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## 2 studies offer new insights from the front lines of battle against malaria

*In most comprehensive review of a decade of data researchers confirm indoor insecticide treatments, dramatically reduce malaria; study finds world's best drug still effective in African malaria 'hot zone' while researchers question for how long*

BURNESS COMMUNICATIONS

Deerfield, IL (July 3, 2012) A pair of provocative studies in the July 2012 issue of *The American Journal of Tropical Medicine and Hygiene* (AJTMH) provides a window into the intense ground war now underway against malaria. In one review, researchers offer new evidence supporting indoor insecticide spraying as a way to dramatically reduce malaria deaths. In another study, scientists in Mali simultaneously affirm the effectiveness of a critical drug to treat malaria infection in the West African malaria "hot zone" amidst concerns that it may follow the path of its predecessors and succumb to resistant parasites already being detected in other parts of the world.

- In the most comprehensive review to date of the malaria-fighting potential of indoor insecticide treatments, researchers at North Carolina Central University (NCCU) and Duke University found that over the last decade on average they have reduced infections in malaria endemic communities by 62 percent--despite rising insecticide resistance among mosquitoes. But the investigators believe the more important contribution of the study is its identification of factors that appear to influence the success of indoor residual spraying (IRS).
- A study led by scientists at the University of Bamako in the West African country of Mali found that the life saving drug artemisinin continues to rapidly cure young children infected with malaria--even as it is showing signs of weakness in Southeast Asia. The researchers raise red flags about gaps in surveillance in Africa as new evidence that drug resistance may be spreading from Thailand to Myanmar renews fears that it could soon cross to Africa and reverse decades of progress against the disease. In an accompanying editorial, experts cite the urgent need for investment in new research and drug development.

"Both of these studies demonstrate the incremental successes and long-term challenges faced by our drive to prevent needless deaths due to malaria. Make no mistake, this is a winnable battle. We can and will ultimately eradicate malaria from its strongholds in Africa and Asia," said James W. Kazura, MD, President of the American Society of Tropical Medicine and Hygiene.

**In House-to-House Combat Against Malaria, Insecticides Emerge as Lethal Weapon**

Researchers at NCCU and Duke University conducted a "meta-analysis"-- a form of research that synthesizes the results from previous studies--of 13 peer-reviewed reports published between 2000 and 2010 that considered the impact of IRS on malaria transmission in various settings, mostly in Africa. IRS involves coating the walls of homes or community buildings with insecticides in an effort to curb infections by killing malaria-carrying mosquitoes.

"Our findings show that during the last decade IRS has remained a powerful tool for fighting malaria, even though mosquitoes, particularly in Africa, are developing the ability to evade widely used insecticides," said Dohyeong Kim, PhD, the study's lead author and a professor in NCCU's Department of Public Administration.

Kim said the fact that IRS can significantly reduce malaria infections is widely accepted. What's less known, he said, are the factors that can influence the magnitude of success.

Kim and his colleagues found that IRS appears to be best at reducing malaria infections in areas experiencing a high rate of disease and where there is a threat from both *Plasmodium falciparum* parasites--the most deadly form of the disease--and *Plasmodium vivax* parasites. Also, IRS campaigns were found to be more effective if they involved several rounds of spraying. Another factor that appeared to improve IRS effectiveness was the use of the controversial insecticide DDT.

"Our (study) results show that DDT is more effective at reducing malaria prevalence than pyrethroids or other insecticides," the authors state. Pyrethroids are the most widely-used class of insecticides in IRS programs. But over the last decade mosquito populations in many malaria-endemic areas have developed genetic traits that make them resistant to these compounds.

DDT has been banned in many countries, including the United States, over concerns about its toxicity to humans and animals. Nevertheless, these dangers were primarily linked to its liberal use in agricultural settings. DDT applications for IRS are relatively small by comparison. However, Kim and his colleagues note that recent studies have provided evidence that even at low levels DDT may still be harmful to those exposed.

Kim said the study's findings indicate DDT may be worth considering in locations where malaria transmission is particularly intense, but the potential health dangers of DDT would need to be weighed against its potential to reduce malaria illnesses and deaths.

While providing some guidance for when indoor spraying is most effective, the IRS review also reveals the critical need for more insights--particularly given the relatively high costs of IRS programs and limited budgets for malaria control.

Kim and his colleagues note that the finding of substantial effectiveness (62 percent with considerable variation) for indoor spraying implies that mosquito control methods have "improved substantially during the past decade." They also called for more studies that consider the effectiveness of IRS and

insecticide-treated bed nets (ITNs) together to see whether "there is any additional benefit of combining" the two in the same households.

### Looking for Signs of Artemisinin Resistance in Africa

Researchers at the University of Bamako in Mali sought a way to quickly detect the emergence in Africa of a malaria parasite resistant to the life-saving drug artemisinin, which several years ago emerged as the most important medicine for treating malaria--in part because parasites have defeated other first-line therapies, such as chloroquine (CQ) and sulfadoxine/pyrimethamine (SP)

Researchers using the synthetic derivative of artemisinin - called artesunate - found that it rapidly purged the deadly malaria parasite *Plasmodium falciparum* from infected children treated in late 2010 and 2011 in a village in Mali that has "high-intensity" seasonal malaria transmission. The median time to "parasite clearance" was 32 hours, compared to 84 hours in tests conducted in areas of Cambodia where *falciparum* parasites are developing resistance. Furthermore, the clearance rate in Mali was very close to what had been observed in the same village in a study conducted several years earlier.

"Our study indicates that in this region of Africa there does not appear to be any artemisinin resistance," said Abdoulaye A. Djimde, PhD with the University of Bamako's Malaria Research and Training Center and the senior author of the study.

But what concerns Djimde is the lack of similarly intensive surveillance underway throughout Africa, particularly in light of an April 2012 article in *The Lancet* that has rattled malaria researchers and clinicians worldwide. Scientists reported finding artemisinin resistance among *falciparum* parasites in Thailand near its border with Myanmar, just a few years after scientists detected artemisinin-resistant parasites on the other side of country along Thailand's border with Cambodia.

Whether these episodes of resistance are distinct cases that arose in isolation or related events illustrative of resistant parasites on the move has yet to be determined, said Christopher Plowe, MD, MPH, a co-author of the Mali study and a malaria expert at the University of Maryland School of Medicine and the Howard Hughes Medical Institute. Past experiences provide reason to be concerned for Africa, he said.

"Historically, parasite resistance to malaria medicines has started in Southeast Asia and then eventually moved into Africa," he said. "We have to be very proactive if we want to avoid a public health disaster in Africa, which is where most of the world's malaria deaths occur and where artemisinin resistance would have its gravest effect."

### Urgent Need For New Research and Drug Development

In an editorial accompanying the Mali study, Caroline L. Ng and David A. Fidock, PhD, of Columbia University Medical Center say one reason there is such alarm over the prospect of artemisinin resistance spreading broadly is that "we are still several years away from any other drugs being

licensed and available to replace artemisinin should they fail." They see an urgent need for increased investments in research focused on discovering new drugs.

Plowe and Djimde pointed out that their effort in Mali probing for drug resistance differs from surveillance occurring elsewhere in Africa in an important way: it studies the reaction of parasites to artemisinin (in the form of the drug artesunate) when administered *by itself*. In African clinics that serve as World Health Organization (WHO) "sentinel" sites for detecting drug-resistance, treatment involves artemisinin combination therapies or ACTs that include other malaria medicines as well.

The combination is intended to make it more difficult for the parasite to develop resistance. Yet, some researchers worry that surveillance focused on ACT efficacy could delay detection of resistance emerging in Africa because other drugs in the compound might mask early signs of the parasite becoming less sensitive to artemisinin.

"We're not recommending clinics use artesunate by itself, but we need to periodically and safely conduct studies in malaria endemic regions of Africa with just artesunate if we want to detect resistance and still have enough time to intervene," Plowe said. "I think everyone agrees that we need more surveillance of this type. The question is where do we get the resources to do more comprehensive and frequent monitoring?"

Plowe said a major boost to the hunt for artemisinin resistance would be the discovery of a tell-tale genetic marker on the malaria parasite, such as the marker that reveals chloroquine resistance. He believes scientists are close to just such a discovery. But in the meantime, they must use a decline in the rate of parasite clearance in clinical studies as the indicator for resistance. Plowe noted that for malaria researchers, one of the key contributions of the Mali study is that it provides a new standard methodology for measuring parasite clearance in areas of intense seasonal transmission that he and his colleagues hope others will adopt.

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Continuously published since 1921, *AJTMH* is the peer-reviewed journal of the American Society of Tropical Medicine and Hygiene, and the world's leading voice in the fields of tropical medicine and global health. *AJTMH* disseminates new knowledge in fundamental, translational, clinical and public health sciences focusing on improving global health.

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