Proposal to the 2025 Expert Committee on Selection and Use of Essential Medicines to classify antibiotics not currently included in the WHO AWaRe classification

Applicant

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Abbreviations used in the document

- AMR: antimicrobial resistance
- AMU: antimicrobial use
- ATC: Anatomical Therapeutic Chemical
- AWaRe: Access, Watch, Reserve
- BL/BLI: beta-lactam/beta-lactamase inhibitor
- CSR: Control and Response Strategies
- DDD: Defined Daily Dose
- DNA: deoxyribose nucleic acid
- EML: WHO Model List of Essential Medicines
- ESBL: extended-spectrum beta-lactamase
- GLASS: Global Antimicrobial Resistance and Use Surveillance System
- LMIC: low- and middle-income country
- N: no
- O: oral
- P: parenteral
- RoA: route of administration
- SPC: Surveillance, Prevention and Control
- UK: United Kingdom
- UNGA: United Nations General Assembly
- UTI: urinary tract infection
- WHO: World Health Organization
- Y: yes

Summary statement

The World Health Organization (WHO) Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support antibiotic stewardship efforts at local, national and global levels. The 2023 classification (1) includes 257 antibiotics, including 87 Access, 141 Watch and 29 Reserve antibiotics. Of these, 41 are on the WHO Model List of Essential Medicines (EML) (2), including 20 Access, 12 Watch and 9 Reserve antibiotics. There are currently 103 antibiotics, including fixed-dose and beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, classified as Not Recommended. The AWaRe classification has been adopted in high-income countries such as the United Kingdom (UK) (3) and Japan (4) and there is increasing use in low- and middle-income countries (LMICs) in antibiotic surveillance and stewardship programmes (5).

The classification of antibiotics by AWaRe has implications on local, national and global efforts to monitor and improve antibiotic use. For example, locally, proportion of antibiotic use by AWaRe classification may be used for benchmarking (6) and broader spectrum antibiotics classified as Watch and Reserve antibiotics have been identified as targets for antimicrobial stewardship programmes (7,8). At the national level, countries may ban the registration, import and use of antibiotics on the Not Recommended list (9). At the global level, the classification of antibiotics by AWaRe may impact on whether Member States achieve the 2024 United Nations General Assembly (UNGA) on antimicrobial resistance (AMR) target of 70% Access antibiotic use in human health by 2030 (10).

A total of 48 antibiotics that are available and used around the world but not yet included in the AWaRe classification have been identified through the Global Antimicrobial Resistance and Use Surveillance System for antimicrobial use (GLASS-AMU). Based on GLASS-AMU methodology, these antibiotics are currently excluded from global AMU monitoring. The technical unit responsible for antimicrobial use and stewardship (AMR/SPC/CSR) in WHO proposes the classification of 27 of these antibiotics by AWaRe as outlined in this document.

Table 1 contains antibiotics that are not currently classified by AWaRe and are proposed to be Access, Watch or Reserve based on the antibiotic class, mechanism of action and classification of other similar antibiotics.

Table 2 contains a novel first-in-class antibiotic (gepotidacin) that is not currently classified by AWaRe. It is a triaza-acenaphthylene antibiotic that selectively inhibits bacterial deoxyribose nucleic acid (DNA) replication by interaction with the bacterial subunits of DNA gyrase and topoisomerase IV (11), similar to the mechanism of action of quinolones. It is given orally and is active against a wide range of pathogens causing urinary tract infection (UTI), including extended-spectrum beta-lactamase producing Enterobacterales. Recent studies suggest it is non-inferior and even superior to nitrofurantoin for the treatment of uncomplicated UTI in women (12). For these reasons, we propose the classification of gepotidacin to be Watch, with review in 2 years according to emerging evidence on its efficacy, safety and real-world use.

Table 3 contains antibiotics that are not currently classified by AWaRe and are proposed to be Not Recommended as the agents are fixed-dose combinations of more than one antibiotic for which there is no evidence to support their co-administration.

Table 4 contains antibiotics not currently classified that require further information before classification can be assigned. These are fixed-dose combinations for which there is insufficient information about the combined substance (do not have a combination ATC code or DDD assigned) to propose a classification. We will approach the WHO International Working Group for Drug Statistics Methodology to discuss the current ATC/DDD methodology with a view to identify each substance in the fixed-dose combination, in order to enable further evaluation and classification by AWaRe. While these are likely to be categorised as Not Recommended, we propose maintaining the unclassified status until further information is available on specific fixed-dose combinations.

Table 5 contains antibiotics not currently classified that should be excluded from classification by AWaRe as these are not systemic antibiotics and therefore not included in WHO AMU surveillance methodology.

Table 6 contains BL/BLI combinations currently classified as Not Recommended. As for the fixed-dose combinations with insufficient information, we will approach the WHO International Working Group for Drug Statistics Methodology to identify all available combinations, so that the classification of each fixed-dose combination may be evaluated as part of a broader review and revision of the AWaRe definitions planned by WHO. In the meantime, we propose maintaining the Not Recommended status of these agents until further information is available on specific fixed-dose combinations.

Table 1: Antibiotics not currently classified by AWaRe that are proposed to be Access, Watch or Reserve based on classification of similar antibiotics

ATC5	Name	RoA	DDD	Combination code	Substances	Current classification	Proposed classification	Rationale
A07AA06	Paromomycin	O	Y			Unclassified	Watch	As for other oral aminoglycosides
J01CE10	Benzathine phenoxymethylpenicillin	O	Y			Unclassified	Access	As for phenoxymethylpenicillin
J01CR03	Ticarcillin and beta-lactamase inhibitor (ticarcillin + clavulanic acid)	P	Y			Unclassified	Watch	As for other BL/BLIs of similar spectrum
J01DF51	Aztreonam and beta-lactamase inhibitor (aztreonam + avibactam)		N			Unclassified	Reserve	Active against carbapenemase producers
J01MB02	Nalidixic acid	O	Y			Unclassified	Watch	As for other quinolones
P01AB04	Azanidazole		N			Unclassified	Access	As for other imidazoles
P01AB05	Propenidazole		N			Unclassified	Access	As for other imidazoles
P01AB06	Nimorazole	O	Y			Unclassified	Access	As for other imidazoles
P01AB08	Satranidazole		N			Unclassified	Access	As for other imidazoles

Table 2: Novel first-in-class antibiotic not currently classified by AWaRe

ATC5	Name	RoA	DDD	Combination code	Substances	Current classification	Proposed classification	Rationale
J01XX13	Gepotidacin		N			Unclassified	Watch	Novel first in class agent, similar mechanism of action to quinolones, covers ESBLs, oral option for uncomplicated UTI

Table 3: Antibiotics not currently classified by AWaRe that are proposed to be Not Recommended

ATC5	Name	RoA	DDD	Combination code	Substances	Current classification	Proposed classification	Rationale
J01AA20	Combinations of tetracyclines	O	Y	J01AA20_1	tetracycline 115.4 mg + chlortetracycline 115.4 mg + demeclocycline 69.2 mg	Unclassified	Not Recommended	Fixed-dose combination
J01CA20	Combinations	O	Y	J01CA20_2	pivampicillin 0.125 g + pivmecillinam 0.1 g	Unclassified	Not Recommended	Fixed-dose combination
J01CA20	Combinations	O	Y	J01CA20_1	pivampicillin 0.25 g + pivmecillinam 0.2 g	Unclassified	Not Recommended	Fixed-dose combination
J01CE30	Combinations	P	Y	J01CE30_1	benzylpenicillin + procaine benzylpenicillin + benzathine benzylpenicillin	Unclassified	Not Recommended	Fixed-dose combination
J01EC20	Combinations	O	Y	J01EC20_1	sulfacarbamide 0.167 g + sulfadiazine 0.167 g + sulfadimidine 0.167 g	Unclassified	Not Recommended	Fixed-dose combination
J01RA01	Penicillins, combinations with other antibacterials		N			Unclassified	Not Recommended	Fixed-dose combination
J01RA02	Sulfonamides, combinations with other antibacterials (excl. trimethoprim)		N			Unclassified	Not Recommended	Fixed-dose combination
J01RA03	Cefuroxime and metronidazole		N			Unclassified	Not Recommended	Fixed-dose combination
J01RA13	Norfloxacin and tinidazole	O	Y	J01RA13_2	norfloxacin 0.4 g + tinidazole 0.6 g	Unclassified	Not Recommended	Fixed-dose combination
J01RA17	Ofloxacin and nitazoxanide		N			Unclassified	Not Recommended	Fixed-dose combination
J01RA18	Ofloxacin and tinidazole		N			Unclassified	Not Recommended	Fixed-dose combination
J01RA19	Tetracycline and nystatin		N			Unclassified	Not Recommended	Fixed-dose combination
P01AB51	Metronidazole and furazolidone	O	Y	P01AB51_1	metronidazole 0.4 g + furazolidone 0.1 g	Unclassified	Not Recommended	Fixed-dose combination

P01AB52	Metronidazole and diloxanide	O	Y	P01AB52_3	metronidazole 0.1 g + diloxanide 0.125 g	Unclassified	Not Recommended	Fixed-dose combination
P01AB52	Metronidazole and diloxanide	O	Y	P01AB52_2	metronidazole 0.2 g + diloxanide 0.25 g	Unclassified	Not Recommended	Fixed-dose combination
P01AB52	Metronidazole and diloxanide	O	Y	P01AB52_1	metronidazole 0.4 g + diloxanide 0.5 g	Unclassified	Not Recommended	Fixed-dose combination
P01AB53	Tinidazole and diloxanide		N			Unclassified	Not Recommended	Fixed-dose combination

Table 4: Antibiotics not currently classified by AWaRe that require further information before classification can be assigned

ATC5	Name	RoA	DDD assigned	Combination code	Substances	Current classification	Proposed classification	Rationale
A07AA51	Neomycin, combinations		N			Unclassified	Unclassified	Need more information on combined substance
A07AA54	Streptomycin, combinations		N			Unclassified	Unclassified	Need more information on combined substance
J01AA56	Oxytetracycline, combinations		N			Unclassified	Unclassified	Need more information on combined substance
J01BA52	Thiamphenicol, combinations		N			Unclassified	Unclassified	Need more information on combined substance
J01CA51	Ampicillin, combinations		N			Unclassified	Unclassified	Need more information on combined substance
J01DD54	Ceftriaxone, combinations		N			Unclassified	Unclassified	Need more information on combined substance
J01EB20	Combinations		N		Intermediate-acting sulfonamide with trimethoprim	Unclassified	Unclassified	Need more information on combined substance
J01ED20	Combinations		N		Long-acting sulfonamide with trimethoprim	Unclassified	Unclassified	Need more information on combined substance
J01XE51	Nitrofurantoin, combinations		N			Unclassified	Unclassified	Need more information on combined substance

Table 5: Antibiotics not currently classified by AWaRe that should be excluded (not systemic antibiotics)

ATC5	Name	RoA	DDD assigned	Combination code	Substances	Current classification	Proposed classification	Rationale
J01XX02	Xibornol		N			Unclassified	Unclassified	Topical antiseptic
J01XX05	Methenamine	O	Y			Unclassified	Unclassified	Not an antibiotic
J01XX06	Mandelic acid	O	Y			Unclassified	Unclassified	Not an antibiotic
J01XX07	Nitroxoline	O	Y			Unclassified	Unclassified	Not an antibiotic
J01XX10	Bacitracin		N			Unclassified	Unclassified	Topical

Table 6: Beta-lactam/beta-lactamase inhibitor combinations currently classified as Not Recommended for which it is necessary to identify all available combinations and evaluate classification

ATC5	Name	RoA	DDD assigned	Combination code	Substances	Current classification	Proposed classification	Rationale
J01DC52	Cefuroxime and beta-lactamase inhibitor	O	Y			Not recommended	Not recommended	Need more information on BLI
J01DD58	Cefixime and beta-lactamase inhibitor		N			Not recommended	Not recommended	Need more information on BLI
J01DD62	Cefoperazone and beta-lactamase inhibitor	P	Y			Not recommended	Not recommended	Need more information on BLI
J01DD63	Ceftriaxone and beta-lactamase inhibitor	P	Y			Not recommended	Not recommended	Need more information on BLI
J01DD64	Cefpodoxime and beta-lactamase inhibitor	O	Y			Not recommended	Not recommended	Need more information on BLI
J01DE51	Cefepime and beta-lactamase inhibitor		N			Not recommended	Not recommended	Need more information on BLI

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