World Health Organization

REGIONAL OFFICE FOR Europe

Consideration of antibacterial medicines as part of the revisions to 2019 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc)

Section 6.2 Antibacterials

including Access, Watch and Reserve Lists of antibiotics

This summary has been prepared by the Health Technologies and Pharmaceuticals (HTP) programme at the WHO Regional Office for Europe.

It is intended to communicate changes to the 2019 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc) to national counterparts involved in the evidence-based selection of medicines for inclusion in national essential medicines lists (NEMLs), lists of medicines for inclusion in reimbursement programs, and medicine formularies for use in primary, secondary and tertiary care.

This document does not replace the full report of the WHO Expert Committee on Selection and Use of Essential Medicines (see The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021). Licence: CC BY-NC-SA 3.0 IGO: https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1) and Corrigenda (March 2020) – TRS1021 (https://www.who.int/medicines/publications/essentialmedicines/TRS1021_corrigenda_March2020.pdf?ua=1).

Executive summary of the report: https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?ua=1.

The revised lists of essential medicines are available here:

- World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1).

- World Health Organization Model List of Essential Medicines for Children, 7th List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1).

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Introduction

This Summary reports the recommendations made by the 2019 WHO Expert Committee on the Selection and Use of Essential Medicines for Section 6.2 antibacterials, describes the deliberations of the EML Antibiotics Working Group, outlines changes to the Access, Watch and Reserve (AWaRe) classification of antibiotics and reports the list of discouraged antibiotics.

The Expert Committee:

- restructured Section 6.2 to align with the AWaRe classification, replacing the sub-sections based on chemical structure (e.g. beta-lactam and other antibacterials)
- added new indications for existing medicines on the EML and EMLc namely, medicines for typhoid and paratyphoid (enteric) fever; for surgical prophylaxis and for oral and dental infections
- recommended the addition of 4 new medicines – cefuroxime for surgical prophylaxis (EML, EMLc); ceftazidime + avibactam, meropenem + vaboractam and plazomicin as Reserve last-resort antibiotics for multi-drug resistant infections (EML)
- rejected applications for the addition of ceftolozone + tazobactam, delafloxacin, eravacycline and omadacycline as last-resort antibiotics
- removed aztreonam, fourth- and fifth-generation cephalosporins (as classes), tigecycline and daptomycin from the Reserve complementary list of the EML and EMLc
- reclassified fourth-generation cephalosporins as Watch group
- reclassified faropenem from Watch to Reserve group
- based on the advice of the EML Antibiotics Working Group, nominated a number of agents as 'not recommended' agents; these are antibiotics whose use is not evidence-based, nor recommended in high quality international guidelines, particularly fixed-dose combinations of multiple broad-spectrum antibiotics.

Recognizing that the EML-listed antibiotics represented a small set of narrow spectrum antibiotics for first- and second-choice empiric treatment of common infections, the Expert Committee endorsed the recommendations of the EML Antibiotics Working Group to classify 177 commonly used antibiotics to Access, Watch and Reserve groups. A database of the 177 agents with ATC codes has been created (https://www.who.int/medicines/publications/essentialmedicines/en/).

A **new target indicator** based on the AWaRe classification was adopted which specifies a country-level target of at least 60% of antibiotic consumption being from the Access group.

A summary of the clinical syndromes reviewed by the Expert Committees in 2017 and 2019 is provided in Annex 1.

Revised structure of Section 6.2 antibacterials

The Expert Committee recommended the re-structuring of Section 6.2 to better accommodate the AWaRe classification, and that antibiotics on the EML be listed in revised sub-sections according to AWaRe groups, replacing the existing sub-sections based on chemical structure (e.g., beta-lactam and other antibacterials). The revised structure is:

- **6.2.1: Access group antibiotics**
- **6.2.2: Watch group antibiotics**
- **6.2.3: Reserve group antibiotics**
- **6.2.4: Antileprosy medicines**
- **6.2.5: Antituberculosis medicines**

This summary focuses on the antibacterial agents classified under sections 6.2.1, 6.2.2, 6.2.3 of the EML and EMLc.

The Expert Committee made no changes to section 6.2.4 (antileprosy medicines) in 2019.

There were a substantial number of changes to section 6.2.5 (antituberculosis medicines) to align the EML and EMLc with WHO guidelines for tuberculosis. The specific changes are outlined in the summary of changes to the EML and EMLc in 2019.

Access, Watch, Reserve (AWaRe) classification of antibiotics

The Expert Committee noted the adoption and utilization of the Access, Watch and Reserve (AWaRe) classification of antibiotics on the EML by several Member States including the endorsement of AWaRe by the G20 Health Ministers in Argentina in October 2018[1]. Furthermore, a new target indicator based on AWaRe was adopted which specifies a country level target of at least 60% of antibiotic consumption being from the Access group. This indicator is intended to monitor access to essential medicines and progress towards Universal Health Coverage under the WHO 13th General Program of Work[2]. The Committee recognized the emerging role of the AWaRe groups for stewardship and quality improvement programs.

The Expert Committee acknowledged that EML-listed antibiotics represent a parsimonious, evidence-based selection of essential narrow spectrum antibiotics for first- and second-choice empiric treatment of most common bacterial infections and a tool for stewardship. However, the AWaRe classification should extend beyond the EML to all commonly used antibiotics globally. The Committee acknowledged the contributions of the EML Antibiotics Working Group and endorsed the Working Group's recommendations for AWaRe classification of 177 commonly used antibiotics, to better support antibiotic monitoring and stewardship activities. The Expert Committee recommended the development

[1] http://www.g20.utoronto.ca/2018/2018-10-04-health.pdf
[2] http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_7-en.pdf

of an AWaRe classification database as a searchable resource for countries. (https://www.who.int/medicines/publications/essentialmedicines/en/

Antibiotics not classified as Access, Watch or Reserve

The Committee recommended, based on the advice of the EML Antibiotics Working Group, that WHO may wish to consider creating an additional group in the AWaRe classification database for antibiotics whose use is not evidence-based, nor recommended in high quality international guidelines, particularly fixed-dose combinations of multiple broad-spectrum antibiotics. Antibiotics in this group are not included on the Model Lists. A list of 'not recommended' is included in the AWaRe classification database. (https://www.who.int/medicines/publications/essentialmedicines/en/

Definitions

Access antibiotics

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first- or second-choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists of Essential Medicines to improve access and promote appropriate use.

Watch antibiotics

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[3] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first- or second-choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists of Essential Medicines.

Reserve antibiotics

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options.

Selected Reserve group antibiotics are listed as individual medicines on the WHO Model Lists of Essential Medicines when they have a favourable risk-benefit profile and proven activity against "Critical

[3] The WHO CIA list is aimed at preserving medically important antimicrobials for human use by decreasing their use in the food chain (http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1).https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/

Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List[4], notably carbapenem-resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable.

These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

Not recommended antibiotics

The use of the fixed-dose combinations of multiple broad-spectrum antibiotics is not evidence-based, nor recommended in high-quality international guidelines. WHO does not recommend their use in clinical practice.

New indications for existing medicines on the EML and EMLc

Typhoid and paratyphoid (enteric) fever

The Expert Committee endorsed listing of ciprofloxacin, ceftriaxone and azithromycin as first-choice treatments for typhoid and paratyphoid (enteric) fever on the core list of the EML and EMLc.

Ciprofloxacin is recommended as first-choice in settings with low prevalence of fluoroquinolone resistance, while ceftriaxone and azithromycin are recommended first-choice treatments in settings where there is a high prevalence of fluoroquinolone resistance.

Ciprofloxacin, azithromycin and ceftriaxone are all classified as Watch group antibiotics (Section 6.2.2).

REJECTED APPLICATION: Following the principle of parsimony, the Expert Committee did not recommend the addition of ofloxacin for this indication, noting that ofloxacin and ciprofloxacin have demonstrated similar clinical performance for this indication in clinical trials.

These recommendations are summarised in the following table:

Typhoid and paratyphoid (enteric) fever	***First-choice***	***Second-choice***
Endorsed existing EML, EMLc medicines	Ciprofloxacin (except where high prevalence of fluoroquinolone resistance exists) [*Watch*] Azithromycin [*Watch*]	

[4]The WHO PPL is tool to guide the research and development (R&D) of new antibiotics, ensuring that R&D responds to public health needs. The list is divided into three tiers – critical, high and medium risk pathogens. Gram negative bacteria are shown to be the most critical priority need (https://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1).

	Ceftriaxone [*Watch*]	

Antibiotics for surgical prophylaxis

The Expert Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion. In line with previous decisions for infectious syndromes, alternatives for use in case of allergy were not recommended.

The Expert Committee endorsed listing of cefazolin, alone or in combination with metronidazole as first-choice options, and of amoxicillin + clavulanic acid and gentamicin as second-choice options for surgical prophylaxis on the core list of the EML and EMLc, as Access group antibiotics (Section 6.2.1).

ADDITION: The Committee also recommended the addition of cefuroxime to the core list of the EML and EMLc as a second-choice option for surgical prophylaxis, as a Watch group antibiotic (Section 6.2.2), as an alternative to cefazolin.

These recommendations are summarised in the following table:

Surgical prophylaxis	***First- choice***	***Second-choice***
Endorsed existing EML, EMLc medicines	Cefazolin [Access] alone or in combination with Metronidazole [Access]	Amoxicillin + clavulanic acid [Access] Gentamicin [Access]
Addition		Cefuroxime [Watch]

Antibiotics for oral and dental infections

NEW INDICATION: The Expert Committee endorsed listing of amoxicillin and phenoxymethylpenicillin on the core list of the EML and EMLc as first-choice treatment for progressive (systemically complicated) apical dental abscess. These antibiotics are also recommended as first-choice treatment of apical dental abscess in medically compromised patients.

Amoxicillin and phenoxymethylpenicillin are classified as Access group antibiotics (Section 6.2.1).

These recommendations are summarised in the following table:

Systemically complicated apical dental abscess	***First-choice***	***Second-choice***
Endorsed existing EML, EMLc medicines	Amoxicillin [Access] Phenoxymethylpenicillin [Access]	

Additions, changes and deletions

Additions

The Expert Committee recommended for inclusion three new recently registered antibiotics for treatment of multi-drug resistant infections caused by pathogens ranked as "Critical Priority" on the WHO Priority Pathogens List[5] and classified under AWaRe as Reserve antibiotics:

ceftazidime + avibactam (ATC Code J01DD52) [Reserve]
meropenem + vaborbactam (ATC Code J01DH52) [Reserve]
plazomicin (ATC Code to be assigned) [Reserve].

Four recently registered antibiotics were not recommended for EML inclusion but were classified under AWaRE for monitoring purposes (ceftolozane + tazobactam, eravacycline and omadacycline as Reserve; delafloxacin as Watch).

Deletions/removals

The Committee recommended the removal of aztreonam, fourth- and fifth-generation cephalosporins (as classes), tigecycline and daptomycin from the EML and EMLc as these antibiotics did not meet the revised criteria for inclusion on the Model Lists as individual Reserve group agents.

Changes

The Committee agreed that fourth-generation cephalosporins should be re-classified as Watch group as they did not meet the revised criteria for classification as Reserve.

The Committee also recommended the re-classification of faropenem from Watch to Reserve due to its high potential for inappropriate use. It is an orally available formulation with a broad-spectrum activity whose inappropriate use may further the spread of carbapenemase-producing *Enterobacteriaceae*.

Section 6.2.1 Access group antibiotics

This category includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups.

The following 19 Access group antibiotics are recommended as first- or second-choice empiric treatment options for infectious syndromes reviewed by the Expert Committee and are listed as individual

[5] The WHO PPL is tool to guide the research and development (R&D) of new antibiotics, ensuring that R&D responds to public health needs. The list is divided into three tiers – critical, high and medium risk pathogens. Gram negative bacteria are shown to be the most critical priority need (https://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1).

medicines on the Model Lists to promote optimal use and with the goal of improving global "access to Access" antibiotics.

Access group antibiotics included on the 2019 Model Lists		
Amikacin	Cefazolin	Nitrofurantoin
Amoxicillin	Chloramphenicol	Phenoxymethylpenicillin
Amoxicillin + clavulanic acid	Clindamycin	Procaine benzylpenicillin
Ampicillin	Cloxacillin	Spectinomycin
Benzathine benzylpenicillin	Doxycycline	Sulfamethoxazole + trimethoprim
Benzylpenicillin	Gentamycin	
Cefalexin	Metronidazole	

A full list of the antibiotics (with ATC codes) included in the Access list is provided in Annex 2.

Section 6.2.2 Watch group antibiotics

The Watch group includes antibiotics that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials (CIA) for Human Medicine[6] and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of national and local stewardship programs and monitoring.

The following 11 Watch group antibiotics are recommended as essential first- or second-choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists.

Watch group antibiotics included on the 2019 Model Lists	
Azithromycin	Ciprofloxacin
Cefixime	Clarithromycin
Cefotaxime	Meropenem
Ceftazidime	Piperacillin + tazobactam
Ceftriaxone	Vancomycin
Cefuroxime	

A full list of the antibiotics (with ATC codes) included in the Watch list is provided in Annex 3.

6.2.3 Reserve group antibiotics

[6] The WHO CIA list is aimed at preserving medically important antimicrobials for human use by decreasing their use in the food chain (http://apps.who.int/iris/bitstream/10665/251715/1/9789241511469-eng.pdf?ua=1).

The Reserve group includes antibiotics that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be considered as "last resort" options.

Seven selected Reserve group antibiotics are listed as individual medicines on the WHO Model Lists as they have a favourable benefit-risk profile and proven activity against "Critical Priority" or "High Priority" pathogens as identified by the WHO Priority Pathogens List, most notably carbapenem-resistant *Enterobacteriaceae*.

These antibiotics should be globally accessible, but their use should be tailored to highly specific patients and settings, when alternatives are not suitable or have failed. To preserve their effectiveness these Reserve group antibiotics should be prioritized as key targets of national and international stewardship programs including regular monitoring and reporting of their use.

Reserve group antibiotics included on the 2019 Model Lists	
Ceftazidime + avibactam	Meropenem + vaborbactam
Colistin	Plazomicin
Fosfomycin (intravenous)	Polymyxin B
Linezolid	

A full list of the antibiotics (with ATC codes) included in the Reserve list is provided in Annex 4. A list of the antibiotics 'not recommended' is shown in Annex 5.

EML ANTIBIOTICS/AWaRe WORKING GROUP

The Expert Committee acknowledged that the existing EML listings and the classification of individual medicines to specific AWaRe groups may change slightly over time, due to the evolving epidemiology of infectious diseases and antimicrobial resistance, changes in the availability of antibiotics and emergence of new scientific evidence. The ongoing revision and consolidation of the antibiotics included on the EML and of AWaRe classification is a key activity of the Working Group, with the aim of balancing the objectives of preserving antibiotic effectiveness while guaranteeing necessary access. Therefore, the Committee recommended the continuation of the activities of the EML Antibiotics/AWaRe Working Group.

The Committee recommended that the Working Group should assess the adoption of AWaRe across countries and further explore how AWaRe can assist in activities to promote optimal antibiotic stewardship. Some areas needing more investigation are the incorporation of AWaRe in national essential medicines lists and clinical practice guidelines, and the adaptation of AWaRe for educational activities to improve antibiotic use.

The Committee recommended the Working Group develop antibiotic stewardship algorithms for Reserve antibiotics to define how these medicines should be used and how their misuse can be prevented. This includes the identification of evidence gaps for the recommended uses in clinical practice.

The Committee noted that the current regulatory approval process for new antibiotics, most of which qualify for the Reserve category due to their activity against priority multidrug-resistant pathogens (usually carbapenem-resistant pathogens), does not result in adequate evidence to judge their role for their optimal clinical use and guide appropriate policy interventions. The Working Group should identify and document these evidence gaps and propose research strategies for how to address them. In general, the AWaRe groups, WHO's Priority Pathogens List and the WHO list of critically important antimicrobials should become more closely aligned with regard to definitions and terminology to avoid confusion and the Working Group should support and expand this effort.

Additional proposed activities of the Working Group include the development of policy documents assessing optimal antibiotic dosage and treatment duration for common infectious syndromes in both adults and children. This information, together with the Model Lists and AWaRe should inform production of a WHO handbook outlining antibiotic treatment guidance for high-burden bacterial syndromes. This information should be made available also in an easily accessible electronic format, e.g. by incorporating this information in the electronic EML.

Annex 1: Summary of reviews of antibiotics conducted for EML and EMLc in 2017 and 2019

In 2017, a comprehensive review of antibiotics in sections 6.2.1 and 6.2.2 of the EML and EMLc was undertaken:

- A review of antibiotics for 21 priority infectious syndromes in adults and children was conducted by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada (the McMaster Group);
- A review of antibiotics for five specific bacterial infections in children, based on a review of WHO guidelines, was conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health;
- A review of antibiotics for specific sexually transmitted infections, based on a review of updated WHO guidelines, was conducted by the WHO Department of Reproductive Health and Research.

In 2019, the Expert Committee reviewed antibiotic options for the treatment of:

- Typhoid and paratyphoid (enteric) fever;
- Antibiotics for surgical prophylaxis;
- Antibiotics for oral and dental infections.

A summary of the clinical conditions reviewed by the Expert Committee in 2017 and 2019 is shown in the following table:

Year	**Clinical conditions reviewed**
2017	*21 priority infectious syndromes in adults and children:* community-acquired pneumonia pharyngitis sinusitis otitis media hospital-acquired pneumonia ventilator-associated pneumonia sepsis in children urinary tract infection (UTI) catheter-associated UTI endocarditis meningitis central-line infections complicated intra-abdominal infections wound, skin and soft-tissue infections surgical site infections cellulitis

	acute infectious diarrhoea sexually transmitted infections exacerbations of chronic obstructive pulmonary disease bone and joint infections febrile neutropenia
2017	*Five specific bacterial infections in children* community-acquired pneumonia sepsis dysentery cholera severe acute malnutrition
2017	*Specific sexually transmitted infections* *Neisseria gonorrhoeae* *Treponema pallidum* (syphilis) *Chlamydia trachomatis*
2019	Typhoid and paratyphoid (enteric) fever Antibiotics for surgical prophylaxis Antibiotics for oral and dental infections

Annex 2: Access group antibiotics and EML status

Medicine	Class of agent	ATC Code	EML 2019
Amikacin	Aminoglycosides	J01GB06	Yes
Amoxicillin	Penicillins	J01CA04	Yes
Amoxicillin/clavulanic Acid	Beta lactam - beta lactamase inhibitor	J01CR02	Yes
Ampicillin	Penicillins	J01CA01	Yes
Ampicillin/sulbactam	Beta lactam - beta lactamase inhibitor	J01CR01	No
Bacampicillin	Penicillins	J01CA06	No
Benzathine benzylpenicillin	Penicillins	J01CE08	Yes
Benzylpenicillin	Penicillins	J01CE01	Yes
Cefacetrile	First-generation cephalosporins	J01DB10	No
Cefadroxil	First-generation cephalosporins	J01DB05	No
Cefalexin	First-generation cephalosporins	J01DB01	Yes
Cefalotin	First-generation cephalosporins	J01DB03	No
Cefapirin	First-generation cephalosporins	J01DB08	No
Cefatrizine	First-generation cephalosporins	J01DB07	No
Cefazedone	First-generation cephalosporins	J01DB06	No
Cefazolin	First-generation cephalosporins	J01DB04	Yes
Cefradine	First-generation cephalosporins	J01DB09	No
Cefroxadine	First-generation cephalosporins	J01DB11	No
Ceftezole	First-generation cephalosporins	J01DB12	No
Chloramphenicol	Amphenicols	J01BA01	Yes
Clindamycin	Lincosamides	J01FF01	Yes
Clometocillin	Penicillins	J01CE07	No
Cloxacillin	Penicillins	J01CF02	Yes
Dicloxacillin	Penicillins	J01CF01	No
Doxycycline	Tetracyclines	J01AA02	Yes
Flucloxacillin	Penicillins	J01CF05	No
Gentamicin	Aminoglycosides	J01GB03	Yes
Mecillinam	Penicillins	J01CA11	No
Metronidazole	Imidazoles	J01XD01	Yes
Metronidazole	Imidazoles	P01AB01	Yes
Nafcillin	Penicillins	J01CF06	No
Nitrofurantoin	Nitrofurantoin	J01XE01	Yes
Oxacillin	Penicillins	J01CF04	No
Penamecillin	Penicillins	J01CE06	No
Phenoxymethylpenicillin	Penicillins	J01CE02	Yes
Pivampicillin	Penicillins	J01CA02	No
Pivmecillinam	Penicillins	J01CA08	No
Procaine benzylpenicillin	Penicillins	J01CE09	Yes

Medicine	Class of agent	ATC Code	EML 2019
Spectinomycin	Aminocyclitols	J01XX04	Yes
Sulfadiazine/trimethoprim	Trimethoprim - sulfonamide combinations	J01EE02	No
Sulfamethizole/trimethoprim	Trimethoprim - sulfonamide combinations	J01EB02	No
Sulfamethoxazole/trimethoprim	Trimethoprim - sulfonamide combinations	J01EE01	Yes
Sulfametrole/trimethoprim	Trimethoprim - sulfonamide combinations	J01EE03	No
Sulfamoxole/trimethoprim	Trimethoprim - sulfonamide combinations	J01EE04	No
Sultamicillin	Beta lactam - beta lactamase inhibitor	J01CR04	No
Tetracycline	Tetracyclines	J01AA07	No
Thiamphenicol	Amphenicols	J01BA02	No
Trimethoprim	Trimethoprim	J01EA01	No

Annex 3: Watch group antibiotics and EML status

Medicine	Class of agent	ATC Code	EML 2019
Arbekacin	Aminoglycosides	J01GB12	No
Azithromycin	Macrolides	J01FA10	Yes
Azlocillin	Penicillins	J01CA09	No
Biapenem	Carbapenems	J01DH05	No
Carbenicillin	Carboxypenicillins	J01CA03	No
Cefaclor	Second-generation cephalosporins	J01DC04	No
Cefamandole	Second-generation cephalosporins	J01DC03	No
Cefbuperazone	Second-generation cephalosporins	J01DC13	No
Cefcapene pivoxil	Third-generation cephalosporins	J01DD17	No
Cefdinir	Third-generation cephalosporins	J01DD15	No
Cefditoren pivoxil	Third-generation cephalosporins	J01DD16	No
Cefepime	Fourth-generation cephalosporins	J01DE01	No
Cefetamet pivoxil	Third-generation cephalosporins	J01DD10	No
Cefixime	Third-generation cephalosporins	J01DD08	Yes
Cefmenoxime	Third-generation cephalosporins	J01DD05	No
Cefmetazole	Second-generation cephalosporins	J01DC09	No
Cefminox	Second-generation cephalosporins	J01DC12	No
Cefodizime	Third-generation cephalosporins	J01DD09	No
Cefonicid	Second-generation cephalosporins	J01DC06	No
Cefoperazone	Third-generation cephalosporins	J01DD12	No
Ceforanide	Second-generation cephalosporins	J01DC11	No
Cefoselis	Fourth-generation cephalosporins	not assigned	No
Cefotaxime	Third-generation cephalosporins	J01DD01	Yes
Cefotetan	Second-generation cephalosporins	J01DC05	No
Cefotiam	Second-generation cephalosporins	J01DC07	No
Cefotiam hexetil	Second-generation cephalosporins	J01DC07	No
Cefoxitin	Second-generation cephalosporins	J01DC01	No
Cefozopran	Fourth-generation cephalosporins	J01DE03	No
Cefpiramide	Third-generation cephalosporins	J01DD11	No
Cefpirome	Fourth-generation cephalosporins	J01DE02	No
Cefpodoxime proxetil	Third-generation cephalosporins	J01DD13	No
Cefprozil	Second-generation cephalosporins	J01DC10	No
Ceftazidime	Third-generation cephalosporins	J01DD02	Yes
Cefteram pivoxil	Third-generation cephalosporins	J01DD18	No
Ceftibuten	Third-generation cephalosporins	J01DD14	No
Ceftizoxime	Third-generation cephalosporins	J01DD07	No
Ceftriaxone	Third-generation cephalosporins	J01DD04	Yes
Cefuroxime	Second-generation cephalosporins	J01DC02	Yes

Medicine	Class of agent	ATC Code	EML 2019
Chlortetracycline	Tetracyclines	J01AA03	No
Ciprofloxacin	Fluoroquinolones	J01MA02	Yes
Clarithromycin	Macrolides	J01FA09	Yes
Clofoctol	Phenol derivatives	J01XX03	No
Delafloxacin	Fluoroquinolones	J01MA23	No
Dibekacin	Aminoglycosides	J01GB09	No
Dirithromycin	Macrolides	J01FA13	No
Doripenem	Carbapenems	J01DH04	No
Enoxacin	Fluoroquinolones	J01MA04	No
Ertapenem	Carbapenems	J01DH03	No
Erythromycin	Macrolides	J01FA01	No
Fleroxacin	Fluoroquinolones	J01MA08	No
Flomoxef	clofocto	J01DC14	No
Flumequine	Fluoroquinolones	J01MB07	No
Fosfomycin (oral)	Phosphonics	J01XX01	No
Fusidic Acid	Steroid antibacterials	J01XC01	No
Garenoxacin	Fluoroquinolones	J01MA19	No
Gatifloxacin	Fluoroquinolones	J01MA16	No
Gemifloxacin	Fluoroquinolones	J01MA15	No
Imipenem/cilastatin	Carbapenems	J01DH51	No
Isepamicin	Aminoglycosides	J01GB11	No
Josamycin	Macrolides	J01FA07	No
Kanamycin	Aminoglycosides	J01GB04	No
Latamoxef	Third-generation cephalosporins	J01DD06	No
Levofloxacin	Fluoroquinolones	J01MA12	No
Lincomycin	Macrolides	J01FF02	No
Lomefloxacin	Fluoroquinolones	J01MA07	No
Lymecycline	Tetracyclines	J01AA04	No
Meropenem	Carbapenems	J01DH02	Yes
Metacycline	Tetracyclines	J01AA05	No
Mezlocillin	Penicillins	J01CA10	No
Micronomicin	Aminoglycosides	Not assigned	No
Midecamycin	Macrolides	J01FA03	No
Minocycline (oral)	Tetracyclines	J01AA08	No
Moxifloxacin	Fluoroquinolones	J01MA14	No
Neomycin	Aminoglycosides	J01GB05	No
Netilmicin	Aminoglycosides	J01GB07	No
Norfloxacin	Fluoroquinolones	J01MA06	No
Ofloxacin	Fluoroquinolones	J01MA01	No
Oleandomycin	Macrolides	J01FA05	No

Medicine	Class of agent	ATC Code	EML 2019
Oxytetracycline	Tetracyclines	J01AA06	No
Panipenem	Carbapenems	Not assigned	No
Pazufloxacin	Fluoroquinolones	J01MA18	No
Pefloxacin	Fluoroquinolones	J01MA03	No
Pheneticillin	Penicillins	J01CE05	No
Piperacillin	Penicillins	J01CA12	No
Piperacillin/tazobactam	Beta lactam - beta lactamase inhibitor (anti-pseudomonal)	J01CR05	Yes
Pristinamycin	Streptogramins	J01FG01	No
Prulifloxacin	Fluoroquinolones	J01MA17	No
Ribostamycin	Aminoglycosides	J01GB10	No
Rifabutin	Rifamycins	J04AB04	No
Rifampicin	Rifamycins	J04AB02	No
Rifamycin	Rifamycins	J04AB03	No
Rifaximin	Rifamycins	A07AA11	No
Roxithromycin	Macrolides	J01FA06	No
Rufloxacin	Fluoroquinolones	J01MA10	No
Sisomicin	Aminoglycosides	J01GB08	No
Sitafloxacin	Fluoroquinolones	J01MA21	No
Sparfloxacin	Fluoroquinolones	J01MA09	No
Spiramycin	Macrolides	J01FA02	No
Spiramycin/metronidazole	Combination of antibiotics	J01RA04	No
Streptomycin	Aminoglycosides	J01GA01	No
Sulbenicillin	Penicillins	J01CA16	No
Tebipenem	Carbapenems	J01DH06	No
Teicoplanin	Glycopeptides	J01XA02	No
Telithromycin	Macrolides	J01FA15	No
Temocillin	Carboxypenicillins	J01CA17	No
Ticarcillin	Carboxypenicillins	J01CA13	No
Tobramycin	Aminoglycosides	J01GA01	No
Tosufloxacin	Fluoroquinolones	J01MA22	No
Vancomycin (IV)	Glycopeptides	J01XA01	Yes
Vancomycin (oral)	Glycopeptides	A07AA09	Yes

Annex 4: Reserve group antibiotics and EML status

Medicine	Class of agent	ATC Code	EML 2019
Aztreonam	Monobactams	J01DF01	No
Ceftaroline fosamil	Fifth-generation cephalosporins	J01DI02	No
Ceftazidime-avibactam	Third-generation cephalosporins	J01DD52	Yes
Ceftobiprole medocaril	Fifth-generation cephalosporins	J01DI01	No
Ceftolozane-tazobactam	Fifth-generation cephalosporins	J01DI54	No
Colistin	Polymyxins	J01XB01	Yes
Dalbavancin	Glycopeptides	J01XA04	No
Dalfopristin-quinupristin	Streptogramins	J01FG02	No
Daptomycin	Lipopeptides	J01XX09	No
Eravacycline	Tetracyclines	J01AA13	No
Faropenem	Penems	J01DI03	No
Fosfomycin (IV)	Phosphonics	J01XX01	Yes
Linezolid	Oxazolidinones	J01XX08	Yes
Meropenem-vaborbactam	Carbapenems	J01DH52	Yes
Minocycline (IV)	Tetracyclines	J01AA08	No
Omadacycline	Tetracyclines	Not assigned	No
Oritavancin	Glycopeptides	J01XA05	No
Plazomicin	Aminoglycosides	Not assigned	Yes
Polymyxin B	Polymyxins	J01XB02	Yes
Tedizolid	Oxazolidinones	J01XX11	No
Telavancin	Glycopeptides	J01XA03	No
Tigecycline	Glycylcyclines	J01AA12	No

Annex 5: Not recommended antibiotics and EML status

Medicine	EML 2019
acetylspiramycin/metronidazole	No
amikacin/cefepime	No
amoxicillin/bacillus coagulans/cloxacillin	No
amoxicillin/bacillus coagulans/dicloxacillin	No
amoxicillin/clavulanic acid/lactic ferments	No
amoxicillin/clavulanic acid/lactobacillus acidophilus	No
amoxicillin/clavulanic acid/nimesulide	No
amoxicillin/cloxacillin	No
amoxicillin/cloxacillin/lactic acid	No
amoxicillin/cloxacillin/lactobacillus acidophilus/serrapeptase	No
amoxicillin/cloxacillin/lactobacillus lactis	No
amoxicillin/cloxacillin/serrapeptase	No
amoxicillin/dicloxacillin	No
amoxicillin/dicloxacillin/saccharomyces boulardii	No
amoxicillin/flucloxacillin	No
amoxicillin/flucloxacillin/lactobacillus acidophilus	No
amoxicillin/metronidazole	No
amoxicillin/pivsulbactam	No
amoxicillin/sulbactam	No
ampicillin/bacillus coagulans/cloxacillin	No
ampicillin/cloxacillin	No
ampicillin/cloxacillin/lactobacillus acidophilus	No
ampicillin/cloxacillin/saccharomyces boulardii	No
ampicillin/dicloxacillin	No
ampicillin/dicloxacillin/lactobacillus acidophilus	No
ampicillin/flucloxacillin	No
ampicillin/lidocaine/sulbactam	No
ampicillin/oxacillin	No
ampicillin/sultamicillin	No
ascorbic acid/metamizole sodium/penicillin g /streptomycin	No
azithromycin/cefixime	No
azithromycin/cefixime/lactobacillus acidophilus	No
azithromycin/cefpodoxime proxetil	No
azithromycin/fluconazole/secnidazole	No
azithromycin/levofloxacin	No
azithromycin/ofloxacin	No
benzyl penicillin/streptomycin	No
bromelains/doxycycline/lactobacillus reuteri/lactobacillus rhamnosus/ornidazole	No

Medicine	EML 2019
bromhexine/sulfamethoxazole/trimethoprim	No
cefaclor/clavulanic acid	No
cefadroxil/clavulanic acid	No
cefadroxil/trimethoprim	No
cefalexin/trimethoprim	No
cefdinir/clavulanic acid	No
cefepime/sulbactam	No
cefepime/tazobactam	No
cefixime/cefpodoxime proxetil	No
cefixime/clavulanic acid	No
cefixime/clavulanic acid/lactobacillus acidophilus	No
cefixime/cloxacillin	No
cefixime/cloxacillin/lactobacillus acidophilus	No
cefixime/dicloxacillin	No
cefixime/lactobacillus acidophilus/ofloxacin	No
cefixime/levofloxacin	No
cefixime/linezolid	No
cefixime/moxifloxacin	No
cefixime/ofloxacin	No
cefixime/ornidazole	No
cefoperazone/sulbactam	No
cefoperazone/tazobactam	No
cefotaxime/sulbactam	No
cefpodoxime proxetil/clavulanic acid	No
cefpodoxime proxetil/cloxacillin/lactobacillus acidophilus	No
cefpodoxime proxetil/dicloxacillin	No
cefpodoxime proxetil/dicloxacillin/lactobacillus acidophilus	No
cefpodoxime proxetil/levofloxacin	No
cefpodoxime proxetil/ofloxacin	No
cefpodoxime proxetil/sulbactam	No
ceftazidime/sulbactam	No
ceftazidime/tazobactam	No
ceftazidime/tobramicin	No
ceftibuten/clavulanic acid	No
ceftriaxone/sulbactam	No
ceftriaxone/tazobactam	No
ceftriaxone/vancomycin	No
cefuroxime axetil/clavulanic acid	No
cefuroxime axetil/linezolid	No
cefuroxime axetil/sulbactam	No

Medicine	EML 2019
cefuroxime/clavulanic acid	No
cefuroxime/sulbactam	No
chloramphenicol/tetracycline	No
ciprofloxacin/metronidazole	No
ciprofloxacin/ornidazole	No
ciprofloxacin/tinidazole	No
doxycycline/tinidazole	No
erythromycin/sulfamethoxazole/trimethoprim	No
erythromycin/trimethoprim	No
fosfomycin/trimethoprim	No
gatifloxacin/ornidazole	No
kanamycin/penicillin g	No
levofloxacin/metronidazole	No
levofloxacin/ornidazole	No
meropenem/sodium/sulbactam	No
meropenem/sulbactam	No
metronidazole/norfloxacin	No
metronidazole/spiramycin	No
metronidazole/tetracycline	No
mezlocillin/sulbactam	No
ofloxacin/ornidazole	No
oleandomycin/tetracycline	No
piperacillin/sulbactam	No
rifampicin/trimethoprim	No
sulfadiazine/sulfamethoxazole/trimethoprim	No

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