The South-East Asia Region Antimicrobial Stewardship 2022 Webinar Series

September 14, 2022

WHO AWaRe Antibiotic Book & the AWaRe classification

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Learning objectives of the webinar

- Develop / deepen the understanding of **WHO's AWaRe classification of antibiotics**
  - How it was developed
  - How it is updated
  - How it can be used to improve antibiotic use in countries
  - How it relates to the WHO Model Lists of Essential Medicines

- Introduce participants to the **WHO AWaRe Antibiotic Book**
  - How it was developed and the underlying principles
  - How it can be locally adapted
  - How it can be used to improve antibiotic use in countries

This is supposed to be an interacrive webinar!

Where are you following this webinar from ?

Mentimeter

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What do you consider the main problem(s) with regard to antibiotic use in your setting ?

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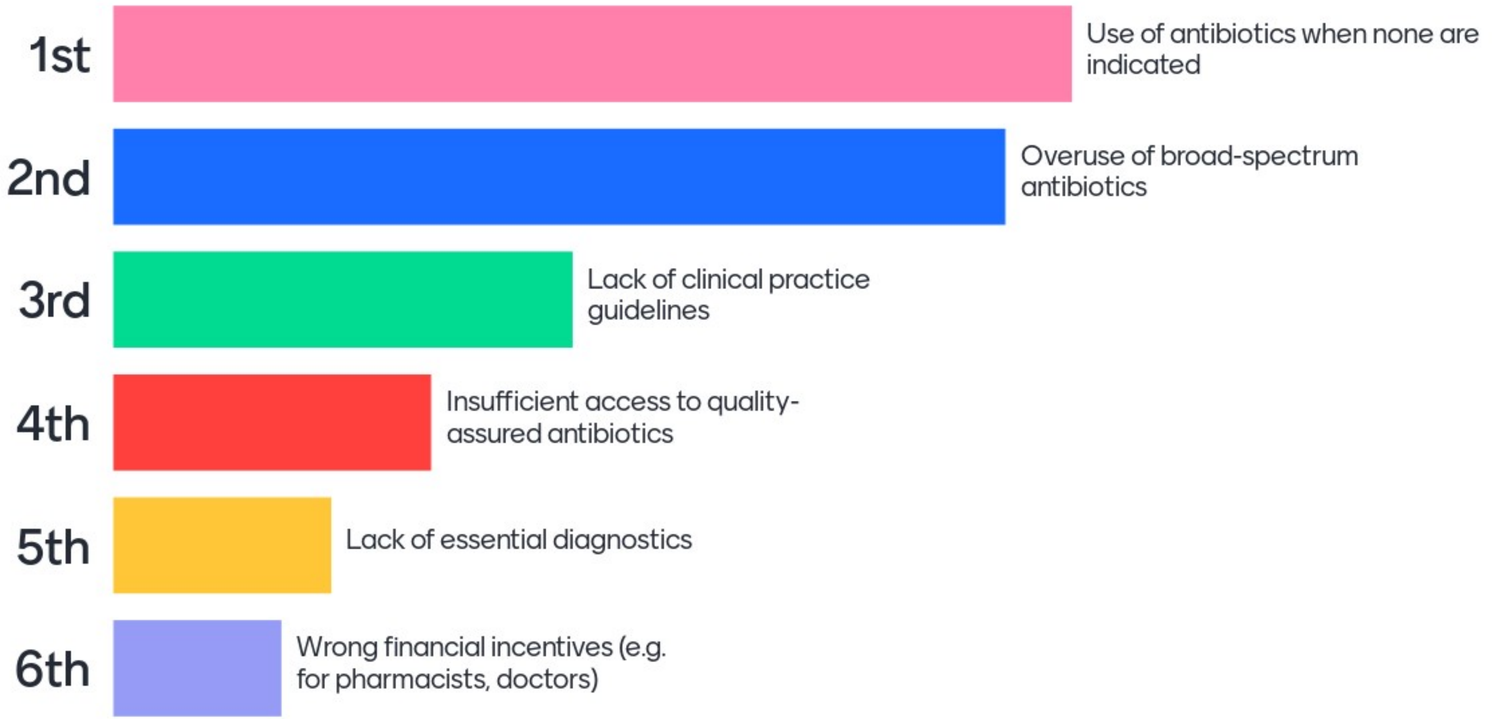

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Antibiotics on the Essential Medicines List (EML)

The WHO Model List of Essential Medicines (EML)

- Updated every two years by the Expert Committee on Selection and Use of Essential Medicines
  - Next Expert Committee Meeting April 2023
- First EML published in 1977
  - First EML for children published in 2007
- Since 2017 extensive update / review of antibiotics on the EML
  - In the context of WHO's global action plan on antimicrobial resistance

How many antibiotics would you consider “essential” (for your country setting)

How many antibiotics are included in the 2021 EML

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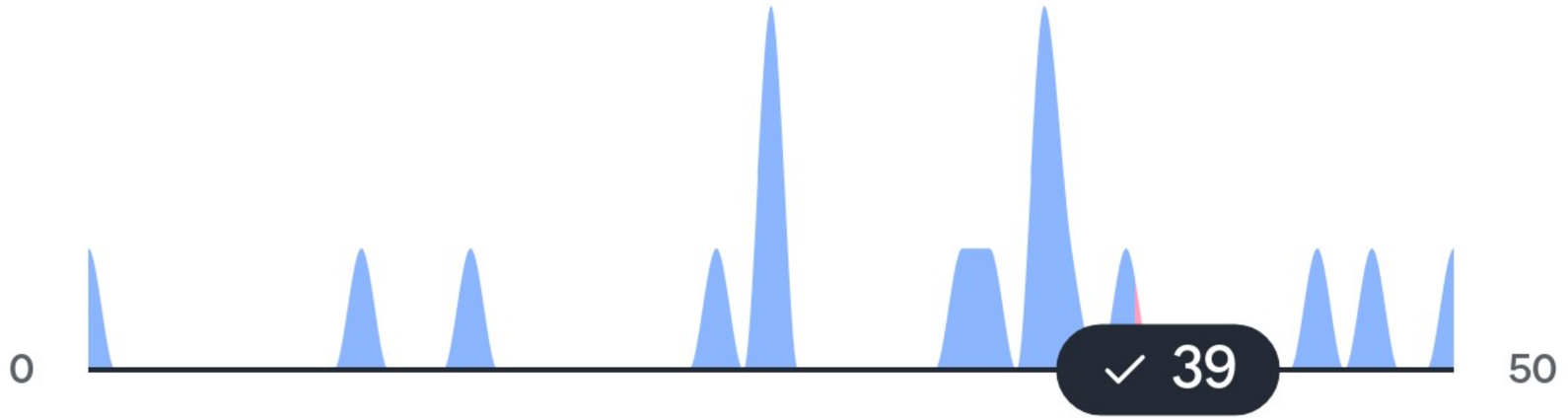

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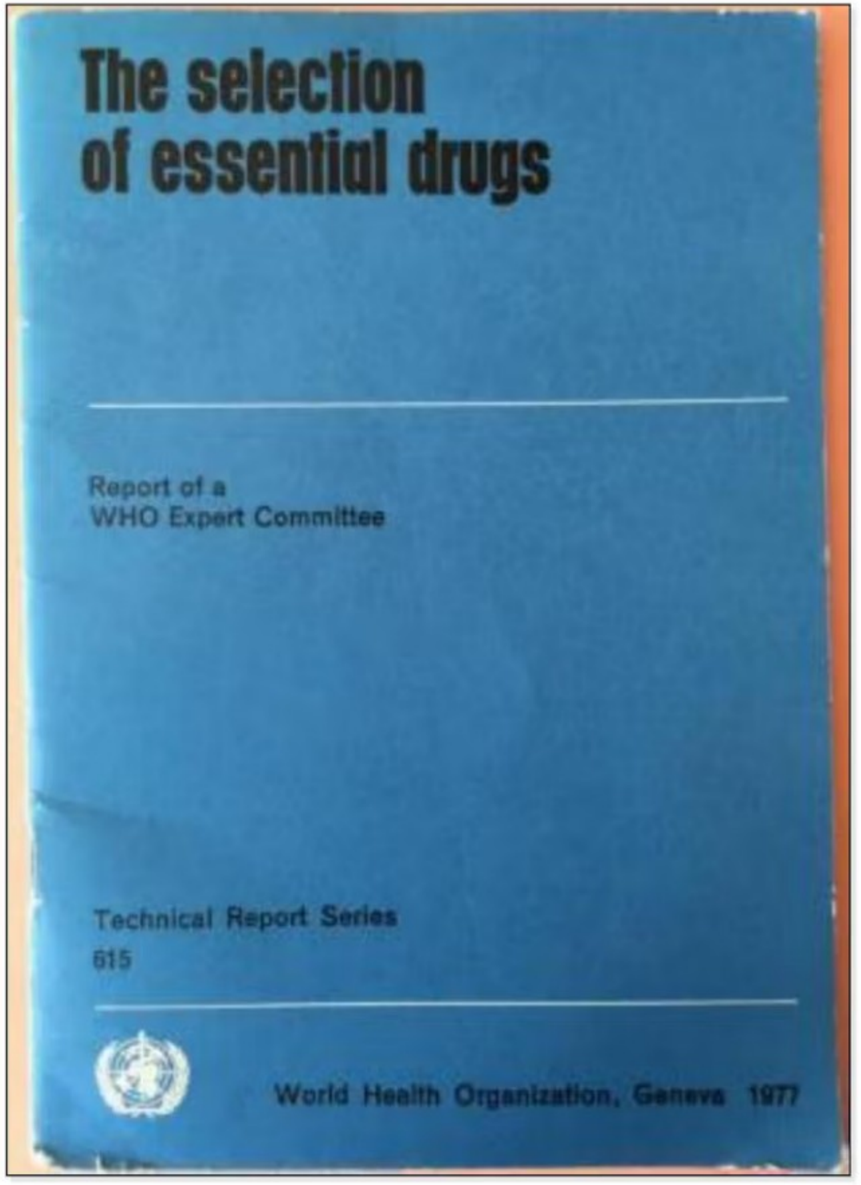

1977

First EML

- 16 antibiotics

(of 240 medicines ≈ 7%)

In a report [1] to the Twenty-eighth World Health Assembly in 1975, the Director-General reviewed the main drug problems facing the developing countries and outlined possible new drug policies. The Director-General also referred to the experience gained in some countries where schemes of basic or essential drugs had been implemented. Such schemes were intended to extend the accessibility of the most necessary drugs to those populations whose basic health needs could not be met by the existing supply system. The Director-General pointed out that the selection of these essential drugs would depend on the health needs and on the structure and development of health services of each country, and that lists of essential drugs should be drawn up locally, and periodically updated, with the advice of experts in public health, medicine, pharmacology, pharmacy and drug management. He also considered that adequate information on the properties, indications and use of the drugs listed should be provided. By resolution WHA28.66, the Health Assembly requested the Director-General to implement the proposals contained in his report and, in particular, to advise Member States on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs.

Antibacterial drugs

ampicillin (1) *
benzathine benzylpenicillin (5) *
benzylpenicillin *

chloramphenicol (7) * *
cloxacillin (penicillinase-resistant, 1)
erythromycin *
gentamicin (4) *
phenoxymethylpenicillin *
salazosulfapyridine
sulfadimidine (1)
sulfamethoxazole + trimethoprim *
tetracycline (1, 4) *

Complementary

amikacin (1, 4, 10) *
doxycycline (6, 5) *
procaine benzylpenicillin (7) *
sulfadiazine (7, 8) *

* On 2021 EML/c

In a report [1] to the Twenty-eighth World Health Assembly in 1975, the Director-General reviewed the main drug problems facing the developing countries and outlined possible new drug policies. The Director-General also referred to the experience gained in some countries where schemes of basic or essential drugs had been implemented. Such schemes were intended to extend the accessibility of the most necessary drugs to those populations whose basic health needs could not be met by the existing supply system. The Director-General pointed out that the selection of these essential drugs would depend on the health needs and on the structure and development of health services of each country, and that lists of essential drugs should be drawn up locally, and periodically updated, with the advice of experts in public health, medicine, pharmacology, pharmacy and drug management. He also considered that adequate information on the properties, indications and use of the drugs listed should be provided. By resolution WHA28.66, the Health Assembly requested the Director-General to implement the proposals contained in his report and, in particular, to advise Member States on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs.

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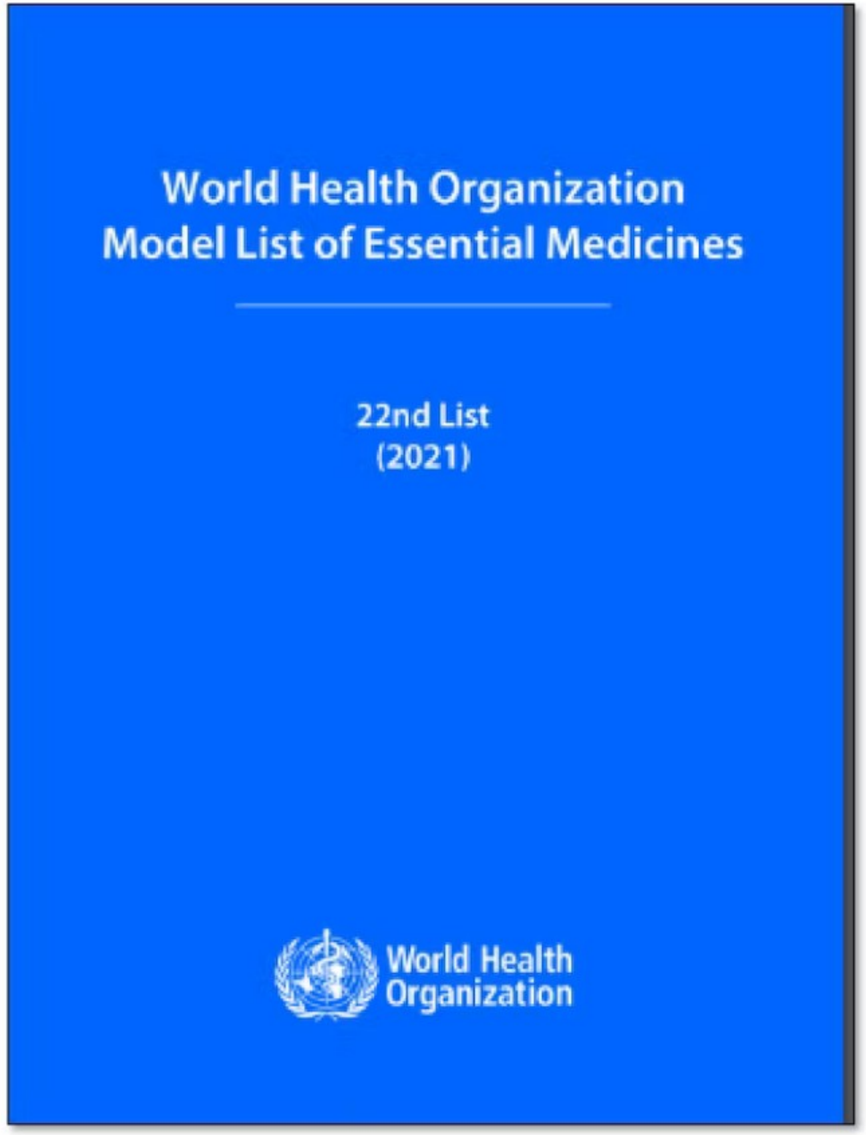
2021



22nd EML

- 39 antibiotics (EMLc 36)

(of 479 medicines ≈ 8%)

SIXTY-EIGHTH WORLD HEALTH ASSEMBLY — WHA68.7

Agenda item 15.1 — 26 May 2015

Global action plan on antimicrobial resistance

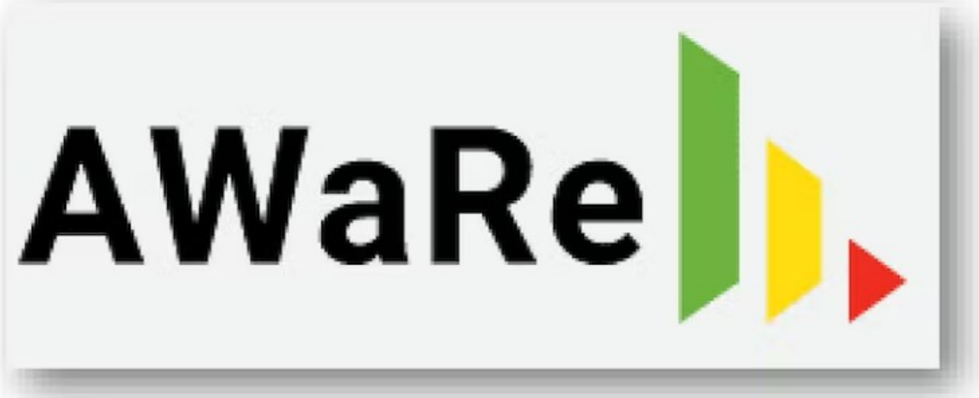
The Sixty-eighth World Health Assembly,

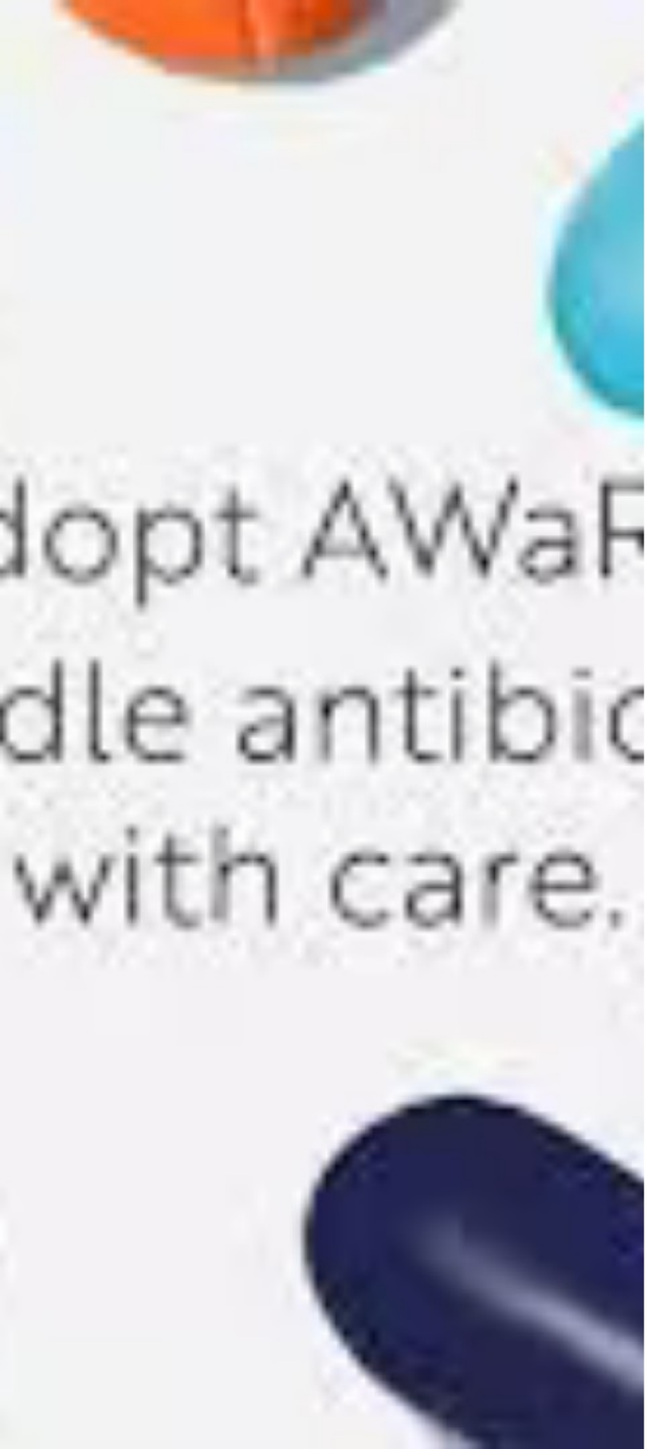
Having considered the summary report on progress made in implementing resolution WHA67.25 on antimicrobial resistance and the report on the draft global action plan on antimicrobial resistance;[1]

Recalling resolutions WHA39.27 and WHA47.13 on the rational use of drugs, resolution WHA51.17 on emerging and other communicable diseases: antimicrobial resistance, resolution WHA54.14 on global health security: epidemic alert and response, resolution WHA58.27 on improving the containment of antimicrobial resistance, resolution WHA60.16 on progress in the rational use of medicines and resolution WHA66.22 on follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination and WHA67.25 on antimicrobial resistance;

ACCESS GROUP	WATCH GROUP	RESERVE GROUP
Amikacin	Azithromycin	
Amoxicillin	Cefixime	
Amoxicillin/clavulanic-acid	Cefotaxime	
Ampicillin	Ceftazidime	
Benzathine-benzylpenicillin	Ceftriaxone	
Benzylpenicillin	Cefuroxime	
Cefalexin	Ciprofloxacin	
Cefazolin	Clarithromycin	
Chloramphenicol	Meropenem	
Clindamycin	Piperacillin/tazobactam	
Cloxacillin	Vancomycin (IV)	
Doxycycline	Vancomycin (oral)	
Gentamicin		Cefiderocol
Metronidazole		Ceftazidime/avibactam
Nitrofurantoin		Colistin (IV)
Phenoxymethylpenicillin		Fosfomycin (IV)
Procaine-benzylpenicillin		Linezolid
Spectinomycin		Meropenem/vaborbactam
Sulfamethoxazole/TMP		Plazomicin
Trimethoprim		Polymyxin B (IV)

The AWaRe classification of antibiotics





The AWaRe classification of antibiotics

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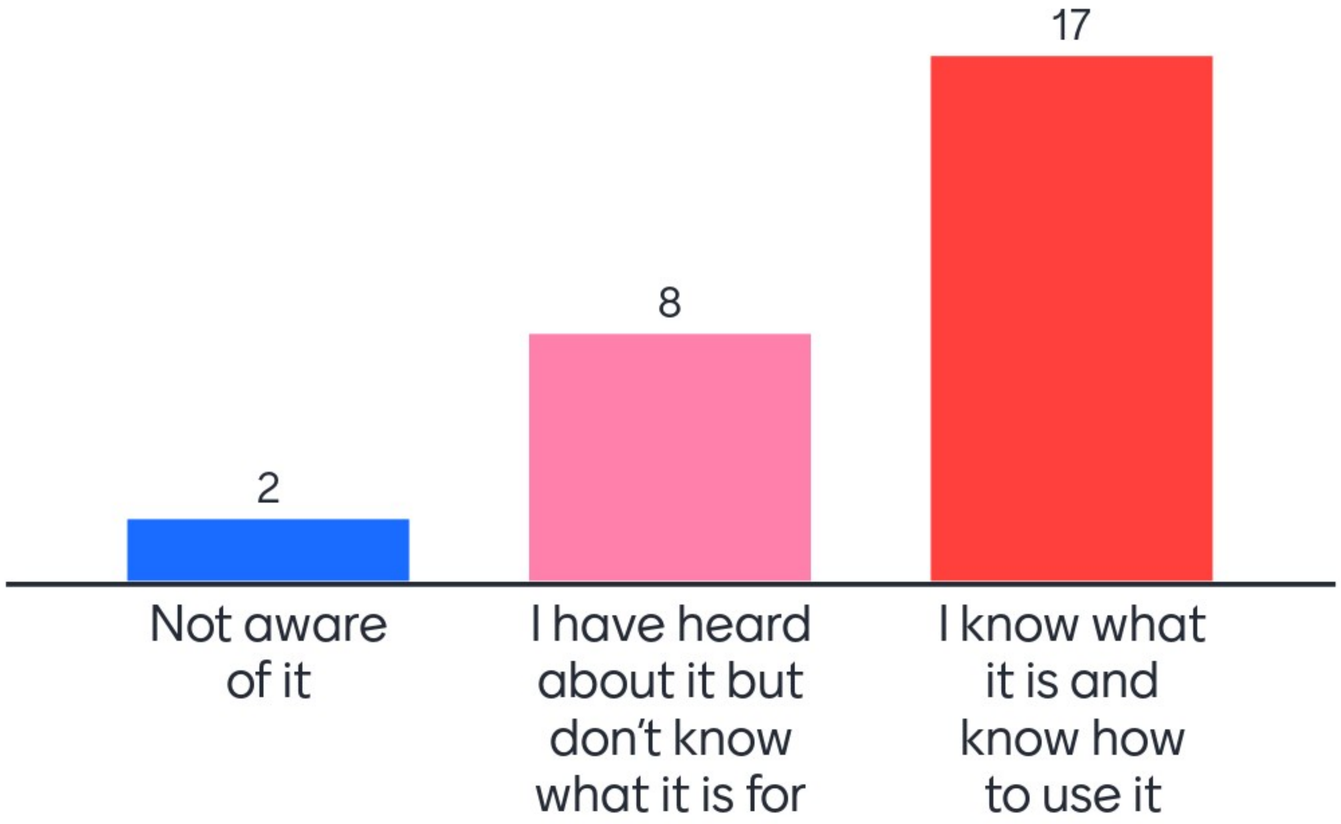

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The classic distinction between narrow and broad-spectrum antibiotics has many limitations (not the least being that there is no standard definition)

Broad- and narrow-spectrum antibiotics: an unhelpful categorization

Clin Microbiol Infect 1997; 3: 395–396

The expression 'broad-spectrum antibiotic' was used in the mid-1950s, when the bacterial spectrum of chloramphenicol and the first tetracyclines could be strikingly opposed to the narrow spectrum of activities of penicillin G, and streptomycin. In the 1960s, amino-penicillins, then ureidopenicillins, became the broad-spectrum penicillins in comparison with penicillin G. Until then, the quality of being broad spectrum or narrow spectrum was given to an antibiotic only when referring to a comparator. Later, the reference to a comparator was omitted, and broad and narrow lost their relativities and became independent character-istics of a compound, used with different meaning and often improperly.

AWaRe: Antibiotics are categorized into three groups

Essential Access, Watch and Reserve antibiotics need to be accessible and affordable for those who need them!

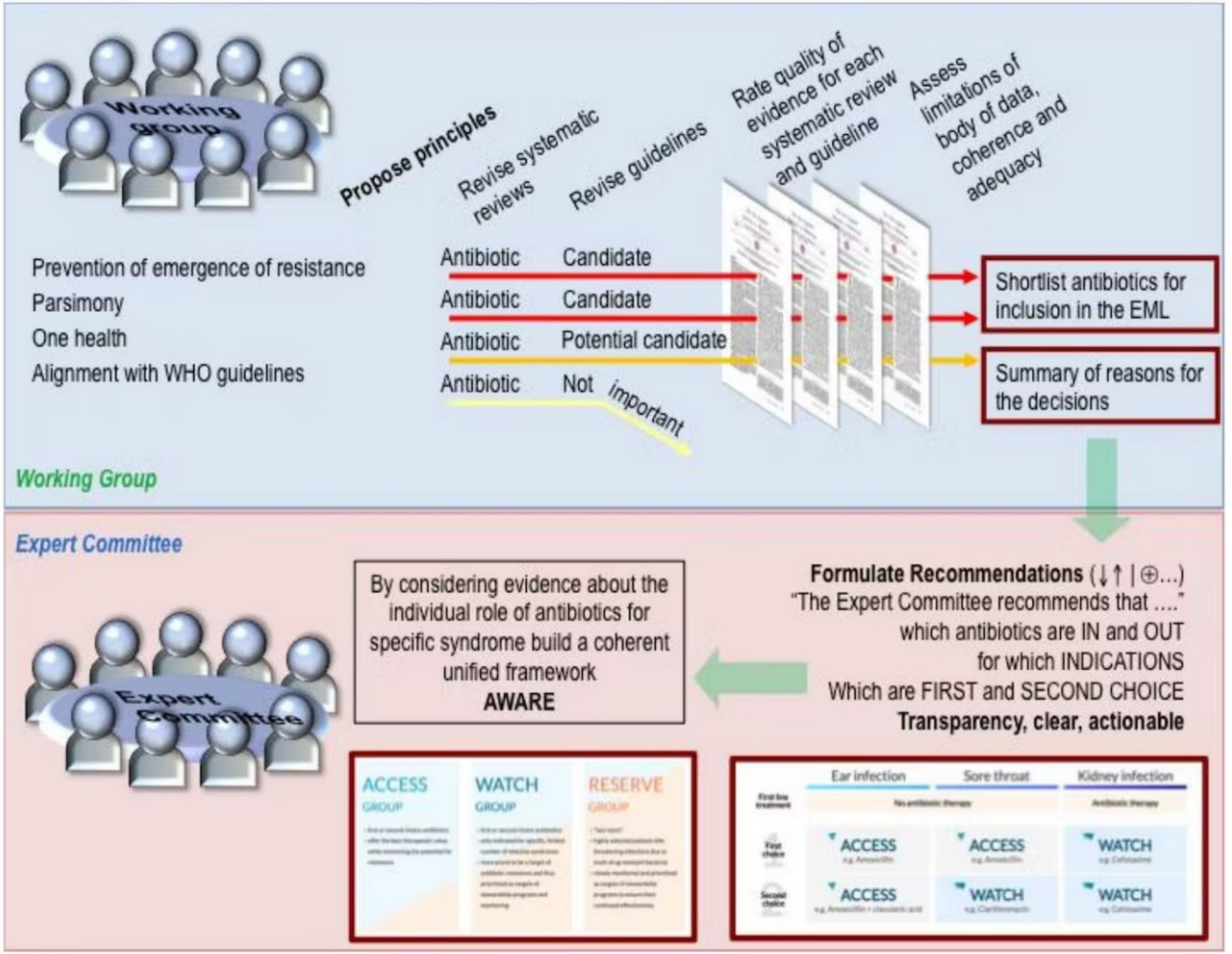
«Last-resort» options against MDRO

Higher "resistance potential"

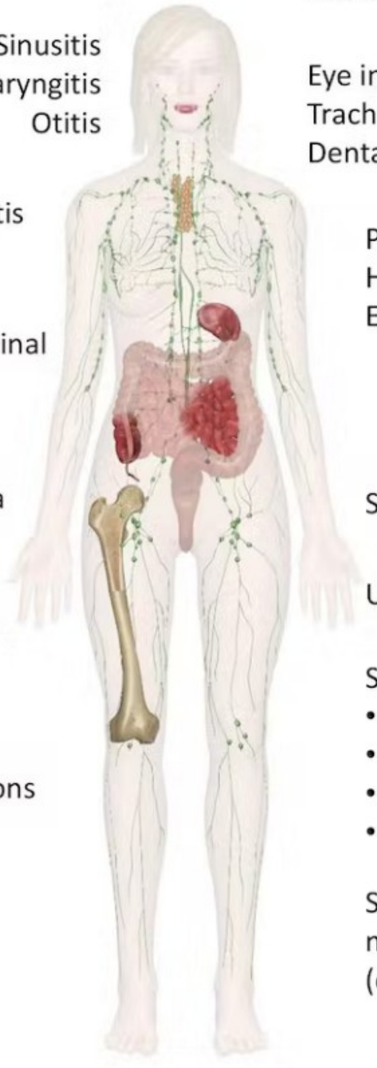
Often 1st or 2nd choice for common infectious syndromes

Lower "resistance potential"

Process for the selection of essential antibiotics



EML updates
2017 / 2019 / 2021



Meningitis

Sinusitis
Pharyngitis
Otitis

Eye infections
Trachoma
Dental infections

Lymphadenitis

Pneumonia (CAP)
HCAP
Exacerbation of COPD

Complicated intraabdominal Infections
Enteric fever

Acute infectious diarrhea
- Cholera
- Shigellosis
- *Clostridoides difficile*

Sepsis

UTI

STD
- *Chlamydia*
- Gonorrhea
- Syphilis
- Trichomoniasis

Bone infections
Septic arthritis
Skin & soft tissue infections

Febrile neutropenia

Severe malnutrition (children)

Surgical prophylaxis

Review of infections

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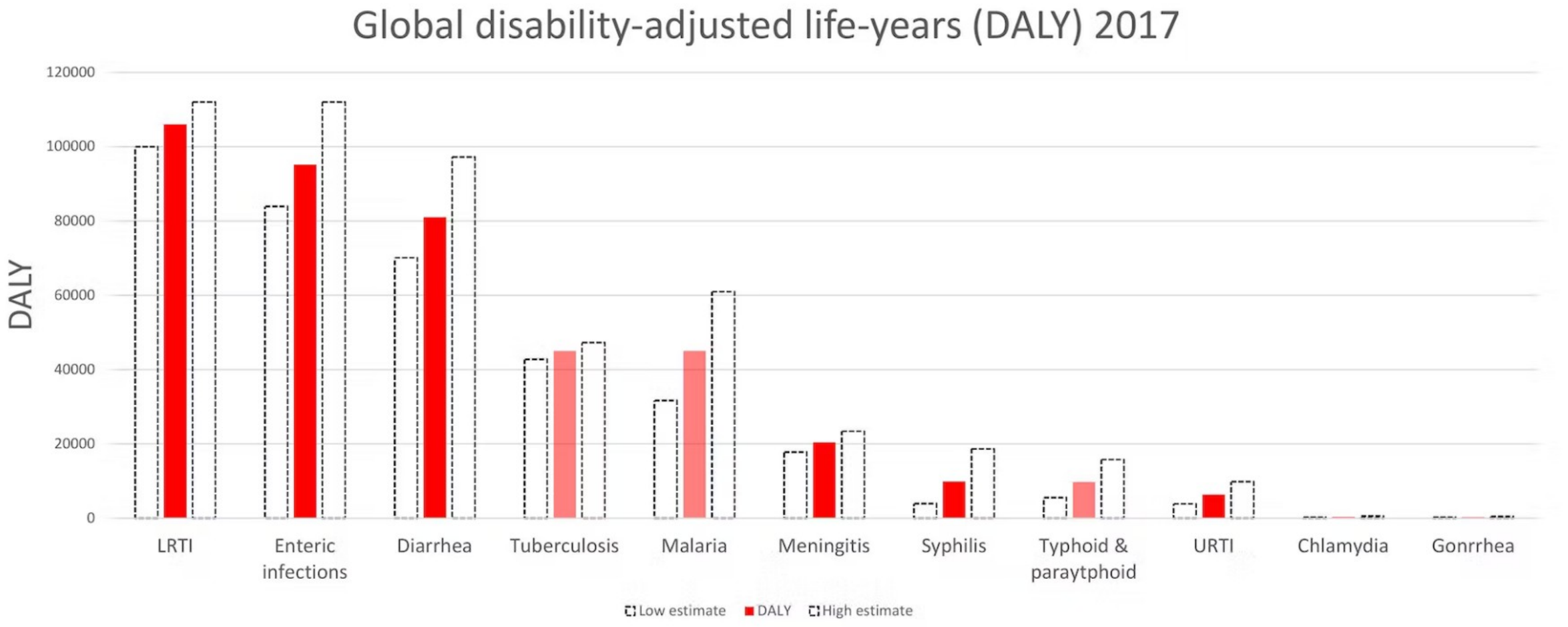
- Frequent infections
  - ✓Mostly community-acquired infections
  - ✓Mostly empiric use
- Certain infections by specific pathogens
  - ✓Syphilis, cholera, gonorrhea, shigellosis,…
- Review of systematic reviews and guidelines

Global burden of infectious diseases



Lancet. 2018 Nov 10;392(10159):1859-1

What is the most important criterion for including an antibiotic on the WHO EML?

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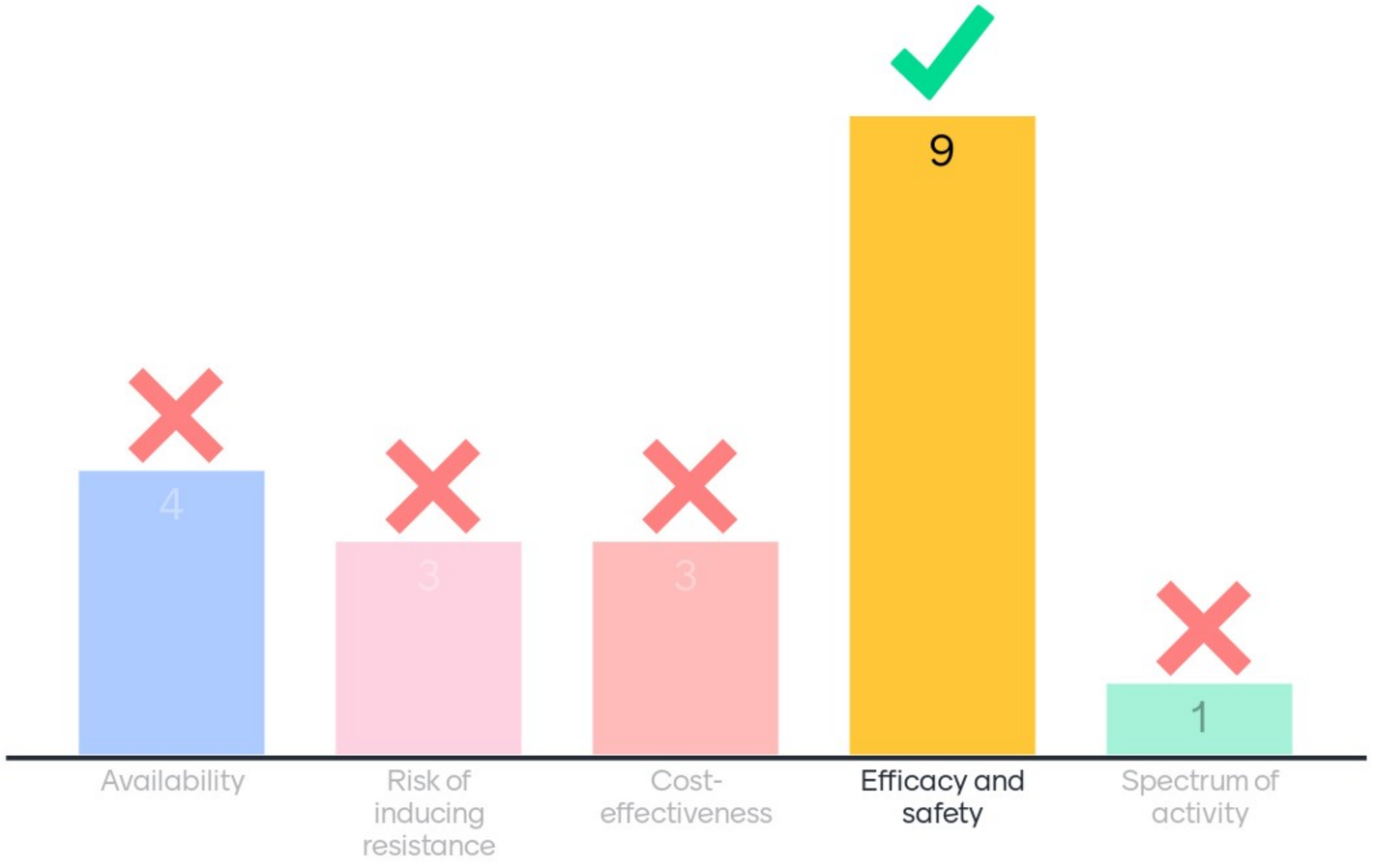

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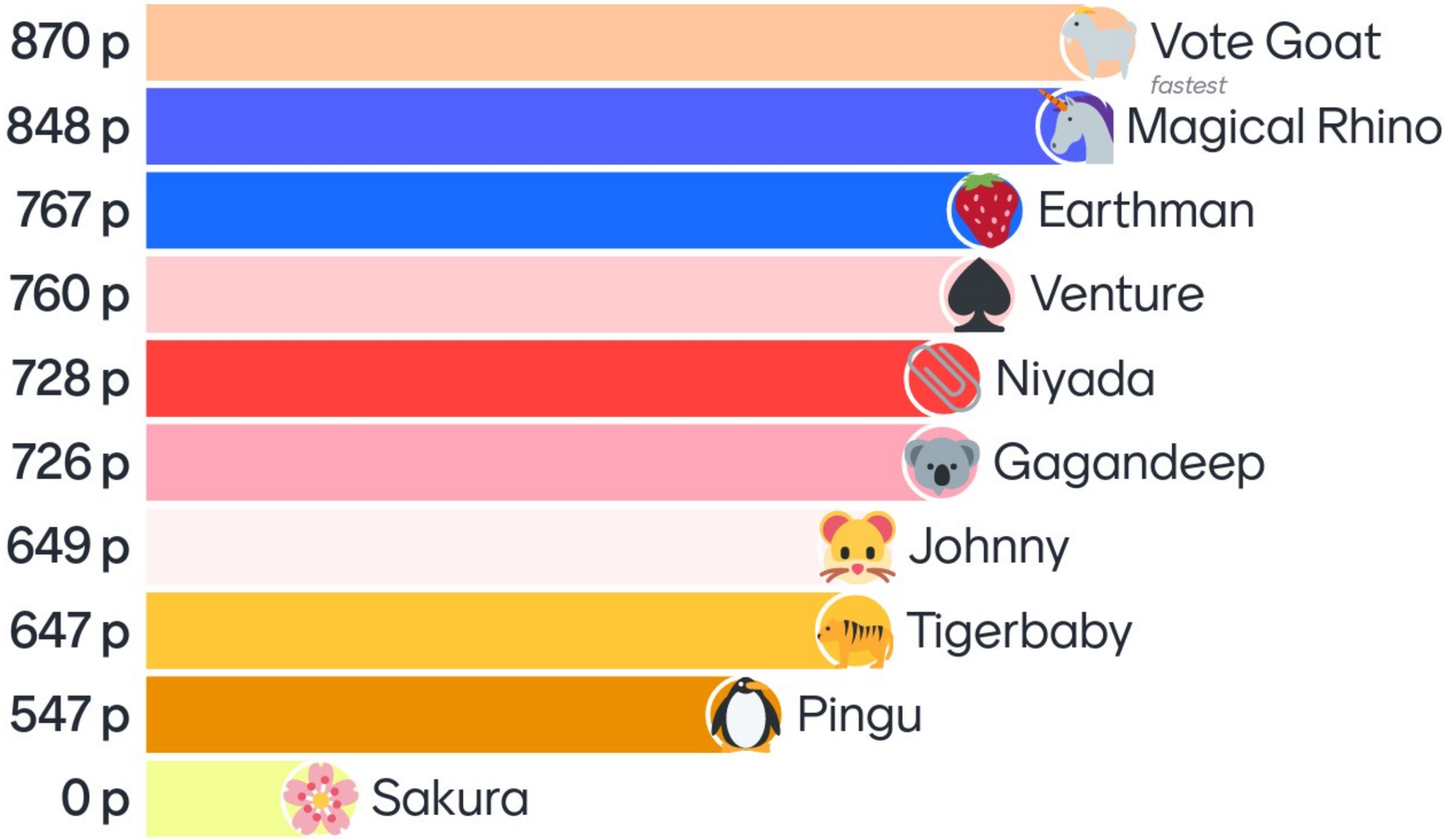
Leaderboard



Selection of 1st and 2nd choice antibiotics

	Ear infection (otitis media)	Sore throat (pharyngitis)	Kidney infection (pyelonephritis)
First line treatment	No antibiotic therapy		Antibiotic therapy
1 First choice	ACCESS e.g. Amoxicillin	ACCESS e.g. Amoxicillin	WATCH e.g. Ciprofloxacin
2 Second choice	ACCESS e.g. Amoxicillin + clavulanic acid	WATCH e.g. Clarithromycin	WATCH e.g. Cefotaxime

https://aware.essentialmeds.org/groups

1st criterion: efficacy

Initial WHO AWaRe Classification (2017)

Access
Amoxicillin
Amoxicillin and clavulanic acid
Ampicillin
Benzathine benzylpenicillin
Benzylpenicillin
Cefalexin or cefazolin
Chloramphenicol
Clindamycin
Cloxacillin
Doxycyline
Gentamicin or amikacin
Metronidazole
Nitrofurantoin
Phenoxymethylpenicillin
Procaine benzylpenicillin
Spectinomycin
Sulfamethoxazole and trimethoprim

Core access antibiotics

Watch
Azithromycin
Cefixime
Cefotaxime
Ceftriaxone
Ciprofloxacin
Clarithromycin
Piperacillin and tazobactam
Meropenem
Vancomycin

* Antibiotics that are also in the Watch group

Watch
Anti-pseudomonal penicillins with beta-lactamase inhibitor (eg, piperacillin and tazobactam)
Carbapenems or penems (eg, faropenem, imipenem and cilastatin, meropenem)
Cephalosporins, third generation (with or without beta-lactamase inhibitor; eg, cefixime, cefotaxime, ceftazidime, ceftriaxone)
Glycopeptides (eg, teicoplanin, vancomycin)
Macrolides (eg, azithromycin, clarithromycin, erythromycin)
Quinolones and fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin)

Reserve
Aztreonam
Cephalosporins, fourth generation (eg, cefepime)
Cephalosporins, fifth generation (eg, ceftaroline)
Daptomycin
Fosfomycin (intravenous)
Oxazolidinones (eg, linezolid)
Polymyxins (eg, colistin, polymyxin B)
Tigecycline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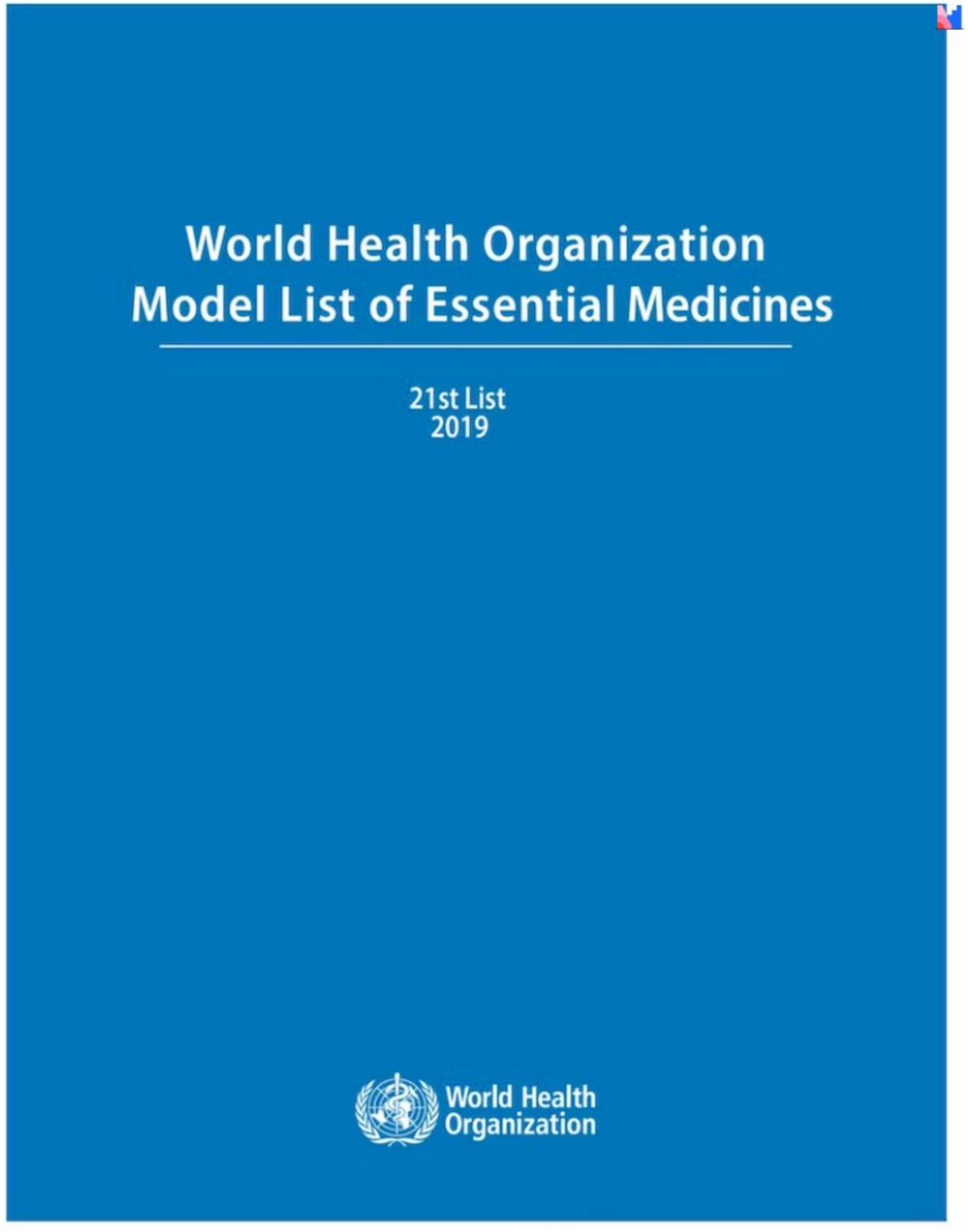
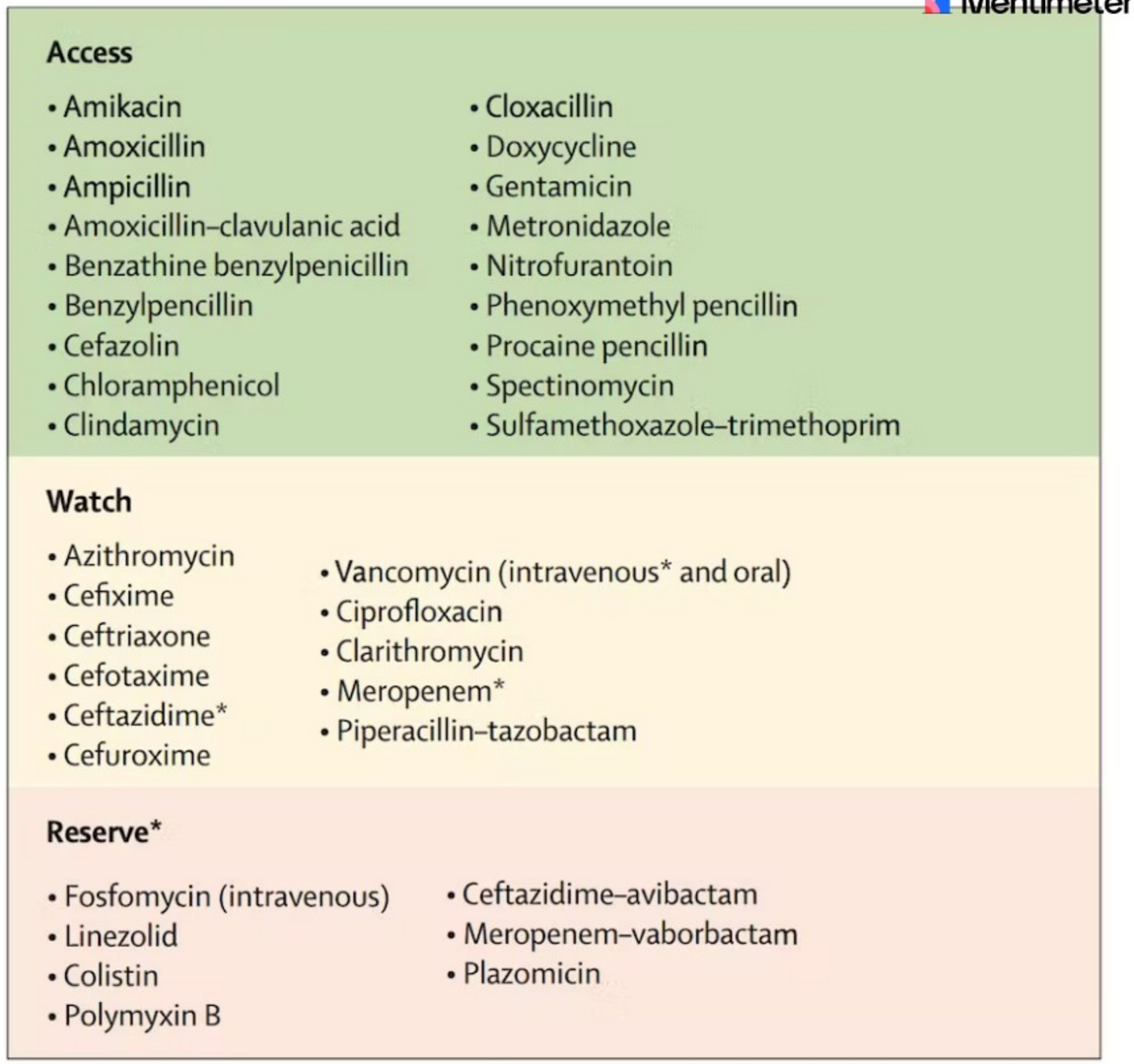
Confused ?
You are not alone

A 2nd revision took place in 2019, further refining (and simplifying) the list and groupings of antibiotics



WHO AWaRe Classification (2019)

- Separation of AWaRe from the EML
- Listing of specific molecules (not classes)
- Classification of most antibiotics classified as “Other” before
- Introduction of a “not recommended” group (e.g. antibiotic combinations without clear indication)
- A further few minor changes in 2021
  - Cefiderocol added as Reserve antibiotic on EML (not EMLc)



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

***Figure:* Antibiotics included in 2019 WHO Essential Medicines List by AWaRe group**

*Antibiotics listed in the complementary list of the 2019 WHO Essential Medicines List, indicating the need for specialist supervision.

Sharland et al. Lancet Infect Dis. 2019 Dec;19(12):1278-1280.

Mentimeter

WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2021

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.
This classification is intended to be used as a tool for countries to better support antibiotic monitoring and stewardship activities. It is not intended as model for the inclusion of antibiotics on national essential medicine lists. Antibiotics classified under AWaRe and also included on the WHO Model Lists of Essential Medicines are indicated in the worksheets.

Antibiotic	Class	ATC code	Category	Listed on EML/EMLc 2021
Amikacin	Aminoglycosides	J01GB06	Access	Yes
Amoxicillin	Penicillins	J01CA04	Access	Yes
Amoxicillin/clavulanic-acid	Beta-lactam/beta-lactamase-inhibitor	J01CR02	Access	Yes
Ampicillin	Penicillins	J01CA01	Access	Yes
Ampicillin/sulbactam	Beta-lactam/beta-lactamase-inhibitor	J01CR01	Access	No
Arbekacin	Aminoglycosides	J01GB12	Watch	No
Aspoxicillin	Penicillins	J01CA19	Watch	No
Azidocillin	Penicillins	J01CE04	Access	No
Azithromycin	Macrolides	J01FA10	Watch	Yes
Azlocillin	Penicillins	J01CA09	Watch	No
Aztreonam	Monobactams	J01DF01	Reserve	No
Bacampicillin	Penicillins	J01CA06	Access	No
Bekanamycin	Aminoglycosides	J01GB13	Watch	No
Benzathine-benzylpenicillin	Penicillins	J01CE08	Access	Yes
Benzylpenicillin	Penicillins	J01CE01	Access	Yes
Biapenem	Carbapenems	J01DH05	Watch	No
Brodimoprim	Trimethoprim-derivatives	J01EA02	Access	No
Carbenicillin	Penicillins	J01CA03	Watch	No
Carindacillin	Penicillins	J01CA05	Watch	No
Carumonam	Monobactams	J01DF02	Reserve	No
Cefacetrile	First-generation-cephalosporins	J01DB10	Access	No
Cefaclor	Second-generation-cephalosporins	J01DC04	Watch	No
Cefadroxil	First-generation-cephalosporins	J01DB05	Access	No
Cefalexin	First-generation-cephalosporins	J01DB01	Access	Yes
Cefaloridine	First-generation-cephalosporins	J01DB02	Access	No
Cefalotin	First-generation-cephalosporins	J01DB03	Access	No
Cefamandole	Second-generation-cephalosporins	J01DC03	Watch	No
Cefapirin	First-generation-cephalosporins	J01DB08	Access	No

Copyright & Disclaimers | AWaRe classification 2021 | Access | Watch | Reserve | Not recommended | 22nd EML 2021 | 8th EMLc 2021

https://www.who.int/publications/i/item/2021-aware-classification

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EML Access group antibiotics

- Core set of **20 antibiotics**
  - 1st or 2nd line choice for ***empirical*** treatment of the priority clinical infection syndromes
- Generally characterized by **narrow-spectrum** (with limited risk of resistance) and/or low toxicity
- Prioritized for use over Watch and Reserve antibiotics
- Should be available everywhere
  - at an appropriate quantity, dose, and formulation

ACCESS on the 2021 EML

Amikacin
Amoxicillin
Amoxicillin/clavulanic-acid
Ampicillin
Benzathine-benzylpenicillin
Benzylpenicillin
Cefalexin
Cefazolin
Chloramphenicol
Clindamycin
Cloxacillin
Doxycycline
Gentamicin
Metronidazole
Nitrofurantoin
Phenoxymethylpenicillin
Procaine-benzylpenicillin
Spectinomycin
Sulfamethoxazole/trimethoprim
Trimethoprim

EML Watch group antibiotics

- Recommended only for a limited number of specific syndromes – **11 antibiotics**
- AB classes that have a **higher potential to drive bacterial resistance**
  - e.g. fluoroquinolones and macrolides
- These antibiotics are also highest priority agents of CIA List
  - (critically important antimicrobials for human medicine)
- Active stewardship important for optimal (specific) uses
- Active monitoring of Watch antibiotics is encouraged
  - e.g., through point-prevalence surveys as a stewardship tool

WATCH on the 2021 EML

Azithromycin

Cefixime

Cefotaxime

Ceftazidime

Ceftriaxone

Cefuroxime

Ciprofloxacin

Clarithromycin (or Erythromycin)

Meropenem (or Imipenem)

Piperacillin + tazobactam

Vancomycin (IV & PO)

EML Reserve group antibiotics

- **Currently 8 "last-resort" antibiotics on EML**
  - proven activity against critical and high priority pathogens (according to WHO PPL)
- Restricted to use in specific patients and clinical settings
  - such as life-threatening infections with MDR- or XDR-resistant bacteria
  - when all Access or Watch group alternatives have failed or not suitable
- Key targets of high intensity national and international stewardship programs
- New antibiotics are likely (but not automatically) to be placed in this group

RESERVE on the 2021 EML

Cefiderocol
Ceftazidime/avibactam
Colistin (IV)
Fosfomycin (IV)
Linezolid
Meropenem/vaborbactam
Plazomicin
Polymyxin-B (IV)

RESERVE group antibiotics (2021)

Listed on EML
Ceftazidime-avibactam
Colistin
Fosfomycin (IV)
Linezolid
Meropenem-vaborbactam
Plazomicin
Polymyxin B
Ceftazidime-avibactam
Cefiderocol

Not listed on EML
Aztreonam
Carumonam
Ceftaroline-fosamil
Ceftobiprole-medocaril
Ceftolozane/tazobactam
Colistin_oral
Dalbavancin
Dalfopristin/quinupristin
Daptomycin
Eravacycline
Faropenem
Iclaprim
Imipenem/cilastatin/relebactam
Lefamulin
Minocycline_IV
Omadacycline
Oritavancin
Polymyxin-B_oral
Tedizolid
Telavancin
Tigecycline

RESERVE group antibiotics

- **Never** listed as first or second-line antibiotic options for any of the 21 infectious syndromes reviewed during the update of the EML

- **BUT:**
  - only empirical treatment was considered for the choice of first or second-line options
  - some important nosocomial infections (such as ventilator associated pneumonia) were excluded from the review.
  - **Use of a RESERVE antibiotic (even empirically) may be appropriate in specific settings**

Not-recommended antibiotics (Fixed-dose combinations)

Table 1. Categories of antibiotic Fixed Dose Combinations (FDCs).

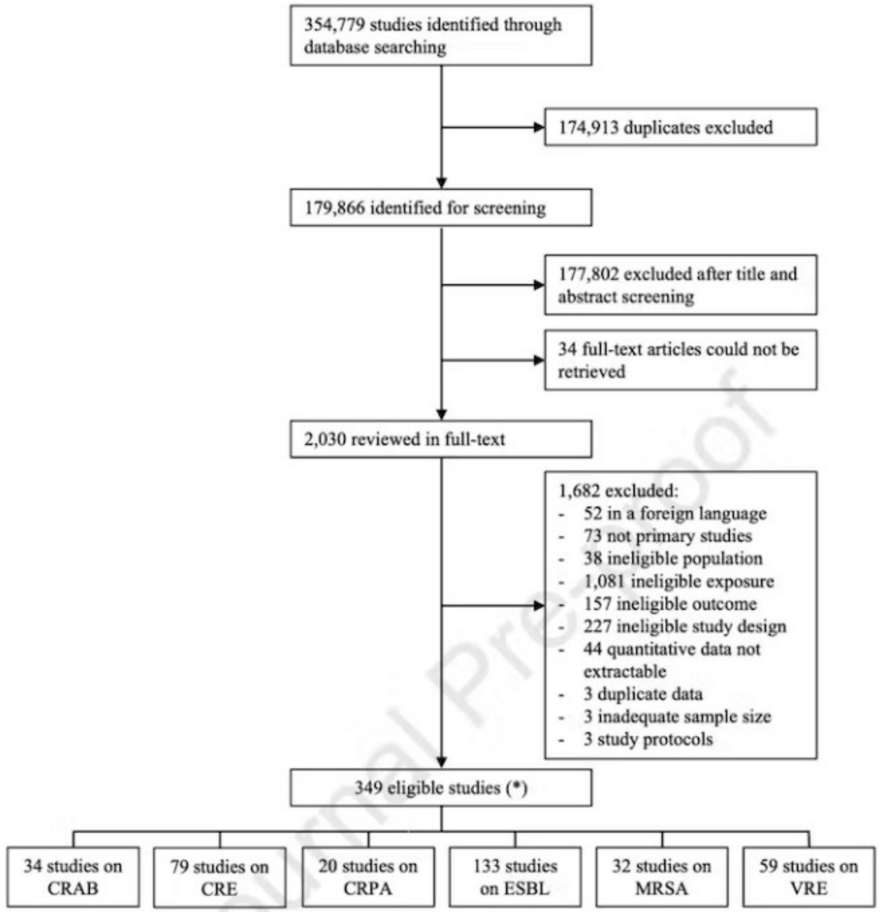
FDC types	Standard Unite sold	Number of FDCs
Aminopenicillin /β-lactamase inhibitor //- other agents	8.60×10^9	8
Sulphonamides/trimethoprim+/- other agents	3.62×10^9	9
Aminopenicillin / β-lactamase resistant penicillin +/- other agents	1.54×10^9	21
Antipseudomonal penicillin /β-lactamase inhibitor	0.95×10^9	4
3^{rd}-4^{th}-5^{th} gen. cephalosporins /β-lactamase inhibitor +/- other agents	0.55×10^9	15
Cephalosporins / fluoroquinolones	0.40×10^9	6
1^{st}-2^{nd} gen. cephalosporins / β-lactamase inhibitor +/- other agents	0.26×10^9	8
Macrolide/ 5-nitroimidazole	0.24×10^9	3
Macrolide/cephalosporin+/-other agents	0.21×10^9	3
Cephalosporin/ β-lactamase resistant penicillin +/- other agents	0.10×10^9	7
Cephalosporin/trimethoprim	0.09×10^9	2
Cephalosporin/oxazolidinone	0.04×10^9	2
Fluoroquinolone/ 5-nitroimidazole	0.04×10^9	8
Macrolide / fluoroquinolone +/- other agents	0.04×10^9	2
Cephalosporin/5-nitroimidazole	0.03×10^9	1
Other combinations	0.01×10^9	20

- Analysis of IQVIA-MIDAS® data for antibiotic FDCs from 75 countries in 2015
- 22% of total antibiotic consumption in 2015
- 92% (110/119) were not approved by the US FDA
- >80% not compatible with EML

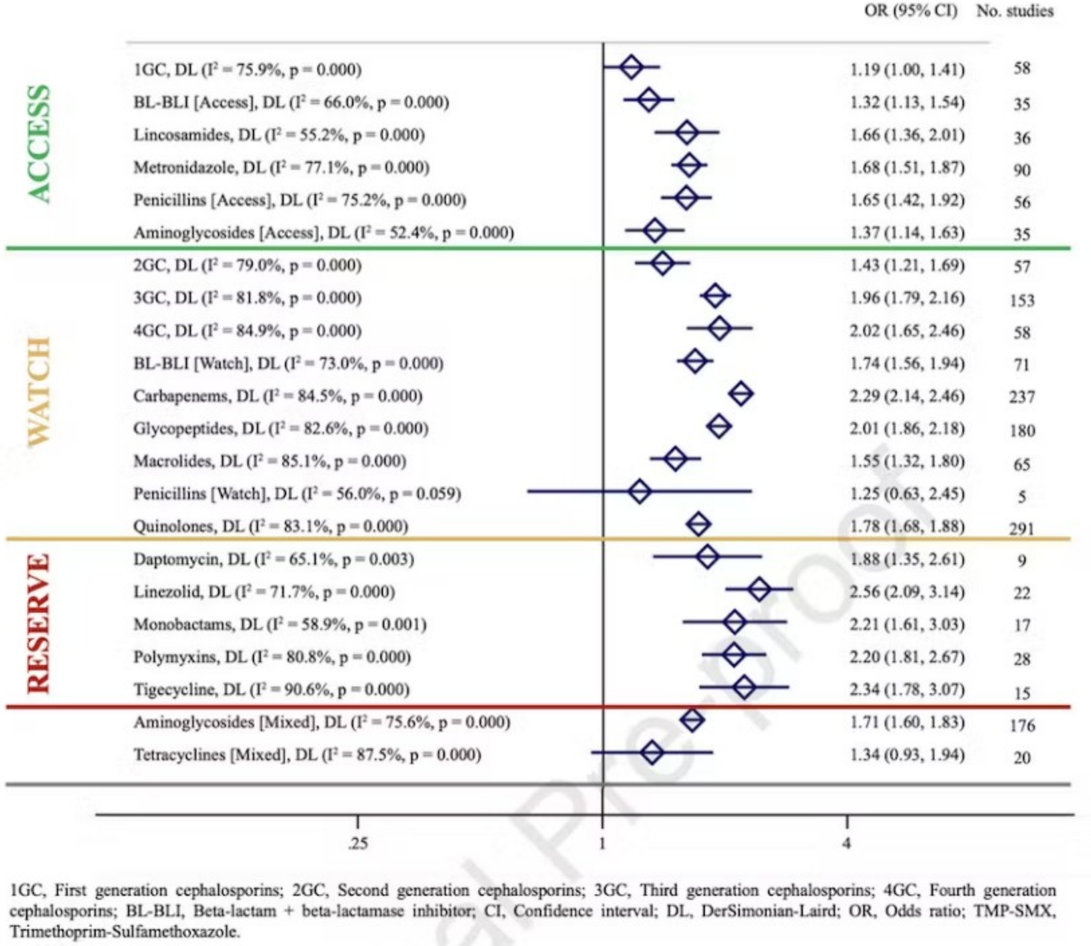
Bortone et al. PLoS One. 2021; 16(1): e0241899.


Mentimeter
What is the evidence base for AWaRe ?

Risk of resistance by AWaRe category: results from a systematic review



* Eight studies reported on two different pathogens



1GC, First generation cephalosporins; 2GC, Second generation cephalosporins; 3GC, Third generation cephalosporins; 4GC, Fourth generation cephalosporins; BL-BLI, Beta-lactam + beta-lactamase inhibitor; CI, Confidence interval; DL, DerSimonian-Laird; OR, Odds ratio; TMP-SMX, Trimethoprim-Sulfamethoxazole.

Sulis et al. Clin Microbiol Infect. 2022 Mar 23;S1198-743X(22)00153-7.

AWaRe – CIA – OIE (WOAH)
One Health ?

Overlap with critically important antibiotics

Critically Important

Antimicrobial class	Criterion (Yes = ●)				
CRITICALLY IMPORTANT ANTIMICROBIALS	C1	C2	P1	P2	P3
HIGHEST PRIORITY					
Highest Priority: *Cephalosporins (3rd, 4th and 5th generation)*	●	●	●	●	●
Highest Priority: *Glycopeptides*	●	●	●	●	●
Highest Priority: *Macrolides and ketolides*	●	●	●	●	●
Highest Priority: *Polymyxins*	●	●	●	●	●
Highest Priority: *Quinolones*	●	●	●	●	●
HIGH PRIORITY					
Aminoglycosides	●	●		●	●
Ansamycins	●	●	●	●	
Carbapenems and other penems	●	●	●	●	
Glycylcyclines	●	●	●		
Lipopeptides	●	●	●		
Monobactams	●	●	●		
Oxazolidinones	●	●	●		
Penicillins (natural, aminopenicillins, and antipseudomonal)	●	●		●	●
Phosphonic acid derivatives	●	●	●	●	
Drugs used solely to treat tuberculosis or other mycobacterial diseases	●	●	●	●	

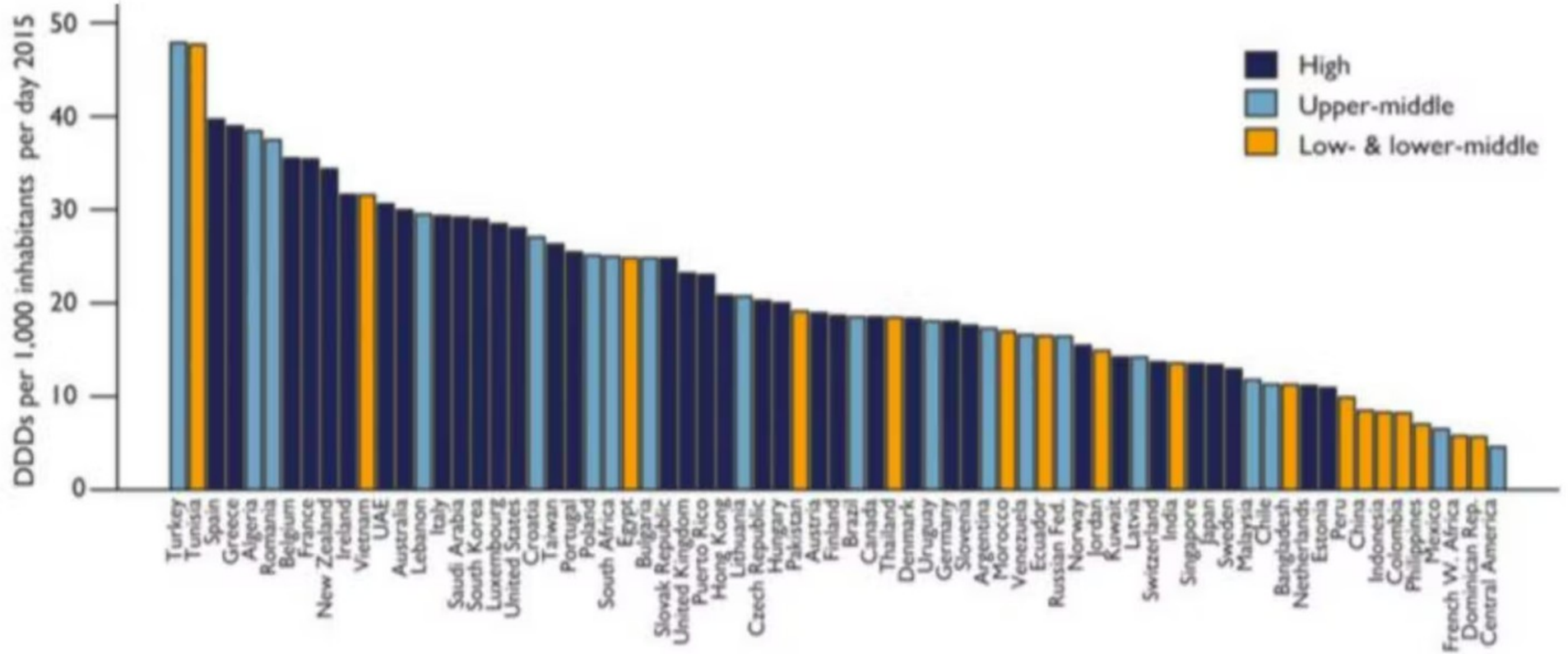
Mentimeter

How to adopt AWaRE

AWaRe for monitoring antibiotic use

Mentimeter

- AWaRe is a relatively “easy” tool that offers more than overall antibiotic use or more conventional classifications (such as broad- vs. narrow-spectrum antibiotics)



Klein et al. Proc Natl Acad Sci U S A. 2018 Mar 26. pii: 201717295.

What is the optimal level of antibiotic use ?

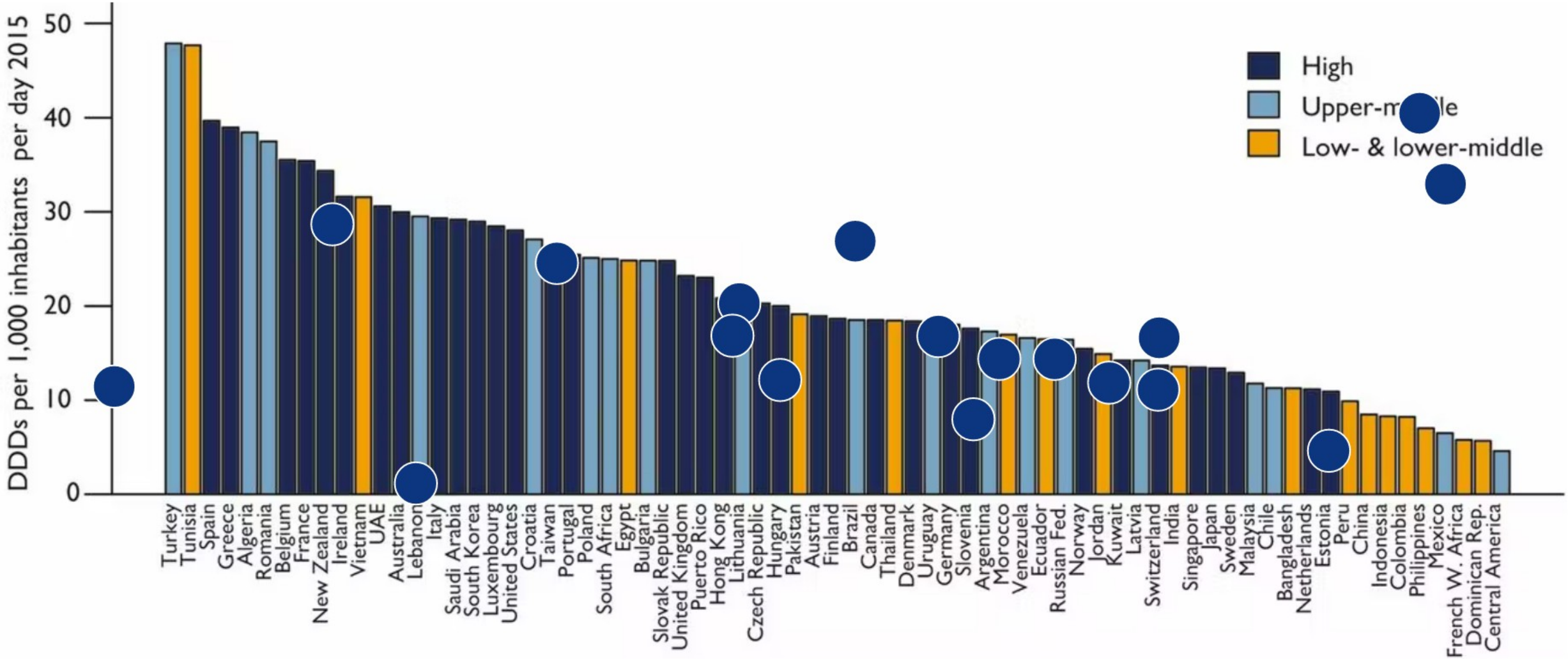
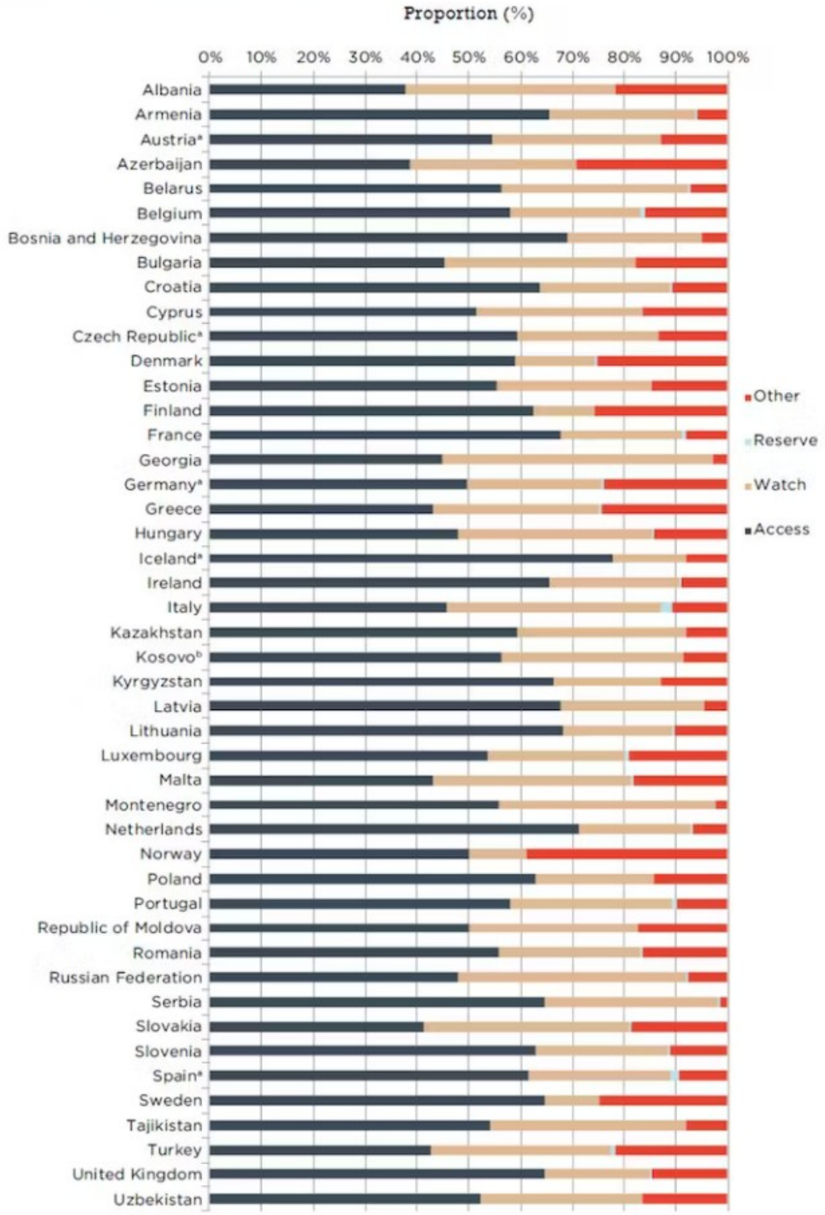


Fig. 4.7 Proportional consumption (%) of antibiotics by AWaRe categorization in 45 countries and Kosovo[b] of the European Region (2015)



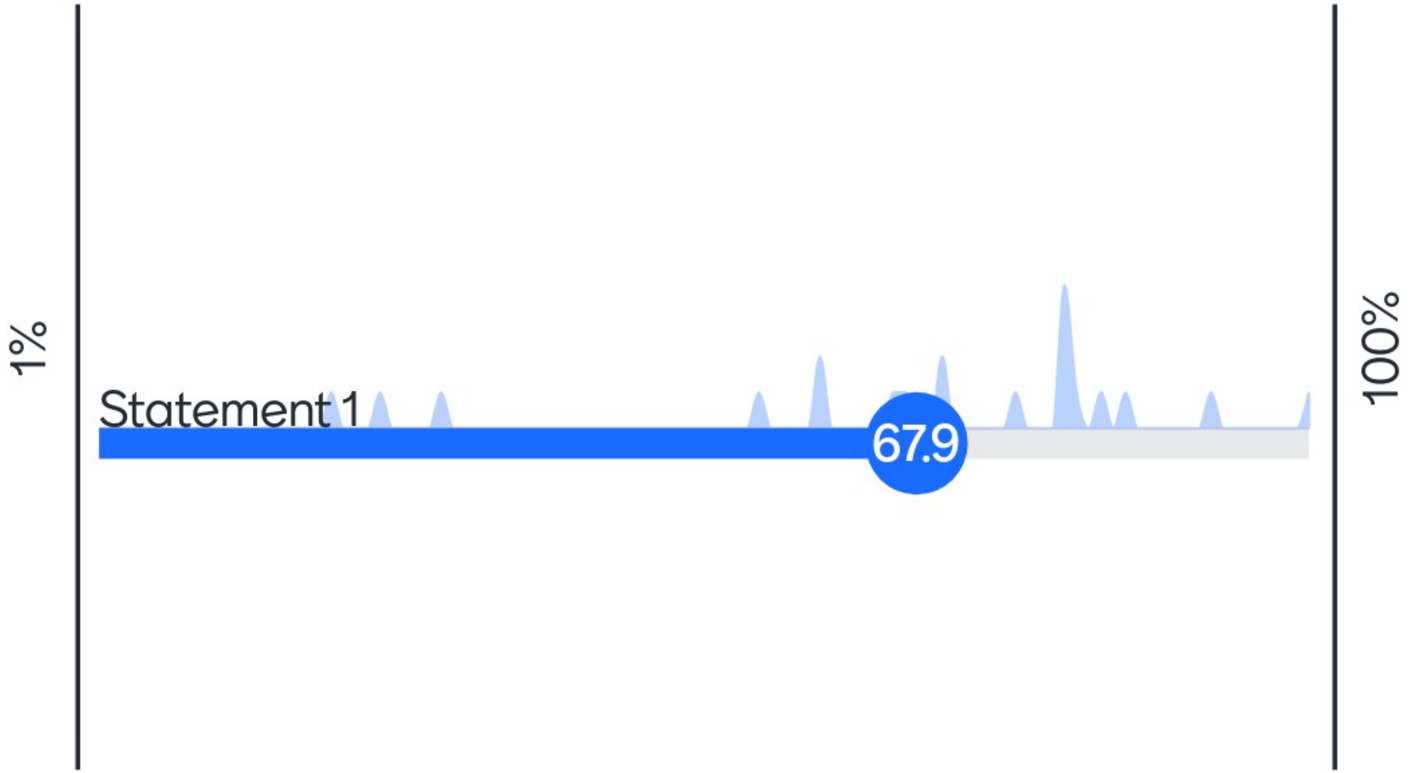
[a] Only community consumption reported.

[b] In accordance with Security Council Resolution 1244 (1999).

GOOD HEALT
AND WELL-BI

What would you consider a "reasonable" target for Access antibiotic use (as % of overall antibiotic use)

Mentimeter



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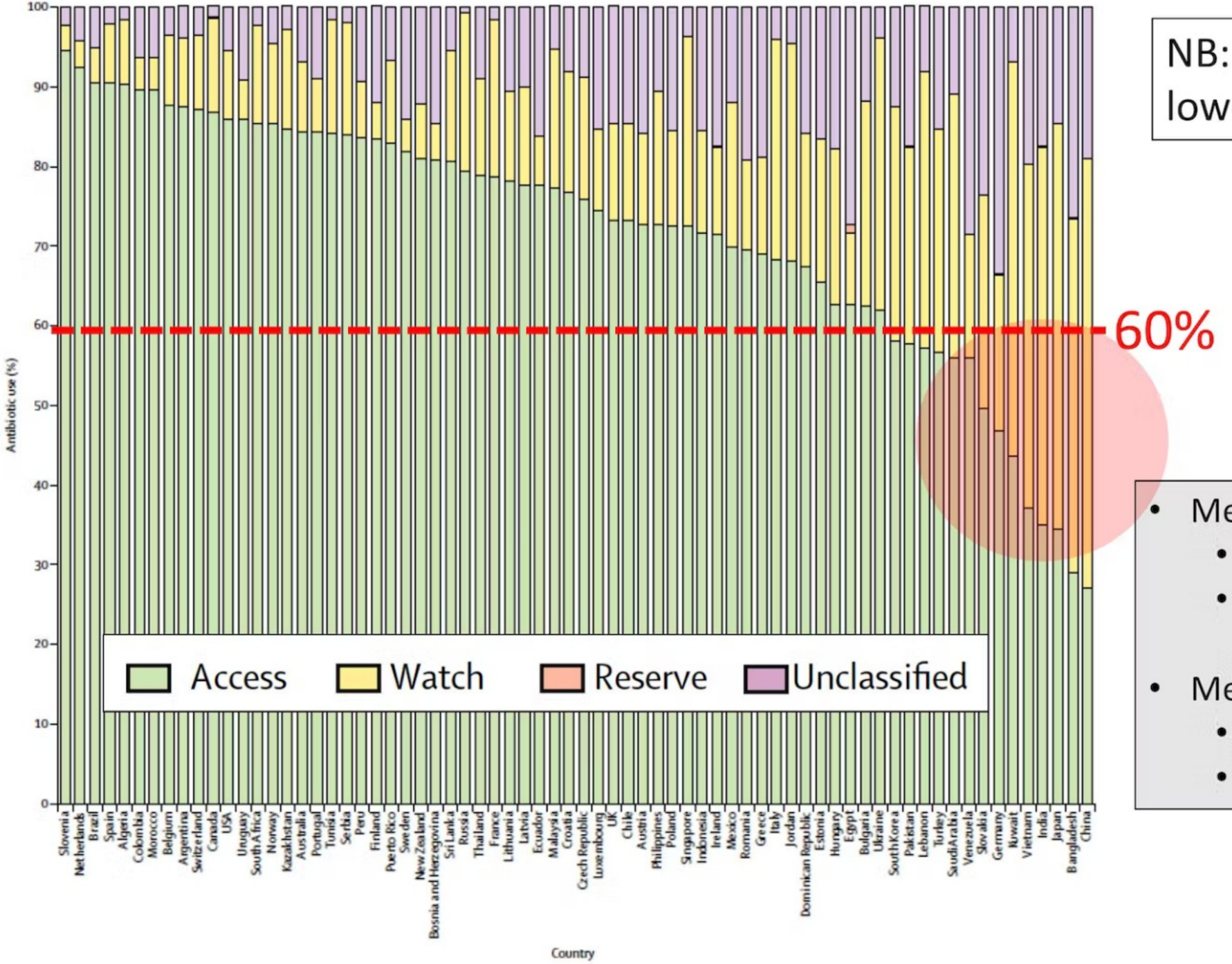
Measuring antibiotic use

Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries

Yingfen Hsia, Mike Sharland, Charlotte Jackson, Ian C K Wong, Nicola Magrini, Julia A Bielicki

Analysis of 2015 wholesale antibiotic sales data from 70 middle-income and high-income countries (IQVIA-MIDAS database)

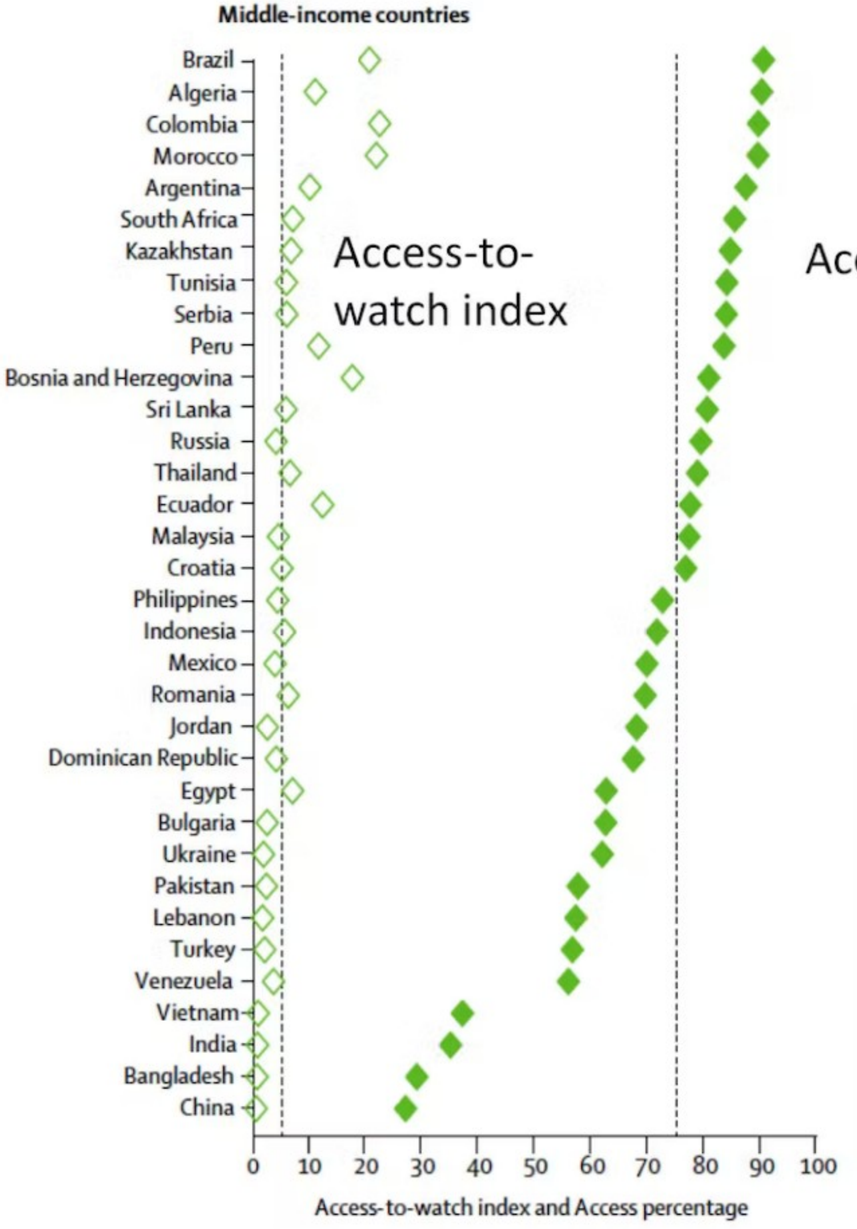
Hsia et al. Lancet Infect Dis. 2019 Jan;19(1):67-75.



60%

NB: No country-level data for low-income countries !

- Median **Access** group use 76·3%
  - Max 94·4% Slovenia
  - Min 27·0% China
- Median **Watch** group use 12·3%
  - Max China 54·0%
  - Min Slovenia 3·3%



Access-to-watch index

Access %

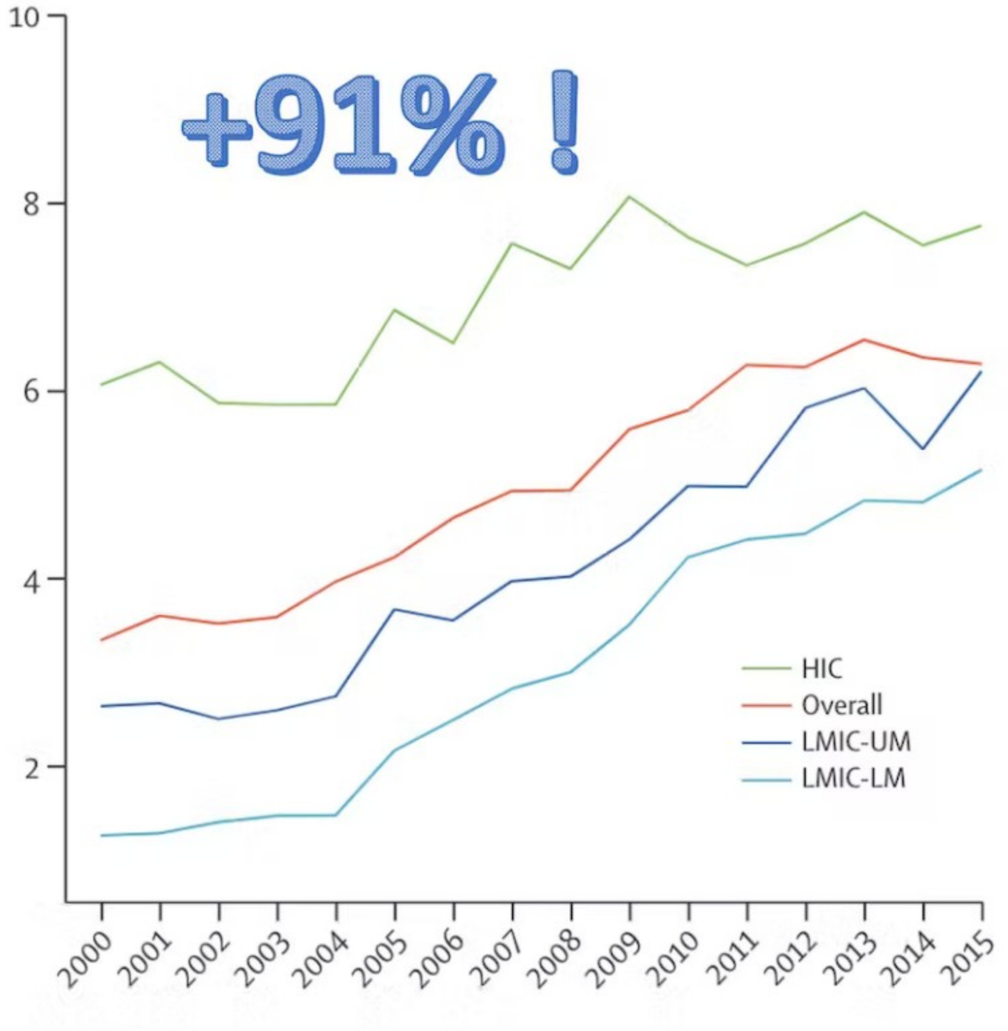
Mentimeter

- Median **Access** group use 76·3%
  - Max 94·4% Slovenia
  - Min 27·0% China
- Median **Watch** group use 12·3%
  - Max China 54·0%
  - Min Slovenia 3·3%

Hsia et al. Lancet Infect Dis. 2019 Jan;19(1):67-75.

Mentimeter

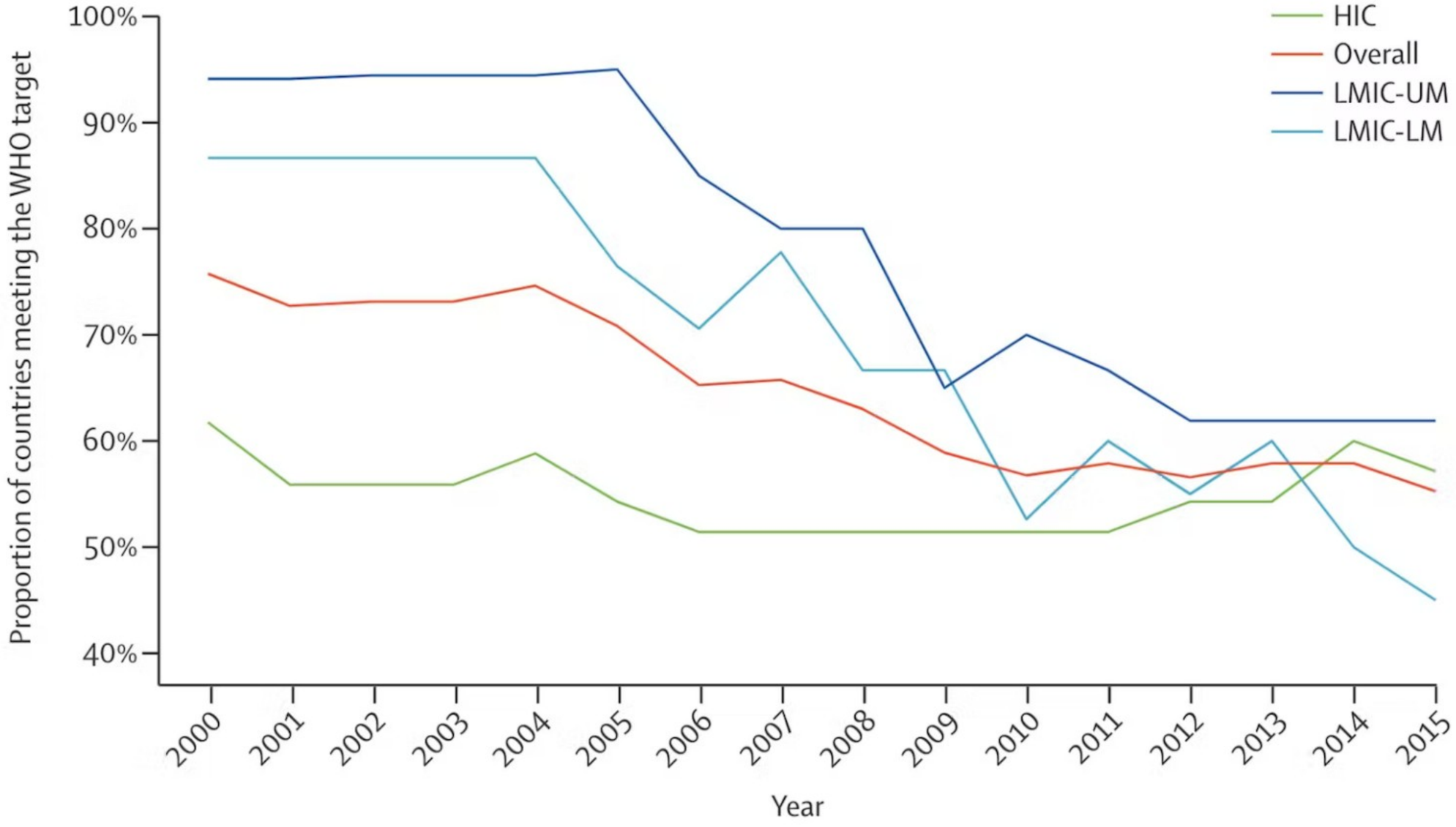
Absolute consumption of Watch antibiotics, 2000–15



Klein et al. Lancet Infect Dis. 2021 Jan;21(1):107-115.

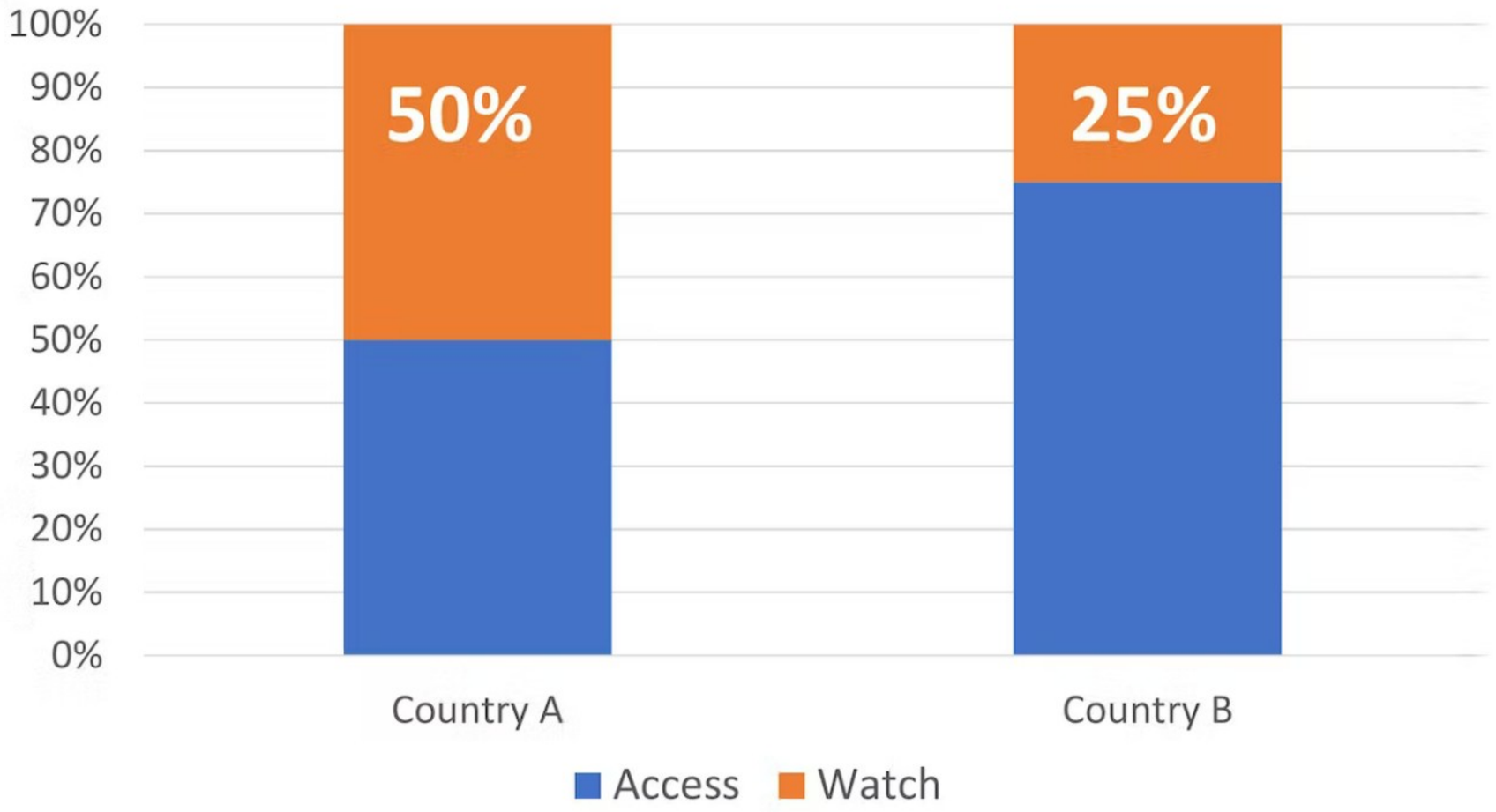
Mentimeter

Proportion of countries that met the WHO target of at least 60% Access antibiotics in total antibiotic consumption, stratified by income level, 2000–15

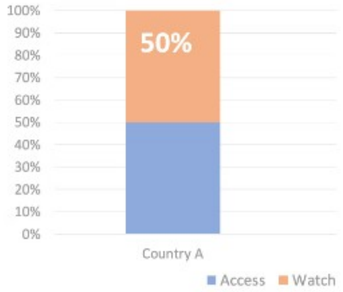


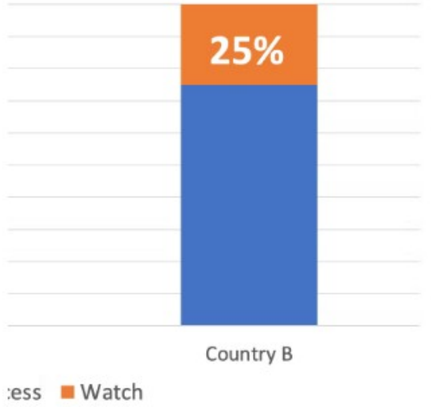
Klein et al. Lancet Infect Dis. 2021 Jan;21(1):107-115.

Relative use



Which country has the "better" antibiotic use ?





Country A

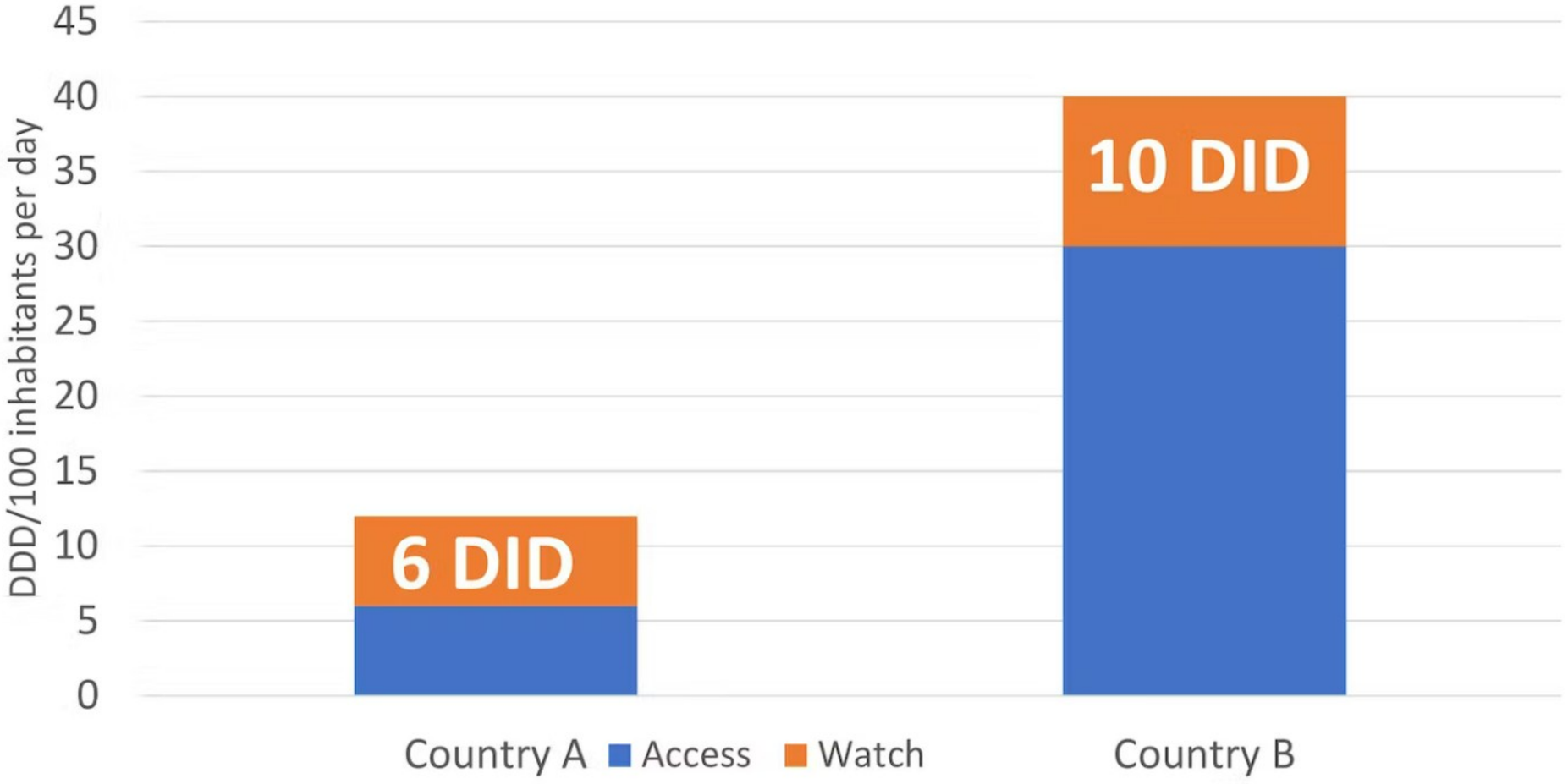
3

Country B

19

22

Overall use also needs to be considered



Consumption of systemic antibiotics in India in 2019

Shaffi Fazaludeen Koya,[a] Senthil Ganesh,[b] Sakthivel Selvaraj,[b] Veronika J. Wirtz,[a] Sandro Galea,[a] and Peter C. Rockers[a]*

[a]Boston University School of Public Health, Boston, MA, USA
[b]Public Health Foundation of India, New Delhi, Delhi, India

The Lancet Regional Health - Southeast Asia 2022;4: 100025
https://doi.org/10.1016/j.lansea.2022.100025

Summary

Background Inappropriate use of antibiotics is a significant driver of antibiotic resistance in India. Largely unrestricted over-the-counter sales of most antibiotics, manufacturing and marketing of many fixed-dose combinations (FDC) and overlap in regulatory powers between national and state-level agencies complicate antibiotics availability, sales, and consumption in the country.

Methods We analyzed cross-sectional data from PharmaTrac, a nationally representative private-sector drug sales dataset gathered from a panel of 9000 stockists across India. We used the AWaRe (Access, Watch, Reserve) classification and the defined daily dose (DDD) metrics to calculate the per capita private-sector consumption of systemic antibiotics across different categories: FDCs vs single formulations; approved vs unapproved; and listed vs not listed in the national list of essential medicines (NLEM).

Findings The total DDDs consumed in 2019 was 5071 million (10.4 DDD/1000/day). Watch contributed 54.9% (2783 million) DDDs, while Access contributed 27.0% (1370 million). Formulations listed in the NLEM contributed 49.0% (2486 million DDDs); FDCs contributed 34.0% (1722 million), and unapproved formulations contributed 47.1% (2408 million DDDs). Watch antibiotics constituted 72.7% (1750 million DDDs) of unapproved products and combinations discouraged by the WHO constituted 48.7% (836 million DDDs) of FDCs.

Interpretation Although the per-capita private-sector consumption rate of antibiotics in India is relatively low compared to many countries, India consumes a large volume of broad-spectrum antibiotics that should ideally be used sparingly. This, together with significant share of FDCs from formulations outside NLEM and a large volume of antibiotics not approved by the central drug regulators, call for significant policy and regulatory reform.

Funding Not applicable.

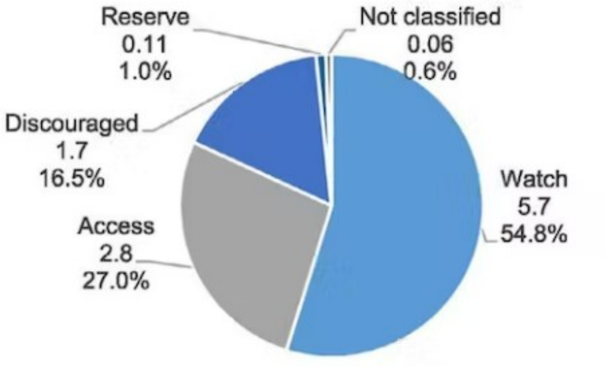


Figure 2. AWaRe composition of antibiotics consumed (DID), 2019.

Table 1. Recategorization of antibiotics within the AWaRe index for use in English national stewardship policy

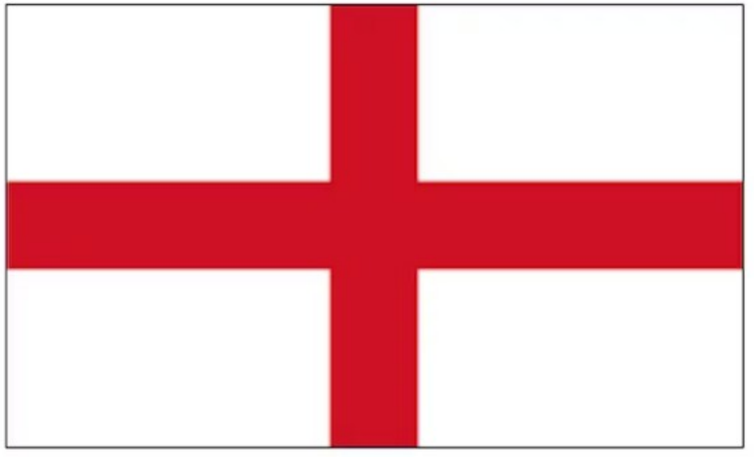
ATC name	ATC code	AWaRe WHO	AWaRe England	Rationale for movement
Amikacin	J01GB06	Access	Watch	antibiotic used for resistant Gram-negative infections
Amoxicillin and enzyme inhibitor	J01CR02	Access	Watch	to avoid overuse as resistance increasing and associated with increased risk of *C. difficile* infections
Ampicillin combinations	J01CA51	Other	Access	similar category as amoxicillin; rare use
Cefaclor	J01DC04	Other	Watch	associated with increased risk of *C. difficile* infections
Cefadroxil	J01DB05	Other	Watch	associated with increased risk of *C. difficile* infections
Cefalexin	J01DB01	Access	Watch	associated with increased risk of *C. difficile* infections
Cefamandole	J01DC03	Other	Watch	associated with increased risk of *C. difficile* infections
Cefazolin	J01DB04	Access	Watch	associated with increased risk of *C. difficile* infections
Cefoxitin	J01DC01	Other	Watch	associated with increased risk of *C. difficile* infections
Cefprozil	J01DC10	Other	Watch	associated with increased risk of *C. difficile* infections
Cefradine	J01DB09	Other	Watch	associated with increased risk of *C. difficile* infections
Cefuroxime	J01DC02	Other	Watch	associated with increased risk of *C. difficile* infections
Ceftazidime and enzyme inhibitor	J01DD52	Watch	Reserve	novel combination reserved for treatment failures
Chloramphenicol	J01BA01	Access	Watch	second-line antibiotic, use in penicillin allergy
Clindamycin	J01FF01	Access	Watch	associated with increased risk of *C. difficile* infections
Dalbavancin	J01XA04	Watch	Reserve	novel antibiotic reserved for treatment failures and OPAT
Doripenem	J01DH04	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Ertapenem	J01DH03	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Fosfomycin (oral)	J01XX01	Other	Access	narrow spectrum, recommended for uncomplicated UTI
Fusidic acid	J01XC01	Other	Access	narrow spectrum
Imipenem	J01DH51	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Lymecycline	J01AA04	Other	Watch	used for acne, alternative non-antimicrobial drugs available
Meropenem	J01DH02	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Minocycline	J01AA08	Other	Watch	used for acne, alternative non-antimicrobial drugs available
Neomycin	J01GB05	Other	Access	not routinely used in England, monitor carefully for change in use
Oxytetracycline	J01AA06	Other	Watch	used for acne, alternative non-antimicrobial drugs available
Piperacillin	J01CA12	Other	Watch	avoid overuse as resistance increasing
Pivmecillinam	J01CA08	Other	Access	narrow spectrum, recommended for uncomplicated UTI
Pristinamycin	J01FG01	Other	Watch	not routinely used in England, monitor carefully for change in use
Quinupristin	J01FG02	Other	Watch	not routinely used in England, monitor carefully for change in use
Telavancin	J01XA03	Watch	Reserve	not routinely used in England, monitor carefully for change in use
Temocillin	J01CA17	Other	Watch	antibiotic used for resistant Gram-negative infections
Tetracycline	J01AA07	Other	Access	narrow spectrum, recommended in treatment guidelines
Ticarcillin	J01CA13	Other	Watch	not routinely used in England, monitor carefully for change in use
Tobramycin	J01GB01	Other	Watch	antibiotic used for resistant Gram-negative infections
Tetracycline combinations	J01AA20	Other	Watch	used for acne, alternative non-antimicrobial drugs available

Any antibiotics categorized as both Access and Watch within the WHO AWaRe index were automatically classified as Watch antibiotics for UK stewardship purposes. The rationale for all other reclassifications is presented in this table. OPAT, outpatient parenteral antimicrobial therapy.

Budd et al. J Antimicrob Chemother. 2019 Nov 1;74(11):3384-3389.

Some countries adapted AWaRe

International comparison goodbye?



WATCH and RESERVE group antibiotics

What to do?

- Monitor use
- Provide feedback on use
- Consider restrictions if overuse
- Develop guidelines when their uses is justified and how they should be used

How familiar do you feel now with AWaRe?

Mentimeter

Not at all

Somewhat

Very much

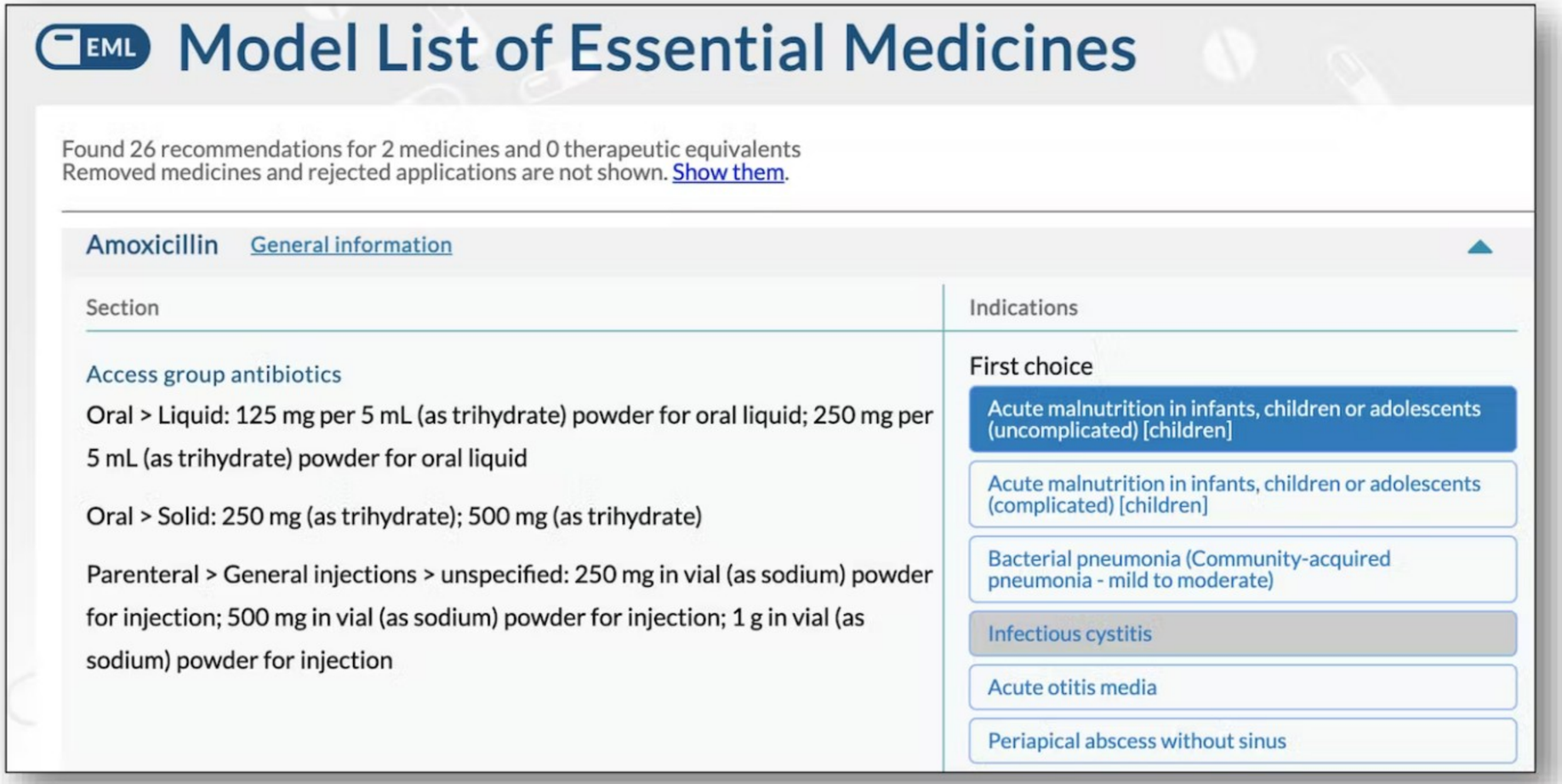
20

Mentimeter

Breathe

Relax, focus and center yourself. Let's take 5 breaths together.

Appropriate use is about more than the choice of the antibiotic



EML Model List of Essential Medicines

Found 26 recommendations for 2 medicines and 0 therapeutic equivalents
Removed medicines and rejected applications are not shown. Show them.

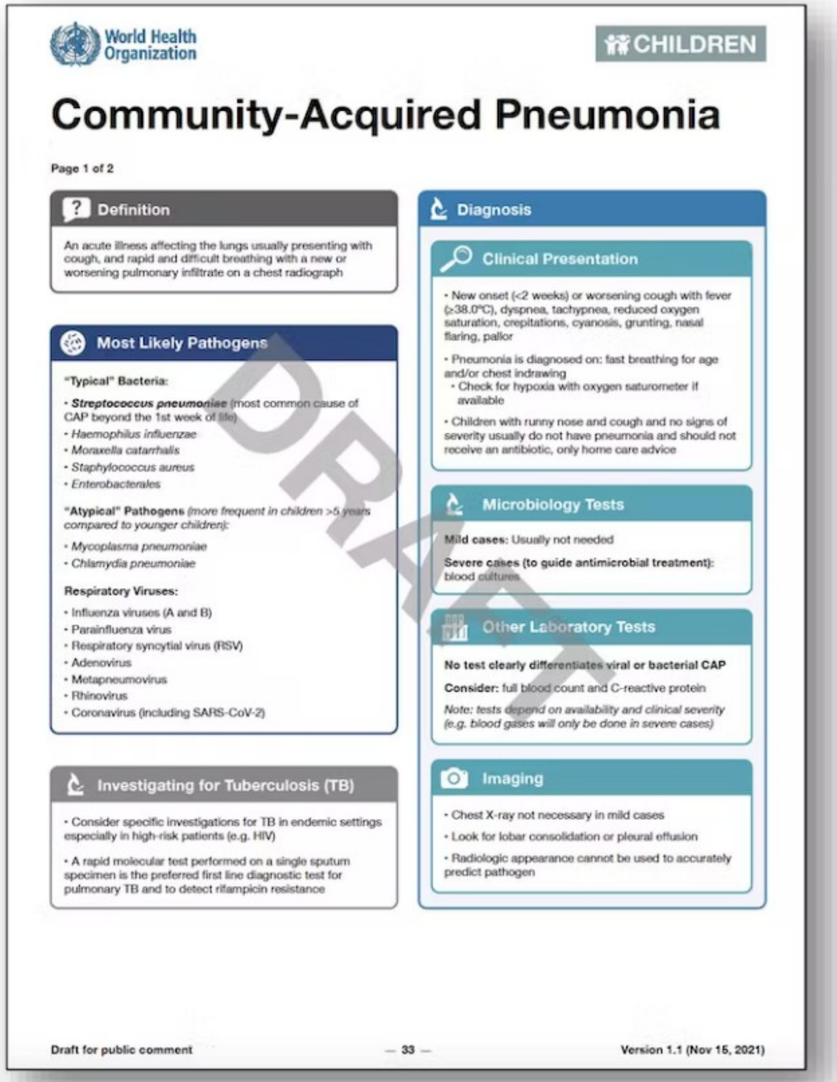
Amoxicillin General information

Section	Indications
Access group antibiotics Oral > Liquid: 125 mg per 5 mL (as trihydrate) powder for oral liquid; 250 mg per 5 mL (as trihydrate) powder for oral liquid Oral > Solid: 250 mg (as trihydrate); 500 mg (as trihydrate) Parenteral > General injections > unspecified: 250 mg in vial (as sodium) powder for injection; 500 mg in vial (as sodium) powder for injection; 1 g in vial (as sodium) powder for injection	First choice Acute malnutrition in infants, children or adolescents (uncomplicated) [children] Acute malnutrition in infants, children or adolescents (complicated) [children] Bacterial pneumonia (Community-acquired pneumonia - mild to moderate) Infectious cystitis Acute otitis media Periapical abscess without sinus

Diagnosis ?
Dose ?
Duration ?

https://list.essentialmeds.org/

The WHO AWaRe Antibiotic Book



World Health Organization

CHILDREN

Community-Acquired Pneumonia

Page 1 of 2

Definition

An acute illness affecting the lungs usually presenting with cough, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

Most Likely Pathogens

"Typical" Bacteria:

- ***Streptococcus pneumoniae*** (most common cause of CAP beyond the 1st week of life)
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Enterobacterales*

"Atypical" Pathogens *(more frequent in children >5 years compared to younger children):*

- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*

Respiratory Viruses:

- Influenza viruses (A and B)
- Parainfluenza virus
- Respiratory syncytial virus (RSV)
- Adenovirus
- Metapneumovirus
- Rhinovirus
- Coronavirus (including SARS-CoV-2)

Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance

Diagnosis

Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever (≥38.0°C), dyspnea, tachypnea, reduced oxygen saturation, crepitations, cyanosis, grunting, nasal flaring, pallor
- Pneumonia is diagnosed on: fast breathing for age and/or chest indrawing
  - Check for hypoxia with oxygen saturometer if available
- Children with runny nose and cough and no signs of severity usually do not have pneumonia and should not receive an antibiotic, only home care advice

Microbiology Tests

Mild cases: Usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures

Other Laboratory Tests

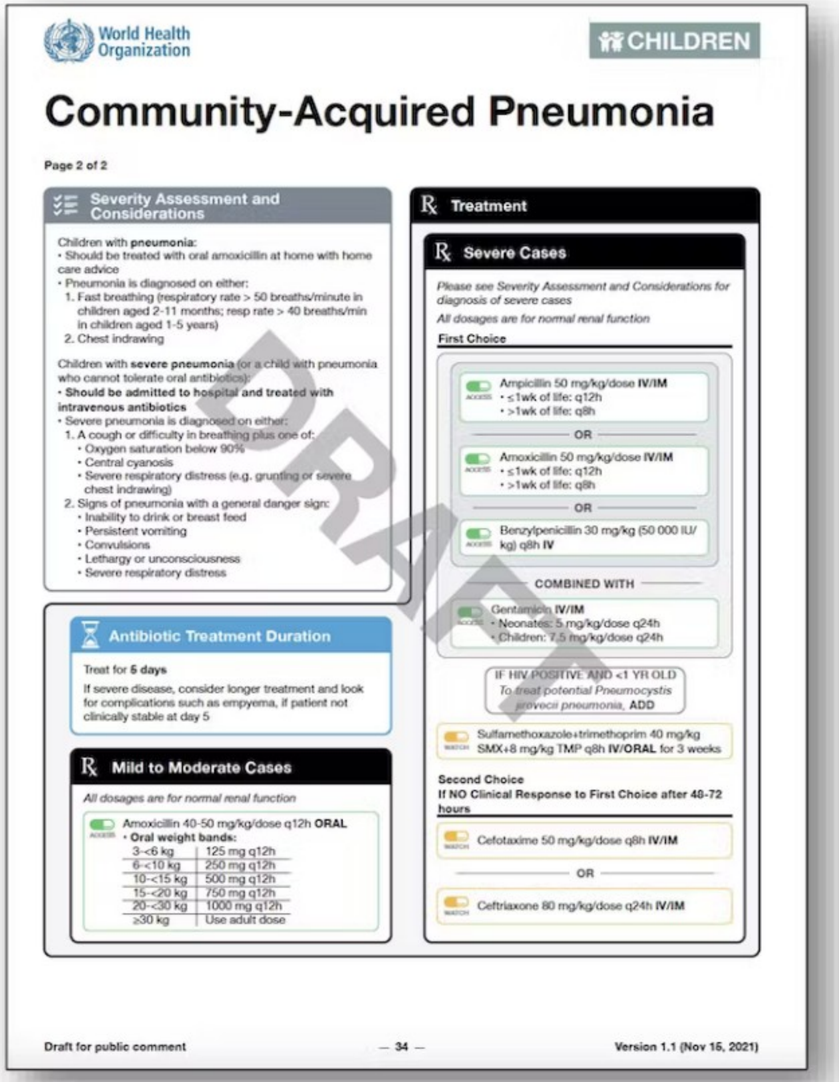
No test clearly differentiates viral or bacterial CAP

Consider: full blood count and C-reactive protein

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

Imaging

- Chest X-ray not necessary in mild cases
- Look for lobar consolidation or pleural effusion
- Radiologic appearance cannot be used to accurately predict pathogen



World Health Organization

CHILDREN

Community-Acquired Pneumonia

Page 2 of 2

Severity Assessment and Considerations

Children with **pneumonia:**
- Should be treated with oral amoxicillin at home with home care advice
- Pneumonia is diagnosed on either:
  1. Fast breathing (respiratory rate > 50 breaths/minute in children aged 2-11 months; resp rate > 40 breaths/min in children aged 1-5 years)
  2. Chest indrawing

Children with **severe pneumonia** (or a child with pneumonia who cannot tolerate oral antibiotics):
- **Should be admitted to hospital and treated with intravenous antibiotics**
- Severe pneumonia is diagnosed on either:
  1. A cough or difficulty in breathing plus one of:
     - Oxygen saturation below 90%
     - Central cyanosis
     - Severe respiratory distress (e.g. grunting or severe chest indrawing)
  2. Signs of pneumonia with a general danger sign:
     - Inability to drink or breast feed
     - Persistent vomiting
     - Convulsions
     - Lethargy or unconsciousness
     - Severe respiratory distress

Antibiotic Treatment Duration

Treat for **5 days**

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Mild to Moderate Cases

All dosages are for normal renal function

Amoxicillin 40-50 mg/kg/dose q12h **ORAL**
- **Oral weight bands:**

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
20-<30 kg	1000 mg q12h
≥30 kg	Use adult dose

Treatment

Severe Cases

Please see Severity Assessment and Considerations for diagnosis of severe cases

All dosages are for normal renal function

First Choice

Ampicillin 50 mg/kg/dose **IV/IM**
- ≤1wk of life: q12h
- >1wk of life: q8h

OR

Amoxicillin 50 mg/kg/dose **IV/IM**
- ≤1wk of life: q12h
- >1wk of life: q8h

OR

Benzylpenicillin 30 mg/kg (50 000 IU/kg) q8h **IV**

COMBINED WITH

Gentamicin **IV/IM**
- Neonates: 5 mg/kg/dose q24h
- Children: 7.5 mg/kg/dose q24h

IF HIV-POSITIVE AND <1 YR OLD
To treat potential Pneumocystis jiroveci pneumonia, **ADD**

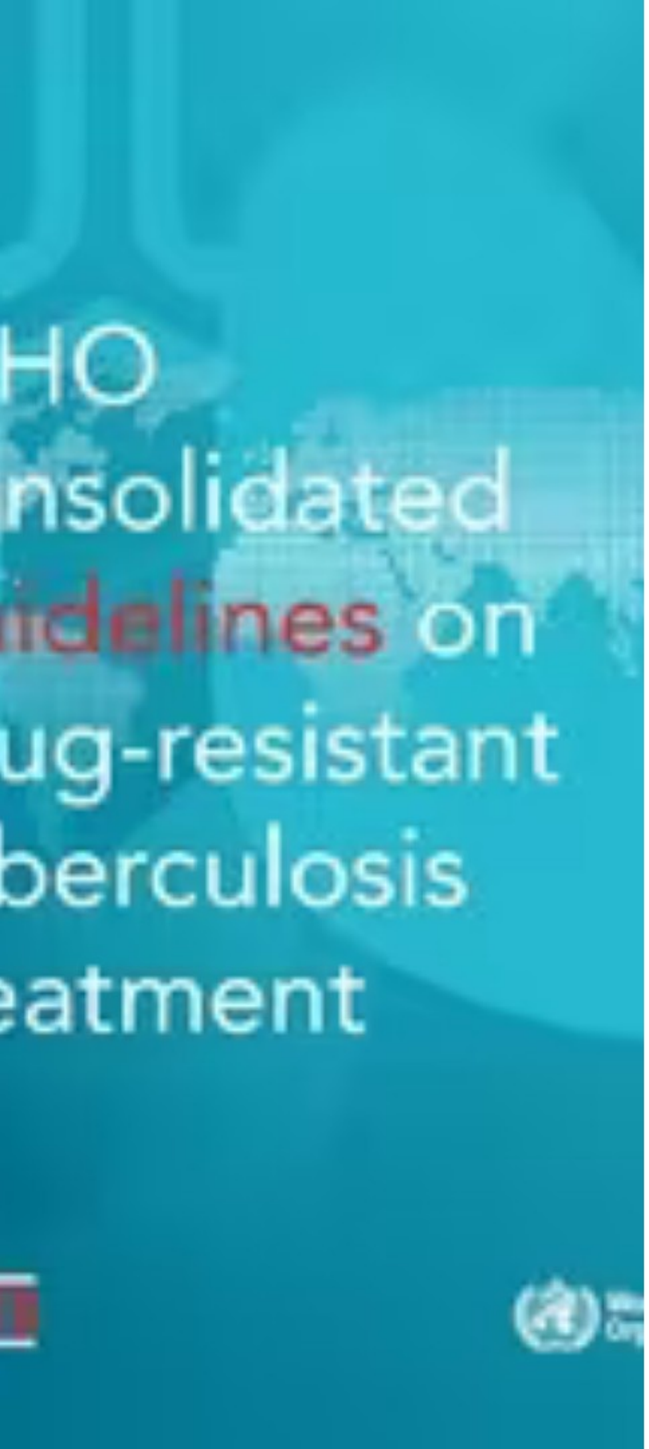
Sulfamethoxazole+trimethoprim 40 mg/kg SMX+8 mg/kg TMP q8h **IV/ORAL** for 3 weeks

Second Choice
If NO Clinical Response to First Choice after 48-72 hours

Cefotaxime 50 mg/kg/dose q8h **IV/IM**

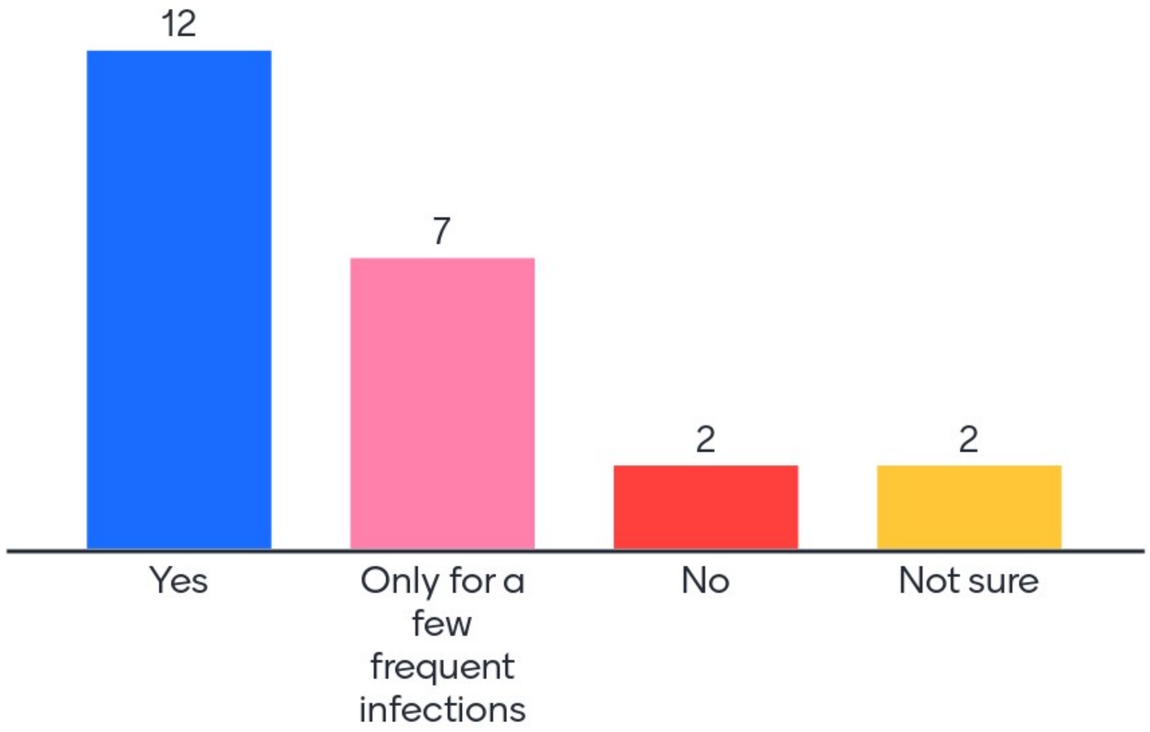
OR

Ceftriaxone 80 mg/kg/dose q24h **IV/IM**



Are there comprehensive national treatment guidelines for the most frequent infections encountered in primary health care in your country?

Mentimeter



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Limited availability of local antibiotic treatment guideline: example African Union

- Review of official websites for published standardized treatment guidelines in the 55 African Union countries
  - Complemented by contact with focal points from African CDC and WHO

- 31 standardized treatment guidelines from 20 countries identified (2001-2018)
  - 35 countries no guidelines identified
  - None developed according to GRADE methodology
  - Important variation in antimicrobial selection and dosage and duration of recommended therapies
  - None stated that antibiotic selection was based on local epidemiology of antibiotic resistance

Craig et al. Bull World Health Organ. 2022 Jan 1;100(1):50-59.

World Health Organization

WHO treatment guidelines

GUIDELINES

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

JUNE 2021

Table 3. Recommended treatment options for urethral discharge syndrome[a]

- Therapy for uncomplicated *Neisseria gonorrhoeae (24)*

Plus

- Therapy for *Chlamydia trachomatis (25)*

Infections covered	First-line options	Effective substitutes
In settings in which local antimicrobial resistance data are not available, the WHO STI guideline suggests dual therapy for gonorrhoea.		
N. gonorrhoeae[a]	**Ceftriaxone 250 mg**, intramuscularly, single dose *Plus* **Azithromycin 1 gram**, orally, single dose	**Cefixime 400 mg**, orally, single dose *Plus* **Azithromycin 1 gram**, orally, single dose
C. trachomatis	**Doxycycline 100 mg**, orally, twice daily for seven days (to be given only if gonorrhoea therapy did not include azithromycin)	**Azithromycin 1 gram**, orally, single dose *or* **Erythromycin 500 mg**, orally, 4 times a day for 7 days *or* **Ofloxacin 200–400 mg**, orally, twice a day for 7 days. (to be given only if gonorrhoea therapy did not include azithromycin)
In settings in which local antimicrobial resistance data reliably confirm the susceptibility of *N. gonorrhoeae* to the antimicrobial agent, singe therapy may be given.		
N. gonorrhoeae	**Ceftriaxone 250 mg**, intramuscularly, single dose	**Cefixime 400 mg**, orally, single dose *or* **Spectinomycin 2 grams**, intramuscularly, single dose (availability makes this antibiotic impractical)
Additional therapeutic options for recurrent or persistent infections		
T. vaginalis	**Metronidazole 2 grams**, orally, single doses	**Metronidazole 400 or 500 mg**, twice daily for 7 days
M. genitalium	**Azithromycin 500 mg**, orally on day 1, 250 mg daily on days 2–5	

[a]Because of increasing antimicrobial resistance to azithromycin in *N. gonorrhoeae* and *M. genitalium* and reduced susceptibility of *N. gonorrhoeae* to cephalosporins, WHO is in the process of revising current treatment recommendations and dosages.

Mentimeter

TREATMENT OF TUBERCULOSIS

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

World Health Organization

WHO Model Prescribing Information (2001)

Drugs used in bacterial infections (177 pages)

Preface

WHO's revised drug strategy, as adopted in resolution WHA39.27 of the Thirty-ninth World Health Assembly in 1986, calls for the preparation of model prescribing information which is being developed to complement WHO's Model List of Essential Drugs.[1] The objective is to provide up-to-date source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material.[2]

The information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug that is appropriate to circumstances prevailing in each of WHO's Member States and that some countries have already formally adopted texts of their own that have a statutory connotation.

This volume has been reviewed by internationally accredited experts and by certain nongovernmental organizations in official relations with WHO, including the International Federation of Pharmaceutical Manufacturers Associations, the International League of Infectious Diseases and the International Society of Chemotherapy.

https://apps.who.int/iris/handle/10665/42372

Acute pharyngitis

Most cases of pharyngitis are caused by viruses and do not require treatment with antimicrobials. The most common bacterial causes of pharyngitis are *Streptococcus pyogenes* (which may be associated with acute rheumatic fever) and *Corynebacterium diphtheriae*.

It may be difficult to distinguish between streptococcal and viral pharyngitis on clinical grounds alone. Tender, enlarged cervical lymph nodes and a scarlet fever-like rash are considered specific for *S. pyogenes*, but uncommon. Presence of the three major signs (fever >38 °C, intense pharyngeal pain, and absence of rhinitis and cough) has a high positive-predictive value for streptococcal pharyngitis. When these three signs are not all present, streptococcal etiology is unlikely. A rapid antigen test and culture techniques are available for the diagnosis of *S. pyogenes* infection, allowing specific therapy, but may not be cost-effective in certain circumstances. Other streptococcal serogroups (e.g. serogroups B, C and G) have also been associated with infections, but they do not cause rheumatic fever. In some cases peritonsillar abscesses may develop and surgical drainage may be needed. Routine testing for allergy to penicillins is not considered necessary.

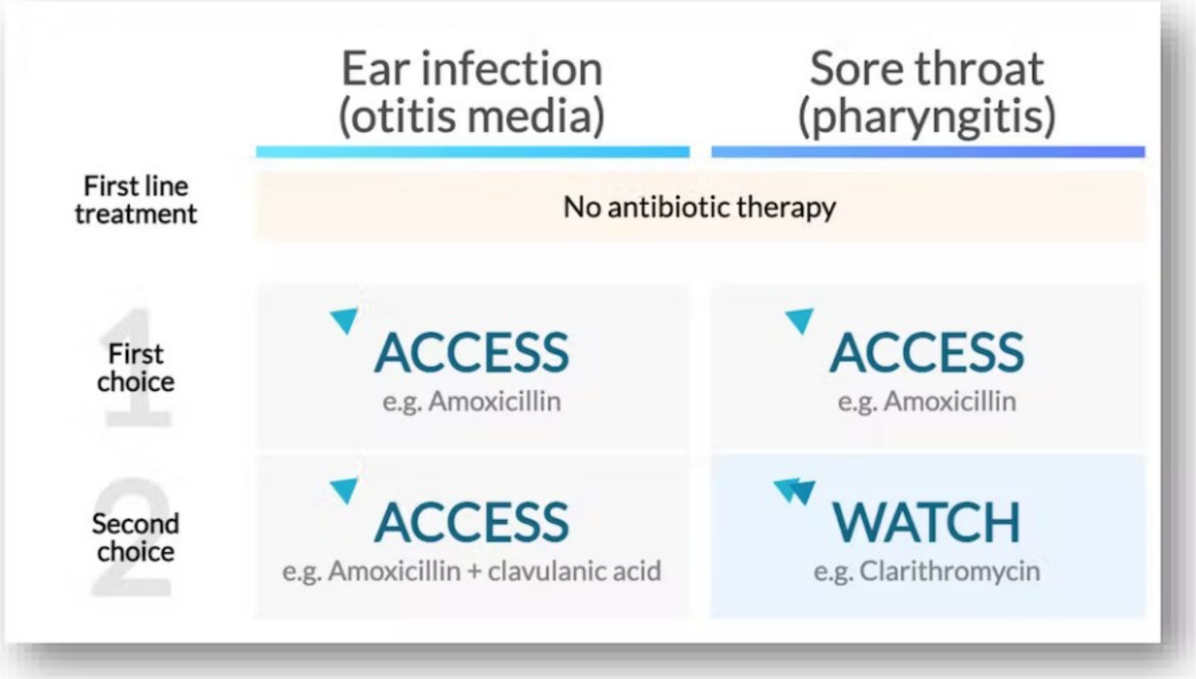
Treatment

Benzathine benzylpenicillin 1.2 million IU i.m. in a single dose for adults and children >30 kg (children ≤30 kg: 30 000 IU/kg (maximum 1.2 million IU) i.m. in a single dose)

The WHO AWaRe antibiotic book

A more comprehensive resource to improve antibiotic use

- First & second choice essential antibiotics



- Additional general information regarding

- Definition(s)
- Epidemiology
- Diagnosis (link with essential diagnostics list)
- Dose (standard; not taking into account renal dosing)
- Duration (favoring shorter duration)
- Based on review of literature and guidelines and expert input (antibiotic working group)
- Separate chapters for Reserve antibiotics on the EML

Key concepts of the WHO EML antibiotic book

- "No antibiotic" strategy whenever adequate
- Focus on all aspects of appropriate antibiotic use (8 D's)
- Standardized dosing whenever possible
- Focus on (oral) Access antibiotics

- **D**iagnosis
- **D**ecide
- **D**rug (medicine)
- **D**ose
- **D**elivery
- **D**own to oral
- **D**uration
- **D**iscuss
- **D**ocument

Focus on empiric (rather than targeted) treatment

Infection	ACCESS (A)/WATCH (W)	First-choice antibiotic option (when an antibiotic is indicated[a])
Bronchitis	No antibiotic	No antibiotic
Community-acquired pneumonia (mild cases)	A	Amoxicillin or Phenoxymethylpenicillin
Chronic obstructive pulmonary disease exacerbations	A	Amoxicillin (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Dental infections	A	Amoxicillin or Phenoxymethylpenicillin (for most cases the first choice is a dental procedure and antibiotics are not necessary)
Infectious diarrhoea[b]	No antibiotic or W	Most mild non-bloody diarrhoea is caused by viral infections and antibiotics are not necessary For acute severe bloody diarrhoea/dysentery - Ciprofloxacin or Azithromycin or Cefixime or Sulfamethoxazole+trimethoprim
Otitis media	A	Amoxicillin (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Pharyngitis	A	Phenoxymethylpenicillin or Amoxicillin (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Sinusitis	A	Amoxicillin or Amoxicillin+clavulanic acid (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Skin and soft tissue infection (mild cases)	A	Amoxicillin+clavulanic acid or Cefalexin or Cloxacillin
Urinary tract infection, lower	A	Nitrofurantoin or Sulfamethoxazole+trimethoprim or Trimethoprim or Amoxicillin+clavulanic acid

Some problems encountered

- How to take into account different prevalence of resistance across settings ?
- How to take into acount different diagnostic (and therapeutic) capactities across settings ?
- How to adapt evidence from high-income countries to the low- (and middle) income setting ?

Egypt

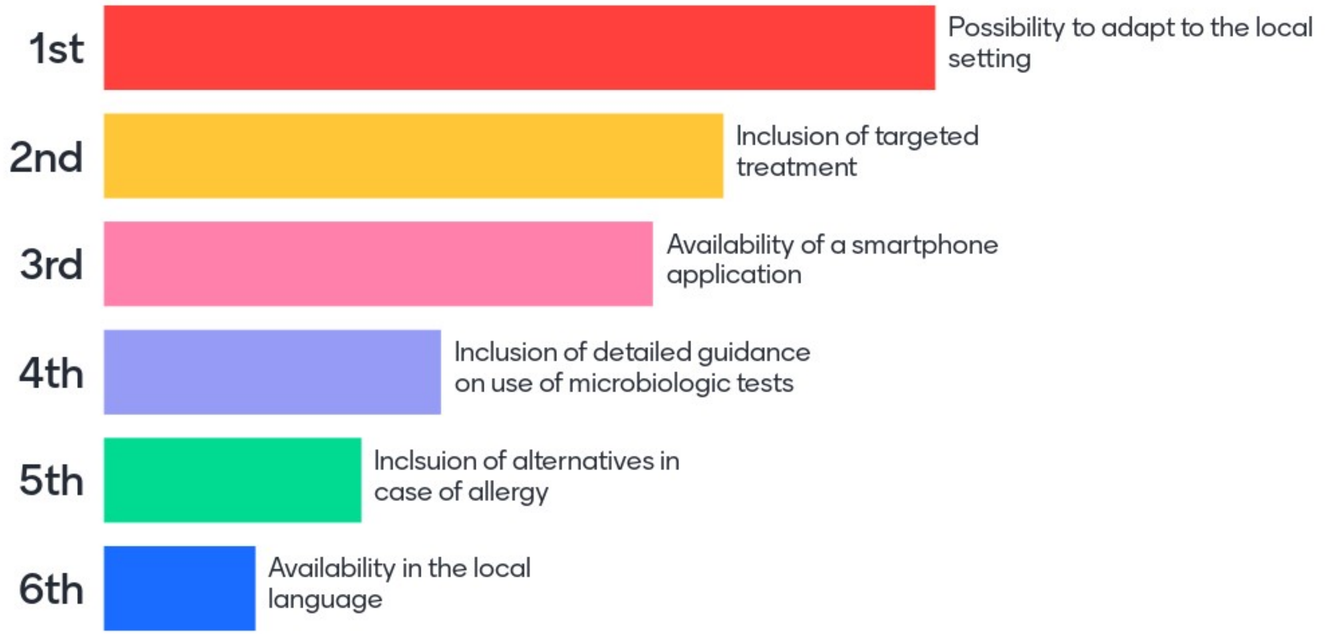
Ethiopia

Pakistan

https://apps.who.int/gho/tableau-public/tpc-frame.jsp?id=2012

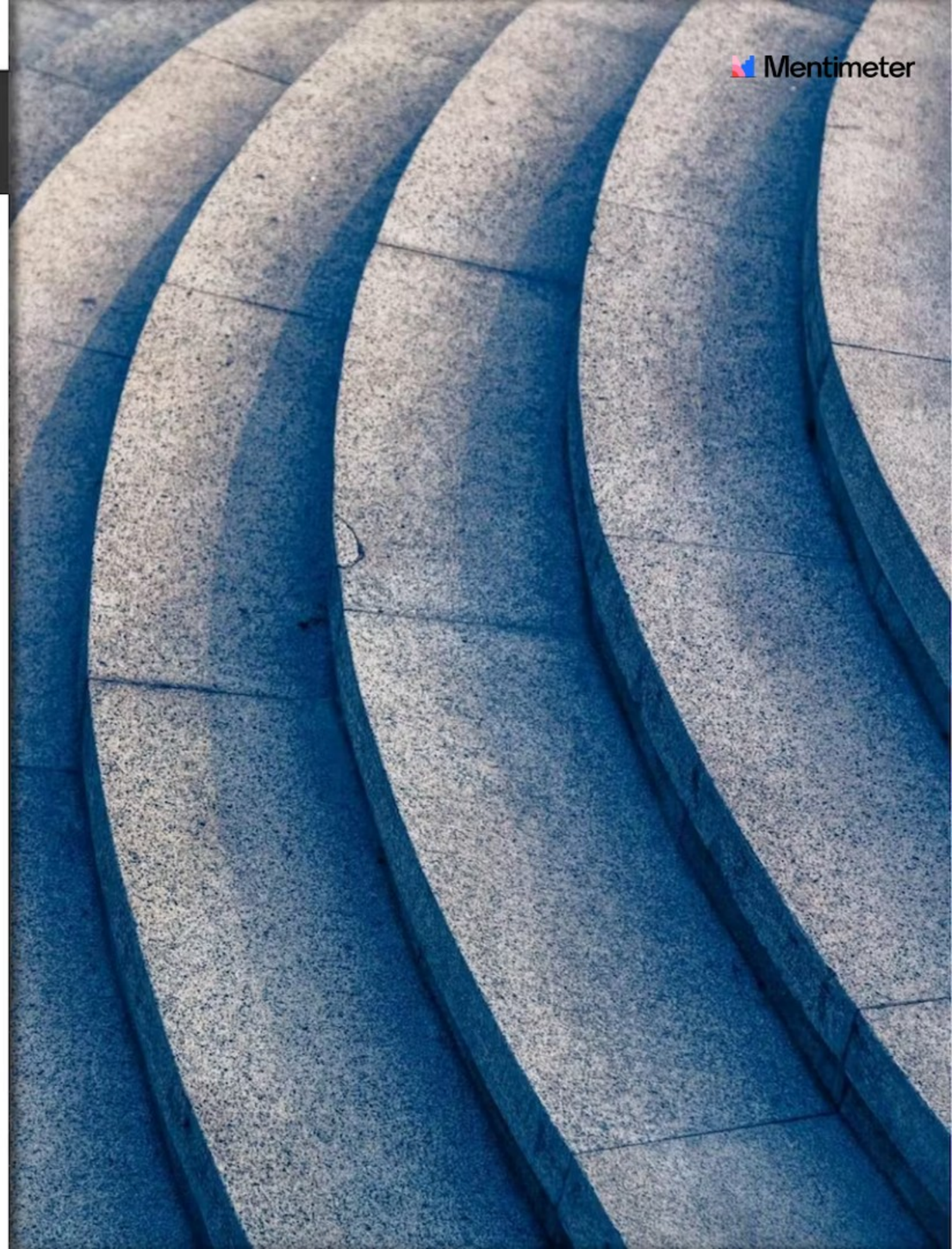
What would you consider as the most important aspects to ensure adoption of the WHO AWaRe antibiotic book by prescribers, countries?

Mentimeter



AWaRe - Next steps

- ✓Finalization of WHO EML antibiotic book
  - taking into account the comments received during the public consultation phase
  - spring / early summer 2022
- ✓Further elaboration of implementation plan
  - including research to improve evidence base
  - in close collaboration with WHO regional/country offices, countries, …
- ✓Development of smartphone application
- ✓Preparation of potential updates for 2023
- ✓Development of new indicators
- ✓….



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- NICE
- …

Ask me anything

1 questions
0 upvotes