AMR and AMS

Containing resistance through good stewardship

Heather Finlayson
Paediatric Infectious diseases Tygerberg Hospital
Finlayson@sun.ac.za

Agenda

- The Burden of AMR
- What is stewardship
- AMS approaches
- Priorities in LMIC

Misuse

Treat and prevent infection

Improve quality of life

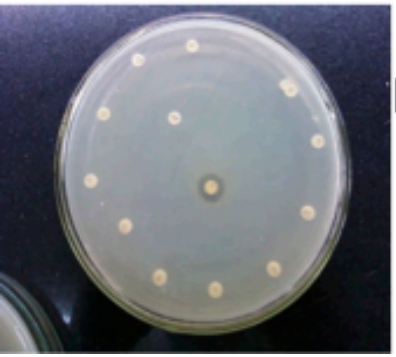
Antibiotics

Risk of toxicity and adverse reaction

Alters the microbiome

Increases healthcare Costs

Drives resistance



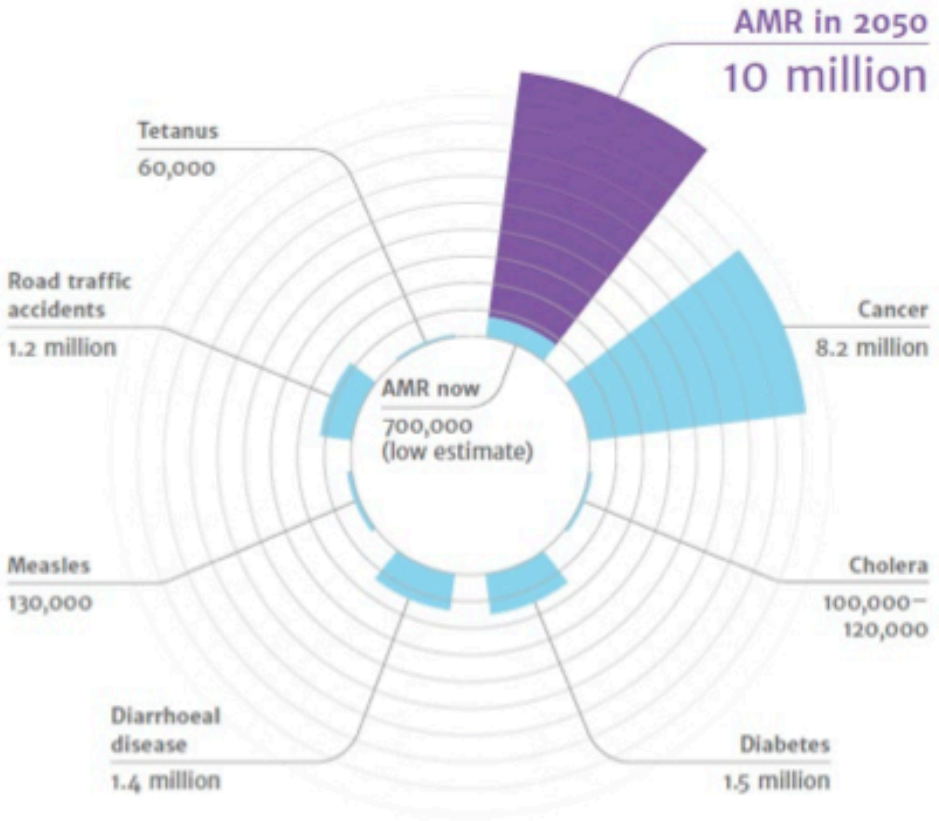
Use

Antimicrobial resistance: WHO Key Facts

- Antimicrobial resistance (AMR) is a global health and development threat. It requires urgent multisectoral action in order to achieve the Sustainable Development Goals (SDGs).
- WHO has declared that **AMR is one of the top 10 global public health threats** facing humanity.
- **Misuse and overuse of antimicrobials are the main drivers** in the development of drug-resistant pathogens.
- Lack of clean water and sanitation and **inadequate infection prevention and control promotes the spread** of microbes, some of which can be resistant to antimicrobial treatment.
- The **cost of AMR to the economy is significant.** In addition to death and disability, prolonged illness results in longer hospital stays, the need for more expensive medicines and financial challenges for those impacted.
- Without effective antimicrobials, the **success of modern medicine in treating infections**, including during major surgery and cancer chemotherapy, **would be at increased risk**.

https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

Deaths Attributable to AMR everv vear



Tackling drug-resistant infections globally: final report and recommendations

19 MAY 2016

Jim O'Neill

PUBLISHER

Government of the United Kingdom

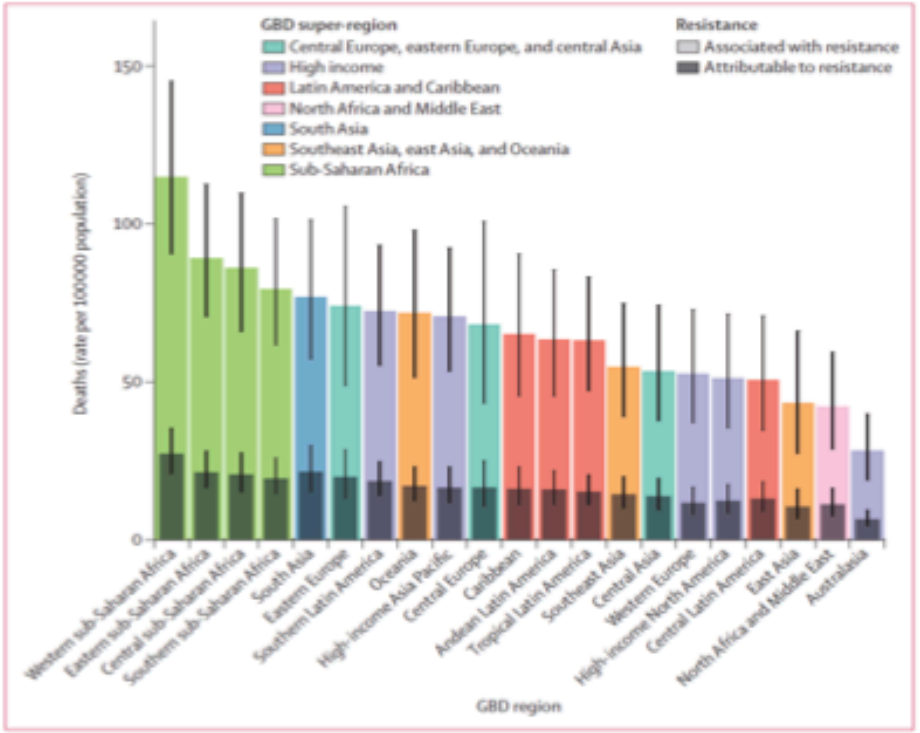
Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

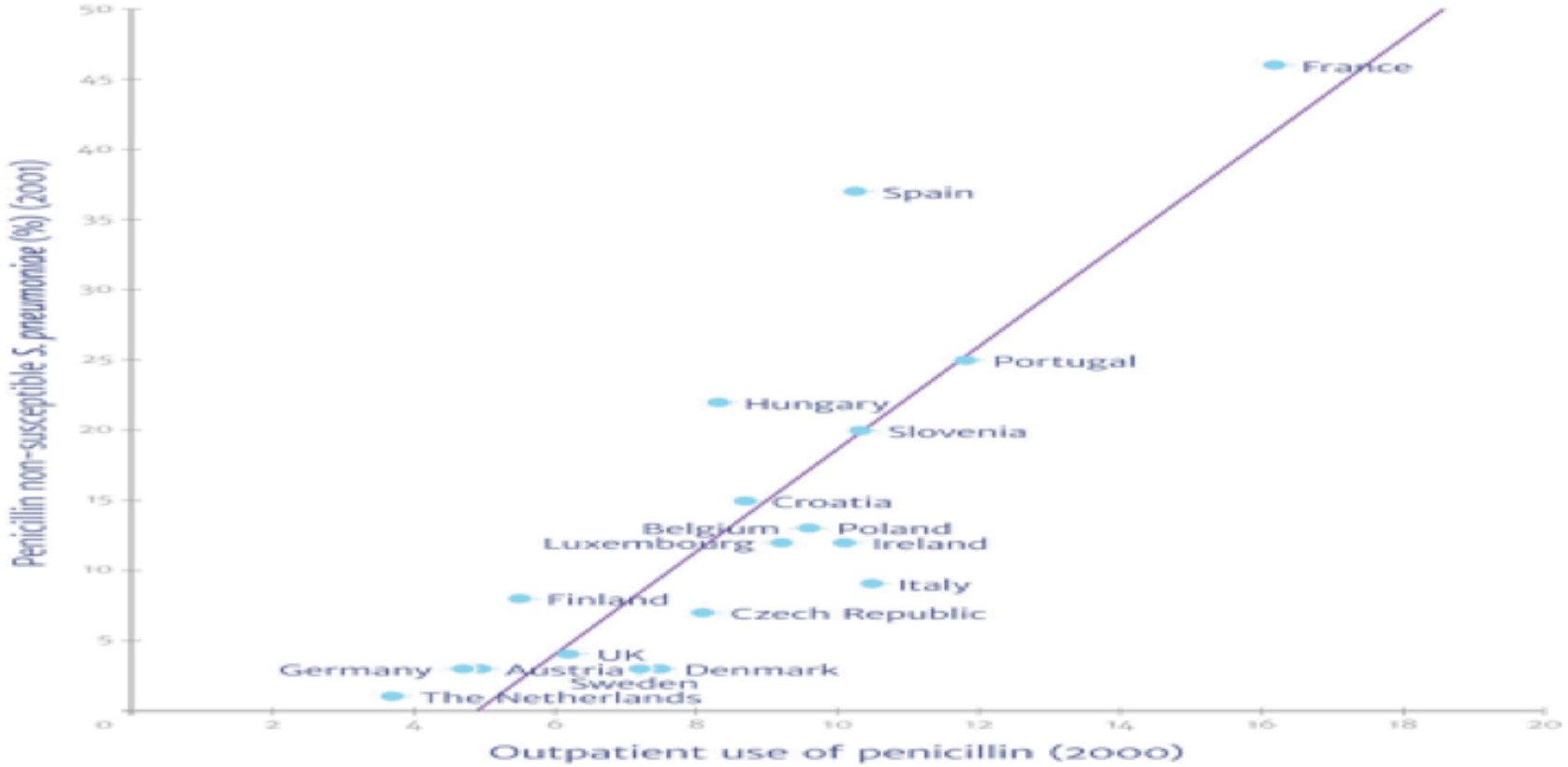
Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators*

- 4.95 (3.62-6.57) million deaths associated with bacterial AMR
- 1.27 million deaths attributable bacterial AMR
- Western SS Africa 27.3 deaths per 100 000
- LRTI > 1.5 million deaths (largest burden)
- Top 6:
  - *E.coli*
  - *S. Aureus*
  - *K. Pneumoniae*
  - *S. Pneumoniae*
  - *A. baumannii*
  - *P. Aeruginosa*



THERE IS A HIGH CORRELATION BETWEEN ANTIBIOTIC USE AND RESISTANCE



Source: Goossens H, Ferech M, Vander Stichele R, et al. *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet 2005; 365(9459): 579–87.

Review on Antimicrobial Resistance

Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study

Annie J Browne, Michael G Chipeta, Georgina Haines-Woodhouse, Emmanuelle P A Kumaran, Bahar H Kashef Hamadani, Sabra Zaraa, Nathaniel J Henry, Aniruddha Deshpande, Robert C Reiner Jr, Nicholas P J Day, Alan D Lopez, Susanna Dunachie, Catrin E Moore, Andy Stergachis, Simon I Hay, Christiane Dolecek

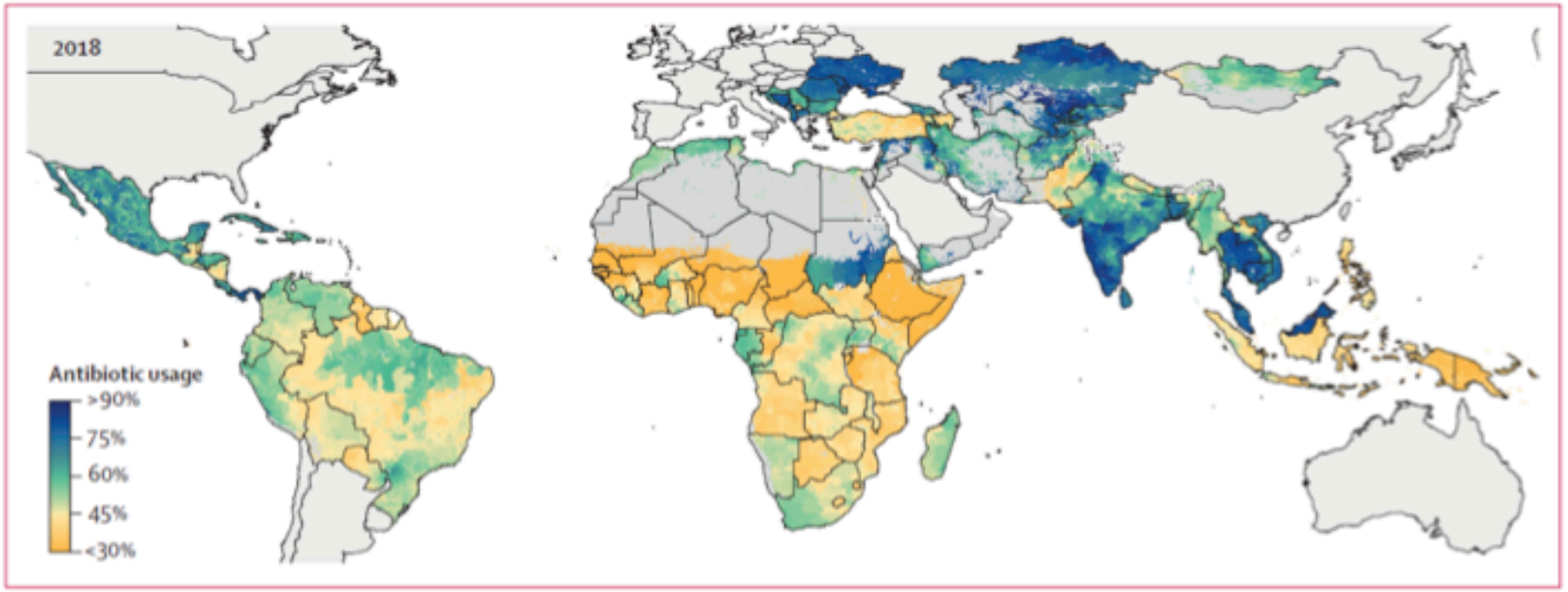


Figure 1: The percentage of children (aged <5 years) with symptoms of lower respiratory tract infections with caregiver-reported antibiotic usage in low-income and middle-income countries, 2018
Modelled estimates are shown by level two administrative divisions. High-income countries and pixels (1×1 km) with populations of less than ten people are shown in grey.

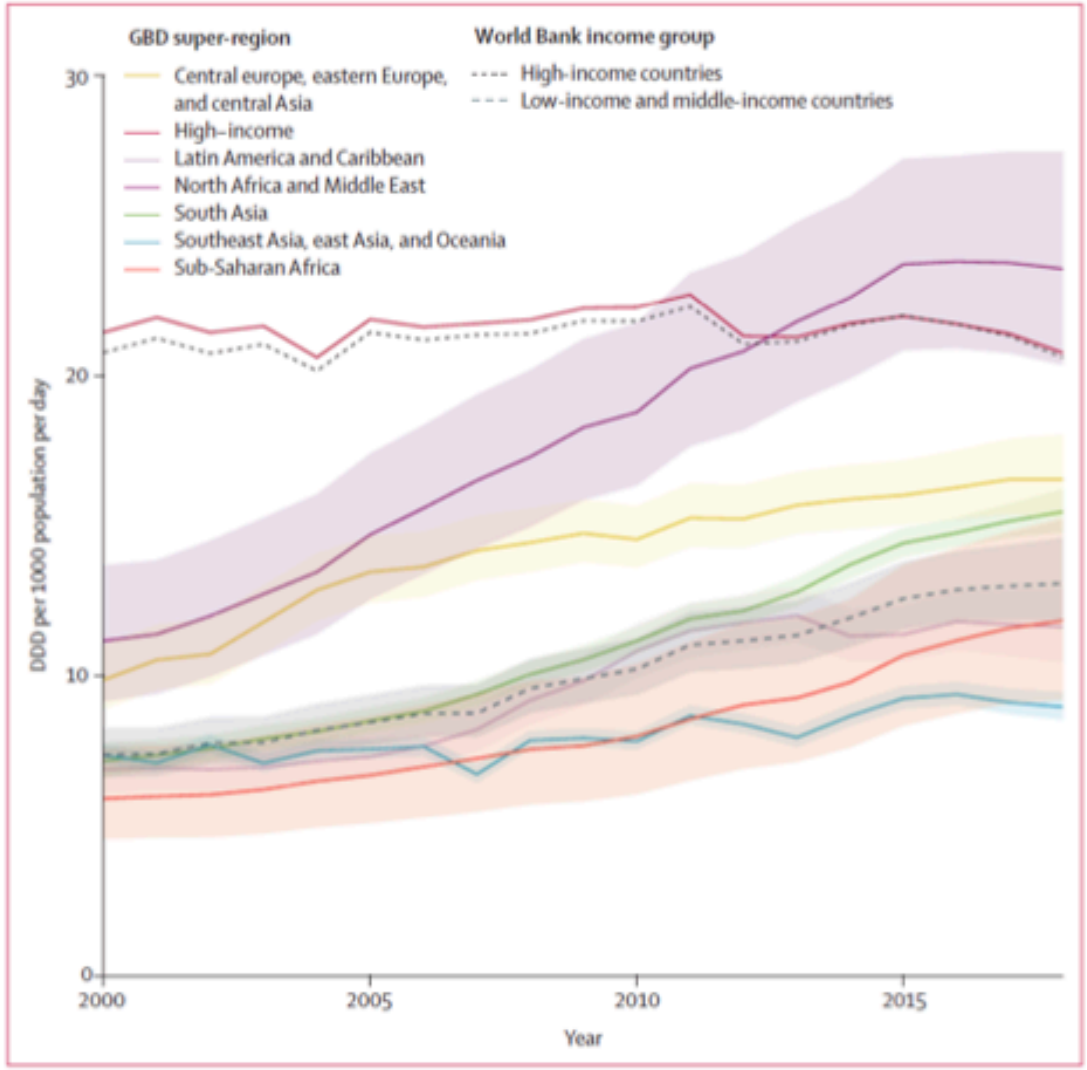


Figure 5: Temporal trends in the total antibiotic consumption rates for GBD super-regions and World Bank income groups

Bacterial Culture:

Bottle: Type	FAN Paediatric Plus	
Result	Positive	
Incubation time	3.0	hours

Gram Stain — Gram negative bacilli

1) *Klebsiella pneumoniae subsp pneumoniae (KLEPP)*

This is a multi-resistant organism. CONTACT PRECAUTIONS are necessary to ensure that this organism does not spread in the ward/unit.

Antibiotic/Culture:	KLEPP
Trimethoprim-sulfamethoxazole	R
Ampicillin / Amoxicillin	R
Amoxicillin-clavulanic acid	R
Ciprofloxacin	R
Cefuroxime (Parenteral)	R
Cefuroxime (Oral)	R
Cefoxitin	R
Cefotaxime / Ceftriaxone	R
Ceftazidime	R
Cefepime	R
Gentamicin	R
Amikacin	I
Piperacillin-tazobactam	R
Ertapenem	R
Imipenem	R
Meropenem	R

MIC by E-test:

Organism	*Klebsiella pneumoniae subsp pneumoniae (KLEPP)*
Antibiotic	Meropenem
MIC corrected	>32 ug/mL
MIC interpretation	Resistant
Antibiotic	Imipenem
MIC corrected	>32 ug/mL
MIC interpretation	Resistant
Antibiotic	Ertapenem
MIC corrected	>32 ug/mL
MIC interpretation	Resistant

Broth dilution MIC:

Organism	*Klebsiella pneumoniae subsp pneumoniae (KLEPP)*
Antibiotic	Colistin
MIC	32 ug/mL
MIC interpretation	Resistant

Bacterial Culture:

Bottle: Type	FAN Paediatric Plus	
Result	Positive	
Incubation time	7.0	hours

Gram Stain — Gram negative cocco-bacilli

1) *Acinetobacter baumannii complex (ACIBC)*

This is a multi-resistant organism. CONTACT PRECAUTIONS are necessary to ensure that this organism does not spread in the ward/unit.

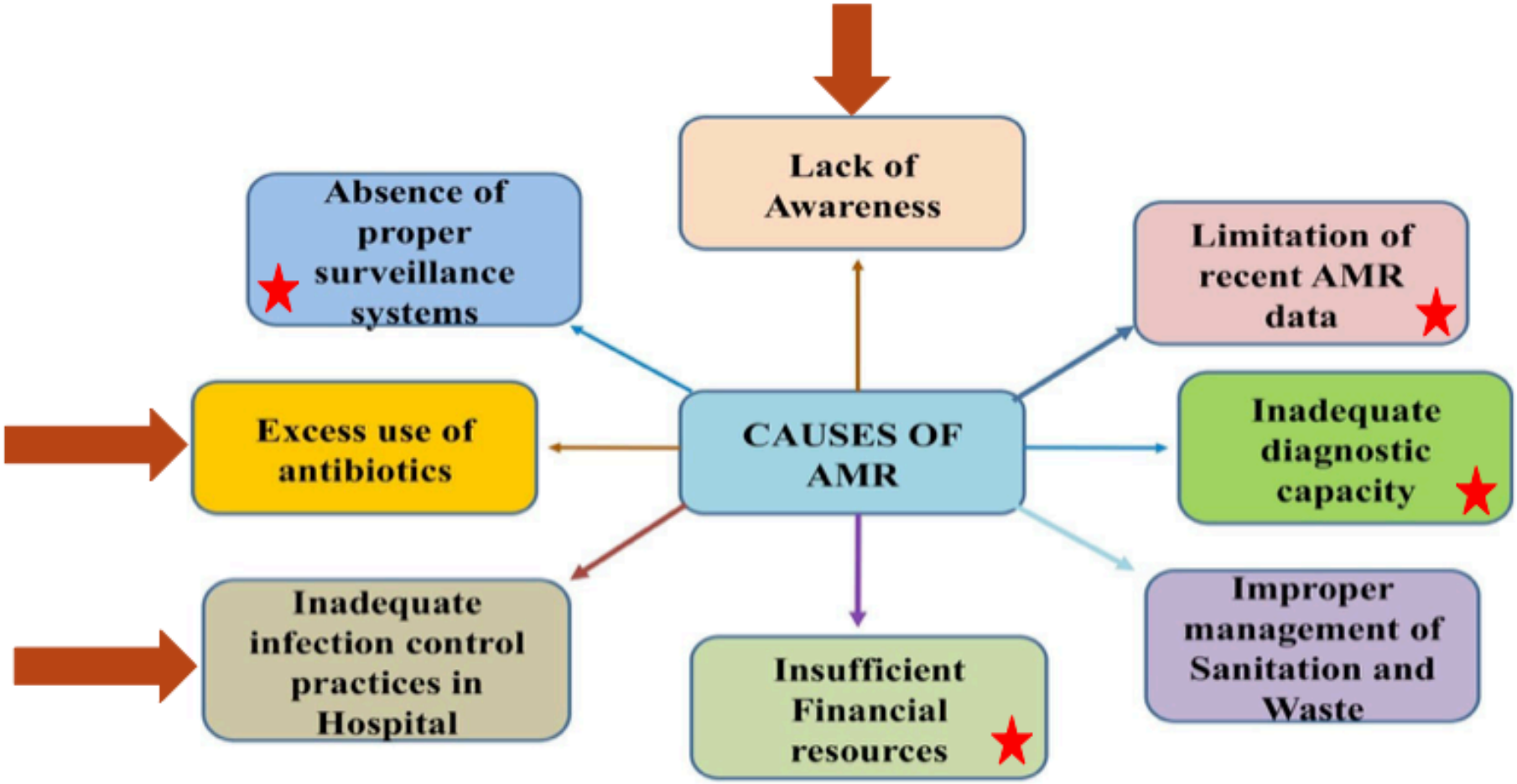
The currently available laboratory methods for performing colistin susceptibility testing are unreliable and may not predict clinical outcome. Based on published data and clinical experience, colistin is a suitable therapeutic alternative for carbapenem-resistant Acinetobacter species. If colistin is clinically indicated, please carefully assess clinical response.

Antibiotic/Culture:	ACIBC
Trimethoprim-sulfamethoxazole	R
Ciprofloxacin	R
Ceftazidime	R
Cefepime	R
Gentamicin	R
Tobramycin	R
Amikacin	R
Piperacillin-tazobactam	R
Imipenem	R
Meropenem	R

Broth dilution MIC:

Organism	*Acinetobacter baumannii (ACIBA)*
Antibiotic	Colistin
MIC	0.5 ug/mL

Causes of AMR in resources-limited countries



Sharma et al. Menace of antimicrobial resistance in LMICs: Current surveillance practices and control measures to tackle hostility, Journal of Infection and Public Health, Volume 15, Issue 2, 2022, 172-181,

Principles of Antimicrobial Stewardship

- Multi-disciplinary, systematic approach to optimising the appropriate use of antimicrobials

Optimizing antibiotic use vs Restricting access

- Right antibiotic at the right time at the right dose via the right route

Impact of Antimicrobial Stewardship Programmes

REVIEW Open Access

Implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review

D. Donà[1,2,3†], E. Barbieri[1*†], M. Daverio[4], R. Lundin[3], C. Giaquinto[1,3], T. Zaoutis[5,3] and M. Sharland[2,3]

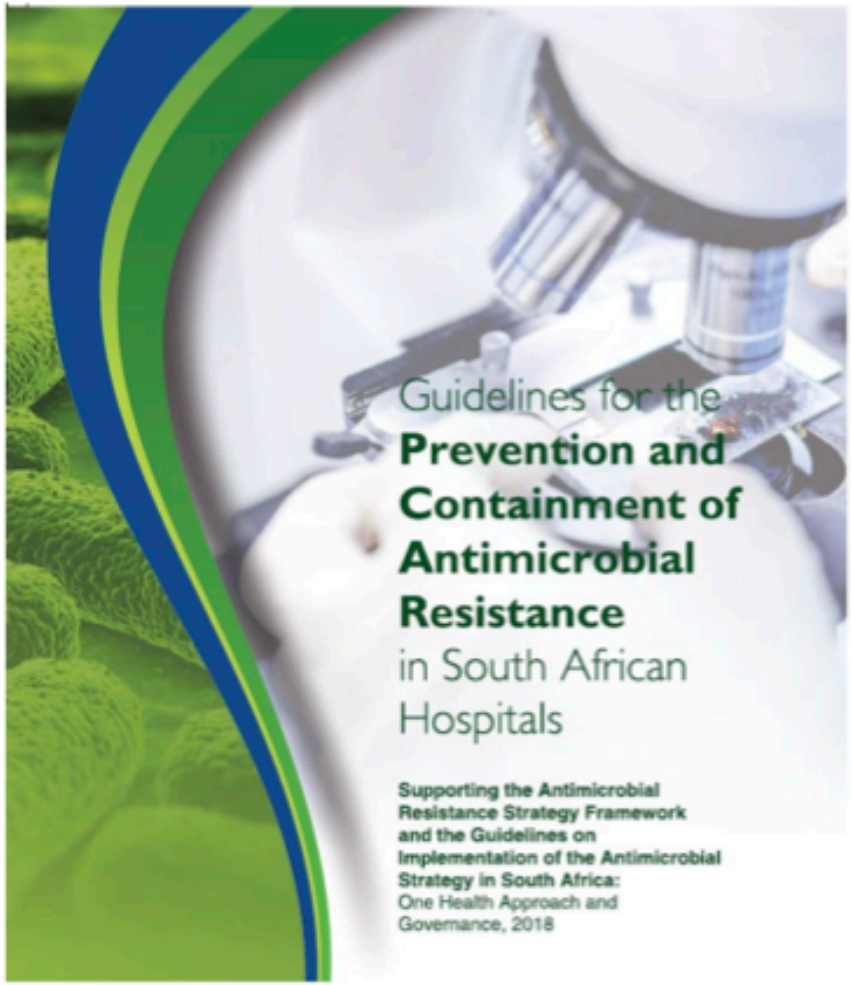
Donà et al. Antimicrobial Resistance and Infection Control (2020) 9:3
https://doi.org/10.1186/s13756-019-0659-3

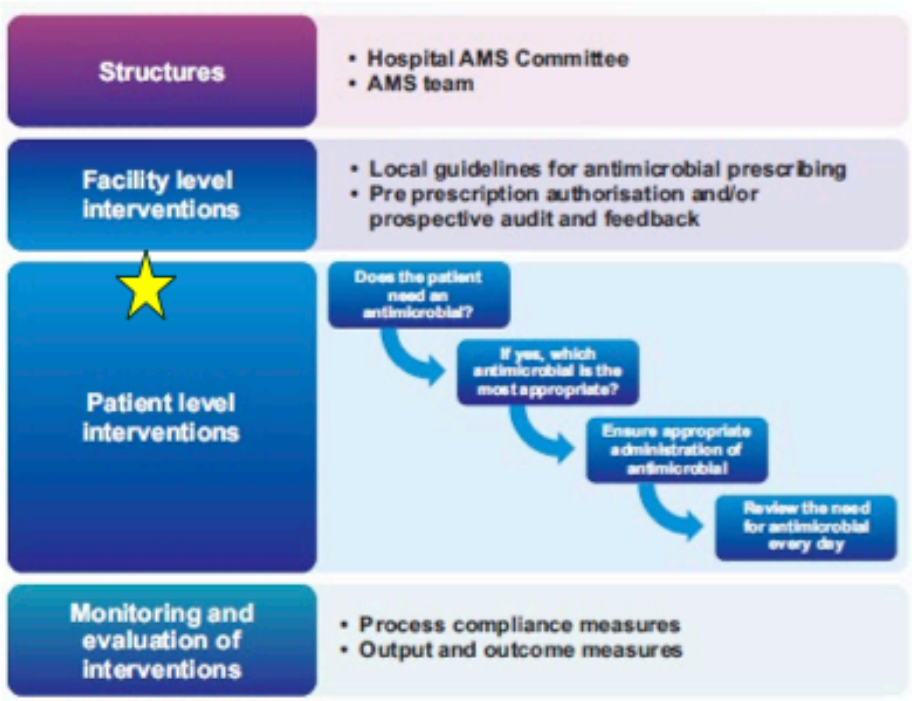
113 studies :

- USA 52%
- Europe 25%
- Asia 18%

- 80% Significant reduction in inappropriate use
- Cost Savings due to decreased use
- Increased susceptibility to antibiotics in Inpatient and outpatient settings

South African Guidelines





health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NDP 2030

https://knowledgehub.health.gov.za/system/files/elibdownloads/2020-03/Guidelines%20for%20the%20prevention%20and%20containment%20of%20AMR%20in%20SA%20hospitals.pdf

WHO 2016

AWARE categories

The overall goal is to reduce the use of Watch Group and Reserve Group antibiotics (the antibiotics most crucial for human medicine and at higher risk of resistance), and to increase the use of Access antibiotics where availability is low.

AWaRe is a useful tool to reduce antimicrobial resistance and ensure access.

First Choice

ACCESS

Which indicates the antibiotic of choice for each of the 25 most common infections. These antibiotics should be available at all times, affordable and quality-assured.

Use Sparingly

WATCH

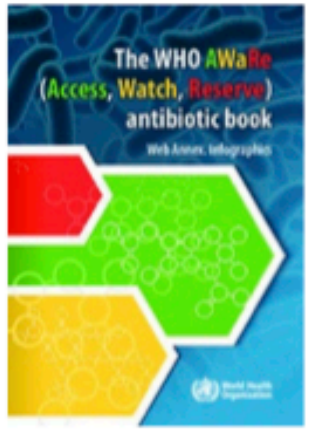
Which includes most of the "highest-priority critically important antimicrobials" for human medicine and veterinary use. These antibiotics are recommended only for specific, limited indications

Last resort

RESERVE

Antibiotics that should only be used as a last resort when all other antibiotics have failed.

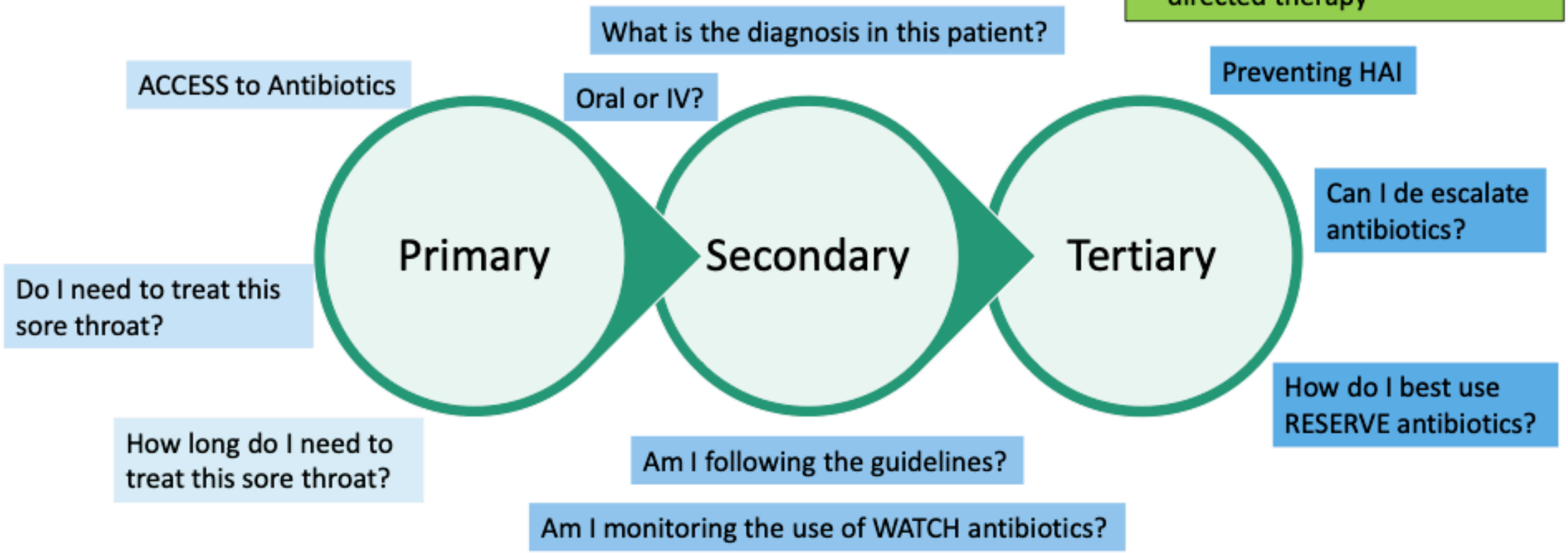
- Provides recommendations for 21 common infectious diseases
- Classifies antibiotics into three groups based on the potential to **induce and propagate resistance**
- Identifies antibiotics that are **priorities for monitoring and surveillance of use**

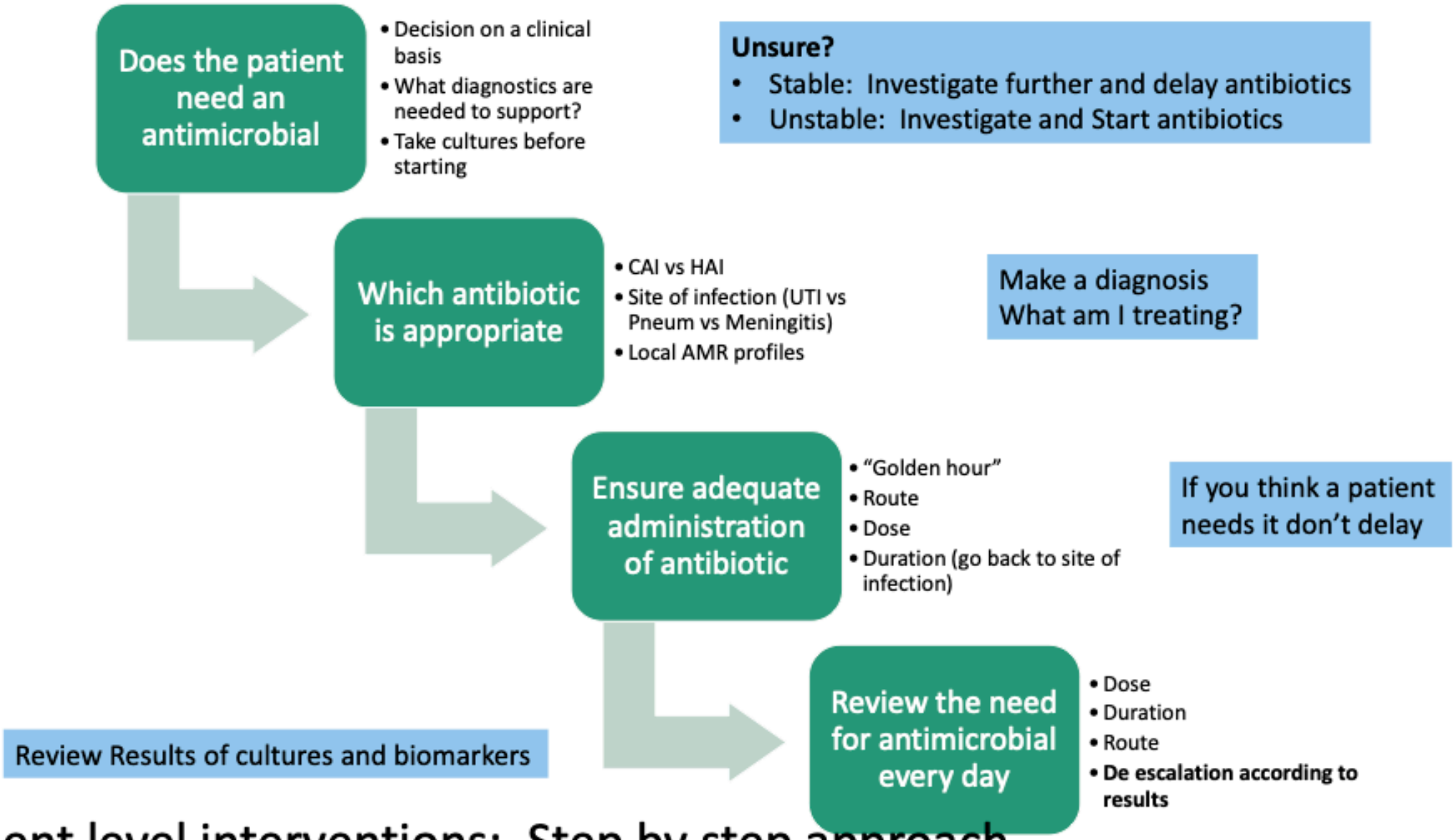


By the end of 2023: 60% of all antibiotics from the Access Category

Stewardship Across the Spectrum

- **5 D's of Antibiotic Stewardship**
- Right Drug,
- Correct Dose
- Right Diagnosis
- Correct Duration
- De-escalation to pathogen-directed therapy





Patient level interventions: Step by step approach

Reacting to blood culture results

Bacterial Culture:

Bottle: Type	FAN Paediatric Plus
Result	Positive
Incubation time	5.0 hours
Gram Stain	Gram negative bacilli

1) *Klebsiella pneumoniae subsp pneumoniae (KLEPP)*

2) *Acinetobacter baumannii (ACIBA)*

Antibiotic/Culture:	KLEPP	ACIBA
Trimethoprim-sulfamethoxazole	S	R
Ampicillin / Amoxicillin	R	
Amoxicillin-clavulanic acid	S	
Ciprofloxacin	S	R
Cefuroxime (Parenteral)	S	
Cefuroxime (Oral)	S	
Cefotaxime / Ceftriaxone	S	
Ceftazidime		R
Cefepime		R
Gentamicin	S	R
Tobramycin		R
Amikacin		R
Piperacillin-tazobactam		R
Imipenem		R
Meropenem		R

Broth dilution MIC:

$ Organism	*Acinetobacter baumannii (ACIBA)*
$ Antibiotic	Colistin
$ MIC	0.5 ug/mL

$ Current CLSI guidelines have set colistin breakpoints for Enterobacterales, P aeruginosa and Acinetobacter spp at <=2 mg/L (intermediate) and >=4 mg/L (resistant), with no susceptible category. Clinical and PK/PD data demonstrate this agent to be of limited clinical efficacy. If available, alternative agents to which the isolate is susceptible are strongly preferred. If these agents are not available, colistin monotherapy (for specific sites and uncomplicated infections) OR colistin in combination with one or more additional antibiotics with the lowest MIC should be used. Please consult a clinical microbiologist or infectious diseases physician if management advice is required.

Patient was started on meropenem, now what?

Think about source control

Bacterial Culture:

Bottle: Type	FAN Paediatric Plus
Result	Positive
Incubation time	4.0 hours
Gram Stain	Gram negative bacilli

1) *Klebsiella pneumoniae (KLEPN)*

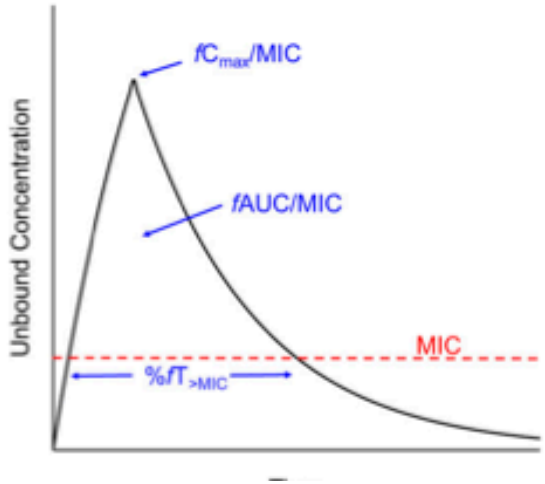
Antibiotic/Culture:	KLEPN
Trimethoprim-sulfamethoxazole	R
Ampicillin / Amoxicillin	R
Amoxicillin-clavulanic acid	S
Ciprofloxacin	S
Cefuroxime (Parenteral)	S
Cefuroxime (Oral)	S
Cefotaxime / Ceftriaxone	S
Ceftazidime	S
Cefepime	S
Gentamicin	S
Tobramycin	S
Amikacin	S
Piperacillin-tazobactam	S
Ertapenem	S
Imipenem	S
Meropenem	S

- In ICU: gram negative bacilli on BC
- Ongoing temps and increasing CRP after 48 hours
- Already in meropenem
- Decision to add colistin
- Next day BC sensitivities comes back

Also has central line in situ

Not just what but how and how much

- pharmacokinetic/pharmacodynamic (PK/PD) principles to antibiotic therapy represents a key point of AMS
- Especially in ICU's, neonates
- Factors affecting dosing (e.g renal function)
- individualization and optimization of antimicrobial therapy using therapeutic drug monitoring (TDM)



Original Research

Evaluation of Meropenem Extended Versus Intermittent Infusion Dosing Protocol in Critically Ill Patients

Journal of Intensive Care Medicine
2020, Vol. 35(8) 763-771

DOI: 10.1177/0885066618784264
journals.sagepub.com/home/jic

RESEARCH ARTICLE

Clinical outcomes of prolonged infusion

Nabeela A
Diana Alts
Vinh P. Ph

antibiotics

MDPI

usion)

nem in

Cor

Review

Extended or Continuous Infusion of Carbapenems in Children with Severe Infections: A Systematic Review and Narrative Synthesis

Pengxiang Zhou [1,2,†], Yahui Zhang [1,3,†], Zhenhuan Wang [3,4], Yingqiu Ying [1], Yan Xing [5], Xiaomei Tong [5,*] and Suodi Zhai [1,2,*]

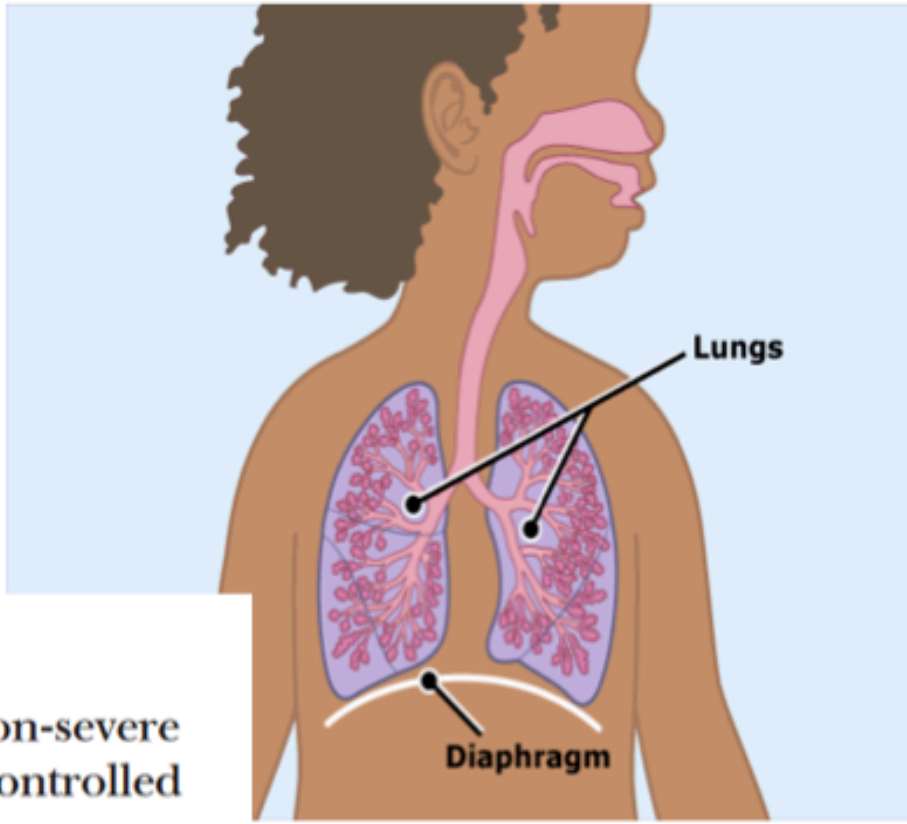
A Randomized Controlled Trial

Abd Elazeez Shabaan, PhD,† Islam Nour, PhD,*† Heba Elsayed Eldegla, PhD,‡§ Nehad Nasef, PhD,*† Basma Shouman, PhD,*† and Hesham Abdel-Hady, PhD*†*

jiang, China,
zhou Third Municipal
Hangzhou, Zhejiang,

Length of treatment

- Least amount of evidence
- Duration (biomarker-guided) of therapy
- Site specific length of treatment
  - Stat dose Surgical prophylaxis



Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial

ISCAP Study Group BMJ 2004; 328 :791 doi:10.1136/bmj.38049.490255.DE

Conclusions Treatment with oral amoxicillin for three days was as effective as for five days in children with non-severe pneumonia.

- **3.8. Universal health coverage**
  - Including financial risk protection,
  - access to quality essential health-care services
  - access to safe, effective, quality and affordable essential medicines and vaccines for all.
- **3.b. Medicines and vaccines**
  - Support the research and development of vaccines and medicines for diseases that primarily affect developing countries.
  - Provide access to affordable essential medicines and vaccines
  - Provide access to medicines for all

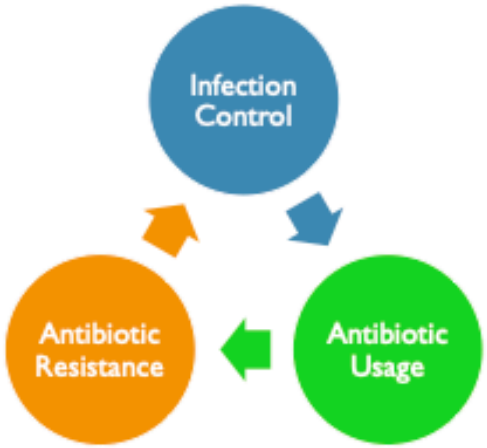
- Reducing inequalities and ensuring no one is left behind
- Highlighted by COVID-19 pandemic

Priorities in LMIC:

Priorities in LMIC

- Political will
  - NAP with implementation policies
  - Improved regulatory frameworks
  - Financial Support
- Data
  - AMR surveillance
  - Antimicrobial usage
- ACCESS to all antibiotics that are needed
  - Improved supply chain
  - Inventive methods for procurement
  - Financial incentive models to promote antibiotic innovation
- Improved diagnostic/laboratory capabilities
- Novel diagnostics and POC tests
- Infection Prevention and Control Strengthening

Driven by the disease profile of the country at hand
We are not the Global North



Thank You