in the United States that will become patients before or after resettlement. This requires skills and knowledge of diseases endemic to country of origin and risk to the foreign born resettling in the United States. Public Health policy and surveillance does not always include preventative health initiatives or programs that consider the health disparities of refugees born in Sub-Sahara Africa.

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RELAPSES VERSUS REINFECTIONS: ASSESSING THE PARASITOLOGICAL AND CLINICAL IMPLICATIONS USING *PLASMODIUM CYNOMOLGI* AS A MODEL FOR *P. VIVAX*

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Plasmodium vivax causes significant morbidity and mortality worldwide and remains a major obstacle to global malaria eradication. One of the obstacles this parasite presents is its liver-stage reservoir comprised of hypnozoites that are capable of reactivating and causing relapses. Relapses are thought to contribute significantly to the prevalence and transmission of *P. vivax*, but it is unclear if either relapses or reinfections are more responsible for clinical vivax malaria cases. To assess the contribution of relapses as well as homologous and heterologous re-infections to clinical vivax malaria, a series of experiments using the rhesus macaque - cynomolgi malaria model were conducted. Clinical and parasitological data were collected daily for 100 days during the initial infection and for 45 – 60 days during the re-infections. Relapses did not induce significant clinical alterations, and when minor changes were observed, they resolved without the need for clinical intervention. Homologous reinfections resulted in considerably lower parasite burden and minimal alterations, if any, in clinical parameters, similar to relapses. Interestingly, infection with a heterologous strain of *P. cynomolgi* did result in significant changes in clinical parameters, although there may have been some clinical protection conferred by the initial infections given the evidence of self-controlled acute parasitemia upon heterologous challenge. Collectively, the data from these experiments suggest that relapses caused by *P. vivax* parasites that are genetically similar to parasites in primary infections and homologous re-infections likely do not contribute significantly to clinical vivax malaria cases. Contrastingly, infections with genetically dissimilar strains of *P. vivax* can have pathological consequences, although severity may be less than with the initial infection. Overall, these studies demonstrate that there is much to learn about the clinical consequences of relapses and re-infections and also highlight that the dynamics of *P. vivax* infections are complicated.

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PLASMODIUM FALCIPARUM FIELD ISOLATES TRIGGER APOPTOSIS PREFERENTIALLY IN HUMAN BRAIN ENDOTHELIAL CELLS COMPARED TO PULMONARY ENDOTHELIAL CELLS

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Plasmodium falciparum infection can progress unpredictably to severe forms including respiratory distress and cerebral malaria. The mechanisms underlying the variable natural course of malaria remain elusive. Here we used cocultured brain and pulmonary endothelial cells challenged with *P. falciparum* field isolates taken directly from malaria patients and scrutinized their capacity of inducing endothelial apoptosis via cytoadherence or not. A total of 27 *falciparum falciparum* isolates were collected from patients with uncomplicated malaria (n=25) or severe malaria (n=2). About half the isolates (n=17) were able to bind brain endothelial cells (12 isolates, 44%) or lung endothelial cells (17 isolates, 63%) or both (12 isolates, 44%). Sixteen (59%) of the 27 isolates were apoptogenic for brain and/or lung endothelial cells. The apoptosis stimulus could be cytoadherence, direct cell-cell contact without cytoadherence, or diffusible soluble factors. While some of the apoptogenic isolates used two stimuli (direct contact with or without cytoadherence, plus soluble factors) to induce apoptosis, others used only one. Among the 16 apoptogenic isolates, eight specifically targeted brain endothelial cells, one lung endothelial cells, and seven both. These results suggest that *falciparum falciparum* field isolates killing brain endothelial cells are more prevalent than those killing pulmonary endothelial cells and may provide new insights into host-parasite interactions.

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CHARACTERIZATION OF ANTIBODIES AGAINST *PLASMODIUM FALCIPARUM* INVASION PROTEIN PFMSP10

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The aim of this study is to evaluate monoclonal antibodies (mAb) generated against pfMSP10 (Merozoite surface protein 10) and their functional role to inhibit the invasion of Peruvian *Plasmodium falciparum* isolates using the Growth inhibition Assay (GIA) *in vitro* as well as the potential use of pfMSP10 in malaria diagnostics. Seven mAb (Gen Script and Abmart) and a polyclonal antisera were evaluated by Western Blot (WB) against the recombinant MSP10 full protein (rMSP10). Synchronized and purified schizonts from *P. falciparum* 3D7 and their concentrated supernatant were obtained by ultrafiltration. Detection of pfMSP10 protein was also evaluated in synchronized ring stage of *P. falciparum* cultures from 1 to 12 hours post-invasion. IFA assays were also carried out. In addition a quantitative direct sandwich ELISA for rMSP10 was developed using all the possible combination of the eight antibodies in evaluation. From all the eight evaluated antibodies, only one mAb (anti pfMSP10-1)

and the polyclonal antisera showed a strong reaction band against pfMSP10 and no cross reaction bands against non-infected RBC. Results by WB showed the presence of an approximately 68 kDa band in purified schizonts and rings stages parasites from 1 to 4 hours post invasion and faint band at 12 hours post-invasion, the binding of these antibodies to mature schizonts was corroborated by IFA. Results from the quantitative ELISA showed that three antibodies combinations were able to detect concentrations from 10,000 - 312.5 pg/ml of rMSP10 (OD 2.0 - 0.5 DS 0.04 R2, 0.92) within a standard curve. Quantification of pfMSP10 will be performed using patient serum and culture samples. GIA *in vitro* assays are underway using Peruvian *P. falciparum* isolates in order to evaluate whether the mAb against MSP10 is capable of binding to erythrocytes to inhibit the invasion of merozoites into erythrocytes.

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CHARACTERIZATION OF A NOVEL ERYTHROCYTE BINDING PROTEIN OF *PLASMODIUM VIVAX*

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Erythrocyte invasion by malaria parasites is essential for blood stage development. In *Plasmodium vivax* the interaction between the Duffy binding protein (DBP) and its cognate receptor, the Duffy antigen receptor for chemokines (DARC), on human erythrocytes is central to blood-stage infection. Contrary to this established pathway of invasion, recent studies have reported evidence of *P. vivax* transmission among Duffy blood-group negative individuals, suggesting that the parasite might have evolved an alternative pathway to infect this group of individuals. Recently, a second distinct DBP-like erythrocyte binding protein (EBP2) that may be the ligand in an alternate invasion pathway has been discovered in *P. vivax*. This study characterizes this novel ligand and determines its potential role in reticulocyte invasion by *P. vivax* merozoites. Our data demonstrates that EBP2 preferentially binds to young (CD71High) Duffy positive (Fy+) reticulocytes with minimal binding capacity for Duffy negative reticulocytes. EBP2 is antigenically distinct from DBP and can be functionally inhibited by anti-EBP2, but not anti-DBP antibodies. Consequently, our results do not support EBP2 as a ligand for invasion of Duffy negative blood cells, but instead EBP2 may be a ligand for an alternate invasion pathway of Duffy positive reticulocytes.

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PATHWAY GROUP LASSO INTEGRATION OF METABOLOMICS AND TRANSCRIPTOMICS TO CHARACTERIZE MALARIA INFECTION IN RHESUS MACAQUES

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We have conducted a detailed systems biology study of malaria using an infection model of *Plasmodium cynomolgi* in rhesus macaques - a model for *P. vivax* malaria. To this end, we have generated a wide array of biological, clinical and multi-omic data sets on NHPs. Among the various -omic data types, transcriptomics and metabolomics are among the most widely used high-throughput technologies. Integration of these two data types is therefore critical to the advancement of contemporary biomedical science. Here, we report a novel approach of such integration in a framework of group LASSO, and demonstrate its application to understand metabolic changes that occur during malaria infection. For this study, five rhesus macaques were infected with P. *cynomolgi* sporozoites and studied for 100 days post inoculation to enable the study of early infection, acute disease, and relapses. Additionally, five uninfected rhesus were studied with antimalarial treatment only. LASSO is widely used for feature selection and shrinkage estimation, which reduces the variance of regression coefficients. Group information from well-curated pathways was added to these regression models, as a means of incorporating prior knowledge into the analysis. The leading principal components of each pathway group from each omic data type were combined into an integrated matrix that was then used to test for association with clinical measures of malaria illness. Using this method, we identified key differences in metabolism between infected and non-infected rhesus macaques. In both groups, changes in porphyrin metabolism, which is central to heme synthesis, was selected as an important biological pathway. Other pathways that were shared between infected and uninfected primates were glycerophospholipid metabolism and linoleate metabolism. Tyrosine and tryptophan metabolism were significantly changed in infected primates, and not in the uninfected animals. Overall, pathway group LASSO is a novel and effective method of integrating metabolomics and transcriptomics data from large-scale studies, and is a useful tool to provide high-quality mechanistic hypotheses.

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MARKERS OF ANEMIA IN KENYAN CHILDREN WITH *PLASMODIUM FALCIPARUM* MALARIA

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Severe malarial anaemia (SMA) is the most common complication of *Plasmodium falciparum* infections, resulting in mortality rates that may exceed 30% in children (less than 5years) living in holoendemic transmission areas. One strategy for reducing the morbidity and mortality associated with SMA is to identify biomarkers that can be utilized for prompt diagnosis and treatment of the disease. Currently, there are no such reliable comprehensive biomarkers for SMA from the inflammatory, iron, hypoxia, and erythropoietic pathways. As such, we measured anemia markers in Kenyan children (3-36 months, n=278) presenting with acute illness at a rural hospital in Siaya, Kenya. Children were categorized into three groups based on anemia status and any density parasitemia: aparasitemic (n=56); non-SMA (Hb>5.0g/dL, n=168); and SMA (Hb<5.0g/dL, n=54). The following measures were obtained and compared across the groups: C-reactive protein (CRP); total iron; total iron binding capacity (TIBC); ferritin, carbon(IV)oxide; creatinine; bilirubin; total bilirubin; and glucose. The results indicated significantly higher median levels in SMA group compared to the other anemia phenotypes for CRP (130mg/dL, p=0.0001), total iron (89ug/dL, p=0.019), ferritin (200ng/ml, p=0.0001), direct bilirubin (2.5mg/dL, p=0.008) and total bilirubin (2.25mg/dL, p=0.0001), while creatinine levels were significantly lower in anemia groups compared to the aparasitemic controls (0.35mg/dL, p=0.030). Data here suggest that the levels of these markers may be useful predictors of anemia disease severity in *P.falciparum* malaria holoendemic transmission areas.

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CLINICAL AND LABORATORY PROFILE OF COMPLICATED MALARIA IN THE COLOMBIAN PACIFIC COAST

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Complicated malaria remains an important public health problem especially in low-income settings, where access to health services is difficult and most of the fatal outcomes occur. Although several studies have been conducted in Colombia, most of them are retrospective and present inherent limitations. A cross-sectional study was performed in

hospitalized patients with complicated malaria in four low-to-moderate endemic regions on the Colombian Pacific Coast during 2014-2016, to describe the clinical, laboratory, and sociodemographic characteristics of study participants. A total of 169 complicated malaria patients between zero and 82 years old were enrolled, including 27 children ≤5 years old and 16 pregnant women. *Plasmodium falciparum* was the main parasite species (70%), followed by *P. vivax* (27%) and mixed malaria (3%). Most common laboratory complications were severe thrombocytopenia (30%), hepatic failure (28%) and severe anemia (16%). Main clinical complications were oral intolerance (33%) and prostration (17%). Two deaths due *to P. vivax* and *P. falciparum* malaria were registered. Patients with *P. falciparum* had significantly higher creatinine levels (1.0 vs 0.6 mg/dL, p=0.0002) and aminotransferases (AST: 102.5 vs 34.0 IU, p<0.0001, ALT: 104.0 vs 47.5 IU, p=0.0014) levels than *P. vivax* cases. In contrast, *P. vivax* patients presented significantly lower hemoglobin levels than *P. falciparum* cases (8.0 vs 9.9 g/dL, p=0.0109). Patients who presented more than one complication simultaneously (52%) had significantly lower platelet counts and higher bilirubin levels regardless of parasite species, as well as higher parasitemias, AST/ALT, creatinine and BUN levels in *P. falciparum* cases. No bacterial co-infections were found. Quibdó was the region with the highest proportion of complicated malaria cases (57%), with transmission of both *Plasmodium* species. Therefore, the high prevalence of complicated malaria in this region, together with more severe anemia in *P. vivax* and worse renal and hepatic function in *P. falciparum* infections, demands particular attention to prevent the higher morbidity and potential mortality.

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PLASMA HAPTOGLOBIN AS A MARKER OF CLINICAL SEVERITY IN GAMBIAN AND MALAWIAN CHILDREN INFECTED WITH *PLASMODIUM FALCIPARUM*

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Elevated cell-free hemoglobin (Hb) is associated with disease severity in adults infected with *Plasmodium falciparum*. However, cell-free Hb can be elevated not only by intravascular hemolysis, but also by hemolysis induced by blood drawing/sample processing. Plasma haptoglobin (Hp), an endogenous Hb scavenging protein, binds cell-free Hb and the Hp-Hb complex is removed from circulation via CD163 on reticuloendothelial cells. Thus Hp falls during intravascular hemolysis, but is minimally affected by *in vitro* red cell lysis. We measured Hp concentration in plasma obtained from children presenting with uncomplicated or severe malaria, as well as healthy children of similar age, using an ELISA (Alpco). Clinical severity was defined per WHO criteria as uncomplicated (UM) or severe malaria (SM). In The Gambia, plasma Hp concentration was 44.5 [15.6-79.9], 4.8 [2.4-50.2], and 2.6 [2.4-5.5] mg/dL among healthy children and children with UM or SM, respectively. ROC curve analysis revealed that a Hp threshold of 24.0 mg/dL distinguished UM from healthy children (AUC 0.68 [0.57-0.79], sens 0.66, spec 0.72), and a threshold of 9.2 mg/dL distinguished SM from healthy children (AUC 0.79 [0.70-0.89], sens 0.77, spec 0.78). A Hp threshold of 4.4 g/dL distinguished UM from SM poorly (AUC 0.60 [0.49-0.70] sens 0.58, spec 0.61). In Malawi, plasma Hp concentration was 177.2 [37.4-330.4], 1.3 [0.5-249.1], and 0.5 [0.01 - 2.4] mg/dL among healthy children, and children with UM or SM, respectively. ROC curve analysis revealed that a Hp threshold of 18.1 mg/dL distinguished UM from healthy children (AUC 0.64 [0.50-0.80], sens 0.57, spec 0.83) and a threshold of 10.6 mg/dL distinguished SM from healthy children (AUC 0.82 [0.71-0.92], sens 0.86, spec 0.77). A threshold of 5.5 mg/dL distinguished UM from SM poorly (AUC 0.63 [0.50-0.77], sens 0.53, spec 0.75). These data reveal that Hp depletion, an indicator of massive intravascular hemolysis, is prevalent not only among patients with severe malaria, but also among patients with uncomplicated malaria. Thus massive hemolysis might be necessary, but it is not sufficient to cause the clinical syndrome of severe malaria.

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CELL-SPECIFIC DELETION OF TISSUE FACTOR ALTERS THE IMPACT OF *PLASMODIUM CHABAUDI CHABAUDI* AS INFECTION ON MURINE PREGNANCY OUTCOME

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Sequestration of *Plasmodium falciparum*-infected erythrocytes in the maternal blood space of the placenta results in a severe clinical manifestations of this disease, placental malaria (PM). PM results in disruption of placental function, leading to low birth weight or fetal loss. Recent evidence of a procoagulant state in PM, including extensive fibrin deposition and Tissue Factor (TF) expression in affected tissues, indicates dysregulated coagulation contributes to malaria pathogenesis, but the molecular basis for these pathologies remains incompletely understood. Timed pregnancy experiments were conducted using female mice with floxed TF expressing Cre-recombinase under the Tie2 promoter (Tie2Cre+) or under the Lysozyme M promoter (LysMCre+) and their phenotypically normal Cre-negative littermates (Tie2Cre- and LysMCre-, respectively). Upon observation of a vaginal plug (gestation day (GD) 0), mice were infected with 1000 *Plasmodium chabaudi* AS-infected erythrocytes. Embryo viability and health were assessed at sacrifice at GD12, and placental pathology was assessed in hematoxylin and eosin-stained histological sections and indirect immunolocalization of TF and fibrin were performed in unstained sections. Malaria-infected, pregnant (IP) Tie2Cre+ mice exhibit improved embryo health and significantly increased pregnancy-associated weight gain (p=0.0338) at GD12 relative to IP Tie2Cre- littermates. Though there is no significant difference in the magnitude of peak percent weight gain or parasitemia between the two strains, IP LysMCre+ mice abort and reach peak parasitemia two days earlier than IP LysMCre- mice. These results indicate that TF on both myeloid cells and either maternal endothelium or fetal-derived trophoblast play a significant role in determining pregnancy outcome during malaria infection. Future experiments seek to understand the mechanisms by which TF on hematopoietic cells may be influencing pregnancy outcome, particularly in how it affects platelet activation and aggregation, and the source of TF causing the phenotype seen in infected Tie2Cre+ mice.

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ANTI-OXIDANT THERAPY SLIGHTLY IMPROVES PREGNANCY OUTCOME IN A MOUSE MODEL OF PLACENTAL MALARIA

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Placental malaria, characterized by sequestration of *Plasmodium falciparum* in the maternal placental blood space and associated inflammatory damage, contributes to poor birth outcomes and ~200,000 infant deaths annually. Specific mechanisms that contribute to placental damage and dysfunction are not completely understood. To assess a potential role of oxidative stress, a marker for lipid peroxidation, 4-hydroxynonenal was quantified by immunohistochemistry in placentas of C57BL/6 mice infected in early pregnancy with *P. chabaudi* AS and malaria-infected Kenyan women. Widespread evidence of lipid peroxidation was observed and was associated with higher anti-oxidant gene expression in

conceptuses of infected mice. To assess the extent to which this oxidative damage and response might contribute to poor birth outcomes and be amenable to therapeutic intervention, infected pregnant mice were injected with N-acetylcysteine (NAC), a free radical scavenger, or tempol, an intracellular superoxide dismutase mimetic, or were given tempol in drinking water. Mice treated with NAC experienced pregnancy loss at the same rate as control animals; in contrast, tempol-treated mice exhibited subtle improvement in embryo survival at gestation day 12. However, immunohistochemical staining for 4-hydroxynonenal was not consistently reduced in placentas of tempol-treated mice. Thus, while oxidative stress is remarkable in placental malaria and its mitigation by anti-oxidant therapy may improve pregnancy outcomes, additional more effective interventions must be tested.

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TEMPERATURE INDUCED CHANGES IN GLOBAL GENE EXPRESSION PROFILES OF MALARIA-CARRYING MOSQUITOES

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By regulating the abundance and distribution of the mosquito vector, environmental factors such as temperature may play a major role in shaping the worldwide incidence of the scourge that is malaria. In general, the relationship is non-linear and indicates distinct temperature optima within which transmission is maintained. Although its effect on vectorial capacity is well appreciated, the patterns and processes underlying the observed phenotypes remain largely obscure. Additionally, its effect on next-generation vector control measures such as transgenic mosquitoes, is even less characterized, but is likely to play a major role in their efficacy. In the current study, we employed RNA-sequencing to investigate global gene expression profiles in the midguts, salivary glands and carcasses of wild-type and transgenic *Anopheles* stephensi mosquitoes infected with *Plasmodium falciparum* at temperatures of 20°C, 27°C and 32°C. Preliminary analyses suggest large scale changes in gene expression in response to temperature, with distinct enrichment in specific pathways. Targeted knockdown of a specific set of genes with RNA interference for instance, will help elucidate their contribution to vectorial competence as well as predict their effects in the face of a variable environment.

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EXPERIMENTAL DESIGN OF *PLASMODIUM KNOWLESI* INFECTION IN SUSCEPTIBLE VERSUS REFRACTORY NON-HUMAN PRIMATE MODEL HOSTS

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The Malaria Host-Pathogen Interaction Center (MaHPIC) and the Host Acute Models of Malaria to study Experimental Resilience (HAMMER) are a large systems biology consortia investigating multi-'omic approaches to study *Plasmodium* species host-pathogen interactions in non-human primate (NHP) hosts, to model human malaria infections. Longitudinal studies with *P. knowlesi* in Macaca mulatta (Rhesus monkey) and *M. fascicularis* (Kra monkey) were designed to identify features at the host-pathogen interface conferring varying degrees of host susceptibility to parasite infection. We expect the susceptible Rhesus (n=8) and refractory Kra monkey (n=8) to manifest different disease profiles and severity at the host-pathogen interface following inoculation with *P. knowlesi* sporozoites, identifying targets unique to disease response. Parasite loads and stages are assessed daily alongside clinical parameters and continuous internal telemetry during the course of infection timeline to anticipate significant points of infection observed during the disease progression. Extensive samples are recovered at each time point to monitor the dynamic changes in the host immune status, erythrocyte phenotype, gene expression and metabolic state by means of immune profiling implementation, transcriptomics, proteomics, lipidomics, microbiome, metabolomics and tissue analysis. To further our understanding of pathological significance during the course of infection, necropsies were performed at various points of infection allowing deeper analysis of affected tissues and organ systems uniquely influenced between these NHP cohorts. Through this set of experiments, we aim to identify host features that confer protection against malaria disease and relate these observations to developments intended to reduce host susceptibility to *Plasmodium* infections.

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POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF LUMEFANTRINE IN YOUNG UGANDAN CHILDREN TREATED IN COMBINATION WITH ARTEMETHER FOR UNCOMPLICATED MALARIA

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Artemether-lumefantrine is the most widely recommended first-line treatment for malaria. The objective of this study was to describe the population pharmacokinetics and pharmacodynamics of lumefantrine when used in the combination therapy, artemether-lumefantrine, in Ugandan children 6 months to 2 years of age. Capillary whole blood samples were collected over 21 days in 105 children treated for 249 episodes of uncomplicated *Plasmodium falciparum* malaria with standard fixed-dose artemether-lumefantrine (twice daily x 6). Population pharmacokinetic analysis of evaluable lumefantrine concentrations (n=806 in 101 children) employed a 2-compartment open model with first-order absorption. Age was found to have a significantly positive correlation with bioavailability in a model that included allometric scaling. Cox proportional multivariate hazards regression was used to explore the relationship between exposure and clinical outcome. A significant interaction between trimethoprim-sulfamethoxazole prophylaxis and a day 7 lumefantrine concentration threshold of 200 ng/mL was present. Children not on trimethoprim-sulfamethoxazole with lumefantrine concentrations below 200 ng/mL had a 3-fold higher hazard of 28-day recurrent parasitemia compared to those with concentrations above 200 ng/mL (p=0.0007). In contrast, the 28-day risk of recurrent parasitemia was not significantly different in children on trimethoprim-sulfamethoxazole based on a lumefantrine threshold of 200 ng/mL (p=0.10). Lumefantrine concentration on day 3 was a stronger predictor of 28-day recurrence compared to day 7 levels. Our data demonstrate that age is a significant determinant of lumefantrine bioavailability, and in the absence of TS, lumefantrine exposure is a determinant of 28-day recurrent parasitemia in this age group. Further refinement of artemether-lumefantrine dosing guidelines in young children may be warranted.

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SURVEILLANCE FOR SULFADOXINE-PYRIMETHAMINE (SP) RESISTANT MALARIA PARASITES IN THE LAKE AND SOUTHERN ZONES, TANZANIA USING POOLING AND NEXT-GENERATION SEQUENCING

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Malaria in pregnancy (MiP) remains a major public health challenge in areas of high malaria transmission; intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is recommended to prevent the adverse consequences of MiP. The effectiveness of IPTp-SP is maintained despite high prevalence of quintuple-mutant haplotypes associated with SP resistance (estimated by the prevalence of mutation at dhps540). The effectiveness of SP for IPTp may be reduced in areas where the dhps581 mutation is found in conjunction with the quintuple mutant background. The dhps581 mutation is common in the Tanga Region of northern Tanzania, but there are limited data from other areas. We investigated the prevalence of molecular markers of SP resistance in malaria parasites in the Lake and Southern Zones of Tanzania. A cross-sectional survey was conducted in 14 health facilities (HF) in seven regions of mainland Tanzania from April to June, 2015. A total of 1,750 dried blood spot (DBS) samples were collected (117 to 160 samples per facility) from consenting patients presenting to the outpatient department who had positive rapid diagnostic tests for malaria. Patients with recent exposure to SP or related drugs were excluded. DNA was extracted from the DBS, pooled by HF, and analyzed by Illumina MiSeq deep sequencing to yield estimates of mutated parasite allele prevalence at each locus of interest. The dhps540 mutation was prevalent across all 14 sites, ranging from 55% to 98.4%, with higher prevalence in Lake Zone compared to Southern Zone. Prevalence of the dhps581 mutation ranged from 0 to 2.4%, with the exception of Kayanga HF (Kagera Region, Lake Zone) where 24.9% of sequences were mutated. The dhfr164 mutation was detected only at Kanyanga HF (0.06%). Although the quintuple mutant was highly prevalent, dhps581 remains geographically restricted, suggesting that IPTp-SP may remain effective in most of Tanzania. However, additional surveillance, particularly in and around Tanga Region is warranted. In addition, a better understanding of the effect of the dhps581 mutant on the efficacy of IPTp-SP is needed.

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UPDATE ON THE ASEXUAL AND SEXUAL STAGE-EFFICACY OF ATOVAQUONE-PROGUANIL AND SINGLE LOW DOSE PRIMAQUINE WITH OR WITHOUT ARTESUNATE IN CAMBODIA

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Atovaquone-proguanil (AP) is a safe, well-tolerated drug for resistant Plasmodium falciparum. However, concerns over rapid development of blood-stage resistance and cost have limited its use to high risk areas in Southeast Asia. While combining AP with artesunate (AS) was previously shown to improve efficacy against MDR P. falciparum in Thailand in 2004, we evaluated current efficacy in Cambodia given recent failures of first-line therapies and assessed the effect of AP use with PQ on gametocyte carriage. Subjects were randomized 1:1 to an open label fixed-dose 3 day AP regimen with or without 3 days of co-administered artesunate (ASAP). Subjects were administered single low dose primaquine (15mg) on day 1 to prevent gametocytemia. A total of 205 subjects with P. falciparum or mixed P. vivax infection were enrolled from December 2014-October 2015 at two sites, Anlong Veng (AV; n=157) and Kratie (KT; n=48) Cambodia. Subjects were followed for 42 days for malaria recurrence and gametocyte carriage. PCR-adjusted ACPR at 42 days was similar for the two regimens - 93% (95% CI = 86-98) for AP vs. 95% (95% CI = 88-98) for ASAP (p=0.73). However, of 17 total P.f. recurrences, 16 (9%; 13 confirmed recrudescences) occurred at the AV site compared with only 1 (3%) in KT. P. falciparum remained sensitive to atovoquone in-vitro, with mean pretreatment IC50 4.76 (95% CI=5.3-8.3) in AV and 3.21 (95% CI=2.9-6.7) in KT (p=0.0096). Median parasite clearance time (PCT) was shortest in KT at 56 hrs (p <0.001) in ASAP-treated subjects and 68 hrs for AP, compared to 72 hrs for both treatment arms in AV. On day 2 post PQ, gametocyte carriage was lower in the ASAP (17%) vs. AP (29%) treatment arm and reached statistical significance by day 3 (11% in ASAP vs. 29% in AP, p=0.0012). Drug level analysis and DNA sequencing analysis for cytb mutations are in progress at the time of submission. While atovaquone-proguanil remains effective in Cambodia both clinically and in vitro, co-administration of AS with PQ in the ASAP arm might have contributed to reduced gametocyte carriage, with potential implications on how AP should be deployed in Cambodia.

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HEMOGLOBIN E RED BLOOD CELLS DO NOT INFLUENCE THE ANTIPLASMODIAL ACTIVITY OF ARTEMISININ *IN VITRO*

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Artemisinin (ART)-resistant Plasmodium falciparum malaria, defined as a parasite clearance half-life >5 h following treatment, is widespread in Cambodia, where hemoglobin E (HbE) is highly prevalent. HbE red blood

cells (RBCs) have excess α-globin chains and Hb degradation products, causing increased oxidative stress. The endoperoxide moiety of ARTs exerts antiplasmodial activity within host RBCs via oxidation reactions, suggesting that interaction effects involving parasites, RBCs, and ARTs may occur. In a clinical study of ART-resistant malaria in Cambodia, parasite clearance half-life was nonsignificantly increased in HbE patients (comprising 43% of the total) compared to HbA patients, but this difference was not significant (0.55 h, P=0.078). Nonetheless, we hypothesized that HbE diminishes the antimalarial activity of dihydroartemisinin (DHA, the active metabolite of ARTs). To explore this, we compared the antiplasmodial activity of DHA in HbE and HbA RBCs using: (i) ART-sensitive/K13-wildtype and ART-resistant/K13-mutant parasites from Cambodia; (ii) the in-vitro ring-stage survival assay (RSA), where higher % survival values associate with longer parasite clearance half-lives; and (iii) HbAA, HbAE, and HbEE RBCs that lack α-thalassemia and G6PD-deficiency genotypes. In all three RBC types, % survival values: were <1% for ART-sensitive parasites and 7-70% for ART-resistant parasites; increased according to K13 mutation (Y493H<C580Y<R539T); and were not significantly different (Kruskal-Wallis test, P>0.05). To test whether senescent, oxidatively-stressed RBCs affect % survival values in the RSA, we used Percoll to fractionate HbAA RBCs into young and old cells. In these cell types, % survival values for ART-sensitive and ART-resistant parasites were also not significantly different. These data indicate that neither HbE nor intraerythrocytic redox status influence the in-vitro antiplasmodial effect of a pharmacologically-relevant dose of DHA, suggesting these factors do not prolong the parasite clearance half-life in patients treated with ART.

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ASSESSING THE IMPACT OF MALNUTRITION ON THE TREATMENT OUTCOME OF ARTEMISININ-BASED COMBINATION THERAPY IN UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

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In children under 5 years of age little is known about the effect of malnutrition on the outcome of *Plasmodium falciparum* (Pf) malaria treatment with an Artemisinin-based Combination Therapy (ACT). Contrasting reports may reflect heterogeneity in the study population, diversity in transmission intensity, use of different growth metrics or small sample sizes. A systematic search of the WWARN data repository and online literature databases identified 35 Pf efficacy studies in which weight and height were both recorded in children under 5 years of age treated with artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ), dihydroartemisinin-piperaquine (DP) or artesunate-mefloquine (ASMQ). Only studies with at least 28 days of follow-up were included in the analysis. Four anthropometric indicators were reviewed: weight-for-height, height-for-age, weight-for-age (calculated using WHO igrowup tool), and the mid-upper arm circumference. An a priori data analysis plan was developed to investigate the association between anthropometric indicators and antimalarial efficacy. Individual patient data were collated from 11,528 children (99% from Africa), treated with AL (44%), ASAQ (27%), DP (23%) or ASMQ (5%). 298 recrudescences and 1,792 reinfections confirmed by PCR were recorded. The overall risk of failure (i.e. recrudescence) was greatest in children with wasting (weight-for-height (whz)<-1). After adjusting for ACT regimen, dose administered and initial parasite density, the treatment failure risk by day 42 was greater in children 1-3 years of age compared to other children (HR=1.50 [95%CI 1.15-1.96]; p=0.0030) and in children with wasting compared to those without wasting (HR=1.41 [95%CI 1.07-1.86]; p=0.013). More severe wasting (whz<-2) was associated with an increased risk of reinfection compared to children without wasting (HR=1.26 [95%CI 1.09-1.45]; p=0.002). This pooled analysis highlights the risk of ACT treatment failure and reinfection in children with wasting, especially in those aged 1-3 years. The consequences on mortality in children suffering from acute global malnutrition warrants further investigation.

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IMPACT OF DIFFERENT MALARIA CHEMOPREVENTION REGIMENS FOR PREGNANT UGANDAN WOMEN ON *PLASMODIUM FALCIPARUM* DRUG RESISTANCE-MEDIATING POLYMORPHISMS

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In a recent randomized trial comparing intermittent preventive therapy regimens to prevent malaria in 300 pregnant women in Tororo, Uganda, dihydroartemisinin-piperaquine given once a month (DPqm) or every 2 months (DPq2m) was superior to sulfadoxine-pyrimethamine given every 2 months (SPq2m). For this study we analyzed the impacts of the different chemoprevention regimens on *Plasmodium falciparum* genetic polymorphisms that affect sensitivity to a number of antimalarial drugs. Blood samples collected monthly from asymptomatic women were analyzed for *P. falciparum* DNA with a highly sensitive loop mediated isothermal amplification (LAMP) assay. All 635 samples positive by LAMP plus samples from all 75 episodes of symptomatic falciparum malaria are now undergoing characterization of polymorphisms in relevant genes encoding putative drug transporters (pfcrt and pfmdr1) and folate enzymes (pfdhfr and pfdhps). We report preliminary data for transporter polymorphisms. The prevalence of mutations at each studied allele (pfcrt K76T and pfmdr1 N86Y, Y184F, and D1246Y) was the same in each arm of the trial in parasites identified before initiation of study drugs. In parasites identified after initiation of study drugs, for pfmdr1 N86Y, the prevalence of a mixed or mutant genotype was higher in the DPqm (91.7%, p<0.001) and DPq2m (50.0%, p=0.001) arms compared to the SPq2m arm (24.9%). For pfmdr1 Y184F, the prevalence of a mixed or mutant genotype was higher in the DPqm (96.2%, p<0.001) and DPq2m (88.6%, p=0.001) arms compared to the SPq2m arm (61.4%). Inconsistent or non-significant trends were seen for the two other studied polymorphisms. Analyses of polymorphisms in pfdhfr and pfdhps are ongoing. Of note, monthly DP strongly selected for the pfmdr1 86Y mutation in subsequent infections. This mutation appears to be associated with decreased activity of AQ, but increased activity of lumefantrine, suggesting that chemoprevention with DP might optimally be utilized when artemether-lumefantrine is the first line drug to treat malaria, so that selection of resistance to partner drugs is minimized.

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DRUG RESISTANCE AND RELAPSE IN CAMBODIAN *PLASMODIUM VIVAX*

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Assessment of antimalarial drug resistance is complicated in *Plasmodium vivax* by the lack of *in vitro* culture system. Most studies of drug resistance in *P. vivax* therefore rely on patient data and the observation of parasites in blood after treatment. However, such studies are complicated by the difficulty to differentiate resistant parasites from re-infections and relapses. To overcome these limitations, we studied *P. vivax*-infected patients treated with chloroquine (CQ) and followed for 80 days in an area without malaria transmission (to exclude reinfections). We tested each patient blood for *P. vivax* DNA by PCR every 8 hours until the parasites were not detectable anymore and then every second day for the rest of the study. Our analyses showed that, for all patients, parasite DNA was not detectable 5 days after drug treatment suggesting that there is little CQ resistance in this population. However, more than half of the patients show re-occurences of *P. vivax* parasites during the 80-day monitoring period suggesting that

relapses occur frequently. Interestingly, none of the relapses occurred when the CQ concentration was above therapeutic level, and the few relapses leading to clinical malaria were successfully cleared by CQ treatment, confirming that these parasites are susceptible to CQ. To further analyze the susceptibility of the parasites to CQ, we genotyped at 100 SNPs parasite DNA extracted from the patient blood samples collected before, 8 hours and 16 hours after treatment and determined, for each infection, the relative susceptibility of each clone to CQ. We also used genotyping and whole genome sequencing to characterize the parasites in the primary infections and relapses to confirm, for a subset of the patients, that the relapses were caused by a parasite that is not detected in the primary infection. Overall, our study did not reveal any CQ resistance among Cambodian *P. vivax* but suggests that pervasive relapses might have confounded previous assessments of drug resistance in patient studies.

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BEHAVIOR OF *PLASMODIUM FALCIPARUM* AGAINST ARTEMISININ-BASED COMBINED THERAPY FOR MALARIA: EVALUATION OF *EX VIVO* SENSITIVITY AND PARASITE DORMANCY

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Approximately 3.3 billion people live at risk of contracting malaria worldwide, with 198 million cases and 584,000 deaths in 2013. There are evidences of decreased efficacy of artemisinin and its derivatives in isolates of *Plasmodium falciparum* in some countries. The dormancy in *P. falciparum* has been proposed as a mechanism of tolerance to artemisinin. In this study, blood samples from patients infected in African and Caribean countries were processed in order to perform *ex vivo* sensitivity assays and *in vitro* dormancy evaluation. For *ex vivo* sensitivity we tested dihydroartemisinin (4-1,000nM), artesunate (0.1-100nM), lumefantrine (3.1-200nM) and mefloquine (0.2-1,000nM). Parasites were incubated in RPMI 1640 with a haematocrit of 5% and parasitemia of 1%. After 96 hours thick blood films were prepared and the number of schizonts/200 parasites was counted. Blood from wells with only rings was transfered to a new microplate for monitoring the dormancy phenomenon for a period of 41 days. Flow cytometry using 1,2,3-Rhodamine and DAPI was performed to assess the viability of parasites. As far as the *ex vivo* sensitivity assays is concerned, minimal inhibitory concentrations ranged from 10.2 to 250nM for dihydroartemisinin, from 50 to 200nM for lumefantrine, from 3.7 to >100nM to artesunate and from 62.5 to 250nM for mefloquine. In the dormancy assays with clinical and reference samples, schizonts were observed after pressure with 62.5, 250 e 1,000nM of dihydroartemisinin. The recovery period of parasites ranged from 4 to 40 days. For lumefantrine, schizonts have emerged only in the reference isolate in days 7 and 12 after exposition to 66.6nM and 200nM respectively. It is worrying to note that parasite growth inhibition was only achieved in high concentrations of dihydroartemisinin and lumefantrine, used worldwide for malaria treatment. As the flow cytometry showed viability of ring stages after drug pressure, our results suggest that the assays based on microscopy could underestimate the response of *P. falciparum* to artemisinin-based combined therapy. To our knowledge, the dormancy phenomenon has never been reported before for lumefantrine.

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ELUCIDATING THE MECHANISM OF PIPERAQUINE RESISTANCE IN *PLASMODIUM FALCIPARUM* MALARIA IN CAMBODIA

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Artemisinin combination therapies (ACTs) are currently the first-line treatments for *Plasmodium falciparum* malaria worldwide. ACTs, which combine a short-acting artemisinin derivative with a long-acting antimalarial partner drug with a different mechanism of action, are designed to efficiently clear parasitemia and prevent the development of drug resistance. In some countries of Southeast Asia (SEA), the current treatment for *P. falciparum* malaria is the ACT dihydroartemisinin (DHA)-piperaquine (PPQ). Unfortunately, the emergence and spread of DHA-PPQ resistance has now been reported at multiple sites in Western Cambodia, which poses a severe risk of widespread resistance to DHA-PPQ and other ACTs. Recent fieldwork by our group identified *P. falciparum* strains that show markedly reduced susceptibility to PPQ in Cambodia. In a genome-wide association study of parasite responses to PPQ exposure *in vitro*, we discovered a single-nucleotide polymorphism (SNP) on chromosome 13 coding for an exonuclease that strongly associates with reduced PPQ susceptibility *in vitro* and DHA-PPQ failures in patients. We are currently using the CRISPR-Cas9 system to edit the wild-type and mutant exonuclease SNP into PPQ-resistant and PPQ-sensitive parasites, respectively. After transfections and successful editing events are verified, we will perform PPQ survival assays to determine whether the mutant SNP confers PPQ resistance. We are also genotyping the exonuclease SNP in contemporary parasite isolates from Cambodia and neighboring countries to monitor the spread of PPQ resistance in SEA. In addition to validating the exonuclease SNP as a molecular marker of PPQ resistance, we aim to identify the causal genetic determinant of PPQ resistance and use appropriate biochemical methods to elucidate its molecular mechanism. These studies will provide novel insights into the mechanism of PPQ resistance in *P. falciparum* and will help to monitor and prevent the further spread of PPQ resistance and DHA-PPQ failures in SEA.

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IMPACT EVALUATION AFTER THREE YEARS OF SEASONAL MALARIA CHEMOPREVENTION IMPLEMENTATION BY MASS CAMPAIGNS IN SOUTHERN SENEGAL

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Seasonal Malaria Chemoprevention (SMC) was piloted in 2013 and extended in Senegal from 2014, in the southern regions where malaria transmission is seasonal and intense with 620,000 children under 10 years eligible. It is however important that scaling up of SMC by national Malaria Control Programs is evaluated to document its coverage, the safety profile, the impact on malaria morbidity and the prevalence of molecular markers of drug resistance. In order to monitor malaria morbidity surveillance, 230 health structures were listed by district, with their catchment populations of 2 million inhabitants based on the 2012 census. A sample of 32 health posts and 16 districts hospitals were selected with probability proportional per size (PPS) using systematic random sampling, with respect to geographical coverage and malaria incidence rates to ensure the sample was representative. One month after the third SMC cycle, a

cross sectional survey targeting 2000 children under 10 years of age in 45 villages selected by PPS were recruited to document SMC coverage and drug resistance markers in 2014 and 2015. Overall 3968 mild adverse events were detected during SMC campaigns including 1026 by the national passive system and 2942 by 2 strategies to strengthen the existing system; and 3 serious adverse events (2 anaphylactic shocks and 1 extra pyramidal syndrome) after the administration of almost 2 million SMC treatments. Ninety eighteen percent of children under 10 years received at least one dose of SMC. The coverage for a full treatment course was 74% for the last cycle. Malaria morbidity surveillance showed in 2014 during the months when SMC was administered, a 66% (95%CI 57%,73%) reduction in outpatient malaria cases and a similar reduction in cases of severe malaria. In 2015, malaria incidence has increased in the targeted group due to several factors including changes in diagnosis flowchart with HRP2 rapid diagnostic test and an exceptional rainy season in 2015 showing the importance of continuous monitoring and evaluation programmes of SMC implementation in the Sahelian region.

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ARTESUNATE TO TREAT SEVERE MALARIA IN TRAVELERS: REVIEW OF EFFICACY AND SAFETY AND PRACTICAL IMPLICATIONS

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Artesunate is recommended by the WHO for the first-line treatment of severe malaria worldwide, in adults and children. However, despite solid evidence that artesunate is safe and more effective than quinine in endemic areas, its deployment in non-endemic areas has been slow, due in part to the absence of a Good Manufacturing Practice (GMP) qualification. Using the Prisma method for bibliographic reports we have analyzed published studies (12 retrospectives 1 prospective) and 7 case reports to assess the safety and efficacy of artesunate in travelers with imported severe malaria. Of 574 patients with reported outcome, 22 died (3.83%). No death was attributed to artesunate toxicity. Relatively few side effects were reported including: neurological syndrome (6 cases), temporary deterioration in renal function (3), cutaneous (3) and cardiac (4) manifestations, high blood pressure (1), elevation of liver enzymes (58) and hyperkaliemia (1). A new side effect of artesunate has been uncovered in travelers: Post-Artesunate Delayed Hemolysis (PADH), defined by delayed hemolytic episodes occurring 7 to 30 days after treatment initiation. PADH occurs in 15% of the treated patients. No death or sequelae were reported but blood transfusion was administered in 45% of patients. Weekly follow-up of hematological parameters during one month post-treatment is now recommended. Our analysis confirms the high efficacy and reasonable safety of artesunate in travelers with severe malaria thereby urging for a wider use in non-endemic countries. GMP qualification for the drug and rapid approval by drug agencies is warranted, backed by clear recommendations for optimal use.

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TRENDS OF HIGH REDUCTION OF MALARIA CASES IN SEDHIOU DISTRICT FOLLOWING SEASONAL MALARIA CHEMOPREVENTION FIRST CAMPAIGN: LESSONS LEARNED

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Following research on efficacy and feasibility, Seasonal Malaria Chemoprevention (SMC) was adopted and scaled up in eligible areas in Senegal. Mass campaigns were launched in 2014 in Sedhiou region and targeted children aged more than 2 months to less than 10 years. The objective of this study was to assess effects of SMC following SMC first mass campaign, launched in August 2014. The study was developed in Sedhiou district, South Senegal. Malaria incidence is still high in the region Most of control strategies are ongoing for a total population of 181,594 inhabitants. Data were collected from January 2013 to December 2014 in all health units and in community units through smart phones with GPS. Patients were localized and malaria confirmation were done by Rapid Diagnostic Test. During these two years, 72,570 patients were visited, 40,548 in 2013 and 32,022 in 2014. Overall 5,055 were malaria positive during these two years, with a 74% total reduction in 2014. There was disparities in malaria morbidity reduction; this was 87% among children more than two months to five years, 80% among those six to ten years, 73% among 11 to 15 years and 65% reduction for patients more than 15 years- 20 years; 70% reduction for more than 20 years. Disparities were also observed among health posts and villages where the reduction varied from 22% to 97%. SMC has been highly effective following first year of implementation in Sedhiou district. Major reduction of malaria cases happened among children under 10, but longer integrated evaluation is needed, especially in epidemiology trends, drugs resistance, mid term acceptability and impact of other interventions like universal coverage of Long Lasting Impregnated Nets.

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MONITORING THE RESPONSES OF *PLASMODIUM FALCIPARUM* TO ANTIMALARIAL DRUGS USING THE DAPI *EX VIVO* TEST: HIGH FREQUENCY OF *P. FALCIPARUM* ISOLATES RESISTANT TO PYRIMETHAMINE IN DIORO, MALI

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The greatest threat to malaria control is the development of resistance to the antimalarial drugs used to treat uncomplicated and severe Plasmodium malaria in human subjects. In order to monitor the response of *Plasmodium falciparum* to the ACTs in current use we performed an *in vivo* study in which blood samples for parasite isolates were obtained from 31 volunteers with uncomplicated malaria who were 2-15 years of age in the rural commune of Dioro within the Segou Region of Mali. To examine the responses of *P. falciparum* in that region to antimalarial drugs, we performed DAPI *Ex vivo* tests for the isolates from the 31 subjects enrolled in that study from 2014 to 2016. The 8 drugs tested in this study were: Chloroquine (CQ), Piperaquine (PIP), Amodiaquine (AMQ), Lumefantrine (LUM), Mefloquine (MEF), Quinine (QN), Artesunate (ARS), Dihydroartemisinin (DHA), Artemether (ATM) and Pyrimethamine (PYR). Among these 8 drugs, the greatest frequency of resistance based

on the IC50 was found with PYR (71% of isolates with an IC50 > 2000 nM), followed by MEF (35.5% with an IC50 > 30 nM), LUM (22.6% with an IC50 > 150 nM), CQ (22.6% with an IC50 > 100 nM) and DHA (16.1% with an IC50 > 12 nM). In contrast, only 6.5% of the *P. falciparum* isolates had an IC50 > 60 nM for AMQ, an IC50 > 800 nM for QN or an IC50 > 30 nM for ATM. The 71% frequency of *P. falciparum* isolates with Pyrimethamine IC50s > 2000 nM indicates this resistance is common in Dioro and suggests that PYR resistance may limit the efficacy of IPTp for pregnant women because IPTp is based on preventive treatment with SP during pregnancy. In addition, the 22.5% frequency of isolates resistant to LUM poses a threat to ACTs with LUM as the partner drug and potentially increases the risk of late recurrences after the initial parasite clearance due to the artemisinins.

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COMBINATORIAL GENETIC MODELING OF PFCRT-MEDIATED DRUG RESISTANCE EVOLUTION IN *PLASMODIUM FALCIPARUM*

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The emergence and spread of drug resistance poses an ongoing threat to the effective treatment and control of *Plasmodium falciparum* malaria. A critical parasite determinant is PfCRT, the primary mediator of CQ resistance (CQR) and a pleiotropic modulator of susceptibility to first-line artemisinin-based combination therapy (ACT) partner drugs. Aside from the validated CQR molecular marker K76T, *P. falciparum* parasites have acquired at least three additional pfcrt mutations, whose contributions to resistance and fitness have remained elusive. Focusing on the quadruple-mutant Ecuadorian PfCRT haplotype Ecu1110 (K76T/A220S/N326D/I356L), we genetically modified the pfcrt locus of isogenic, asexual blood stage *P. falciparum* parasites using zinc-finger nucleases (ZFNs), producing all possible combinations of intermediate pfcrt alleles. Our analysis included the related quintuple-mutant PfCRT haplotype 7G8 (Ecu1110+C72S) that is widespread throughout South America and the Western Pacific. Drug susceptibilities and *in vitro* growth profiles of our combinatorial pfcrt¬-modified parasites were used to simulate the mutational trajectories accessible to parasites as they evolved CQR. Our results uncover unique contributions to parasite drug resistance and growth for mutations beyond K76T and predict critical roles for the CQ metabolite monodesethyl-chloroquine and the related quinoline-type drug amodiaquine in driving mutant pfcrt evolution. Modeling outputs further highlight the influence of parasite proliferation rates alongside gains in drug resistance in dictating successful trajectories. Our findings suggest that *P. falciparum* parasites have navigated constrained pfcrt adaptive landscapes by means of probabilistically rare mutational bursts that led to the infrequent emergence of pfcrt alleles in the field. We recently extended this in an analysis of pfcrt resistance alleles that distinguish the evolution of CQR in Asia and Africa.

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COMPARISON OF HIGH RESOLUTION MELT (HRM) ANALYSIS TO TA CLONING AND SEQUENCING FOR THE ANALYSIS OF A CLINICAL TRIAL USING AN INVESTIGATIONAL AMINOQUINOLINE, AQ-13, TO CIRCUMVENT CHLOROQUINE RESISTANCE IN SUBJECTS WITH UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN MALI

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Chloroquine resistance, which was first described in Southeast Asia and South America, has now complicated malaria control for more than 50 years. To address this problem, we have developed an analogue of chloroquine (CQ) which is active *in vitro* against CQ-resistant parasites and is safe in human subjects (AQ-13). To test the efficacy and therefore the potential clinical value of this investigational antimalarial, it has been compared for efficacy with the current first-line treatment for patients with uncomplicated *Plasmodium falciparum* malaria (Coartem = Artémether + Luméfantrine, A+L) in a randomized, blinded clinical trial. As part of that process, the efficacy of A+L and AQ-13 has been examined in subjects infected with CQ-resistant vs. CQ-susceptible parasites, based on the K76T single nucleotide polymorphism responsible for CQ resistance. The HRM analyses performed in Mali have shown that parasite isolates obtained from subjects in both groups had specimens with only K76 parasites, only T76 parasites and mixtures of K76 and T76 parasites. Because all subjects in the A+L and AQ-13 treatment groups cleared all asexual parasites from the blood within 3 days, both A+L and AQ-13 were efficacious against CQ-resistant and CQ-susceptible parasites. Based on that information, these samples are now being cloned and sequenced in order to compare the codon present at position 76 of the *Plasmodium falciparum chloroquine resistance transporter* gene (*pfcrt*) in these samples to the results of HRM analyses for the same samples. We anticipate that these results will be available within 2 months and that they will add to the information now available on comparisons of HRM with sequencing for important loci such as position 76 of *pfcrt*.

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ARTEMISININ-COMBINATION THERAPY VERSUS CHLOROQUINE FOR THE TREATMENT OF *PLASMODIUM MALARIAE* IN SABAH, MALAYSIA: A RANDOMIZED CONTROLLED TRIAL

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Background. Human infection with *Plasmodium malariae* is uncommon but remains present in the Asia-Pacific region, Africa and South America, and can cause severe anaemia. There have been no previous randomised trials to evaluate the optimal treatment for uncomplicated malaria due to *P. malariae*. Methods. An open-label, randomised controlled trial was conducted at three district hospitals in Sabah, Malaysia. Patients aged 1 year or older with uncomplicated *P. malariae* on screening microscopy were randomly assigned to receive oral artesunate–mefloquine (ASMQ; target dose 12 mg/kg artesunate and 25 mg/kg mefloquine) or chloroquine (CQ; target dose 25 mg/kg). The primary endpoint was parasite clearance at 24 h. Analysis was by modified intention to treat. Secondary analysis