Antimicrobial Resistance in the Tropics

Update Course in Clinical Tropical Medicine & Travelers' Health

September 27-28, 2024, 1:15 p.m. – 2 p.m. U.S. Eastern Time, Virtual

Miriam Stegemann, Berlin

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Antimicrobial Stewardship Charité, Chief Medical Office

Travel is an important risk factor for the acquisition of AMR bacteria

1. ~ 30% of travelers return with an acquired AMR bacterium

2. Major risk factors for acquisition:

→travel destination

→antimicrobial usage

→infectious diseases acquired abroad

Destination matters

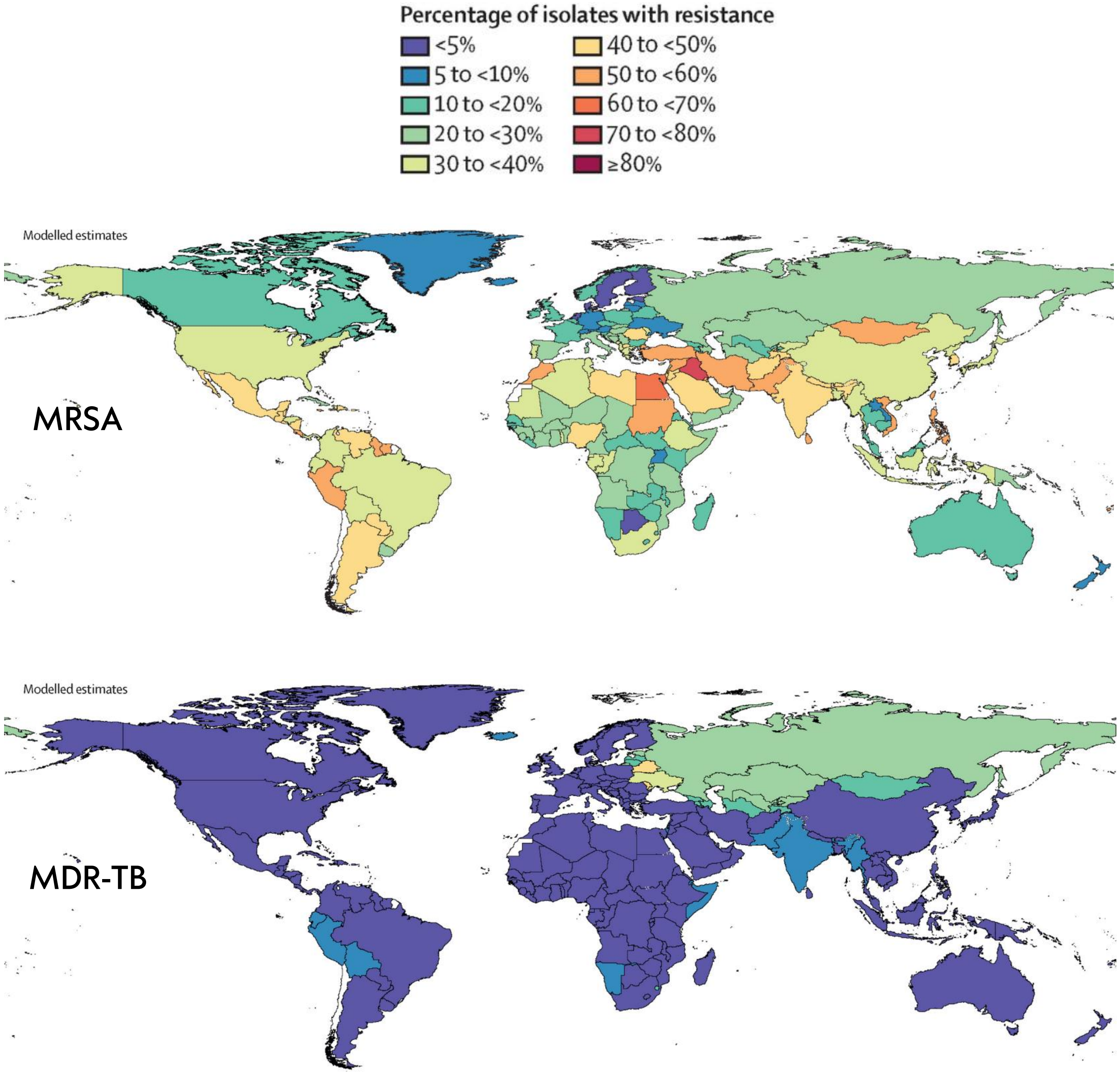
Resistance rates vary substantially by country and territory

Methicillin-resistant *Staphylococcus aureus* MRSA:

- 60 - 80% in north Africa and the Middle East (eg, Iraq and Kuwait)

MDR *M. tuberculosis:*

- 10 - 30 % in eastern Europe



Murray, Cet al., The Lancet, Vol. 399, Issue 10325, 629 – 655, 2022

Agenda and objectives

1. Antimicrobial Resistance in low-income and middle-income countries
2. Antimicrobial Resistance - actions and strategies
3. Patient management: Preparation and posttravel considerations in the context of AMR

1

Antimicrobial Resistance in low-income and middle-income countries

Global success in improving health

Life expectancy increased globally

- From 48 years (1950) to 71 years (2017) in men
- From 53 years (1950) to 76 years (2017) in women

Mortality in children < 5 years decreased globally

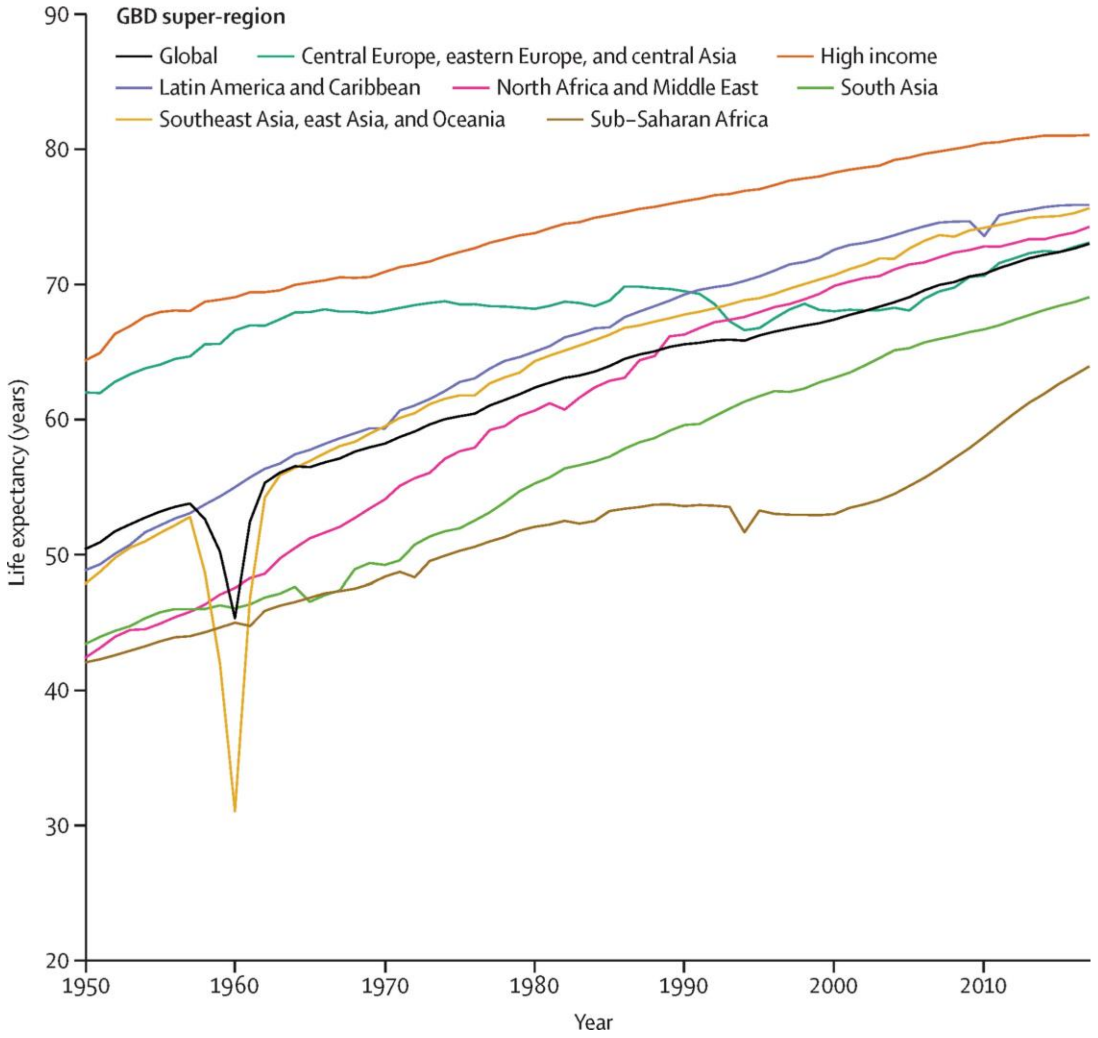
- 216 deaths / 1000 live births (1950) vs.
- 39 deaths / 1000 live births (2017)

GBD 2017 Mortality Collaborators. Lancet. 2018 Nov 10;392(10159):1684-1735. Burstein, R. et al, Nature 574, 353–358 (2019)

Substantial regional variation

Life expectancy at birth in 2017

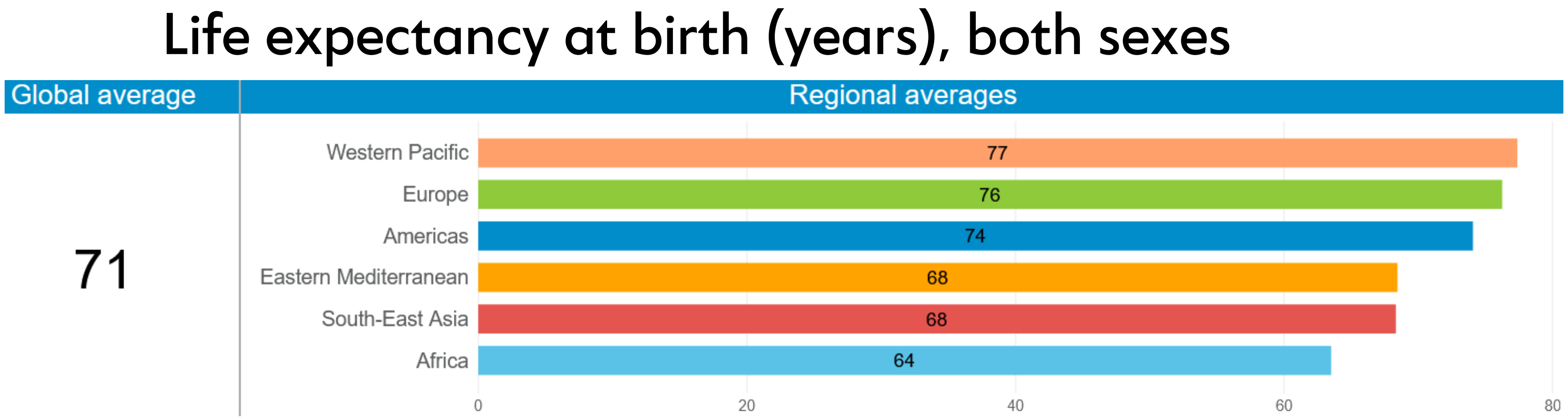
- 49 years for men in Central African Republic
- 88 years among women in Singapore



GBD 2017 Mortality Collaborators. Lancet. 2018 Nov 10;392(10159):1684-1735. Burstein, R. et al, Nature 574, 353–358 (2019)

Main contributors to increase of life expectancy

Antimicrobials are life-saving drugs



- Antimicrobials
- Nutrition
- Clean Water
- Hygiene
- Sanitation
- Vaccination

The Global Health Observatory, acc. Sept 26, 2024 World Health Organization

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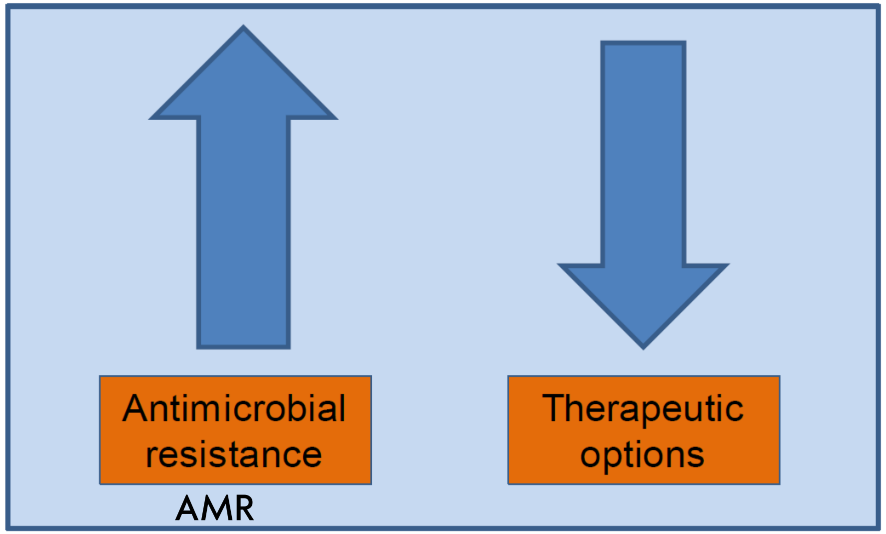
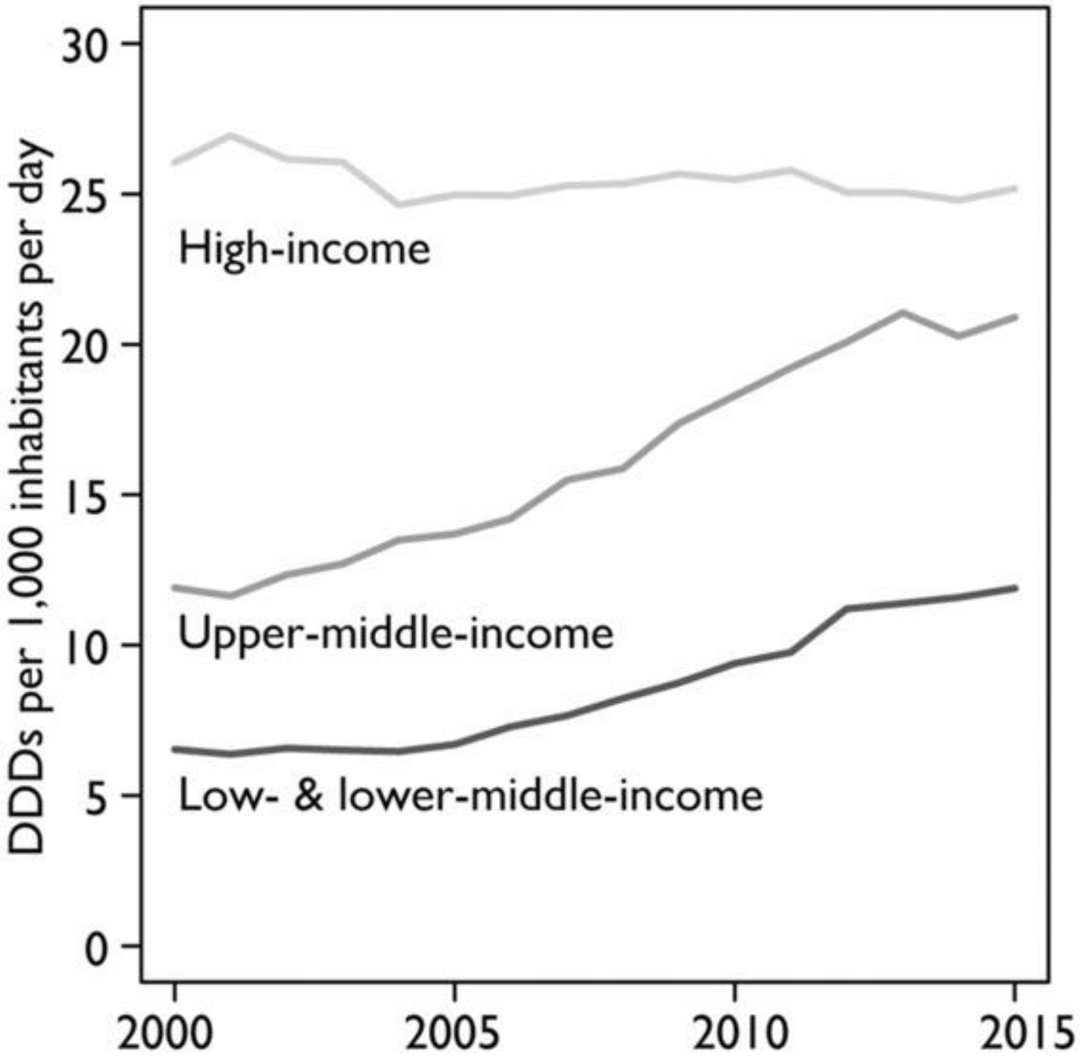
Antimicrobials are life-saving drugs



Infections due to drug resistant organisms

- Longer illnesses
- Increased mortality
- Prolonged hospitalizations
- Increased costs

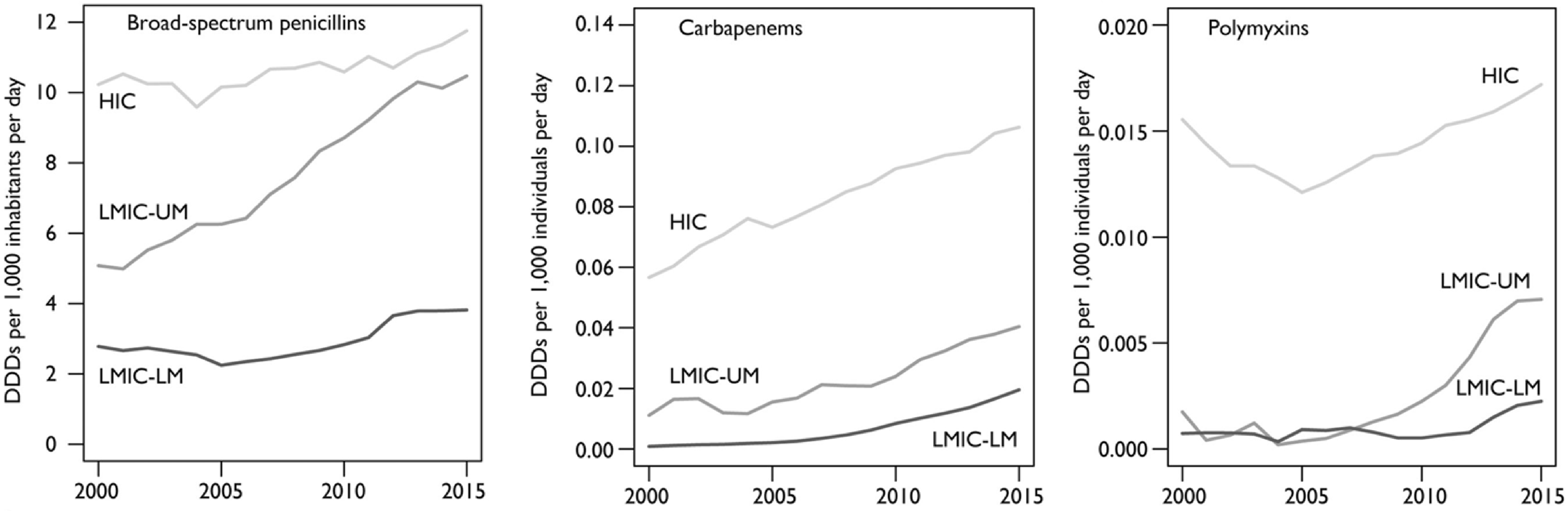
Increase of global antibiotic consumption



DDD: *statistical measure of drug consumption, used to standardize the comparison of drug usage between different drugs or between different health care environments*

Klein E et al, PNAS 2018;115

Increase of global consumption of reserve antibiotics



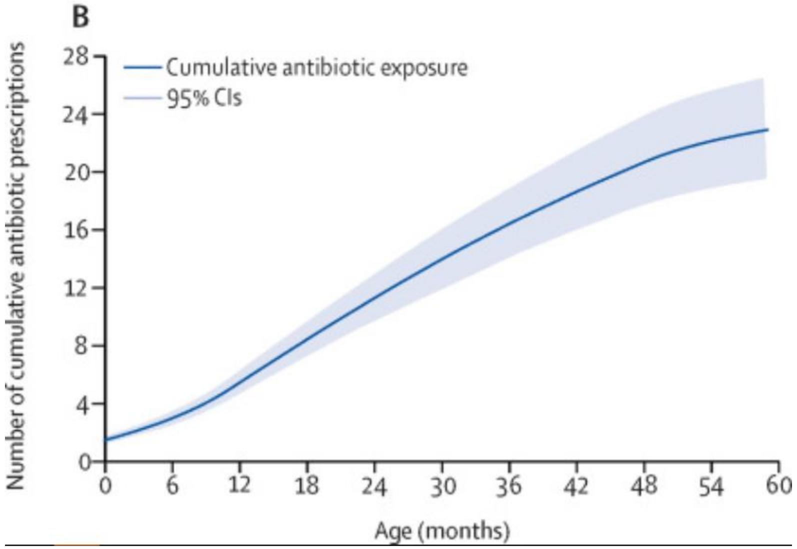
The overuse and misuse of antimicrobials contribute to the emergence of antimicrobial resistance

Klein E et al, PNAS 2018;115

Antibiotic consumption in LMIC

- Many countries lack effective surveillance capacity, but statistical methods estimate global antibiotic consumption over time
- Substantial increase antibiotic consumption over the past 2 decades
- Prescribing practices are reportedly poor, robust antibiotic stewardship programmes are often non-existent
- Often, indications for empirical antibiotic therapy are inappropriate
- Children in LMIC receive ~25 antibiotic prescriptions during their first 5 years of life

→ excessive amount that causes harm (e.g. side effects) & increase AMR



Estimated age-specific and cumulative antibiotic exposure of children from birth up to age 5 years in LMICs

Sulis G et al. PLoS Med. 2020 Jun 16;17(6):e1003139. doi: 10.1371/journal.pmed.1003139
Fink G et al. Lancet Infect Dis. 2020 Feb;20(2):179-187. doi: 10.1016/S1473-3099(19)30572-9

Antibiotic consumption is increasing worldwide but limited access is still an issue

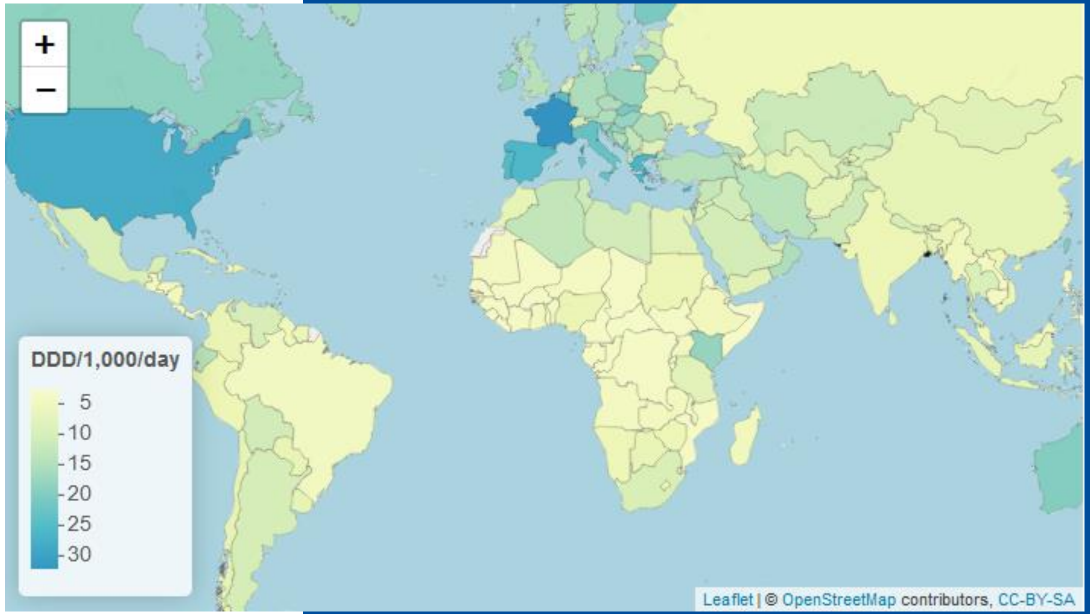
Patients in many LMIC are often unable to access antibiotics because

→Antibiotics not affordable

→Low government funding for health

→Unreliable supply chains

→Poor quality control to deliver antibiotics to patients in need



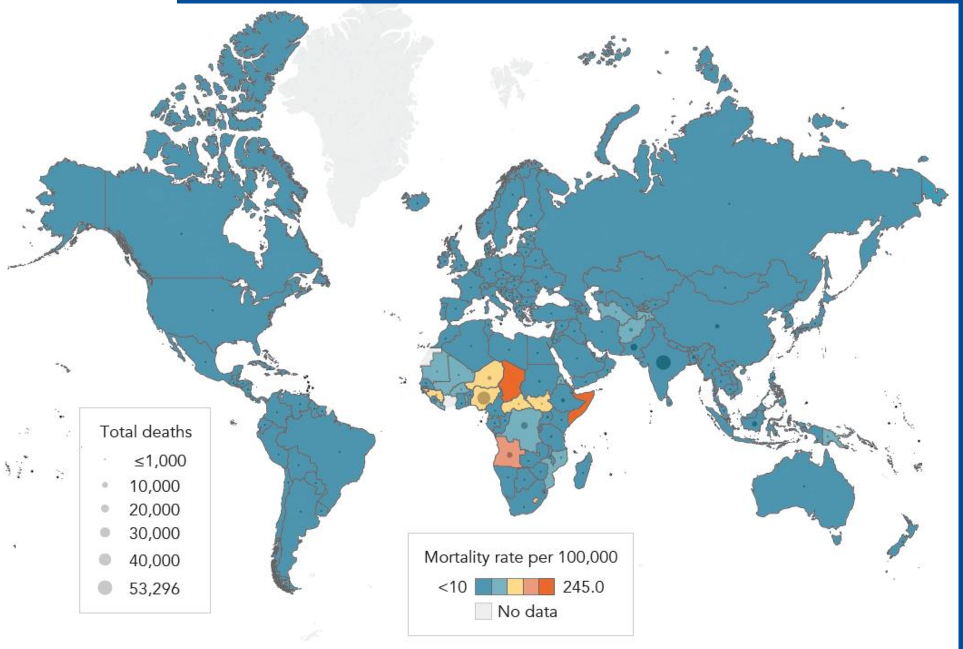
Total antibiotic consumption in each country: inequitable antibiotic consumption between HICs and LMICs

Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Lancet Planetary Health 2021

Consequences of limited access to antibiotics in LMIC

- Bacterial infections go untreated
- Increase in morbidity & mortality
- Increase of rates of preventable deaths
- Suboptimal dosing
- Poor pharmaceutical quality
- AMR development and propagation
- Improving access to antibiotics vital to better health outcomes

The majority of the world's antibiotic-treatable deaths occur in LMIC



1000s of people in LMIC continue to die from treatable pneumococcal infections

Streptococcus pneumoniae deaths and mortality rates per 100,000 (HIV-negative) children aged 1–59 months.
Data from Wahl et al. 2018

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Antimicrobial resistance (AMR):

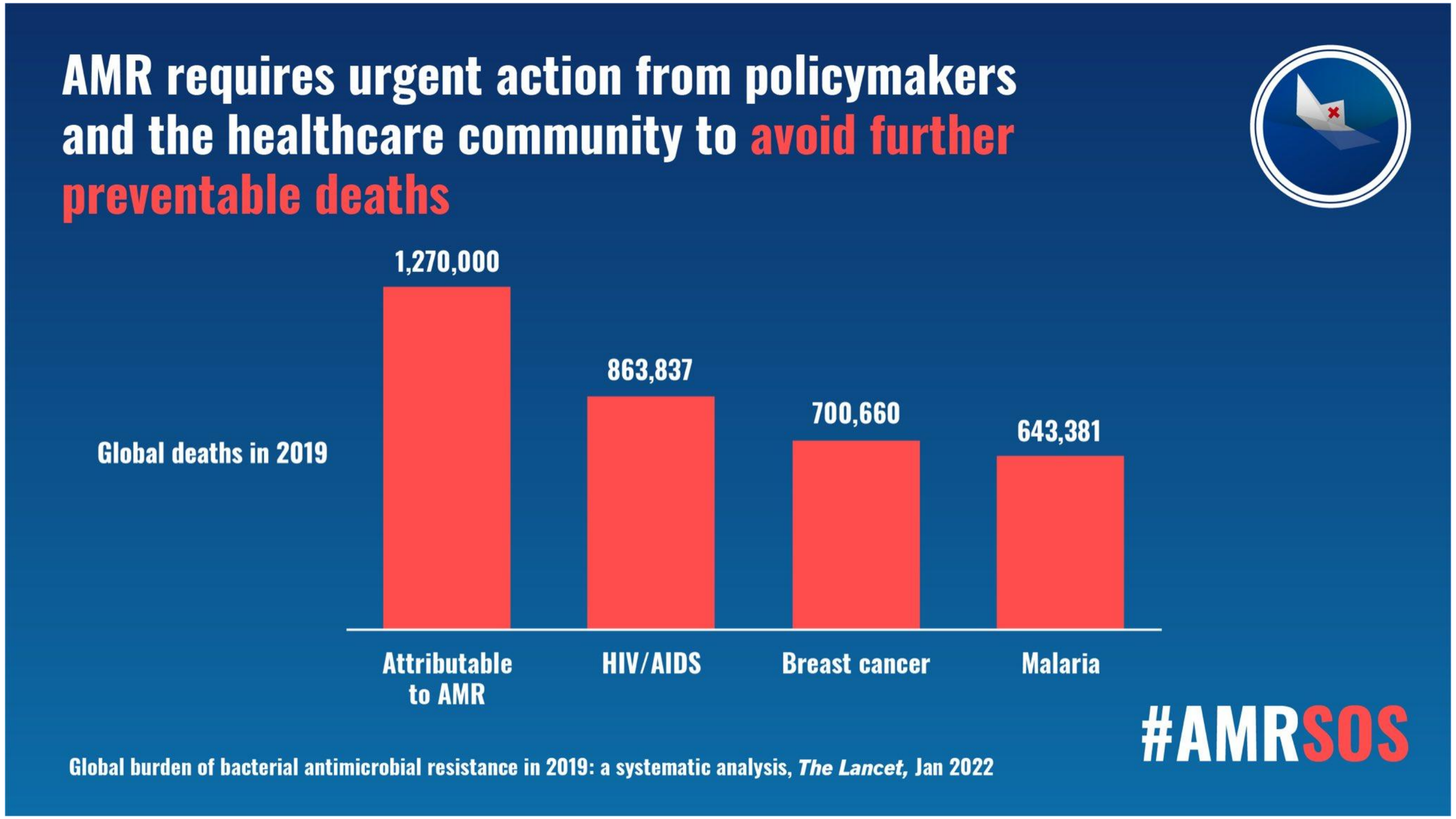
Lack of susceptibility of bacteria, fungi, viruses and parasites to antimicrobial agents.

Global burden of AMR

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

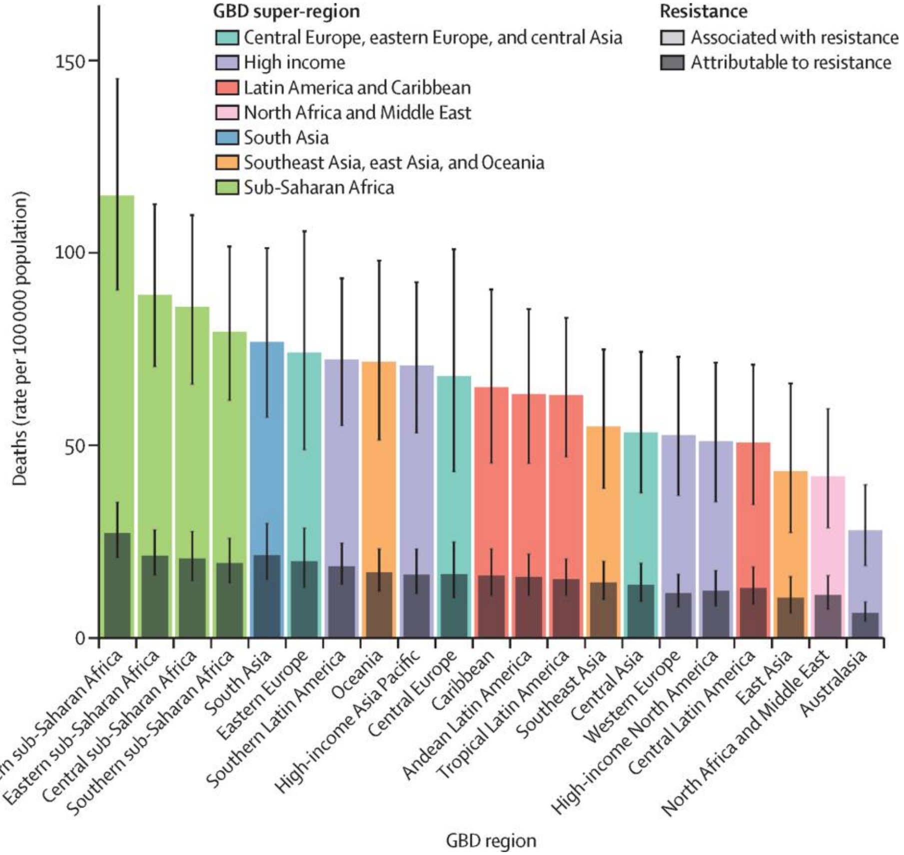
*Antimicrobial Resistance Collaborators**

Published Online
January 20, 2022
https://doi.org/10.1016/
S0140-6736(21)02724-0



Lancet. 2022 Feb 12, Erratum in: Lancet. 2022 Oct 1; PMID: 35065702; PMCID: PMC8841637

AMR: highest burdens in low-resource settings



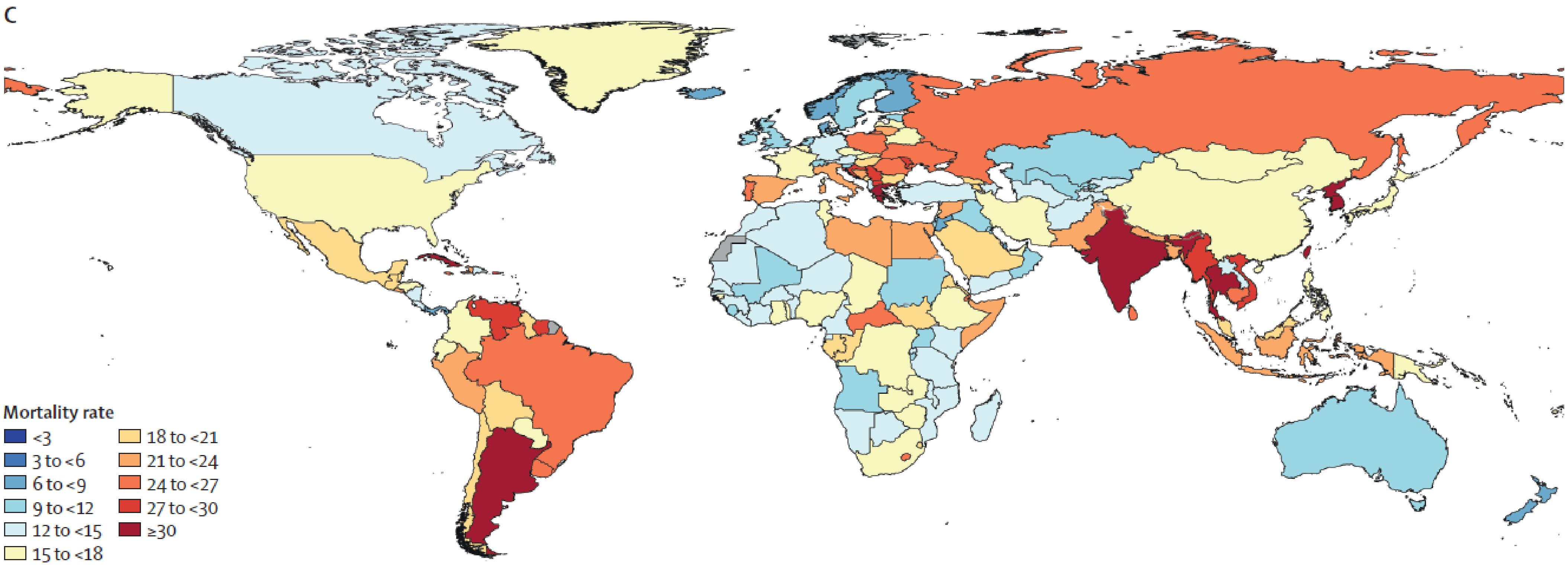
Lancet. 2022 Feb 12, Erratum in: Lancet. 2022 Oct 1; PMID: 35065702; PMCID: PMC8841637

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

*GBD 2021 Antimicrobial Resistance Collaborators**

www.thelancet.com Published online September 16, 2024

Death rate attributable to AMR, all ages, 2050



Global deaths could reach 39 million between 2025 and 2050 = 3 deaths / minute

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https://doi.org/10.1016/S0140-6736(24)01867-1

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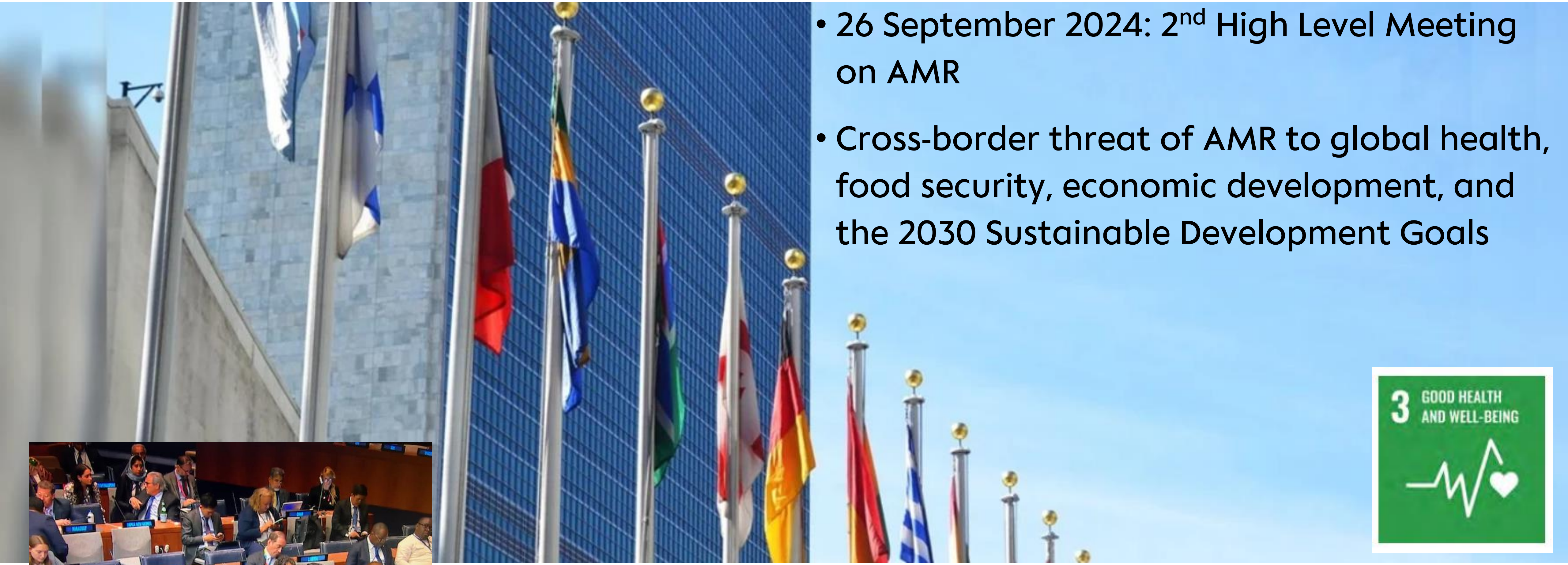
Antimicrobial Resistance – actions and strategies

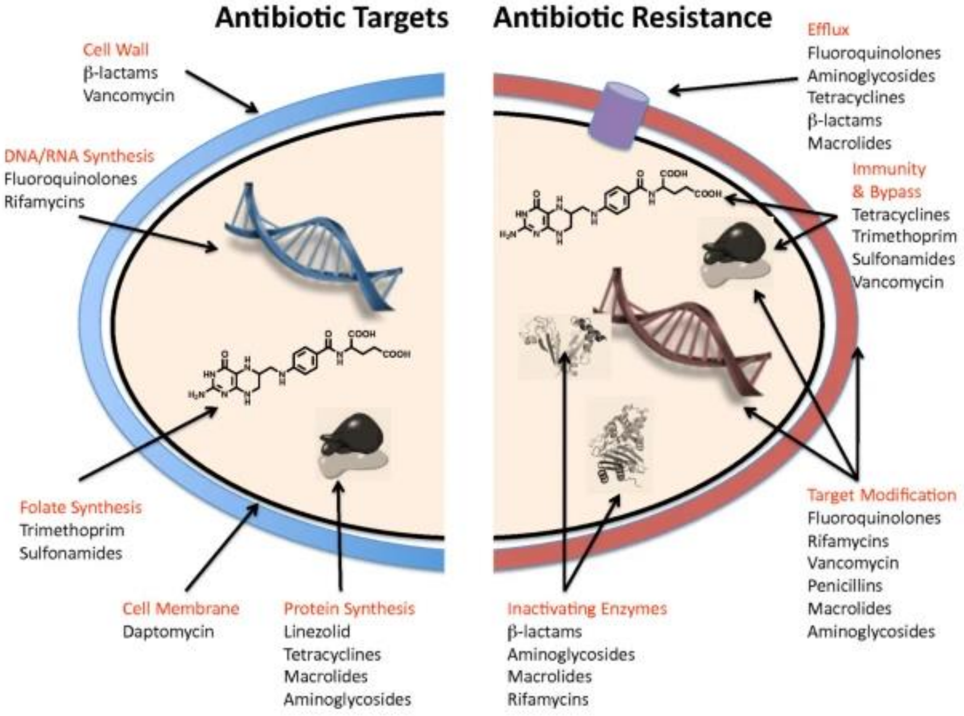
UN General Assembly High-Level Meeting on antimicrobial resistance 2024



- 26 September 2024: 2nd High Level Meeting on AMR
- Cross-border threat of AMR to global health, food security, economic development, and the 2030 Sustainable Development Goals

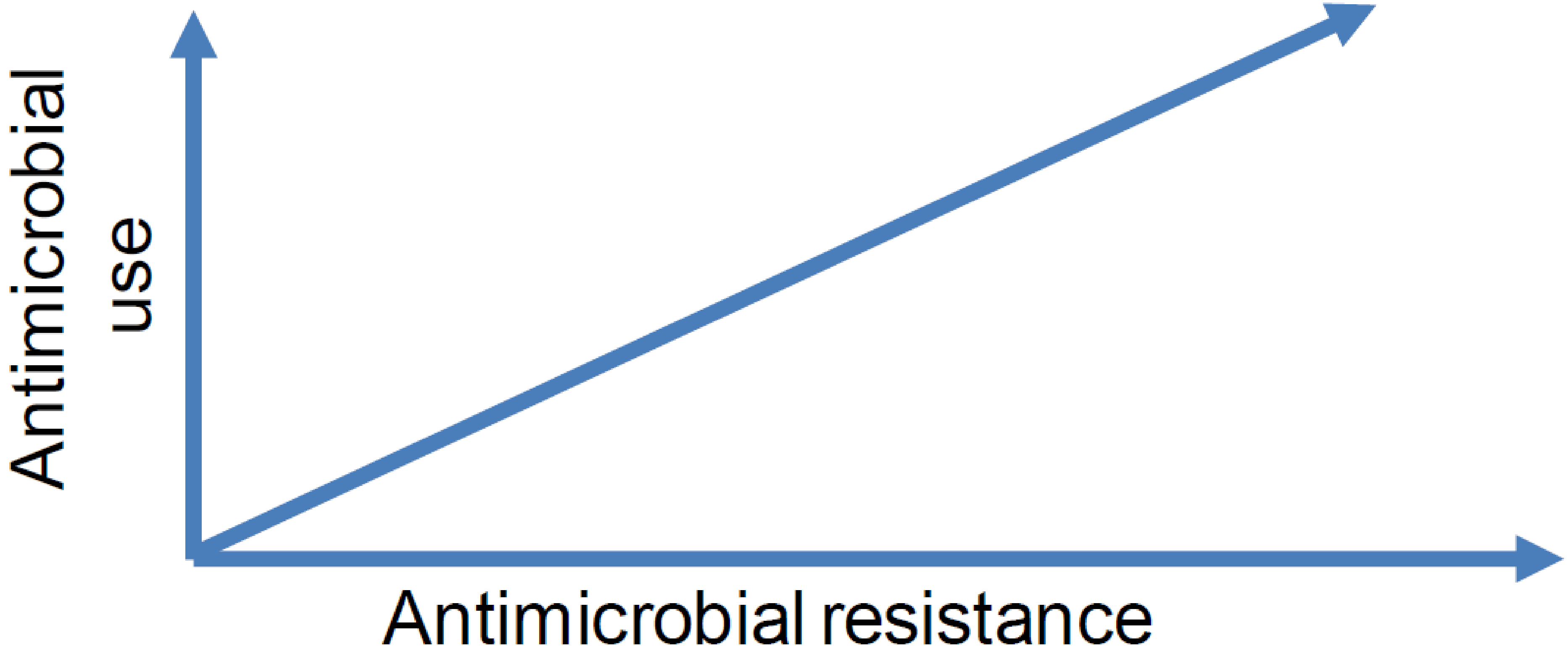
Development of antibiotic resistance

- Natural process
- Genetic changes in pathogens: mutation or acquisition of resistance genes
- Spread of AMR: transfer of resistant organisms and resistance genes



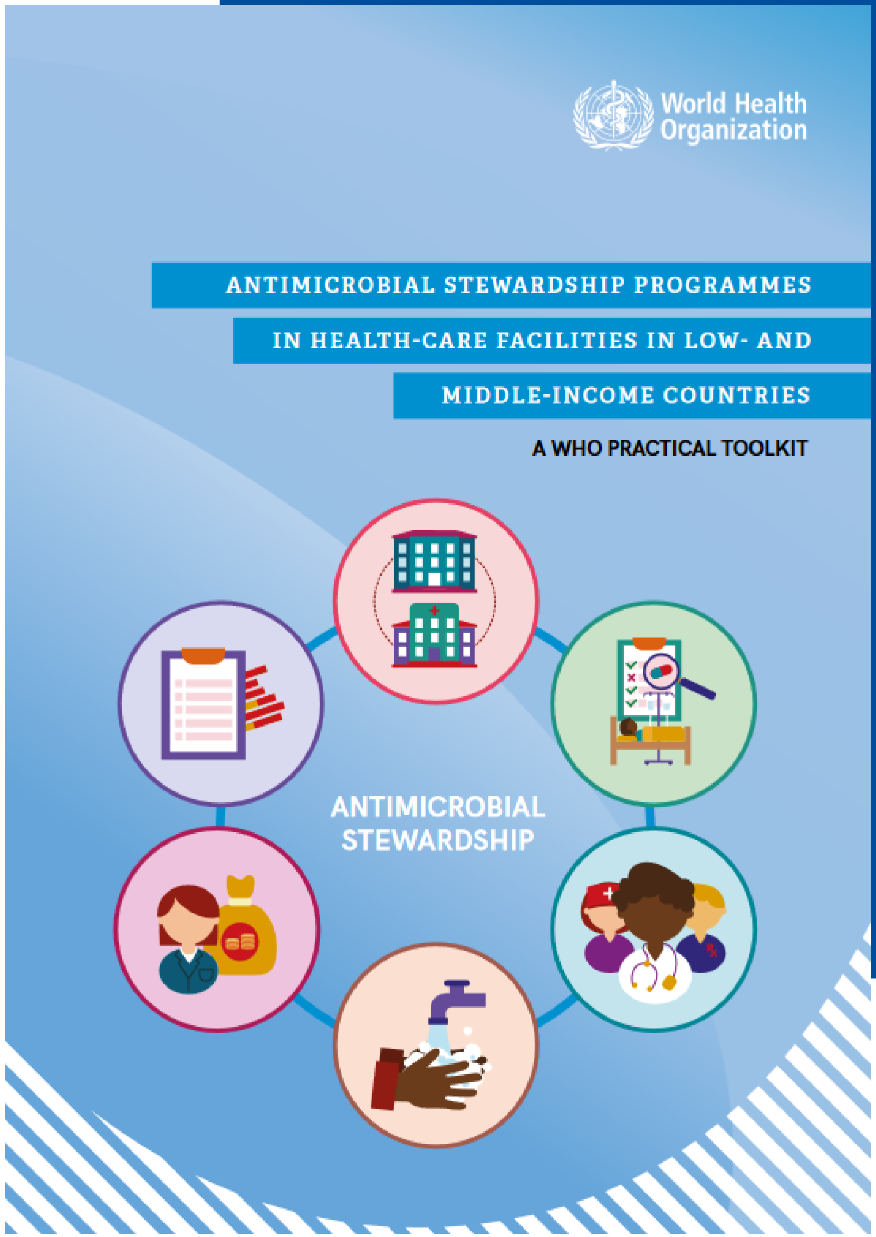
Antibiotic targets and mechanisms of resistance
Wright, G.D. *BMC Biol* **8**, 123 (2010). https://doi.org/10.1186/1741-7007-8-123

What accelerates the emergence and spread of AMR?

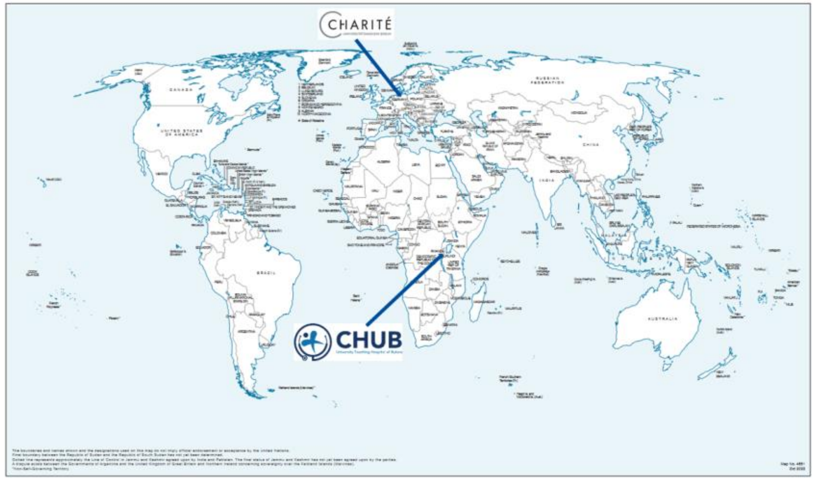


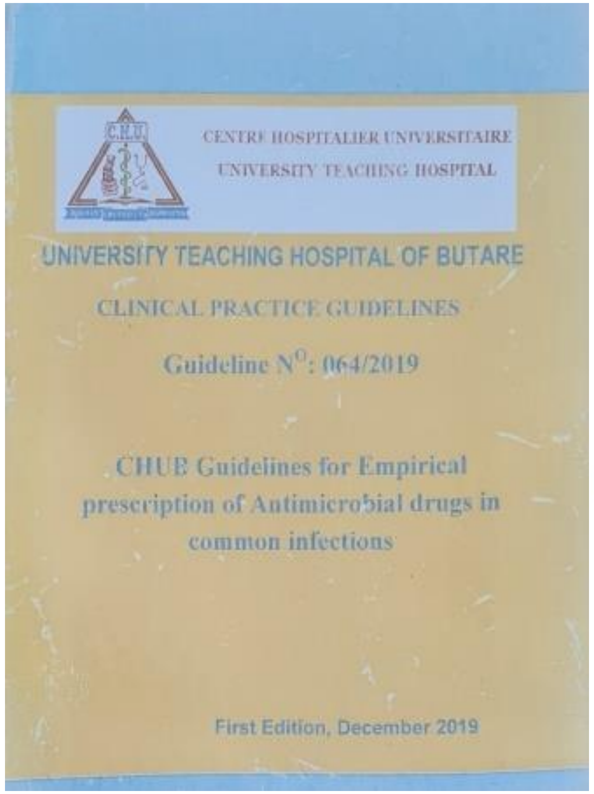
Antimicrobial Stewardship Programmes

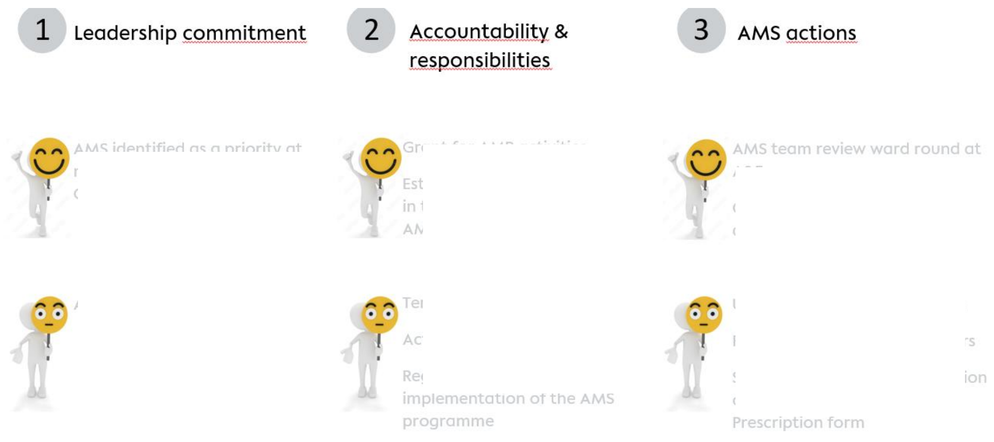
- Optimize the use of antimicrobials
- Improve patient outcomes
- Reduce AMR, health-care-associated infections
- Save health-care costs

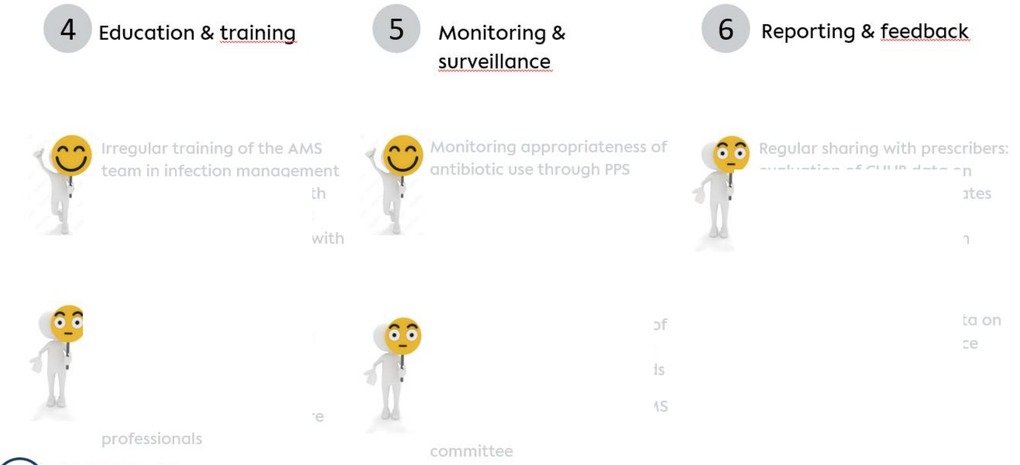


International collaborative AMS – Hospital partnership Germany – Rwanda

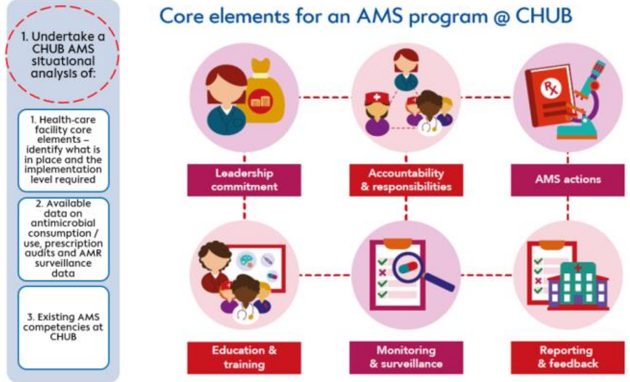






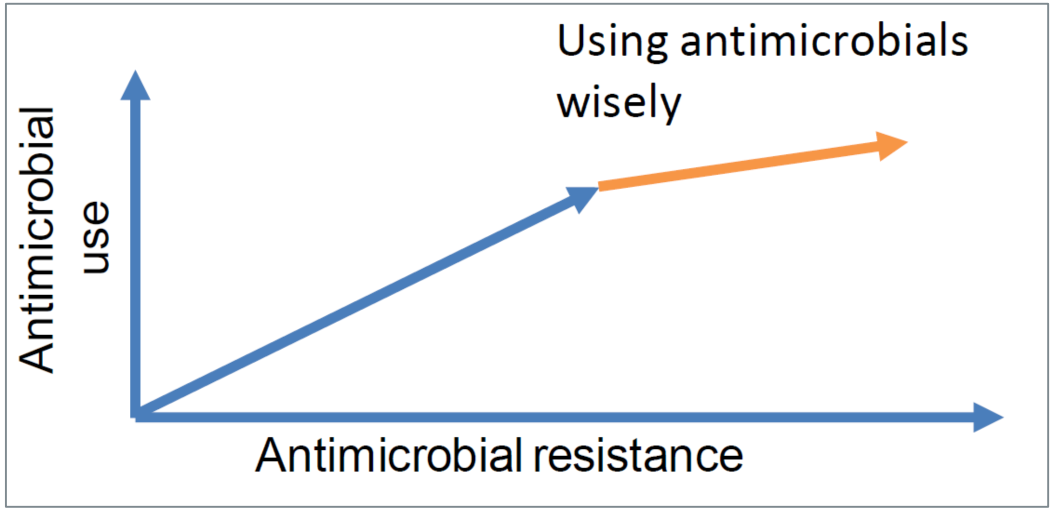


Implementation of an AMS programm @ CHUB: situational analysis



Objective:
To guide the CHUB management in building the structures needed to enable implementation of a sustainable AMS program @ CHUB

Antimicrobial Stewardship



We must all be antimicrobial stewards

Stewardship:
the careful and responsible management of natural resources

We must all be antimicrobial stewards

Microbiology guides therapy wherever possible
Indications should be evidence based
Narrowest spectrum required
Dosage appropriate to the site and type of infection
Minimise duration of therapy
Ensure monotherapy in most cases

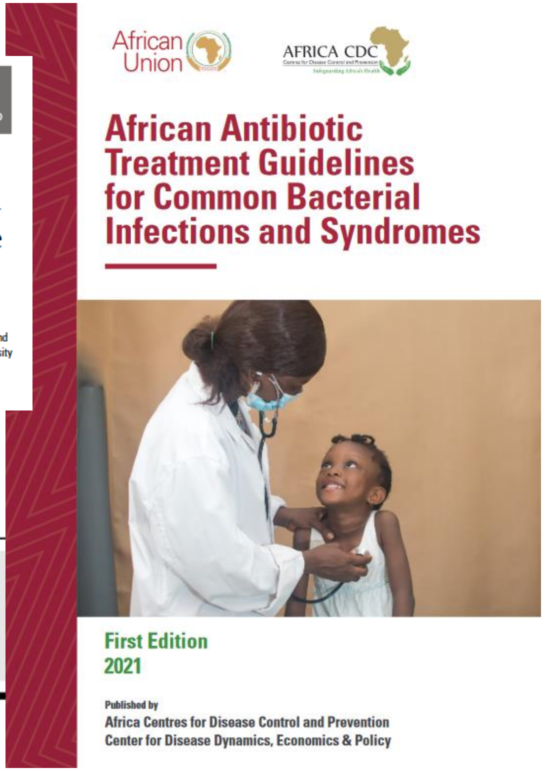
How can we be antimicrobial stewards?

Clinical Infectious Diseases
IDSA GUIDELINES
IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Department of Practice, Sciences, and Health-Outcomes Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA; [3]Department of Pharmacy, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, USA; [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA; [5]Department of Medicine, Weill Cornell Medicine, New York, New York, USA; and [6]Medical Service and Center for Antimicrobial Resistance and Epidemiology, Louis Stokes Cleveland Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA

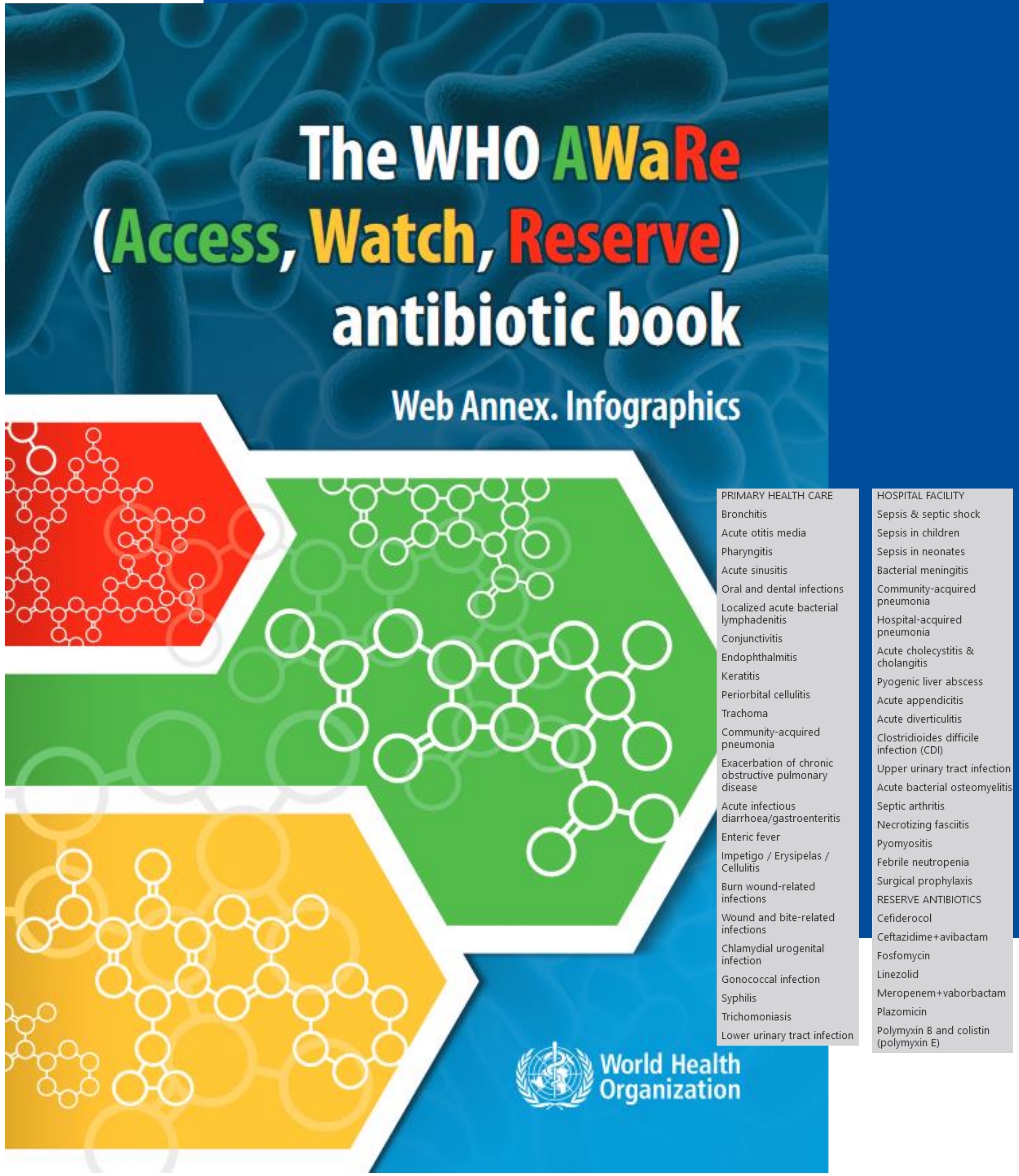


ELSEVIER
Contents lists available at ScienceDirect
Clinical Microbiology and Infection
journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

European society of clinical microbiology and infectious diseases guidelines for antimicrobial stewardship in emergency departments (endorsed by European association of hospital pharmacists)

Teske Schoffelen [1,2,*,†], Cihan Papan [3,4,†], Elena Carrara [5], Khalid Eljaaly [6,7], Mical Paul [8], Emma Keuleyan [9,10], Alejandro Martin Quirós [11)], Nathan Peiffer-Smadja [12,13,14], Carlos Palos [15], Larissa May [16], Michael Pulia [17], Bojana Beovic [18], Eric Batard [19,20], Fredrik Resman [21], Marlies Hulscher [22], Jeroen Schouten [1,23], on behalf of the ESCMID Study Group for Antimicrobial Stewardship (ESGAP)



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Antimicrobial Resistance – individuals travelling

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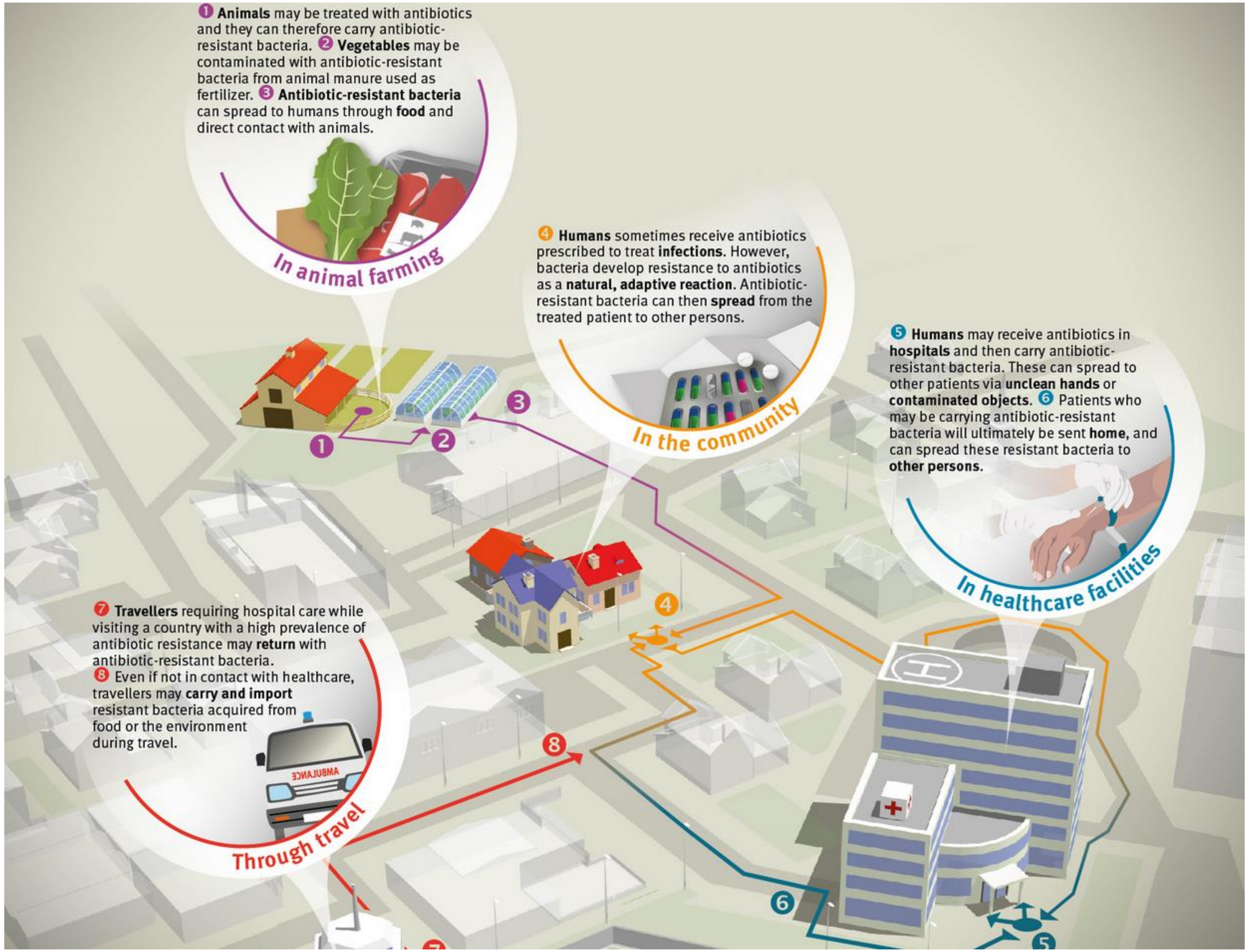
How does antibiotic resistance spread?



Intercontinental travel contributes to the global spread of AMR

Intestinal colonization with extended-spectrum beta-lactamase producing Enterobacterales (ESBL-PE) during long distance travel: A cohort study in a German travel clinic (2016–2017) Travel Medicine and Infectious Disease 33 (2020)

Lynn Meurs[a,b,*,1], Felix S. Lempp[c,1], Norman Lippmann[d], Henning Trawinski[c], Arne C. Rodloff[d], Matthias Eckardt[b,2], Anja Klingeberg[b], Tim Eckmanns[b], Jan Walter[b], Christoph Lübbert[c,d], Rai Study group (Muna Abu Sin, Esther-Maria Antão, Michael Behnke, Jutta Bleidorn,

Risk factor analysis for ESBL-PE colonization upon return from long distance travel, Germany 2016–2017, n = 230.

Risk factors		n	Adjusted OR[a]
Age	< 20 years	11	1.8 (0.3–10)
	20–29 years	66	4.8 (1.9–12)
	30–49 years	75	1.6 (0.7–4.0)
	≥ 50 years	78	Ref.
Accommodation	Hotel	107	4.4 (1.6–12)
	Private	32	3.8 (1.2–12)
	Other tourist accommodation (e.g. hostel, camping or guest house)	58	Ref.
	Missing/multiple[b]	33	2.3 (0.6–8)
Destination Eastern, Southern or Western Asia	Yes	34	4.6 (1.9–11)
	No	196	Ref.
Diarrhoea during travel	Yes	83	1.7 (0.9–3.5)
	No	146	Ref.
Antibiotics during travel	Yes	18	0.9 (0.2–3.4)
	No	212	Ref.

53/230 (23%) that were ESBL negative before travelling, returned positive

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 382;14 NEJM.ORG APRIL 2, 2020

Acquisition of Antibiotic-Resistant Bacteria by U.S. International Travelers

Patient No.	Age	Sex	Trip Duration	Destination	Diarrhea during Trip†	Antibiotic Use during Trip	Type of Antibiotic Resistance	
							Phenotype‡	Resistance Genes§
	yr		no. of days					
1	29	Female	14	Thailand	No	No	MCRE	*mcr-3.1, mcr-1.1*
2	68	Female	20	Kenya, Tanzania	Yes	Ciprofloxacin	MCRE	*mcr-1.1*
3	79	Male	19	Vietnam	No	No	MCRE	*mcr-1.1*
4	29¶	Male	19	Thailand, Cambodia, Vietnam	Yes	Azithromycin	ESBL-MCRE (2)	*mcr-3.1*, $bla_{CTX-M-55}$; *mcr-3.1*, $bla_{CTX-M-55}$
5	60	Female	10	Vietnam	No	No	MCRE (2)	*mcr-1.1*; *mcr-1.1*
6	59	Female	10	Peru	Yes	Ciprofloxacin	MCRE	*mcr-1.1*
7	55	Female	8	Singapore, Cambodia	No	No	MCRE	*mcr-1.1*
8	34	Male	23	Hong Kong, Vietnam	Yes	No	MCRE	*mcr-1.1*
9	24	Female	45	Japan, Vietnam	Yes	No	MCRE	*mcr-1.1*
10	56	Male	25	Liberia	No	No	MCRE	*mcr-1.1* variant
11	74	Male	18	Peru	Yes	No	ESBL-MCRE	*mcr-1.1*, $bla_{CTX-M-55}$
12	64	Female	14	Peru	Yes	No	MCRE	*mcr-1.1*
13	66	Male	39	Vietnam, Laos, Cambodia	No	No	MCRE (2); ESBL-MCRE	*mcr-1.1*; *mcr-1.1*; *mcr-1.1*, $bla_{CTX-M-14}$
14	58	Female	11	Rwanda, Tanzania	No	No	MCRE	*mcr-1.1*
15	64	Male	30	Peru	Yes	No	ESBL-MCRE	*mcr-1.1*, $bla_{CTX-M-55}$
16	85	Female	8	Nigeria	Yes	Azithromycin	MCRE	*mcr-1.1*
17	27	Male	30	Peru	Yes	No	ESBL-MCRE	*mcr-1.1*, $bla_{CTX-M-55}$
18	76	Female	9	Peru	No	No	MCRE	*mcr-1.1*
19	55	Female	8	Peru	Yes	Azithromycin	MCRE	*mcr-1*
20	54	Male	8	Peru	Yes	Ciprofloxacin	MCRE	*mcr-1*
21	74	Female	17	Hong Kong, Vietnam, Cambodia, Thailand, Singapore	Yes	Doxycycline	CP-CRE	bla_{NDM-5}, $bla_{CTX-M-15}$
22	48	Female	9	India	Yes	No	CP-CRE	bla_{NDM-5}, $bla_{CTX-M-15}$

5% in 412 travelers acquired bacteria with mobile colistin resistance (mcr) gene (primarily community-associated)

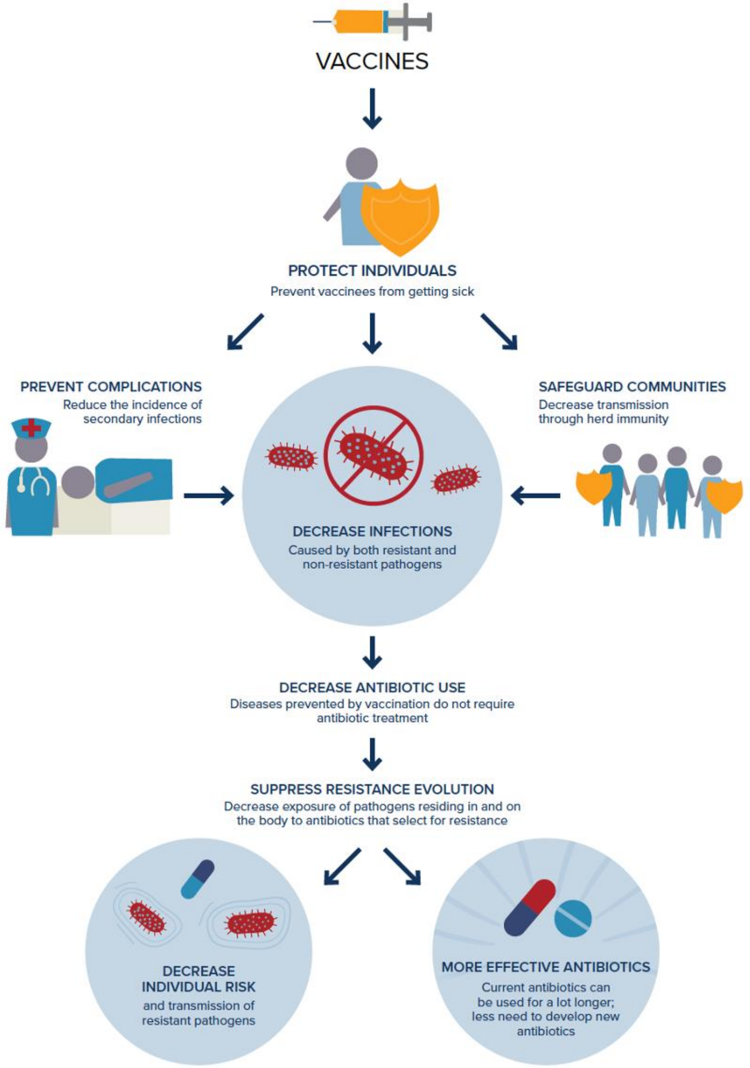
Conclusion:

- raise awareness in returning high-risk travelers, about possible AMR bacteria colonization in the weeks after travel
- effective prevention of spread basic hand hygiene

Prevention and reduction of travel-related infections due to AMR bacteria

PLoS ONE 11(7): e0159863. doi:10.1371/journal.pone.0159863

Vaccines play a role in preventing AMR



Prevention and reduction of travel-related infections due to AMR bacteria

- Safe food choices
- Good hand hygiene
- Ensure safe drinking water

→ Less enteric pathogen exposures among travelers, including AMR bacteria in food (e.g. mcr), and water (e.g. *Campylobacter* spp., *E. coli*, *Salmonella* spp., *Shigella* spp. with AMR)

- Avoid antibiotics for self-treatment without prescription

→
- Might be ineffective
- Risks of side effects
- Disruption of microbiota
- Promotion of resistant organisms

- If admitted to health care facility abroad*, choose one with IPC programme

→
- Reduce risk for pathogen transmission

*Medical tourism

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PLoS ONE 11(7): e0159863. doi:10.1371/journal.pone.0159863

Posttravel considerations

- Be aware of the risk to international travelers for acquiring AMR organisms
- Travel history

→identify effective treatments for infections

→ensure infection control interventions to prevent spread of AMR (e.g. Carbapenem-resistant enterobacterales (CRE), Candida auris)

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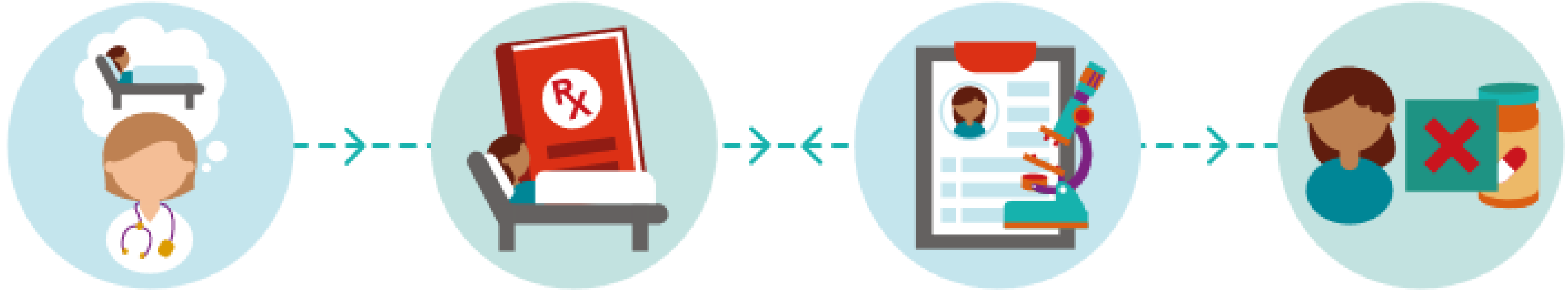
Pereira RT, Malone CM, Flaherty GT. Aesthetic journeys: a review of cosmetic surgery tourism. J Travel Med. 2018 Jun 1;25(1)

Care of individuals who have become ill during travel or who are living “abroad”

Four moments of antibiotic decision making

Antibiotic treatment



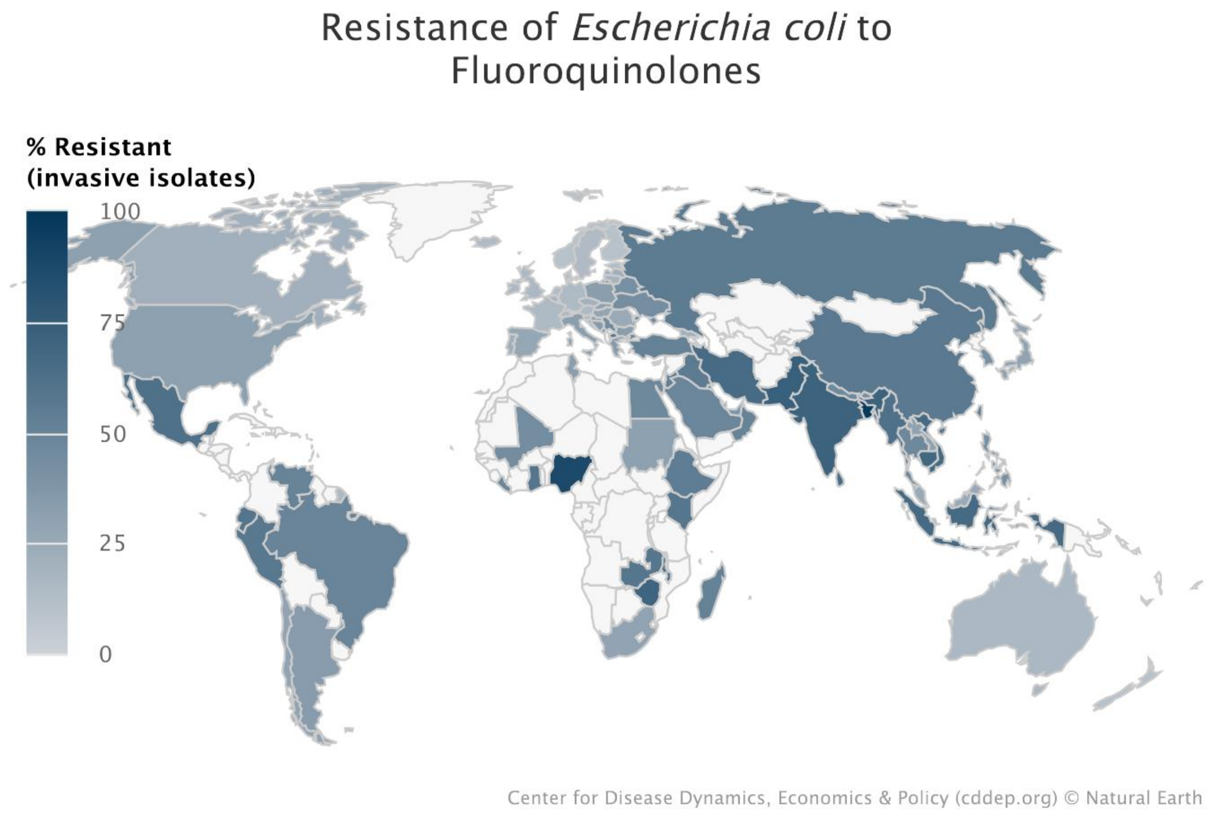
Indication
Bacterial infection?
Viral infection?
Colonization?
Inflammation?
Microbiology testing?

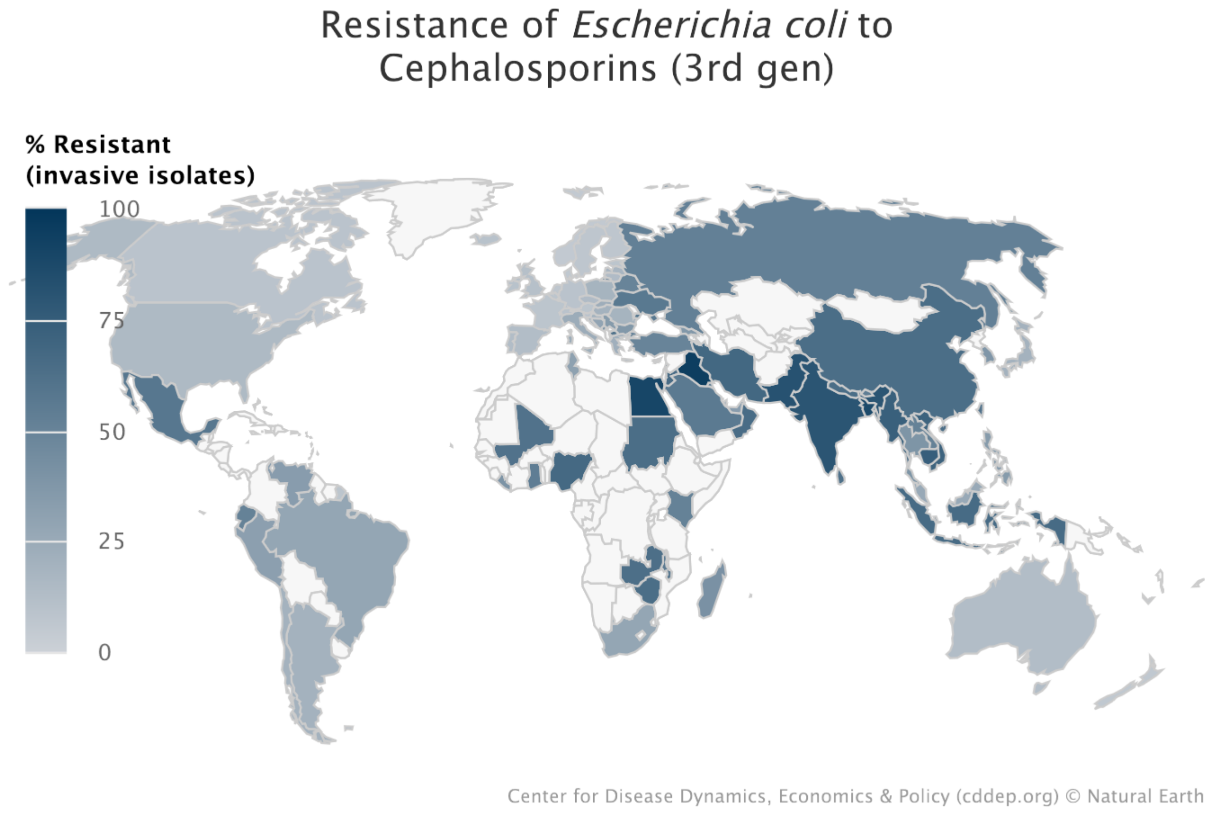
Prescribe
Probable pathogen?
Empirical treatment?
Severe disease?
Comorbidities?
Allergy?

Review
Right indication?
Right antibiotic(s)?
IV-to-oral switch?
Microbiology results?

Stop
Treatment duration?

Antibiotic Resistance, data visualization tools





Further resources: https://epi-net.eu/
CDC Yellow Book 2024

Thank you for your attention!

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