GLOBAL AMR..U?
Thinking the unthinkable

(Improving AWaRe-ness)

Professor Mike Sharland
St George's University London

Improving antibiotic use in humans

- Where we are with policy and politics..
- What's been going on meanwhile..
- What could be done..maybe..
- Why this is going to be even harder than we thought..

GLOBAL ACTION PLAN
ON ANTIMICROBIAL RESISTANCE

World Health Organization

Objective 1:
Improve awareness and understanding of antimicrobial resistance through effective communication, education and training

Objective 2:
Strengthen the knowledge and evidence base through surveillance and research

Objective 3:
Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

Objective 4:
Optimize the use of antimicrobial medicines in human and animal health

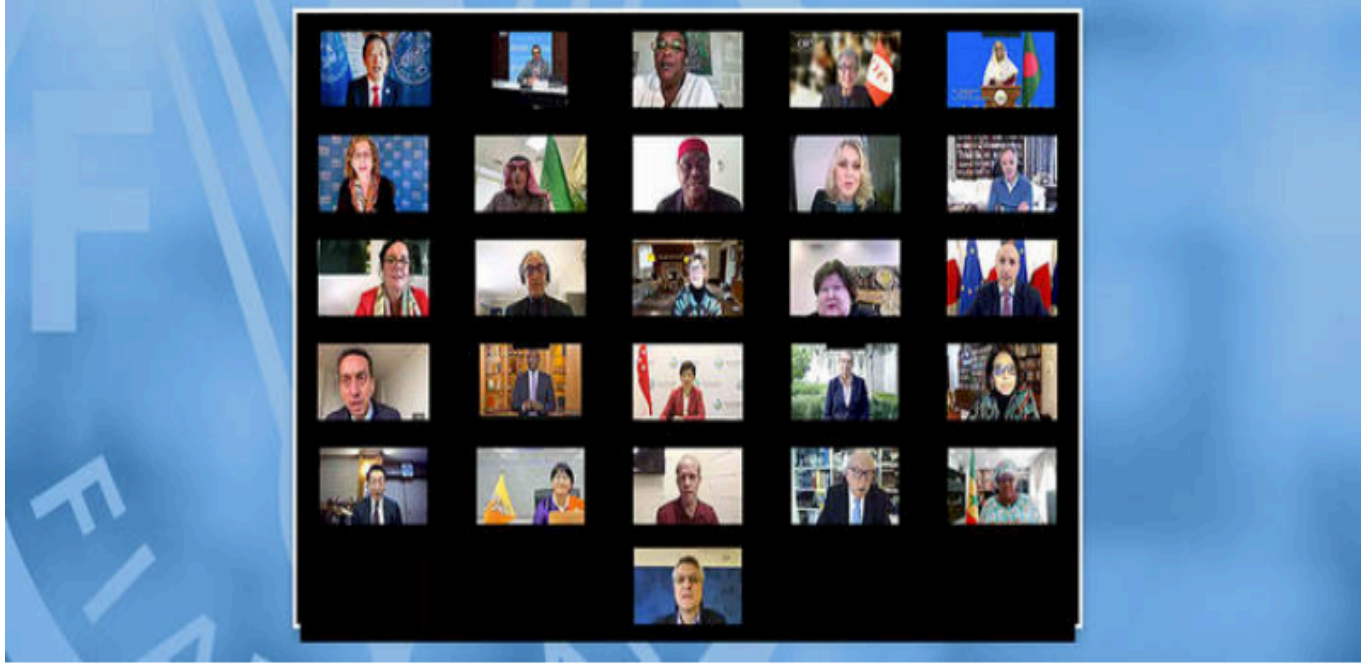
Objective 5:
Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

NO TIME TO WAIT:
SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS

REPORT TO THE SECRETARY-GENERAL OF THE UNITED NATIONS

APRIL 2019

IACG | Interagency Coordination Group on Antimicrobial Resistance



Composite photo from the first meeting of the One Health Global Leaders Group on Antimicrobial Resistance (AMR).

26 January 2021, Rome - Prominent global leaders in science, industry and government joined today a United Nations effort to fight antimicrobial resistance, described as a slow-moving pandemic by the Director-General of the Food and Agriculture Organization of the United Nations (FAO), QU Dongyu.

The *One Health Global Leaders Group on Antimicrobial Resistance (AMR)*, co-chaired by Mia Amor Mottley, Prime Minister of Barbados and Sheikh Hasina, Prime Minister of Bangladesh, held its first meeting, bringing together as members about 20 government ministers, prominent scientists, and leaders of foundations and corporations from around the world. The full list of members of the One Health Global Leaders Group is available here.

Launched in November 2020 by FAO, the World Organisation for Animal Health (OIE) and the World Health Organization (WHO), who will now also be joined by the UN Environment Programme (UNEP), the Group aims to catalyze global attention and efforts to combat antimicrobial resistance across all sectors and ensure the availability of important medicines for the future.

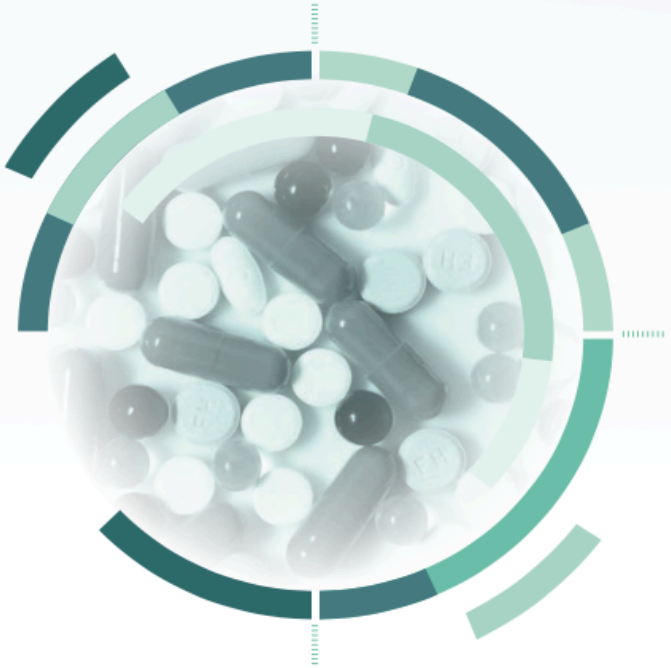
Supported by the Independent Panel on Evidence for Action Against Antimicrobial Resistance (IPEAAAG)

Food and Agriculture Organization of the United Nations

WORLD ORGANISATION FOR ANIMAL HEALTH

World Health Organization

International instruments on the use of antimicrobials across the human, animal and plant sectors



Responsible and prudent use

- WHO *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses* ('the Blue Pocketbook') (2nd edition) (2010)
- FIP/WHO *Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services* (2011)
- WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (2014)
- WHO *Revised WHO classification and treatment of childhood pneumonia at health facilities* (2014)
- WHO *Guidelines for treatment of drug-susceptible tuberculosis and patient care* (2017)
- WHO *AWaRe classification of antibiotics for evaluation and monitoring of use* (2019)

MONITORING AND EVALUATION OF THE GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

Framework and recommended indicators

ANNEX 3. Methodology sheets for recommended indicators

Food and Agriculture Organization of the United Nations

WORLD ORGANISATION FOR ANIMAL HEALTH

World Health Organization

Outcome 4: Optimized use of antimicrobials in human and animal health, with growth promotion phased out for animal use

REFERENCE SHEET	
Indicator name and number	**4.1 a & b: Use of antimicrobials in humans** a: Total human consumption of antibiotics for systemic use (ATC J01) in Defined Daily Doses (DDD) per 1000 population (or inhabitants) per day b: The proportion of ACCESS antibiotics for systemic use, relative to total antibiotic consumption in DDD
DESCRIPTION	
Definition/s	Total human consumption of antibiotics for systemic use
Disaggregation	The proportion of ACCESS antibiotics for systemic use, relative to total antibiotic consumption in DDD. Distinction between Access, Watch and Reserve antibiotics (AwARe categorization) can be used as defined by the 2017 WHO Essential Medicine List (see references). Differentiation between level of care (community vs hospital) and between sector (public vs private). Sub-national data (by geographical area, e.g. disaggregated by state, region or province or by socio-economics stratus) are useful to study the heterogeneity of consumption within the country.
DATA COLLECTION SOURCES	
Data Sources (data collected by FAO/WHO/ OIE)	Import and domestic production. Distribution (wholesalers, central medical stores etc.) Please refer to the manual "WHO Program on Surveillance of Antimicrobial Consumption" for further information on data sources.
Country Level Data Sources, if applicable	Hospitals, pharmacies, insurance data
Secondary data sources, if applicable	
DATA COLLECTION	

PLOS MEDICINE

RESEARCH ARTICLE

Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map

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Author summary

Why was this study done?

- Despite global commitments to reduce antimicrobial resistance and protect the effectiveness of antimicrobials, most countries have not yet started implementing government policies to reduce their overuse and misuse of antimicrobials.
- To the best of our knowledge, no evidence syntheses have attempted to identify the policy options available to government policy makers to tackle antimicrobial resistance by reducing antimicrobial use in humans.

What did the researchers do and find?

- We searched 7 academic databases to identify impact evaluations of government policy interventions aiming to reduce human antimicrobial use that were published in any language before January 28, 2019.
- We found 69 studies that evaluated government policy interventions to reduce antimicrobial use around the world. From these, we were able to describe 17 different types of policies that governments have used to tackle this major driver of antimicrobial resistance in humans.
- Commonly used policy strategies included public awareness campaigns and antimicrobial guidelines; however, other policy strategies focused on vaccination, stewardship, and changing regulations around prescribing and reimbursement.
- We found 4 randomized controlled trials and 35 studies using rigorous quasi-experimental designs. The remaining 30 studies used uncontrolled and descriptive study designs.

What do these findings mean?

- Our systematic evidence map suggests that governments have a variety of policy options at their disposal to respond to the growing threat of antimicrobial resistance.
- Unfortunately, most existing policy options have not been rigorously evaluated, which limits their usefulness in planning future policy interventions.
- To avoid wasting public resources, governments should ensure that future antimicrobial resistance policy interventions are evaluated using rigorous study designs, and that study results are published.

PROGRESS IN OPTIMISING ANTIBIOTIC USE

HEALTH AND SCIENCE

New $1 billion fund aims to steer antibiotic companies in a tough market

PUBLISHED THU, JUL 9 2020•9:15 AM EDT | UPDATED THU, JUL 9 2020•1:12 PM EDT

REUTERS

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KEY POINTS

- A new $1 billion fund backed by 20 drugmakers is aiming to bolster struggling antibiotic companies and sustain a pipeline for new treatments, an industry group said.
- Antibiotic makers have struggled with anemic investment and bankruptcies as fears of drug-resistant microbes force hospitals to adopt a more conservative approach toward such treatments.
- The new fund, led by the International Federation of Pharmaceutical Manufacturers & Associations, has raised nearly $1 billion so far and aims to help shore up

Non-profits fill gaps in the broken market for antibiotics

Promising treatments in pipeline despite lack of financial incentives for pharma industry

Research is producing new antibiotics using technologies ranging from conventional chemistry to biological approaches that enlist other microbes or viruses to attack harmful bacteria

New antibiotics; clinical pipeline

- 11 new antibiotics licenced by EMA or FDA in last 5 years (9/11 existing classes with well established resistance mechanisms)
- Now around 25 antibiotics in Phase 1/2/3 active against WHO Priority Pathogens
- Around half are Beta Lactam/Beta Lactam Inhibitors - very few are oral – very few focussed on ESBL's.
- Very few have innovative modes of action against Multi Drug Resistant Gram Negatives
- Only 3 have activity against Metallo Beta Lactams - commonest genotype causing carbapenem resistance in LMICs

https://www.nature.com/articles/s41579-019-0288-0 - WHO Antibiotic Pipeline

New antibiotics; pre-clinical pipeline

- Wider and more innovative portfolio of around 500 antibacterial agents (traditional/non-traditional) but..
- Shift to very limited spectrum agents..half targeting single pathogen – will require expensive companion diagnostics
- Only around 50 target MDR Gram Negative bacteria, of which the great majority target *Acinetobacter/Pseudomonas* (Hospital/Ventilator Acquired Pneumonia – ICU).
- <5% focus on *Klebsiella spp or E coli.*

2017 WHO EML Expert Committee developed the AWaRe classification of Essential Antibiotics on the EML/c as Access/ Watch/Reserve (Traffic light)

ACCESS group: narrow spectrum affordable antibiotics widely available.

WaTCH group: broader spectrum antibiotics used for specific and limited indications due to higher resistance and toxicity potential.

ReSERVE group: last resort antibiotics that should be used only when other antibiotics have failed or for treatment of multi-resistant bacteria.

"EML - WHAT TO USE "

Access

- Amikacin
- Amoxicillin
- Ampicillin
- Amoxicillin–clavulanic acid
- Benzathine benzylpenicillin
- Benzylpencillin
- Cefazolin
- Chloramphenicol
- Clindamycin
- Cloxacillin
- Doxycycline
- Gentamicin
- Metronidazole
- Nitrofurantoin
- Phenoxymethyl pencillin
- Procaine pencillin
- Spectinomycin
- Sulfamethoxazole–trimethoprim

Watch

- Azithromycin
- Cefixime
- Ceftriaxone
- Cefotaxime
- Ceftazidime*
- Cefuroxime
- Vancomycin (intravenous* and oral)
- Ciprofloxacin
- Clarithromycin
- Meropenem*
- Piperacillin–tazobactam

Reserve*

- Fosfomycin (intravenous)
- Linezolid
- Colistin
- Polymyxin B
- Ceftazidime–avibactam
- Meropenem–vaborbactam
- Plazomicin

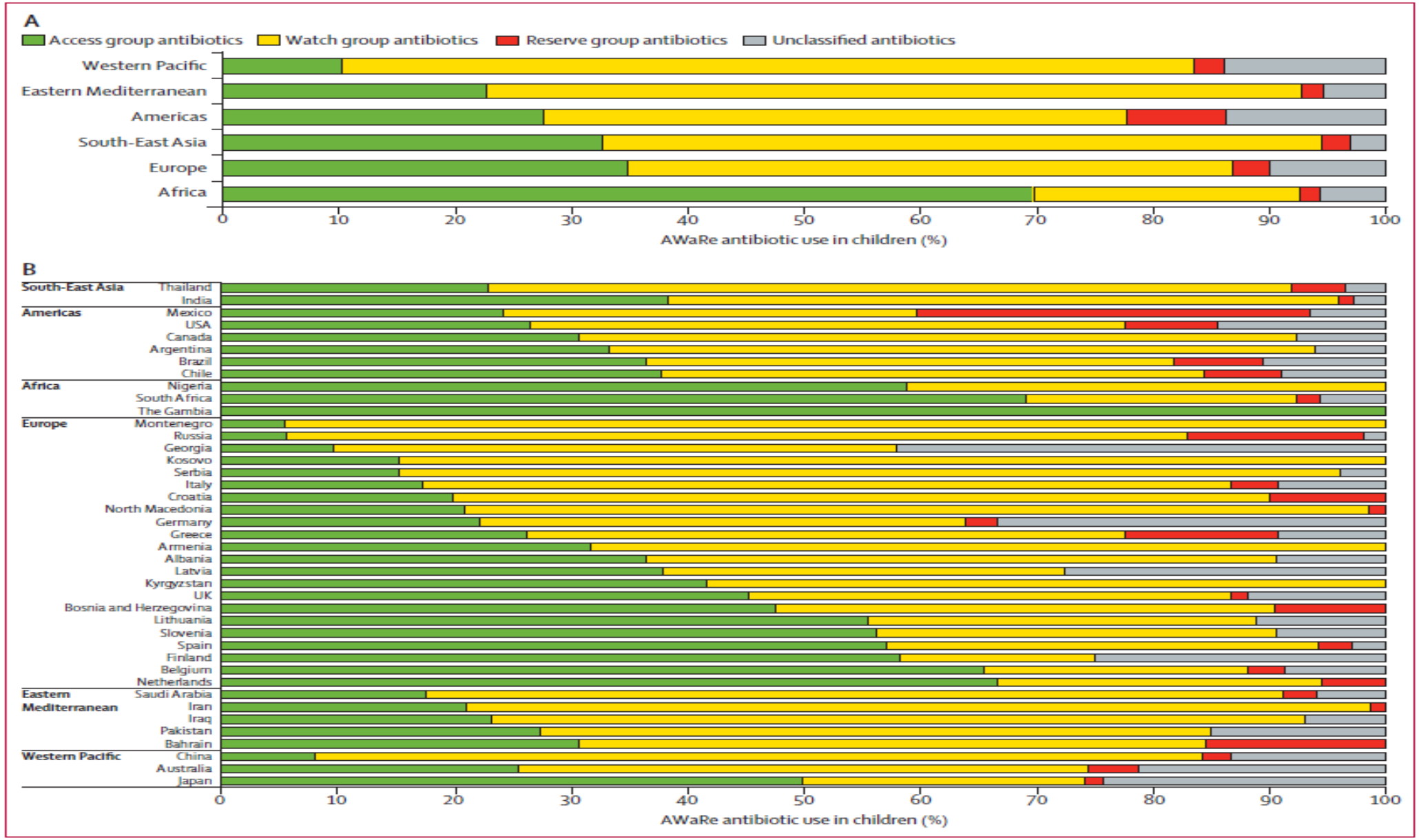
- **2019 EML** committee expanded the AWaRe classification to over **200 antibiotics (around 35 on EML)**
- A new category of Not Recommended was added – mainly inappropriate Fixed-Dose Combinations of multiple broad-spectrum antibiotics.
- WHO General Programme of Work (GPW) now includes a Target indicator that the proportion of Access antibiotics should be more than **60%** of total antibiotic use at country level
- https://adoptaware.org/

Sharland et al. Lancet Infection Disease 2019

Major data limitations - LMIC

- WHO GLASS Consumption data
- Hospital procurement data - only link to indication through Point Prevalence Survey's
- Community data – import/wholesale data, many source of bias..no link to indication.
- Only broad comparison of proportions eg AWaRe possible.
- Innovative with data..eg formulation as proxy for use..courses..to assist local/national groups to understand their own patterns of use.
- Many, many, many caveats with interpretation/bias..(many)

Hospital AWaRe AB in LRTI in children – GARPEC Point Prevalence Survey



Hsia Y et al LGH 2019

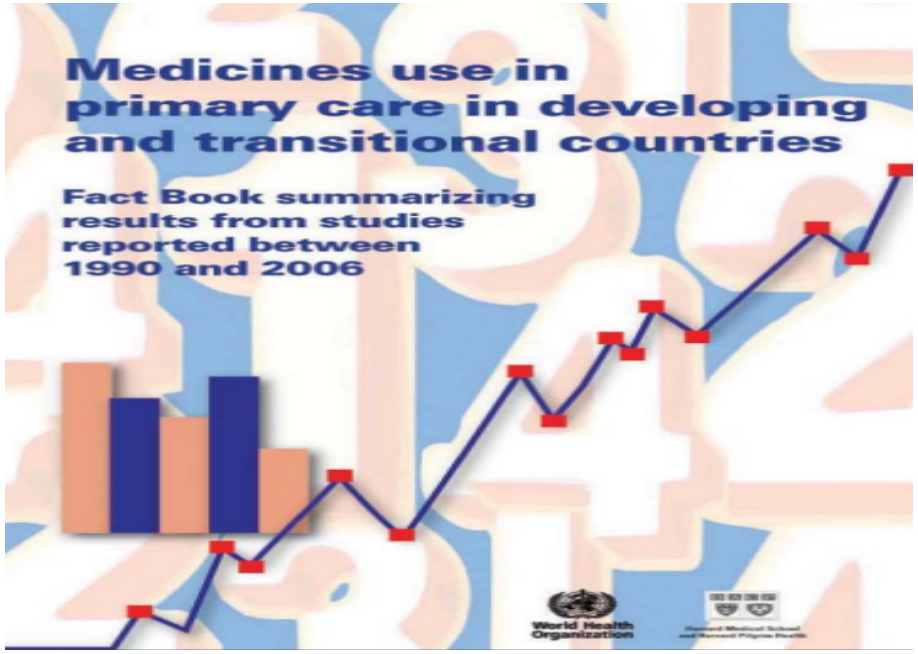


Figure 4.4: Rates of adherence to clinical guidelines over time, by World Bank region

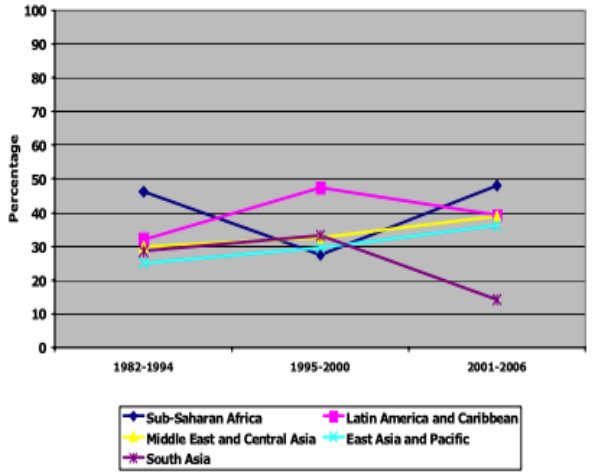
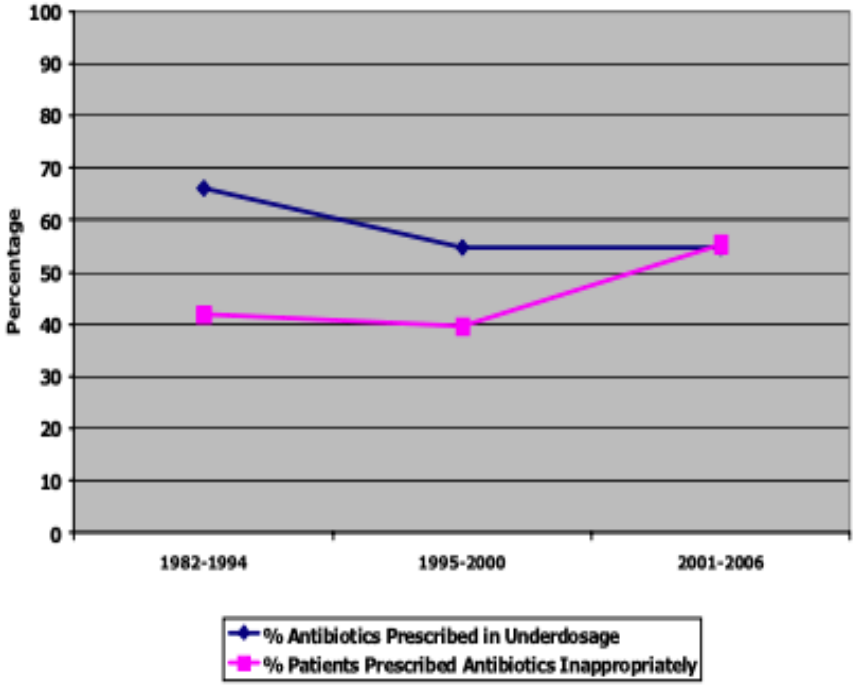


Figure 9.1: Inappropriate prescribing of antibiotics over time



Key Points:

- Results suggest a large, persistent and growing problem of inappropriate use of antibiotics.
- The percentage of patients prescribed antibiotics inappropriately increased to over 50% in studies conducted between 2001 and 2006, up from 40% in earlier studies.
- The percentage of antibiotics prescribed in underdosage remained over 50% in all time periods.

Trends in AWaRe use - marked increase in LMIC use of Watch antibiotics

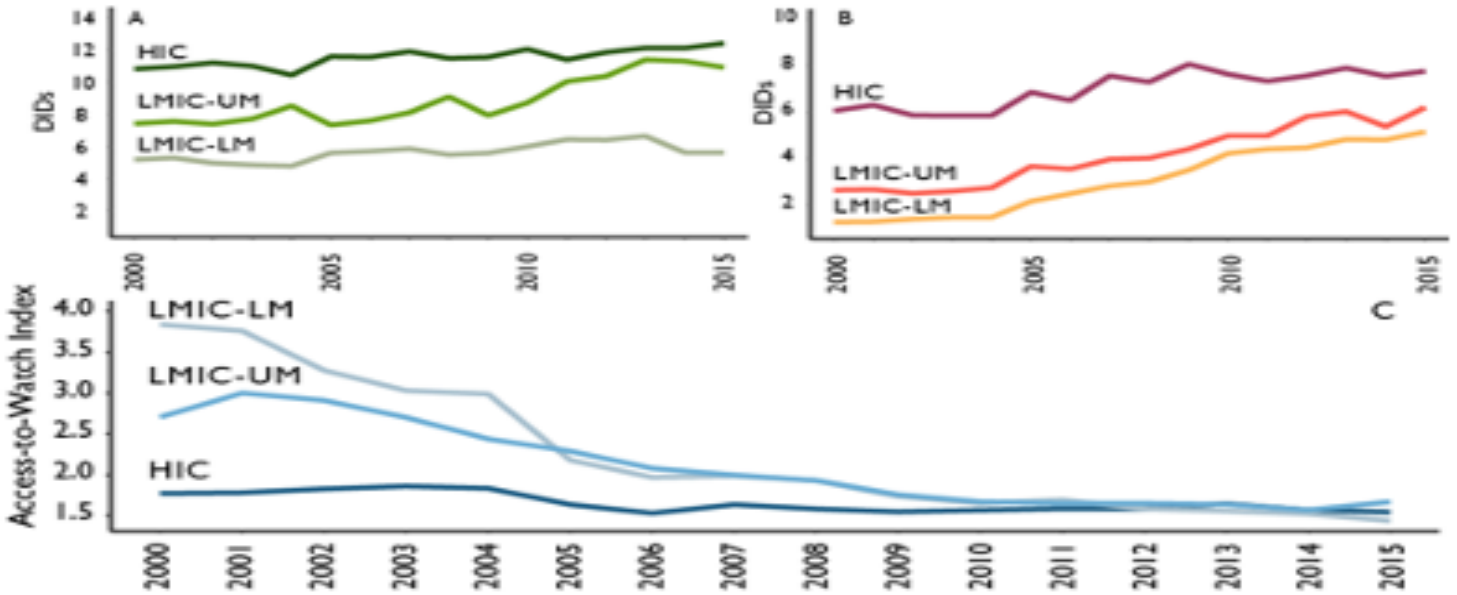


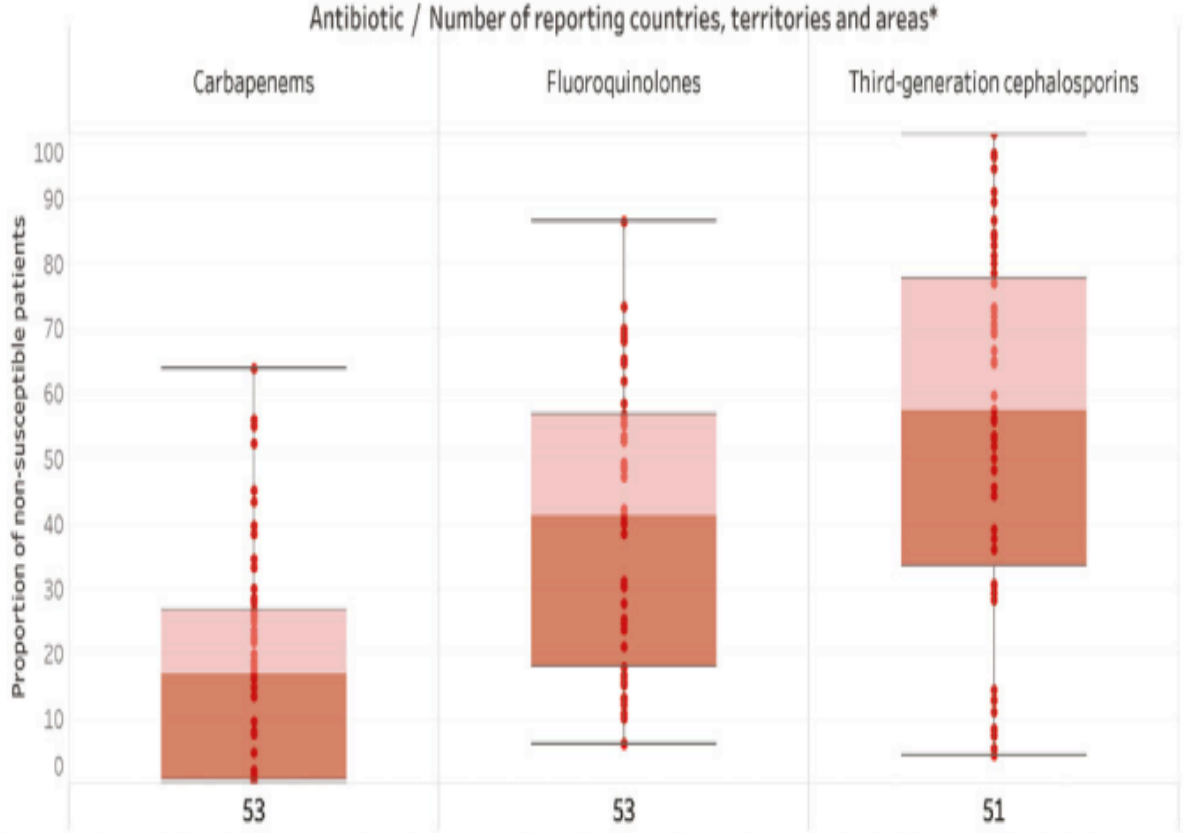
Figure 2. Relative and absolute consumption of Access and Watch antibiotics, 2000-2015
Median consumption in high-income countries (HICs), upper-middle low- and middle-income countries (LMIC-UM), and lower-middle low- and middle-income countries (LMIC-LM) expressed in defined daily doses (DDDs) per 1,000 inhabitants per day (DIDs) for (A) Access and (B) Watch antibiotics. The Access-to-Watch Index (C), which measures the ratio of DIDs of Access to Watch antibiotics, saw large declines in both LMIC-UM and LMIC-LM, which reflects the relatively larger increase in use of Watch antibiotics compared to Access antibiotics. Source: IQVIA MIDAS, 2000–2015, IQVIA Inc. All rights reserved.

Klein EY LID 2020

2021 - WHO EML Antibiotic Handbook

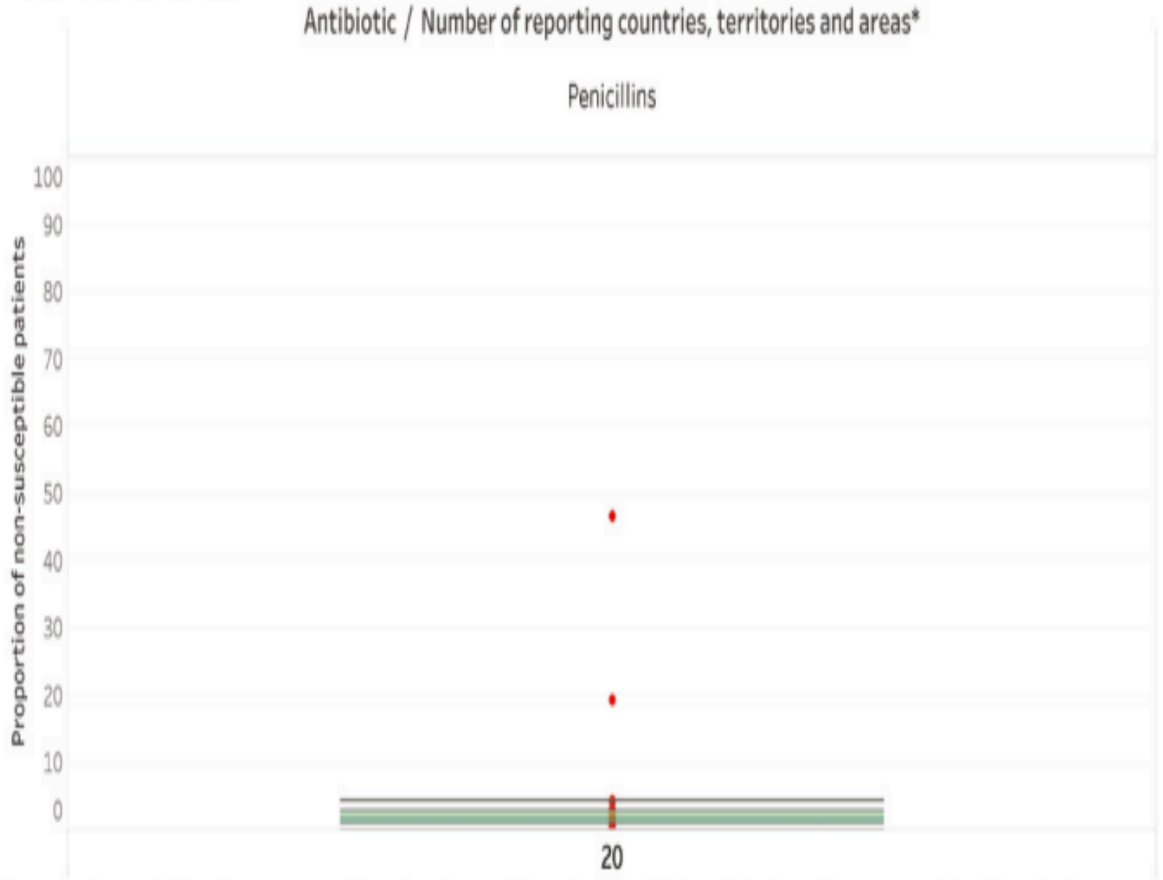
- To provide simple guidance on "HOW TO USE the antibiotics on the EML to manage common infections
- Guidance for 36 infections; a **strong focus on primary care** also facility/hospital setting, children and adults.
    - acute bacterial infections (Not TB/viral/fungal/parasitic infections)
  - **Recommendations on empiric antibiotic treatment** (i.e. presumptive diagnosis not requiring any laboratory diagnostic)
  - Includes guidance on making the clinical Diagnosis, the Decision if antibiotic needed, the choice of Drug, Dose, Duration
  - Short summaries of key features of microbiology, epidemiology, clinical presentation, diagnostics (in collaboration with EDL), prevention
  - **Target audience: all health professionals giving antibiotics**

Blood - K. Pneumoniae



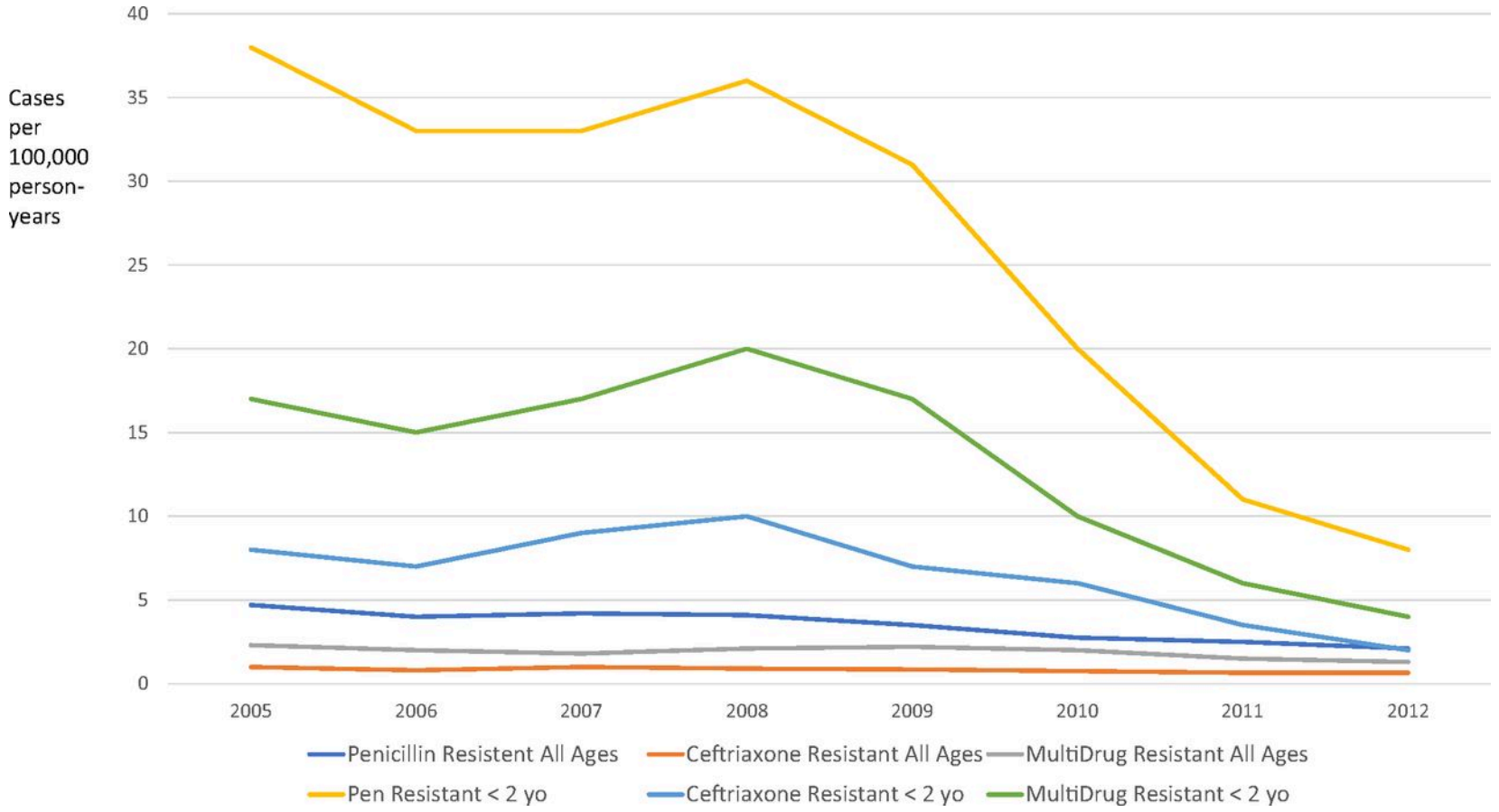
*Rates are shown only if results were reported for > 10 patients and for pathogen–antibiotic combinations with > 10 AST results and < 30% unknown results. Single antibiotic results are shown only if data were submitted by at least 50% of the countries reporting on the specimen-pathogen combination.

Blood - S. pneumoniae



*Rates are shown only if results were reported for > 10 patients and for pathogen–antibiotic combinations with > 10 AST results and < 30% unknown results. Single antibiotic results are shown only if data were submitted by at least 50% of the countries reporting on the specimen-pathogen combination.

Trends in invasive pneumococcal disease in South Africa pre- and post-PCV introduction.



Keith P. Klugman, and Steven Black PNAS 2018;115:51:12896-12901

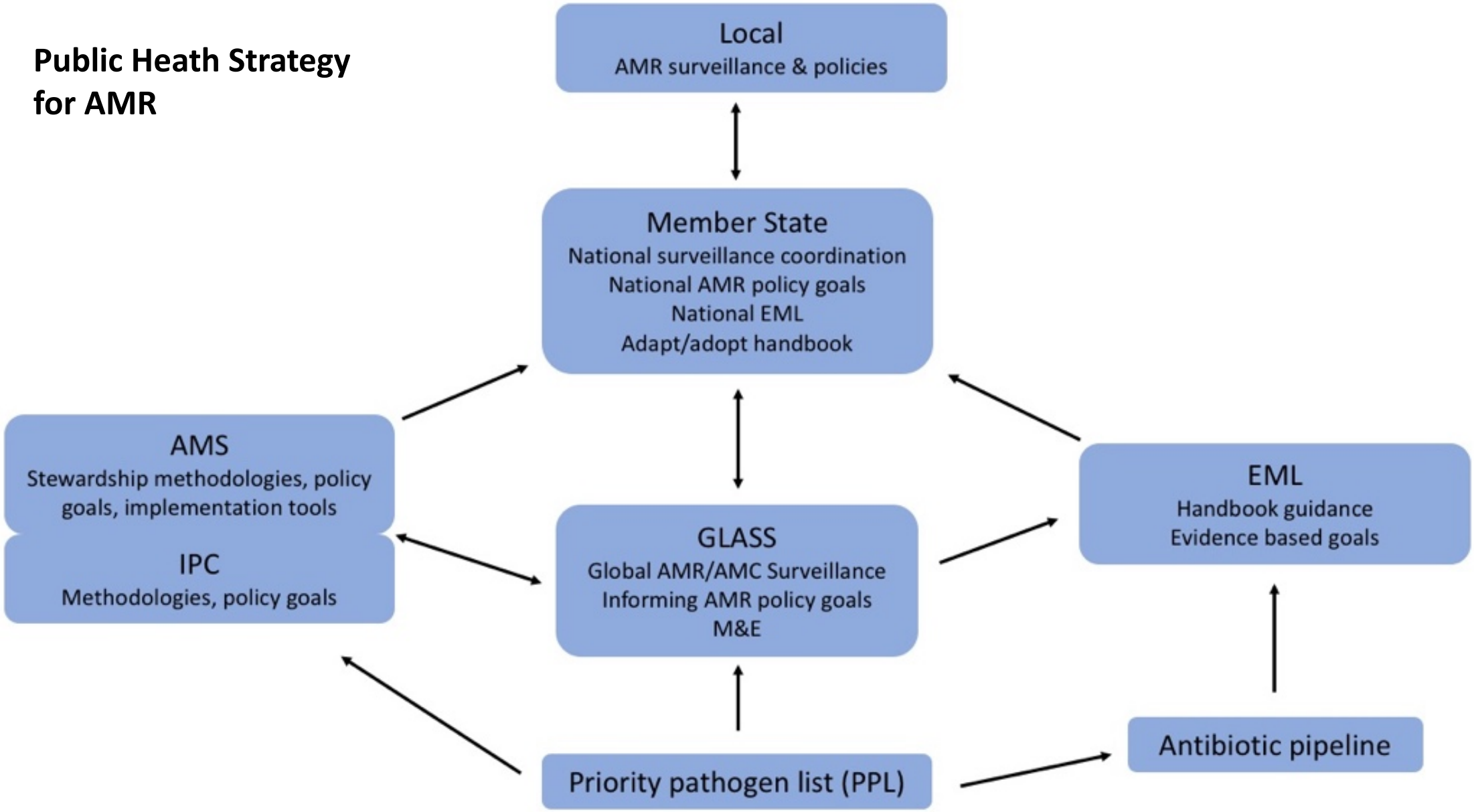
Improving Guidance

- Complex issues of adapting guidance for varying patterns of resistance locally/nationally
- Most microbiology surveillance data aggregate, with limited clinical information, underlying disease, severity, pre-treatment, outcome
- Will need to develop global clinical AMR surveillance, efficacy studies, sentinel sites (malaria..)
- Need to improve models of “antibiotic modifiable” mortality and morbidity
- In HICs around a quarter of Blood Stream Infection is Hospital Acquired..in LMICs?
- Strategic public health focussed trials with clinical, toxicity, selection of resistance/impact on microbiome outcomes.

So, what can be done..

- Over 90% of LMIC antibiotic use is oral used in the primary healthcare setting..(similar for HICs)
- The great majority of primary care prescribing can safely be Access antibiotics
- The great majority of minor infections in primary care can safely be managed without an antibiotic
- Now possible to develop and implement more formal **policy goals and clear targets** focusing on safely reducing Total and oral Watch antibiotic use.
- Model “ideal” patterns of community and hospital use, risk adjusted for disease burden and varying levels of resistance
- Develop wide range of AWaRe based tools for optimal implementation of policy goals and monitoring outcomes (including potential adverse effects on vulnerable populations)
- Conduct LMIC focussed global trials to define and test policy strategies, their safety and impact on resistance to build a more convincing evidence base for national policy leadership

Public Heath Strategy for AMR



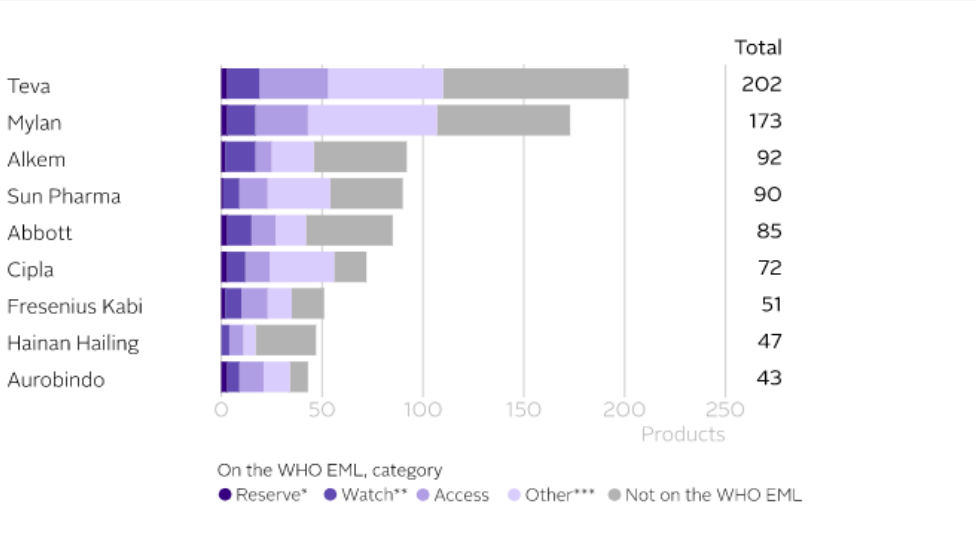
Global antibiotic markets – not so easy..

- Global antibiotic market $40-50 billion/year (5%/year growth)
- Asia Pacific 40% of market (higher growth)
- 90% oral generic

Which generic medicine manufacturers produce the most products?

Generic medicine manufacturers have larger portfolios on average, and a greater proportion of Watch and Reserve antibiotics than other company groups. The generic medicine manufacturers evaluated in the Benchmark have just over 850 antibacterial and/or antifungal medicine and vaccine products on the market. The largest producer of these products is Teva, followed by Mylan.

Generic medicine manufacturers

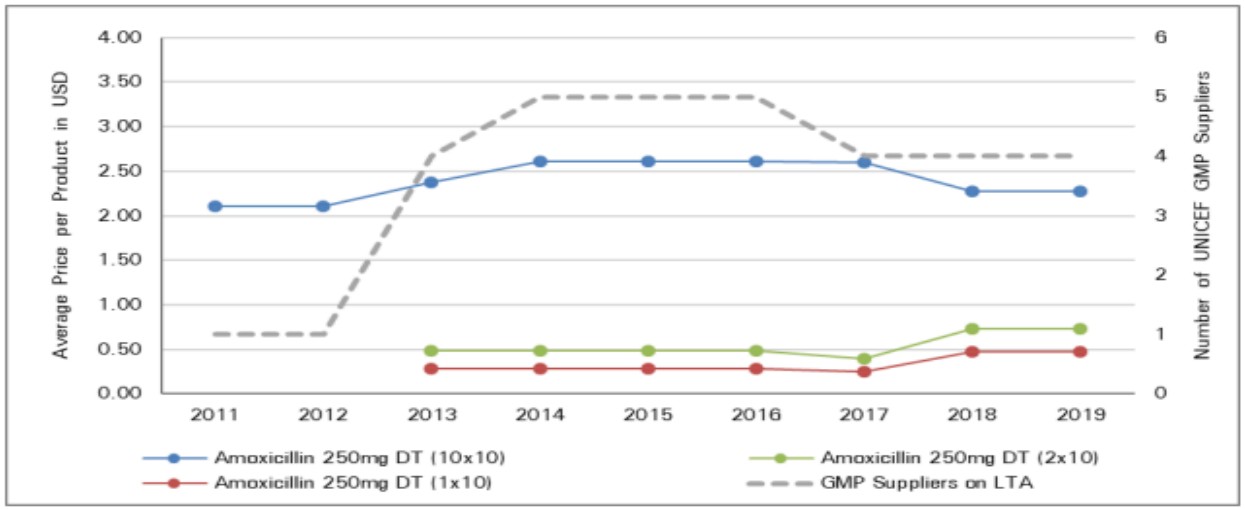


Access to Medicine Federation AMR Benchmark 2020

3.3 Pricing

Figure 1 describes the average price trend per amoxicillin 250mg products UNICEF has procured since 2011. UNICEF increased the number of good manufacturing practice (GMP) approved suppliers to increase product availability to meet growing demand. Price increases reflect UNICEF including European suppliers, which have higher prices as production costs are higher, compared to India (Figure 2).

Figure 2 Amoxicillin 250mg DT Average Price per Product 2011-2019



Source: UNICEF Supply Division

UNICEF's indicative price per treatment course for a child under-one year of age is USD 0.22, and USD 0.44 for a child over one year age. [16,17] The different packaging options available through UNICEF have different price and cost implications, and choices to select the appropriate option depend on what best suits end-users, their context, and environment (Table 4).

Amoxicillin DTs UNICEF 2018

So how to think the unthinkable..

- The great majority of acute bacterial infections in primary care can be treated effectively and safely with our current narrow spectrum Access antibiotics – the primary problem for 90% of global antibiotic prescribing is not antimicrobial resistance but antimicrobial use.
- The novel antibiotic clinical and pre-clinical antibiotic pipeline is likely not closely aligned with the global unmet public health need (which is not clearly defined)
- Insufficient attention is being given to healthcare facilities as drivers of nosocomial MDR infections.
- There is a clear lack of human AMR policy goals and detailed targets, without which impedes progress in tackling the serious threat of AMR on global health.

MANY THANKS

- **ALL MEMBERS OF EML SECRETARIAT AND ANTIBIOTIC WG (Prof Nicola Magrini).**
- **GLASS :** participated in meetings and exchanged ideas on how AMR surveillance data could be used (including for future updates)
- **AMR/AMS group:** participated in meetings and exchanged ideas for possible future implementation of the Handbook and linkage with Toolkit.
- **NICE:** assisted meetings based on their summaries of the evidence (particularly on symptomatic care)
- **McMaster University** (WHO Collaborating Center): reviewed the evidence for the EML application, updated the reviews and conducted new reviews.
- **SGUL team and all collaborators**