Update of the 2019 WHO AWaRe classification of antibiotics

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Proposal

The Expert Committee is requested to consider the recommendations of the EML Antibiotics Working Group for updating the 2019 WHO AWaRe classification of antibiotics.

Background

The AWaRe classification of antibiotics was first introduced in 2017 for EML-listed antibiotics. It was expanded beyond the EML in 2019 to include over 170 commonly used antibiotics globally, to better support monitoring of antibiotic use and stewardship activities. A general summary of the 2019 AWaRe classification groupings[1] is presented below. The full 2019 AWaRe classification database is available at https://apps.who.int/iris/handle/10665/327957.

Access group	Aminoglycosides (unless included in Watch or Reserve) Amphenicols Beta-lactams with beta-lactamase inhibitors First-generation cephalosporins Penicillins (unless included in Watch) Tetracyclines (unless included in Watch or Reserve) Trimethoprim, alone or in combination with sulfonamides Clindamycin Metronidazole Nitrofurantoin Spectinomycin
Watch group	Aminoglycosides (unless included in Access or Reserve) Anti-pseudomonal penicillins with beta-lactamase inhibitors Carbapenems (unless included in Reserve) Carboxypenicillins Fluoroquinolones Glycopeptides (unless included in Reserve) Macrolides (unless included in Reserve) Penicillins (unless included in Access) Tetracyclines (unless included in Access or Reserve) Second generation cephalosporins Third generation cephalosporins (unless included in Reserve)

[1] World Health Organization. (2019). 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). World Health Organization. https://apps.who.int/iris/handle/10665/330668. License: CC BY-NC-SA 3.0 IGO

	Fourth generation cephalosporins Rifamycins Clofoctol Fosfomycin (oral formulation) Fusidic acid
Reserve group	Carbapenems (unless included in Watch) Monobactams Third generation cephalosporins (unless included in Watch) Polymyxins Glycopeptides (unless included in Watch) Macrolides (unless included in Watch) Oxazolidinones Tetracyclines (unless included in Access or Watch) Daptomycin Faropenem Fosfomycin (IV formulation) Tigecycline

Methodology to update the AWaRe classification of antibiotics

The WHO ATC/DDD Index[2] (2020 and 2021) was utilized to identify systemic antibacterial agents that are not included in the 2019 AWaRe classification database. The following ATC groups were reviewed:

J01 ANTIBACTERIALS FOR SYSTEMIC USE

A07A INTESTINAL INFECTIVES

P01AB ANTIPROTOZOALS

Antibiotics for which regulatory approval was granted in 2019 and 2020 were also identified from the FDA and EMA websites[3,4,5.]

Antibacterial agents that are not included in the 2019 AWaRe list were identified and categorized using the current definitions of the 3 groups listed below.

ACCESS: 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.

[2] https://www.whocc.no/atc_ddd_index/

[3] https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019

[4] https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020

[5] https://www.ema.europa.eu/en/committees/chmp/chmp-agendas-minutes-highlights

WATCH: 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 Medicine1 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: 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 Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List[1], 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.

Antibacterial agents identified were reviewed by the EML Antibiotics Working Group. The agents proposed for addition to the AWaRe database, and their recommended classification as Access, Watch or Reserve is presented in Table 1.

Table 1: Recommended AWaRe classification of antibiotics

ATC Code	Medicine	RoA	Comments
ACCESS			
J01CA07	epicillin	O, P	Similar to aminopenicillins
J01CA14	metampicillin	O, P	Hydrolized to ampicillin
J01CA15	talampicillin	O	Hydrolized to ampicillin
J01CA18	hetacillin	O	Hydrolized to ampicillin
J01CE03	propicillin	O	Similar to penicillin
J01CE04	azidocillin	O	Similar to penicillin
J01CF03	meticillin	P	Similar to oxacillin
J01CG01	sulbactam	P	Beta-lactamase inhibitor
J01DB02	cefaloridine	P	First gen cephalosporin
J01EA02	brodimoprim	O	Derivative of trimethoprim
J01EB01	sulfaisodimidine	O, P	Sulfonamide
J01EB02	sulfamethizole	O	Sulfonamide
J01EB03	sulfadimidine	O	Sulfonamide
J01EB04	sulfapyridine	O	Sulfonamide
J01EB05	sulfafurazole	O, P	Sulfonamide
J01EB06	sulfanilamide		Sulfonamide
J01EB07	sulfathiazole		Sulfonamide
J01EB08	sulfathiourea	O	Sulfonamide
J01EC01	sulfamethoxazole	O	Sulfonamide
J01EC02	sulfadiazine	O	Sulfonamide
J01EC03	sulfamoxole	O, P	Sulfonamide
J01ED01	sulfadimethoxine	O	Sulfonamide
J01ED02	sulfalene	O	Sulfonamide
J01ED03	sulfametomidine		Sulfonamide
J01ED04	sulfametoxydiazine	O	Sulfonamide
J01ED05	sulfamethoxypyridazine	O	Sulfonamide
J01ED06	sulfaperin	O	Sulfonamide
J01ED07	sulfamerazine	O	Sulfonamide
J01ED08	sulfaphenazole	O	Sulfonamide
J01ED09	sulfamazone	O, R	Sulfonamide
J01EE05	sulfadimidine and trimethoprim		Sulfonamide combination
J01EE06	sulfadiazine and tetroxoprim		Sulfonamide combination
J01EE07	sulfamerazine and trimethoprim		Sulfonamide combination
J01XD02	tinidazole	P	Imidazole, similar to metronidazole

P01AB02	tinidazole	O	Imidazole, similar to metronidazole
J01XD03	ornidazole	P	Imidazole, similar to metronidazole
P01AB03	ornidazole	O	Imidazole, similar to metronidazole
J01XE02	nifurtoinol	O	Similar to nitrofurantoin
J01XE03	furazidin	O	Similar to nitrofurantoin
P01AB07	secnidazole	O	Imidazole
WATCH			
A07AA01	neomycin	O	Similar to IV
A07AA04	streptomycin	O	Similar to IV
A07AA08	kanamycin	O	Similar to IV
A07AA12	fidaxomicin	O	Not a lot of C. difficile resistance known
A07AA13	rifamycin	O	Similar to IV
J01CA05	carindacillin	O	Prodrug of carbenicillin
J01CA19	aspoxicillin	P	Similar to piperacillin
J01CG02	tazobactam	P	Beta-lactamase inhibitor - Watch
J01DC08	loracarbef	O	Second gen cephalosporin
J01DD03	cefsulodin	P	Third gen cephalosporin
J01FA08	troleandomycin	O	Similar to erythromycin
J01FA11	miocamycin	O	Similar to erythromycin
J01FA12	rokitamycin	O	Macrolide
J01FA14	flurithromycin	O	Macrolide
J01FA16	solithromycin		Macrolide. Did not receive FDA approval for CAP and not as effective for Gonorrhea
J01GA02	streptoduocin	P	Aminoglycoside - combination of streptomycin and dihydrostreptomycin
J01GB13	bekanamycin	P	Similar to kanamycin
J01MA05	temafloxacin	O	Quinolone
J01MA11	grepafloxacin	O	Quinolone
J01MA13	trovafloxacin	O	Quinolone
J01MA13	trovafloxacin	P	Quinolone
J01MA24	levonadifloxacin		Quinolone, activity against MRSA- approved in India only
J01MA25	lascufloxacin	O	Quinolone, activity against MRSA- Japanese drug
J01MB01	rosoxacin	O	Quinolone
J01MB03	piromidic acid	O	Quinolone
J01MB04	pipemidic acid	O	Quinolone
J01MB05	oxolinic acid	O	Quinolone
J01MB06	cinoxacin	O	Quinolone
J01MB08	nemonoxacin		Quinolone
J01AA01	demeclocycline	O	Tetracycline, limited use as antibiotic, vasopressin inhibitor (SIADH)

J01AA09	rolitetracycline	P	Prodrug of tetracycline, most tetracyclines in Watch except doxycycline and tetracycline
J01AA10	penimepicycline		Salt of tetracycline pipacycline
J01AA11	clomocycline	O	Tetracycline, used for acne.
J01AA14	sarecycline	O	Tetracycline, used for acne.
RESERVE			
A07AA05	polymyxin B	O	Similar to IV
A07AA10	colistin	O	Similar to IV
J01DF02	carumonam	P	Similar to aztreonam
J01DH56	Imipenem, cilastatin, relebactam	P	Active against CRE, MDR PSA
J01DI04	cefiderocol	P	Active against CRE, CRAB, MDR PSA
J01EA03	iclaprim	P	Intravenous, active against MRSA, VRSA
J01XX12	lefamulin		Active against MRSA, VISA/VRSA, VRE
NOT CLASSIFIED			
J01XX02	xibornol		No systemic use, exclude from AWaRe
J01XX05	methenamine	O	Urinary antiseptic, exclude from AWaRe
J01XX06	mandelic acid	O	Urinary antiseptic, exclude from AWaRe
J01XX07	nitroxoline	O	Available in Europe. Used to prevent biofilm esp Pseudomonas. Exclude from AWaRe
J01XX10	bacitracin		Not systemic therapy, exclude from AWaRe
A07AA06	paromomycin	O	Mainly parasite coverage, exclude from AWaRe
P01AB04	azanidazole	O	Used mainly for antiprotozoal activity, exclude from AWaRe
P01AB05	propenidazole	O	Used mainly for antiprotozoal activity, exclude from AWaRe
P01AB06	nimorazole	O	Used mainly for antiprotozoal activity, exclude from AWaRe