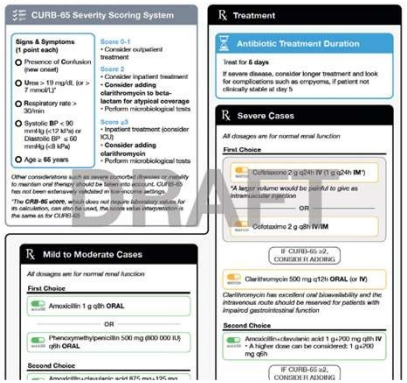
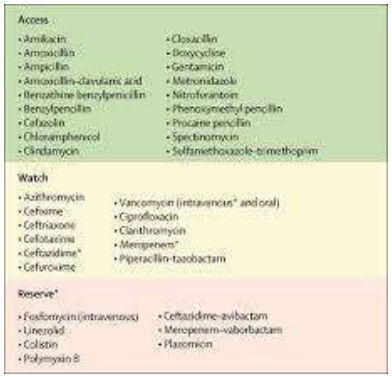
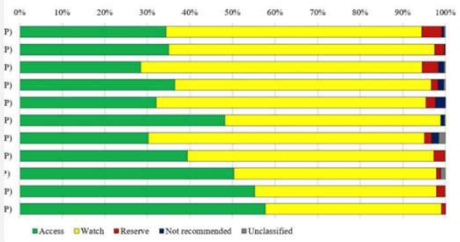




AWaRe



World Health Organization

The WHO EML AWaRe Book Webinar – November 18, 2021

Benedikt HUTTNER
Secretary EML
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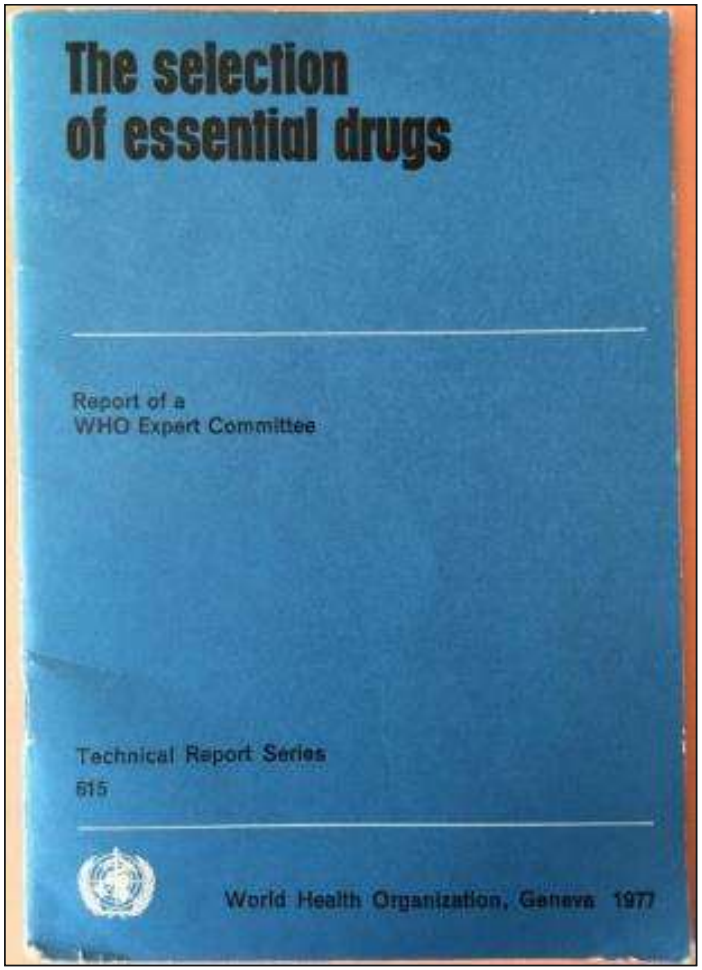
Antibiotics on the Essential Medicines List (EML)



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.

"...adequate information on ... indications and use of the drugs listed should be provided"

Antibacterial drugs

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

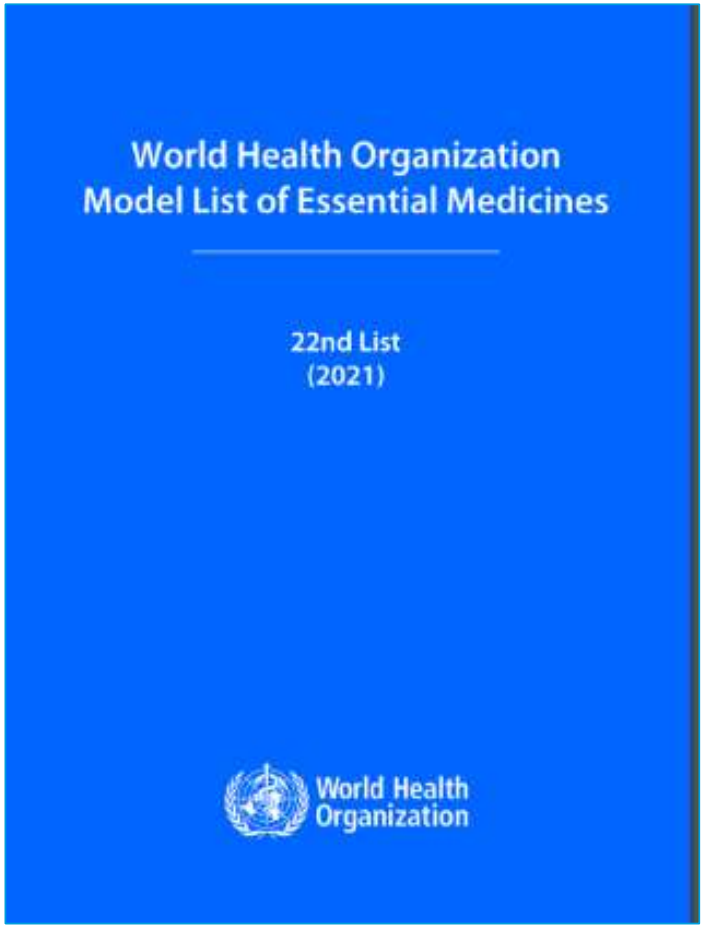
chloramphenicol (7) * *
cloxacillin (penicillinase-resistant, 1)
erythromycin *
gentamicin (4) *
phenoxymethylpenicillin *
salazosulfapyridine
sulfadimidine (1)
sulfamethoxazole + trimethoprim *
tetracycline (1, 4) *

Complementary

amikacin (1, 4, 10) *
doxycycline (6, 5) *
procaine benzyl-penicillin (7) *
sulfadiazine (7, 8) *

* On 2021 EML/c

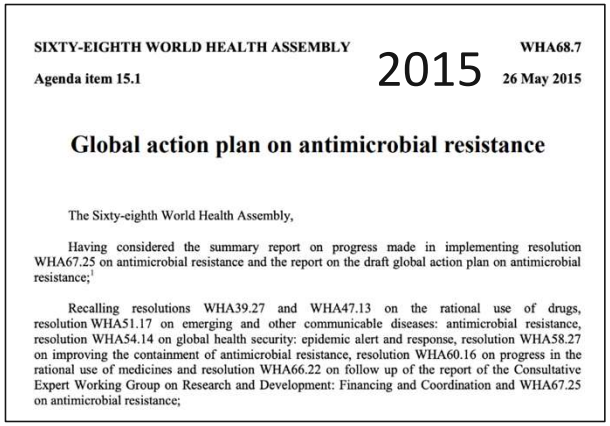
2021



22nd EML

- 39 antibiotics

(of 479 medicines ≈ 8%)



SIXTY-EIGHTH WORLD HEALTH ASSEMBLY — WHA68.7

Agenda item 15.1 — 2015 — 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;

AWaRe since 2017

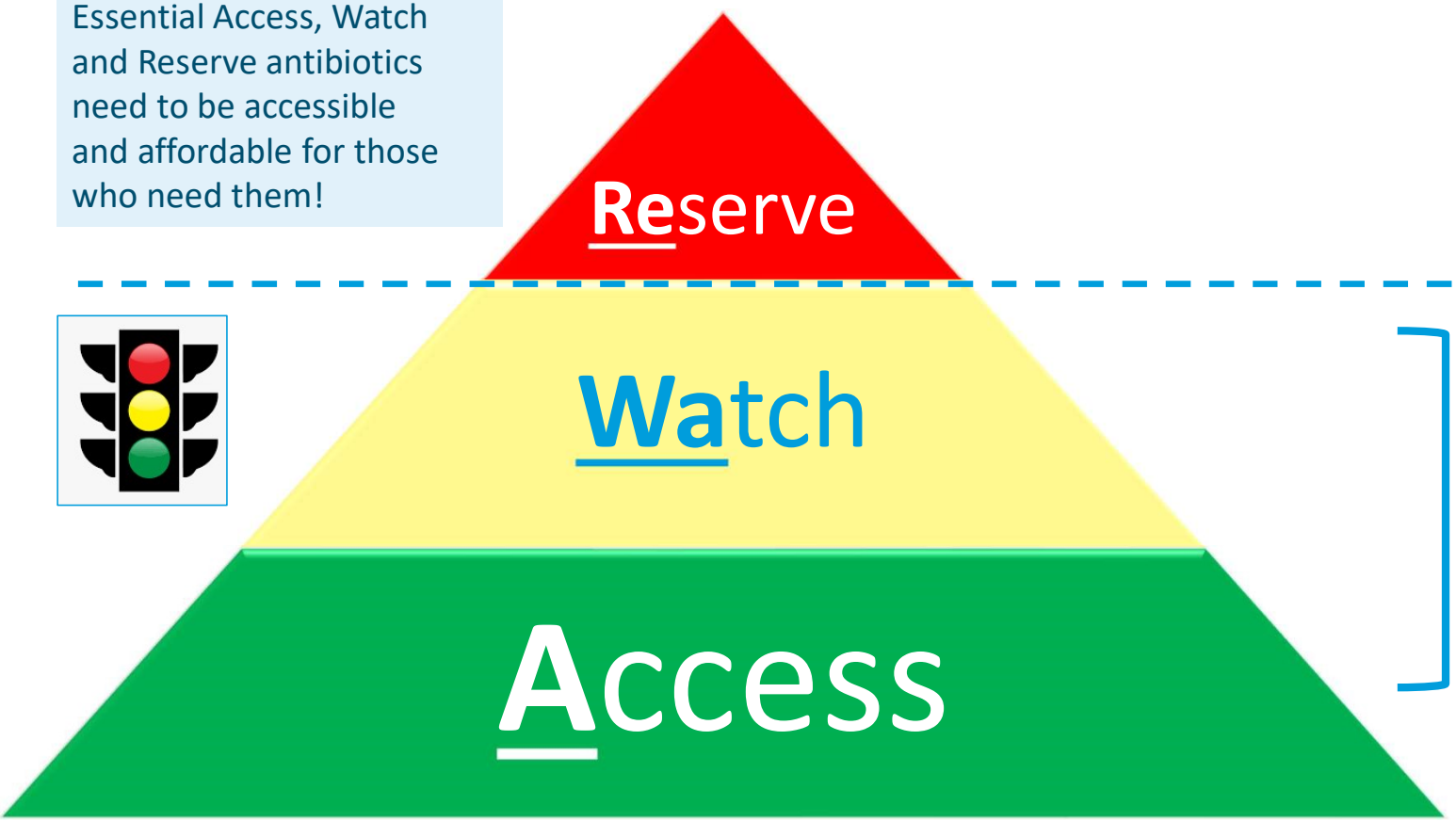
ACCESS GROUP	WATCH GROUP	RESERVE GROUP
Amikacin	Azithromycin	Cefiderocol
Amoxicillin	Cefixime	Ceftazidime/avibactam
Amoxicillin/clavulanic-acid	Cefotaxime	Colistin (IV)
Ampicillin	Ceftazidime	Fosfomycin (IV)
Benzathine-benzylpenicillin	Ceftriaxone	Linezolid
Benzylpenicillin	Cefuroxime	Meropenem/vaborbactam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

The AWaRe classification

As framework underlying the WHO EML antibiotic book

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 multidrug-resistant bacteria

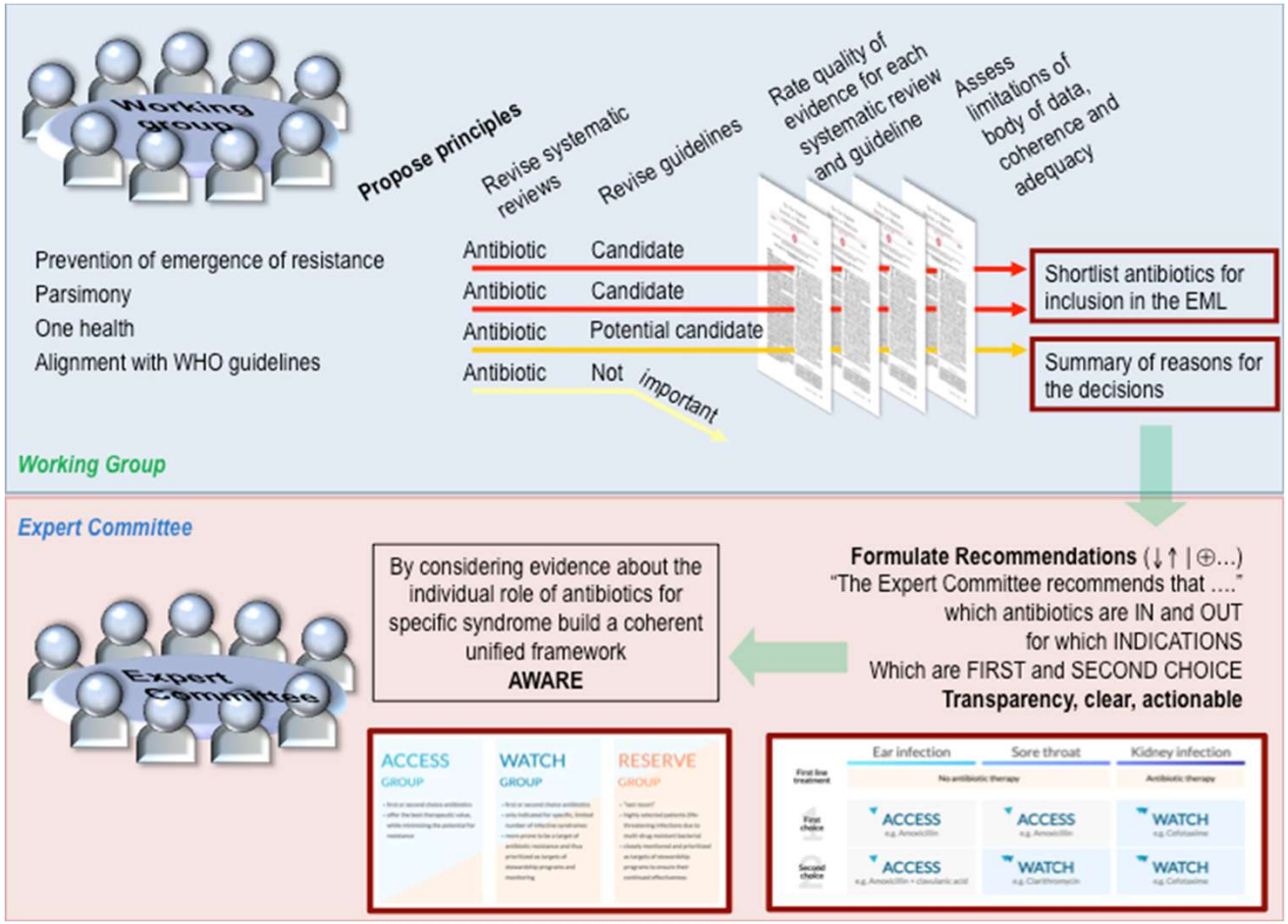
Higher "resistance potential"

1st or 2nd choice for common infectious syndromes

Lower "resistance potential"

https://aware.essentialmeds.org/list

Process for the selection of essential antibiotics



https://aware.essentialmeds.org/list

https://list.essentialmeds.org/

EML updates
2017 / 2019 / 2021

Sinusitis
Pharyngitis
Otitis

Lymphadenitis

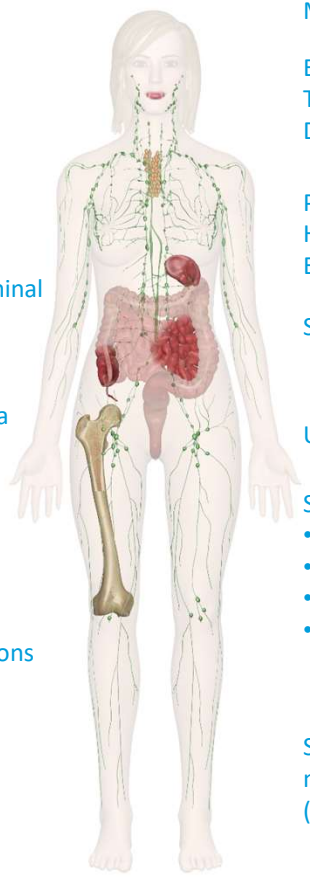
Complicated intraabdominal Infections
Enteric fever

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

Bone infections
Septic arthritis
Skin & soft tissue infections

Febrile neutropenia

Surgical prophylaxis



Meningitis

Eye infections
Trachoma
Dental infections

Pneumonia (CAP)
HCAP
Exacerbation of COPD

Sepsis

UTI

STD
- *Chlamydia*
- Gonorrhea
- Syphilis
- Trichomoniasis

Severe malnutrition (children)

Review of infections

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

Selection of 1st and 2nd choice antibiotics

Mild to moderate severity

	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

World Health Organization

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/

World Health Organization

ADULTS

Community-Acquired Pneumonia

CURB-65 Severity Scoring System

Signs & Symptoms (1 point each)

- Presence of **C**onfusion (new onset)
- **U**rea > 19 mg/dL (or > 7 mmol/L)*
- **R**espiratory rate > 30/min
- Systolic **B**P < 90 mmHg (<12 kPa) or Diastolic BP ≤ 60 mmHg (<8 kPa)
- Age ≥ **65** years

Score 0-1
- Consider outpatient treatment

Score 2
- Consider inpatient treatment
- **Consider adding clarithromycin to beta-lactam for atypical coverage**
- Perform microbiology tests

Score ≥3
- Inpatient treatment (consider ICU)
- **Consider adding clarithromycin**
- Perform microbiology tests

Other considerations such as severe comorbid illnesses or inability to maintain oral therapy should be taken into account. CURB-65 has not been extensively validated in low-income settings.

The **CRB-65 score, which does not require laboratory values for its calculation, can also be used, the score value interpretation is the same as for CURB-65*

Mild to Moderate Cases

All dosages are for normal renal function

First Choice

ACCESS Amoxicillin 1 g q8h **ORAL**

OR

ACCESS Phenoxymethylpenicillin 500 mg (800 000 IU) q6h **ORAL**

Second Choice

ACCESS Amoxicillin+clavulanic acid 875 mg+125 mg q8h **ORAL**

OR

ACCESS Doxycycline 100 mg q12h **ORAL**

Treatment

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

Severe Cases

All dosages are for normal renal function

First Choice

WATCH Ceftriaxone 2 g q24h **IV** (1 g q24h **IM***)

**A larger volume would be painful to give as intramuscular injection*

OR

WATCH Cefotaxime 2 g q8h **IV/IM**

IF CURB-65 ≥2, CONSIDER ADDING

WATCH Clarithromycin 500 mg q12h **ORAL** (or **IV**)

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Second Choice

ACCESS Amoxicillin+clavulanic acid 1 g+200 mg q8h **IV**
- A higher dose can be considered: 1 g+200 mg q6h

IF CURB-65 ≥2, CONSIDER ADDING

WATCH Clarithromycin 500 mg q12h **ORAL** (or **IV**)

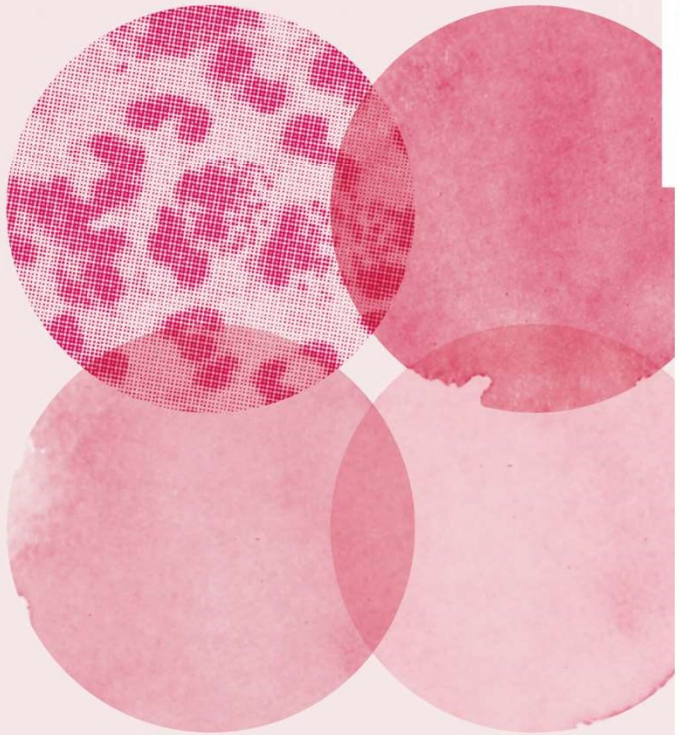
Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

The WHO Essential Medicines List Antibiotic Book

World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Neisseria gonorrhoeae*



02 METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the WHO handbook for guideline development *(8)* (see Annex B for a detailed description).

2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

To update the WHO guidelines for the prevention, treatment and management of STIs, a GDG was established, comprising 33 international STI experts, including clinicians, researchers and programme managers (Annex A). A core subgroup to focus on the guidelines related to gonorrhoea was created within the GDG, to provide more intensive feedback throughout the process (Annex A). The GDG

2.2 QUESTIONS AND OUTCOMES

In December 2013, the first GDG meeting was held to identify and agree on the key PICO (population, intervention, comparator, outcome) questions that formed the basis for the systematic reviews and the recommendations. Following this meeting, a survey of GDG members was conducted to prioritize the questions and outcomes according to clinical relevance and importance. Six PICO questions were identified for the update on the treatment of genital, anorectal and oropharyngeal gonococcal infections, management of treatment failure, and prevention and treatment of neonatal ophthalmia (see Annex B). These questions pertained to adults and other special populations, namely adolescents, pregnant women, people living with HIV, and populations at high risk of acquiring and transmitting STIs, such as men who have sex with men (MSM) and sex workers. Only outcomes that were ranked as critical or important to patients and decision-making were included: clinical and microbiological cure and adverse effects (including maternal and fetal effects in pregnant women).

2.3 REVIEWS OF THE EVIDENCE

The systematic reviews for each priority question were conducted by McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy. Evidence for desirable and undesirable outcomes, patient values and preferences, resources, acceptability, equity and feasibility were reviewed from published and unpublished literature. Comprehensive searches for previously conducted systematic reviews, randomized controlled trials and non-randomized studies were performed from March to October 2015. Additional searches were conducted to identify studies on patient values and preferences (e.g. qualitative research designs) and resources (e.g. cost of intervention, cost-benefits and cost-effectiveness studies). Two members of the Systematic Review Team screened studies, extracted and analysed the data, and assessed the quality/certainty of the evidence

	Judgement	Research evidence
Problem	**Is the Problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** The World Health Organization (WHO) recently reported that the global estimate of gonorrhoea is 0.8% (0.6–1.0%) and regional estimates range from 0.3% to 1.7%. Infection of the genital tract causes local inflammation that can result in dysuria, discharge, genital discomfort, and pain. In women, it may spread to the fallopian tubes and ovaries causing pelvic inflammatory disease (PID). Complications include infertility, chronic pelvic pain, and ectopic pregnancy and infection, which can result in considerable physical and emotional morbidity in addition to a significant financial burden on healthcare services. Complications of gonorrhoea are usually seen when the infection remains untreated for a prolonged period, or with inappropriate treatment, and are more common in settings where access to medical care is suboptimal. It has consistently been identified as a risk factor for incident HIV infection in both heterosexual and MSM populations. **Additional considerations:** Gonococcal resistance to many antibiotics is increasing and is cause for concern. It includes resistance to ceftriaxone, cefixime, azithromycin and ciprofloxacin.
Desirable effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • **Moderate** • Large • Varies • Don't know	**Research evidence:** For adults, adolescents, HIV-positive patients and MSM, 108 studies were found (including foreign languages articles): 14 randomized and 94 non-randomized studies (including 3 non-randomized studies with 2 or more groups and 91 non-randomized studies with 1 group). See the evidence profile below for the summary of the results. For pregnant women, 3 studies were included: 2 randomized and 1 non-randomized. The results from adults (non-pregnant people) were also used to inform the recommendations. See the evidence profile below for the summary of the results.
Undesirable effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	**Additional considerations:** The GDG agreed that much of the data for effects of gonorrhoea treatments is dated with the emergence of resistance. This data would therefore be indirect today. The GDG also noted that there is little data comparing dual therapy to increased doses of single therapy. Dual therapy indicates that the same class of antibiotic should not be used for both drugs. Different dosages were assessed across studies, with little difference in effects. The cure rates of azithromycin 1 g or 2 g were similar. The cure rates of gentamicin and kanamycin were above 95%, but the cure rates varied across studies (and were fragile depending on which studies were included in the analysis), but this data is also dated. The cure rates were similar for cefixime 400 mg and 800 mg. The GDG noted that in many countries, doses much higher than what is considered standard are given. Therefore, standard doses as "minimum" should be described, but higher doses may be used in some cases. There was no data in high-risk groups (e.g. MSM or sex workers). Side-effects were generally non-serious. Side-effects are probably greater with azithromycin (1 or 2 g) and spectinomycin (2 g) than with ceftriaxone. The GDG agreed that when measured, the side-effects were trivial. There is global resistance to quinolones and emerging resistance to single therapies. Therefore, in order to successfully treat gonococcal infection with a single therapy, susceptibility should be known. Resistance to azithromycin is emerging, and resistance to gentamicin and kanamycin are not being measured. For pregnant women, doxycycline and tetracyclines cannot be used due to adverse effects.

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.

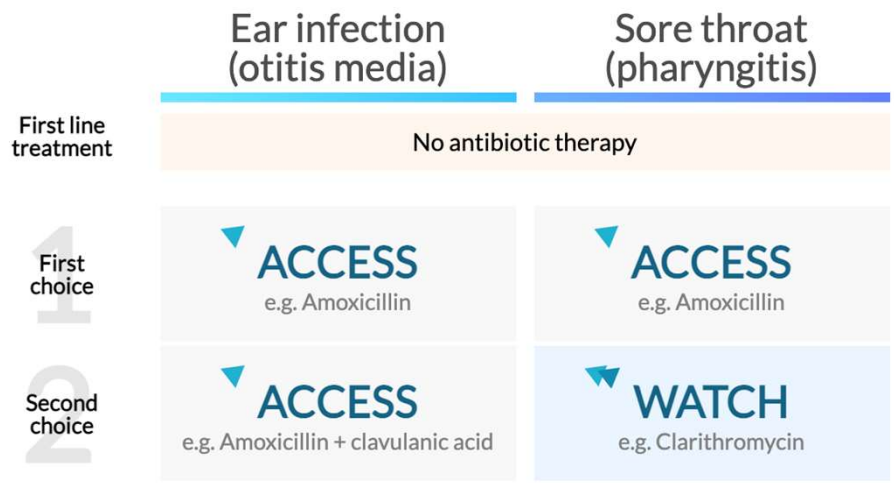
Treatment

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 EML antibiotic book

A more comprehensive resource to improve antibiotic use

First & second choice essential antibiotics



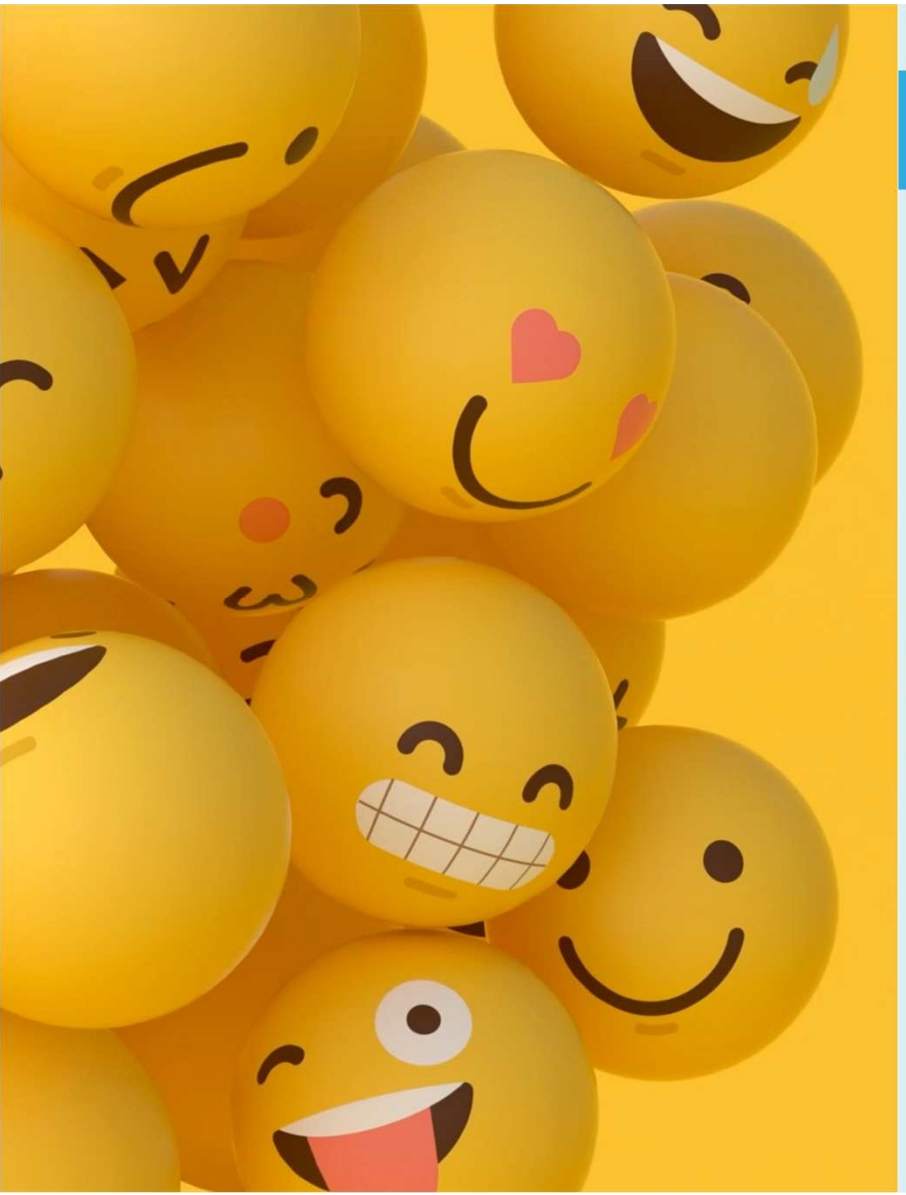
Additional general information regarding

- 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



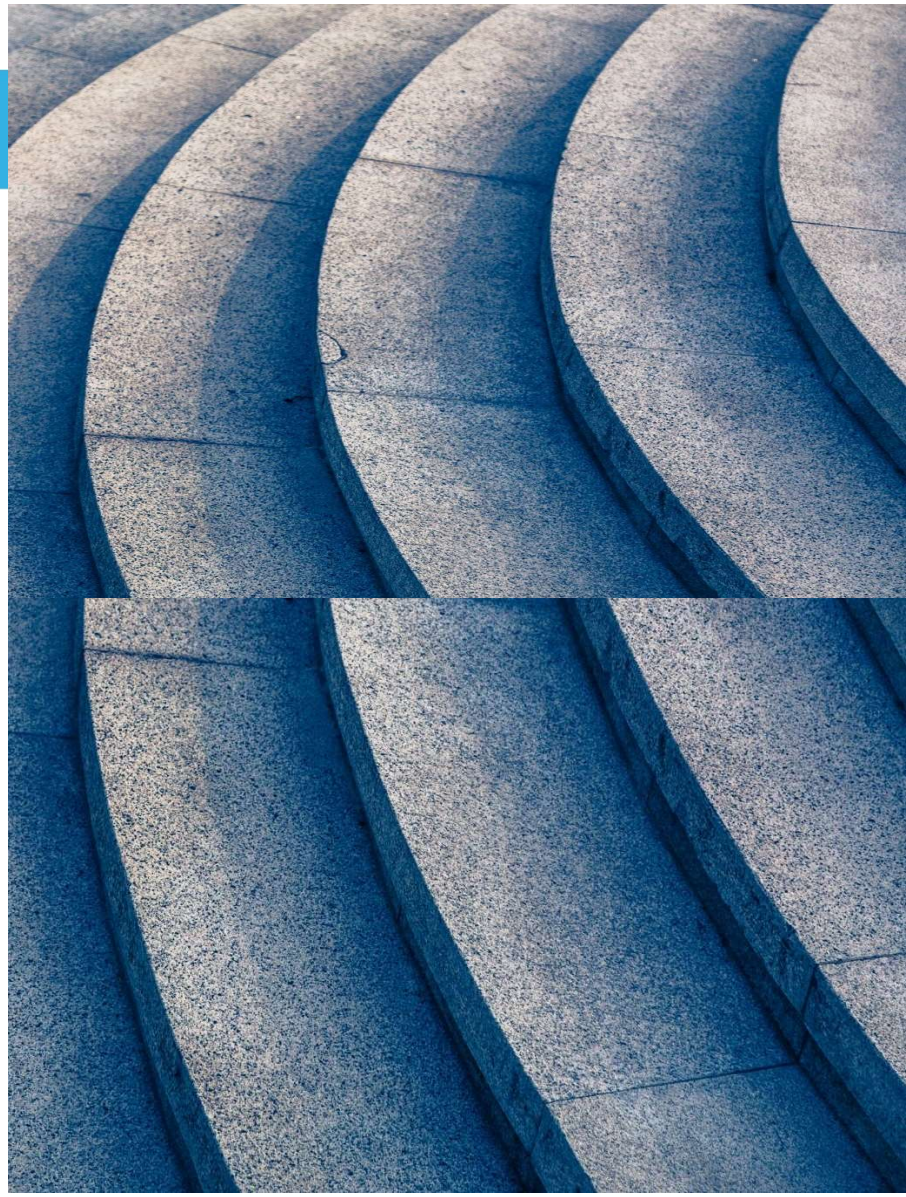
The public consultation phase

Public consultation phase

- Open until **January 31, 2022**
- Please use the dedicated link to provide feedback https://forms.office.com/r/ZgS4xqhwBH
- If you have questions / need to send documents please use aware@who.int
- Whenever possible also indicate **evidence** underlying requests for change of content
- Comments including the names of the person / organization commenting will be published unless sepcifically requested otherwise

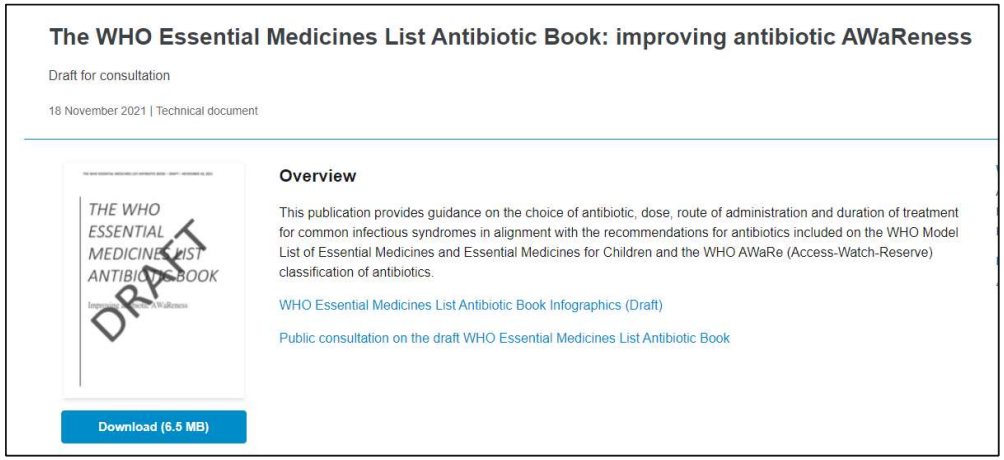
Next steps

- ✓ 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
- ✓ ….



Where to download the book and infographics

https://www.who.int/publications/m/item/the-who-essential-medicines-list-antibiotic-book-improving-antibiotic-awareness



Acknowledgments

- Veronica Zanichelli
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- Government of Germany
- GARDP
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- …