AWaRe definitions: Focus on Reserve and Watch "plus"

WHO EML Secretariat, Health Products Policy and Standards Department with input from WHO Control and Response Strategies (CSR), Surveillance, Prevention and Control (SPC) Department

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Background

In 2017, the WHO developed AWaRe, which categorizes antibiotics into three groups (Access, Watch and Reserve), as a tool with two aims: to guide the selection of antibiotics that offer the best payback in terms of clinical benefits, and to support antimicrobial stewardship and surveillance related to their use [1]. AWaRe considers the impact of different antibiotics on antimicrobial resistance (AMR) to emphasize the importance of their appropriate use in humans and is part of a global people-centered strategy to address AMR [1, 2]. Access antibiotics are generally used as the first choice for common infections (when an antibiotic is needed). Watch antibiotics are the first choice only for specific infections as they have a higher (than Access) potential to develop resistance and for inappropriate use in indications where narrower spectrum antibiotics are preferable. Finally, Reserve antibiotics should only be used when all alternatives are likely to fail [1]. A fourth category includes Not Recommended antibiotics which are fixed-dose combinations of antibiotics without clear indication or clinical merit. While initially only antibiotics on the WHO Model List of Essential Medicines (EML) were categorized, since 2019 both essential antibiotics and those not listed on the EML are categorized, extending AWaRe beyond the 41 antibiotics recommended in the 2023 EML to 257 antibiotics used in humans. The fact that AWaRe incorporates, rather than simplifies, much of the complexity associated with the clinical use of these molecules has been described as a merit [3].

AWaRe is closely linked to the essential medicines concept and tools like the WHO EML which inform national essential medicines lists [1, 4, 5]. Essential medicines lists are a fundamental strategy in healthcare systems to ensure that limited resources are used effectively. Further, they consider that medicines deemed essential are of assured quality and available, support economic efficiency and improve health outcomes. By focusing on essential medicines and essential antibiotics, healthcare systems can better meet the health needs of their populations, mitigating the risk of AMR.

Between 2017 and 2019, the definitions of AWaRe groups were refined to reflect the health needs and selection of antibiotics to be added to the WHO EML at that time (e.g., antibiotics in combination with beta-lactamase inhibitors to treat carbapenem-resistant *Enterobacterales*) [1]. WHO defines Reserve antibiotics as "… 'last resort' antibiotics to use only for highly selected patients with confirmed or suspected life-threatening infections due to multidrug-resistant (MDR) bacteria." It is also stated that Reserve antibiotics "… should be only used when other therapeutic alternatives have failed or are unsuitable." Finally, only

Reserve antibiotics with "proven activity against critical or high priority pathogens identified by the WHO Priority Pathogens list notably carbapenem-resistant *Enterobacterales*" can qualify for inclusion on the WHO EML as essential Reserve antibiotics [1, 6, 7].

Antibiotics categorized by AWaRe are updated on the same biennial cycle as the WHO EML. As of 2023 – the last update – 257 antibiotics not listed on the WHO EML and 41 antibiotics listed on the WHO EML have been classified into an AWaRe group. For those listed on the Model Lists, which should be prioritized for public procurement and policy decisions, WHO has developed guidance (AWaRe antibiotic book) to empirically treat over 30 clinical infections in both the primary and tertiary health care settings based on the WHO EML and the AWaRe system [1, 6].

Along with decisions regarding which Reserve antibiotics to list on the WHO EML, the categorization of specific antibiotics within AWaRe groups has also caused debate. For instance, some advocate to re-categorize amoxicillin-clavulanate as Watch, as done in the national adoption of AWaRe for the United Kingdom, or to move the carbapenems from Watch to Reserve since in many low resource settings they are the last available treatment option and a priority for antimicrobial stewardship interventions [8]. The call to deliberate current definitions and selection of antibiotics to the WHO EML is motivated by how to pursue the goals of AWaRe. Changes could be beneficial for the future updates and success of the WHO EML and AWaRe classification. Finally, the potential of AWaRe goes beyond surveillance of antibiotic use and antibiotic stewardship, and the selection of antibiotics to the WHO EML. Issues related to access, in particular to essential Reserve antibiotics is a dimension that could be better considered so as to have more equity in the distribution of newer antibiotics, which are almost totally absent in some parts of the world. Improvements could be made to further extend the use of the AWaRe classification to other antibiotic policies, for instance using AWaRe to orient compelling research questions, especially those related to the appropriate use of Reserve group antibiotics.

Expert considerations

The WHO Technical Unit on AMR and WHO EML Secretariat engaged Experts, including some serving on the multidisciplinary and globally representative WHO Technical Advisory Group on AWaRe (TAG-AWaRe) [9], to develop this proposal. This section reflects on three areas for improvement that emerged during the first round of consultation between WHO

and Experts: 1) essential Reserve antibiotic definition and selection to the WHO EML; 2) Watch "plus" subgroup; and 3) re-categorization of specific antibiotics.

Essential Reserve antibiotic definition and selection to the WHO EML

The current essential Reserve antibiotic definition is presented in **Box 1**. Seven opportunities for clarification associated with the essential Reserve antibiotic definition were identified by the Experts; of which, three apply to Reserve antibiotics in general as well. They are summarized in **Table 1** and detailed, along with potential solutions, herein.

Box 1. Current definition of essential Reserve antibiotics.

*'Last resort' antibiotics with **proven activity** against **critical or high priority pathogens identified by the WHO Priority Pathogens list** to be used only for highly selected patients with **confirmed or suspected life-threatening infections** due to **multidrug-resistant bacteria**. They should be **only used** when other **therapeutic alternatives have failed or are unsuitable**. To ensure their continued effectiveness, they should be closely monitored and prioritized as targets of stewardship programs*.

Table 1. Elements of the 2025 essential Reserve antibiotic definition where changes are possible.

1. Level of evidence needed to demonstrate *"proven activity"* against critical or high priority pathogens identified by the WHO Bacterial Priority Pathogens List is not always clear;
2. The relationship between the current definition and the WHO Bacterial Priority Pathogens List is not univocal; e.g. some antibiotics with consistent in vitro activity against priority pathogens are not classified as Reserve;
3. Evidence to develop guidance on the appropriate empiric use of Reserve antibiotics to treat life-threatening infections due to suspected multidrug-resistant bacteria is limited;*
4. The definition for multidrug-resistant bacteria has long been debated;*
5. Use of the same principles for selecting all antibiotics on the WHO Essential Medicines Lists regardless of AWaRe classification; e.g. Reserve antibiotics might deserve different criteria;
6. WHO innovation criteria for novel antibiotics and research and development antibacterial pipeline not explicitly considered;*
7. Access issues and strategies to increase access not considered

* Elements open to reflection that also apply to Reserve antibiotics in general (i.e. 29 antibiotics not listed in the EML but in which the AWaRe categorization has been extended)

1. *Level of evidence needed to demonstrate "proven activity" against critical or high priority pathogens identified by the WHO Bacterial Priority Pathogens List is not always clear*

For essential Reserve antibiotics, it is not clear what level of evidence, in terms of "*proven activity"* against critical or high priority pathogens identified on the WHO Bacterial Priority Pathogens List (BPPL), is needed (e.g., in vitro, in humans) to list a Reserve antibiotic on the WHO EML [1, 7]. The Reserve group, as the Access and Watch, is characterized by the co-presence of older and newer antibiotics. In general evidence supporting "old" antibiotics is weak, lacking high-quality clinical studies. Newer antibiotics might be better supported in terms of data related to evolving epidemiology and resistance. However, the most recent pivotal trials supporting marketing approval by stringent regulatory authorities have been often criticized as not providing clear evidence demonstrating *"proven activity"* against critical or high priority pathogens [10]. Phase 2 and 3 randomized controlled trials conducted for regulatory approval often lack representativeness, prioritize statistical significance over clinical relevance, and frequently omit prespecified analytical methods. There is a notable scarcity of robust post-marketing studies that assess the real-world effectiveness and safety of these antibiotics, limiting guidance for their optimal clinical use.

The situation is therefore far from ideal: it is always possible to ask for stronger levels of evidence, but then decisions have to be made with the evidence that is available, clarifying the degree of confidence one has. Confusion can further arise as some antibiotics with consistent in vitro activity against priority pathogens are not classified as Reserve, such as carbapenems (Watch antibiotics) to treat third-generation cephalosporin-resistant *Enterobacterales* (critical priority). The instructions for applicants preparing a submission for the 2025 meeting of the WHO Expert Committee on Selection and Use of Essential Medicines presents a hierarchy for the type of evidence addressing benefits and harms applicants should include (e.g., randomized trials are preferred over non-randomized studies) [11]. The Experts proposed a similar approach to address this limitation, where demonstration of *"proven activity"* in studies with human participants would be preferred over in vitro studies, acknowledging that these data may not always be available.

2. *The relationship between the current definition and the WHO Bacterial Priority Pathogens List is not univocal; e.g. some antibiotics with consistent in vitro activity against priority pathogens are not classified as Reserve*

An additional criterion only valid for listing Reserve antibiotics on the WHO EML is *"proven activity against critical or high priority pathogens identified by the WHO Priority Pathogens list"* [1]. However, not all these high and critical priority pathogens are so resistant that they need a Reserve antibiotic to be effectively treated (both for the 2017 and 2024 editions) [6, 7]. For example, Watch antibiotics such as meropenem and vancomycin are appropriate to treat third-generation cephalosporin-resistant *Enterobacterales* (critical priority) and methicillin-resistant *Staphylococcus aureus* (MRSA) (high priority), respectively. In other words, "*proven activity against critical or high priority pathogens*" is not exclusive to Reserve antibiotics. The BPPL was originally developed to guide research and development (R&D) of new antibiotics, not WHO EML decisions [7]. Therefore, the Experts considered that if the WHO EML Expert Committee decision to list Reserve antibiotics is to be linked to the WHO BPPL, the relationship between pathogen priority status and AWaRe group, and its role in the WHO EML decision-making process, should be better defined. The Experts proposed the second round of consultations consider the complete delinking of the definition of essential Reserve antibiotics from the BPPL, especially since the relevance of high and critical priority pathogens varies between settings.

3. *Evidence to develop guidance on the appropriate empiric use of Reserve antibiotics to treat life-threatening infections due to suspected multidrug-resistant bacteria is limited;**

This point has raised a debate that can be divided into two main lines, the first relating to appropriate empirical use and the second relating to which antibiotics should be considered lifesaving. The current Reserve definition is emphatic of the empiric use of 'last resort' antibiotics for suspected MDR infections. Prominence given to use as lifesaving could be interpreted differently depending on setting resource level. In low- and lower middle-income countries, carbapenems or vancomycin could be the only available last resort therapeutic options. Against this scenario, the Reserve definition is primarily aligned with high income countries.

The current Reserve definition only partially helps with defining appropriate use of these antibiotics (that is using them only for highly selected cases with no valid therapeutic

alternatives) but potential for misinterpretation remains, especially when a pathogen is not identified, which is a common situation, exacerbated by the lack of microbiologic diagnostic capacity and frequent antibiotic pretreatment before cultures are taken in many settings. It is challenging to develop guidance given the lack of high-quality clinical evidence and differences in local epidemiology. The Infectious Disease Society of America (IDSA) took a pragmatic approach to provide guidance on how to treat antimicrobial resistant Gram-negative infections, based on comprehensive reviews of the literature, clinical experience, and expert opinion [12]. Acknowledging limitations in the evidence, guidance is also provided in the AWaRe handbook for essential Reserve antibiotics [6] and could be expanded to other Reserve antibiotics, based on a similar pragmatic approach.

Finally, *"confirmed or suspected"* in the statement *"used only for highly selected patients with confirmed or suspected life-threatening infections due to multidrug-resistant bacteria"* was intended to refer to the presence of MDR bacteria, rather than life-threatening infection. The Experts judged that the statement can be reordered to the following to clarify: "*used only for highly selected patients with life-threatening infections due to confirmed or suspected multidrug-resistant bacteria*."

4. The definition for multidrug-resistant bacteria has long been debated

In the statement "*used only for highly selected patients with confirmed or suspected life-threatening infections due to multidrug-resistant bacteria"* multidrug resistance is not clearly defined. Some Authors have sought to bring clarity, at least for public health and epidemiological purposes, by proposing definitions for MDR, extremely (or extensively) drug-resistant (XDR) and pandrug-resistant (PDR) for select bacteria (*Enterobacterales, Pseudomonas aeruginosa*, *Acinetobacter* spp., *Staphylococcus aureus* and *Enterococcus* spp.) [13]. However, the definitions they proposed are inconsistently used, and most practitioners and policy makers probably remain unfamiliar with them or have developed alternative definitions based on local epidemiology and availability, leaving room for discussion about whether multidrug resistance should be defined globally or locally.

In 2018, the difficult-to-treat resistance (DTR) definition was proposed for Gram-negative bacteria as a new practical paradigm to capture bacterial resistance to all first-line, highly safe and effective antibiotics, which would then require last resort antibiotic options, if available [14]. For a Gram-negative pathogen to be categorized as having DTR, it must test intermediate or resistant to all reported agents in carbapenem, beta-lactam, and fluoroquinolone classes. This clinical definition is already used in some guidelines including

the IDSA guidelines for the treatment of resistant Gram-negative infections [12] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by MDR Gram-negative bacilli [15].

To some experts the lack of definition seems problematic: no consensus has yet been reached on a standardized internationally adopted definition. Standardizing what bacteria and infection syndromes are considered the most difficult to treat due to AMR and require use of Reserve antibiotics could be then a priority. It is not uncommon to discuss a possible role for the WHO to coordinate rounds of consultations to come to a consensus on multidrug resistance, for instance adopting DTR. However, this long-standing debate might not have direct implications on the essential Reserve antibiotic definition. In fact, given the principle of multiple resistance is inherently more significant. For these Experts, it is more significant that the broad concept behind multiple resistance is widely shared than a widely accepted narrow definition or definitions. In other words, the definition of Reserve antibiotics can continue even without an unambiguous definition of multidrug resistance. Following this approach, clinical definitions used in national guidelines or in local contexts could be acceptable as face value and could have implications for the local adaptation of Reserve listed antibiotics.

5. *Use of the same principles for selecting all antibiotics on the WHO Essential Medicines Lists regardless of AWaRe classification*

As of 2023, 10 out of 29 Reserve antibiotics are listed on the WHO EML (**Table 2**); of which eight are active against Gram negative MDR bacteria and two (linezolid and tedizolid) are active against Gram positive MDR bacteria. The list of essential antibiotics is subject to change as the WHO EML is updated every two years based on applications made by WHO departments or organizations external to WHO that can request the additions or removals of antibiotics. Decisions to list Reserve antibiotics on the WHO EML are made by the WHO EML Expert Committee based on agreed upon principles that apply to all AWaRe group antibiotics such as benefits, harms, and parsimony i.e., not listing too many antibiotics with a similar efficacy and safety profile [1].

Some Experts challenged the idea that Access, Watch and Reserve antibiotics should have the same principles supporting their selection as essential medicines. The parsimony criterion has been proposed primarily to guide the selection of Access and Watch antibiotics, to not inflate the number of options with similar characteristics. This criterion had important

implications, for instance, leading to not listing alternative antibiotics in cases of allergy to first-choice antibiotics. This latter decision was also supported by the rarity of true allergy (immune-mediated allergic reactions) to antibiotics. Reserve antibiotic selection could potentially benefit from a more flexible application of the criterion of parsimony. This could, for example, facilitate the uptake in some countries' markets of the new antibiotics recommended as Reserve and included in the WHO EML.

Another element that generated discussion is the operationalization of principles like benefits and harms: it is not fully clear for Reserve antibiotics what specific elements or data should be presented in the application and then evaluated by the WHO EML Expert Committee, or which comparator(s) should be chosen, particularly when a Reserve antibiotic with a comparable spectrum of activity is already listed on the WHO EML. In this document, for brevity, we limit to one aspect associated with the assessment of benefits associated with Reserve antibiotics, this being the choice of the primary outcome. The reliability of primary outcomes in randomized controlled trials is frequently uncertain, even when these outcomes are prespecified between pharmaceutical companies and regulatory agencies [10]. They generally fall into three categories: clinical cure, microbiological cure, and mortality. However, inconsistencies in definitions, measurement approaches, metrics, analysis strategies, and timing lead to considerable heterogeneity with regard to the first two categories—particularly in studies on infections such as pneumonia, urinary tract, intraabdominal, and bloodstream infections. This variability complicates meta-analyses and WHO EML decision making. Surrogate outcomes (like microbiologic response) often fail to capture true clinical benefit, and subjective or composite endpoints can overstate an antibiotic's efficacy. Short-term mortality—despite being reliable and broadly comparable across clinical trials —is often not prioritized as an outcome of interest by trialists. However, mortality is a relatively infrequent event, even in serious infections, thanks to supportive care and existing treatments. Detecting a statistically significant difference in mortality between treatment groups would require a large sample, which would increase the cost and complexity of trials.

Another aspect related to the operationalization of principles supporting the selection of Reserve antibiotics were the roles of data from routine use and real-world evidence and if they can provide further information on benefits (e.g., increased adherence due to ease of administration, superior effectiveness compared to older agents) and harms (e.g., increased incidence of resistance, fewer side effects). The operationalization of principles requires additional work to identify which aspects may support selection, being practical and policy-oriented.

Table 2. Reserve antibiotics by WHO EML listing status (as of 2023).

Reserve Antibiotic	Listed on the EML / EML for Children
Aztreonam	No
Carumonam	No
Cefiderocol	Yes
Ceftaroline-fosamil	No
Ceftazidime/avibactam	Yes
Ceftobiprole-medocaril	No
Ceftolozane/tazobactam	Yes
Colistin IV	Yes
Colistin oral	No
Dalbavancin	No
Dalfopristin/quinupristin	No
Daptomycin	No
Eravacycline	No
Faropenem	No
Fosfomycin IV	Yes
Iclaprim	No
Imipenem/cilastatin/relebactam	No
Lefamulin	No
Linezolid	Yes
Meropenem/vaborbactam	Yes
Minocycline IV	No
Omadacycline	No
Oritavancin	No
Plazomicin	Yes
Polymyxin-B IV	Yes
Polymyxin-B oral	No
Tedizolid	Yes
Telavancin	No
Tigecycline	No

6. *WHO innovation criteria for novel antibiotics and research and development antibacterial pipeline not explicitly considered;**

The AWaRe classification and decisions to list Reserve antibiotics on the WHO EML can have implications for the R&D of novel antibiotics, and vice versa. Every two years, the WHO R&D antibacterial pipeline is updated to reflect the landscape of antibacterials in clinical development. Reserve antibiotics represent the vast majority of recently approved antibacterials in that document. All agents that gained market authorization between July 2017 and December 2023 are reported with their assigned AWaRe group. Seven out of 13 new antibacterials are classified as Reserve and three as Watch [16]. In that list, contezolid and the combination sulbactam + durlobactam have not been evaluated yet but are likely to fall within the Reserve group, like other medicines of their class. The Experts considered that integration with the WHO R&D antibacterial pipeline can aid researchers and pharmaceutical companies in identifying gaps where new antibiotics are most needed, particularly in the Reserve group, which is intended for last resort treatments.

The WHO has indicated four innovation criteria for novel antibiotics: 1) no cross resistance to other antibiotic classes; 2) new chemical class; 3) new target/binding site; and 4) new mode of action [17]. Contextualizing this information against the AWaRe classification, particularly Reserve antibiotics, and the WHO EML, may identify unmet health needs that could be considered essential to address. For example, vaborbactam, a beta-lactamase inhibitor, approved in combination with meropenem, represents a new chemical class, is classified as Reserve in combination with meropenem, and is the only agent since 2017 that met at least one of the innovation criteria and was subsequently listed on the WHO EML [6, 16].

Experts mentioned the scarce attention to innovation as a possible cause of plazomicin commercial challenges. Plazomicin is a next-generation aminoglycoside antibiotic developed to combat MDR Gram-negative bacteria, particularly carbapenem-resistant *Enterobacteriaceae*. It was designed to overcome common resistance mechanisms that compromise older aminoglycosides like gentamicin and amikacin. In 2023, plazomicin was included in the WHO EML, categorized under the Reserve group, underscoring its importance. Despite its clinical promise, plazomicin faced significant commercial hurdles. Achaogen, the biotech company who developed plazomicin, filed for bankruptcy in 2019, less than a year after the medicine's approval, due to challenges in market uptake and reimbursement [18]. Subsequently, the rights to plazomicin were acquired by Cipla USA, but it is unclear if plazomicin will be marketed any longer.

The Experts judged that the role of these innovation criteria in the AWaRe classification and WHO EML selection principles should be urgently deliberated to better inform decisions around AWaRe classification, listing of Reserve antibiotics to the WHO EML and R&D of novel antibiotics.

7. Access issues and strategies to increase access not considered

The actual definition mentions “last resort”, emphasizing the lifesaving role of Reserve antibiotics. In low resource settings, carbapenems or vancomycin (Watch antibiotics) could be the only available last resort options. Against this scenario, the Reserve definition is primarily aligned with high income countries. Access to Reserve antibiotics is not the same across jurisdictions and is especially limited in low resource settings [19, 20]. Limited access to essential Reserve antibiotics often prompts countries to adapt their national EML and deviate from the WHO EML. For example, meropenem (Watch) is often listed as Reserve in settings where third-generation cephalosporin-resistant *Enterobacterales* are endemic and/or Reserve antibiotics are unavailable [21], which for the purposes of AWaRe is an incorrect use of the classification (where antibiotics are not supposed to move between groups based on local epidemiology, priorities, or availabilities). A future iteration of the definition may place value on access as this dimension is likely to have important implications for low- and middle-income countries. To ensure patients globally benefit from essential Reserve antibiotics, Experts considered that comprehensive implementation strategies that direct the path to not only increased equitable access, but appropriate use with diagnostic support, need to follow. One such example is SECURE, a collaboration between the Global Antibiotic Research & Development Partnership (GARDP) and the WHO, that seeks to not only expand access to essential antibiotics but also ensure their appropriate use [22].

Watch “plus” subgroup

By revising the definition of Reserve antibiotics, complementary changes to the Watch group could also be necessary. Currently the Watch group is very broad and includes antibiotics with a higher (than Access) resistance potential that are recommended as first choice only for a limited number of infections. This group includes antibiotics from a wide variety of classes, some of them among the most commonly used globally, such as fluoroquinolones, macrolides, second and third generation cephalosporins, and carbapenems. These antibiotics are also considered critically important in the WHO list of medically important

antimicrobials and active monitoring for specific uses and targeted stewardship programs are encouraged [23].

To facilitate monitoring and stewardship initiatives, the Experts considered the potential of a subgroup within the Watch group: Watch "plus". This subgroup could include antibiotics generally given in the hospital setting and active against selected priority pathogens that cause severe infections, particularly MRSA, third-generation cephalosporin-resistant *Enterobacterales* and vancomycin-resistant *Enterococcus*. This subgroup could include linezolid (now Reserve), carbapenems, cefepime, vancomycin and delafloxacin – most of which have a Reserve antibiotic as a backup in case of treatment failure. Specifically, unavailability of Reserve antibiotics prompts many countries to have meropenem listed as a Reserve (not Watch) antibiotic. Moving carbapenems, such as meropenem, to a new Watch "plus" subgroup could help clarify their role in the context of AWaRe.

Some Experts considered that splitting the Watch group could help solve some of the ambiguities of the current definitions. However, other Experts raised concerns. Part of the recognized success of AWaRe is due to its simplicity. Therefore, the Experts considered that adding a new subgroup could create confusion and face resistance in a phase where the system is still being implemented for the first time in some countries. Instead of creating a subgroup, the idea of explicitly prioritizing antibiotic classes within AWaRe groups (i.e., giving guidance on which classes should be prioritized when the pathogen is susceptible to antibiotics in more than one class) was suggested. As another alternative, the Experts considered refining the Reserve definition and then removing the problematic antibiotics from the Reserve group and adding them to the Watch group instead. Ultimately, there was no clear consensus about the utility of adding a Watch "plus" subgroup.

Re-categorization of specific antibiotics

For stewardship purposes (though not related with the Reserve definition), the need to reclassify certain antibiotics from the Access to the Watch group to preserve their use was debated. However, there is no consensus. In many healthcare systems, particularly in high- and middle-income countries, amoxicillin-clavulanic acid is overprescribed, often for conditions where narrower-spectrum options (like plain amoxicillin) would suffice—e.g., for uncomplicated respiratory infections or dental issues. In low-resource settings, where bacterial resistance profiles differ and access to diagnostics is limited, amoxicillin-

clavulanic acid may still be a practical and essential alternative. Reclassifying it as "Watch" could inadvertently limit availability where it is still appropriate and needed.

Future directions building on past success

The AWaRe classification is gaining momentum as evidenced by its impact on surveillance, stewardship, and education. Its application in the R&D of new antibiotics, including pre- and post- approval trials of Reserve antibiotics, is promising. A revision to the AWaRe classification, particularly the essential Reserve definition, could strengthen its use as a tool for prioritization, surveillance, and stewardship, along with extend its use to other antibiotic policies.

Surveillance and stewardship

The success of the AWaRe classification is founded in part because of its use as a tool for monitoring antibiotic use and targets for stewardship policies. Uptake of the AWaRe classification has occurred at the local, national and global levels. For example, AWaRe has been used to interpret antibiotic use in primary and secondary research studies [24-26], surveillance reports by public health agencies [27], and the Global Antimicrobial Resistance and Use Surveillance System (GLASS) [19] and Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS) [19, 28]. All these data are valuable to address variability in patterns of antibiotic use (even among similar settings and providers), support strategies to improve antibiotic use and assess progress towards targets in stewardship policies. A revision to the Reserve group that addresses existing ambiguities in the definition and limitations could ultimately improve the accuracy of these data.

WHO set a country-level target such that antibiotics from the Access group should account for at least 60% of total antibiotic use by 2023. In September 2024, at the United Nations General Assembly, this target was expanded with a stricter commitment by countries that decided to *"ensure, by 2030, that the use of WHO Access group antibiotics is expanded from the 2023 global target, and in that regard, taking into account national contexts, aim to achieve at least 70 per cent overall human antibiotic use globally, through investing in and strengthening stewardship programmes"* [29]. This metric is based on country-level antibiotic use data which can be collected with different methodologies. For example, the

way in which WHO collects antibiotic use data through GLASS requires countries to provide three types of information: (1) a list of registered antimicrobial medicines; (2) the quantities of medicines used in the public and/or private sectors and in community and/or hospital settings for 1 year (January–December); and (3) related contextual information to clarify the data being sent to WHO and their relevance. According to the chosen methodology, WHO estimates antimicrobial use by using the international Anatomical Therapeutic Chemical (ATC) classification and expresses the quantities of antimicrobials in defined daily doses (DDD) for humans and metric tons (t) for comparison with data on use in animal health [19]. By prioritizing the use of Access group antibiotics as first-line treatments and reserving Watch and Reserve group antibiotics for specific indications, healthcare providers can optimize patient outcomes while mitigating the development of AMR.

In the past years, progress was made towards the 2023 WHO target. For example, in 2022 the European Union reached the 60% WHO Access target even though 10 out of 28 countries were still below the 60% Access threshold [27]. This variability is also confirmed on the GLASS dashboard that presents the percentage of Access use in 60 countries for the year 2022 [30]. Despite variability between settings in using Access antibiotics and with more representation expected in the future, the fact a subset of countries did reach the proposed target supports the decision for a more ambitious goal [29, 31]. The recent increase in the AWaRe Access target confirms the dynamic nature of AMR policies acting strategically to improve antibiotic stewardship. This can further be interpreted as a signal of global acceptance of the AWaRe classification [32].

Finally, comparing use of antibiotics in the different AWaRe groups (e.g. Access-to-Watch ratio) between countries or over time can be very informative, allowing for example the evaluation of strategies to optimize antibiotic use in the context of local and national stewardship interventions.

Education

Educational interventions have significantly enhanced awareness and understanding of the AWaRe classification among healthcare professionals. A hospital-based study conducted in Amman, Jordan, demonstrated that after targeted educational sessions, the percentage of clinical staff familiar with the AWaRe classification increased from 22% to 56%. Additionally, the proportion of participants who acknowledged the importance of adhering

to the AWaRe framework in their practice rose from 22% to 59%. These findings underscore the effectiveness of educational initiatives in promoting the adoption of AWaRe guidance [33].

To facilitate the practical application of the AWaRe classification, the WHO has developed a suite of resources, including normative guidance, technical documents, and tools. These materials support Member States in implementing antimicrobial stewardship policies and interventions, encompassing planning, monitoring, and evaluating impact. The AWaRe antibiotic book, for instance, provides concise, evidence-based guidance on antibiotic selection, dosing, and duration for common infections encountered in both primary care and hospitals, aiding clinicians in making informed prescribing decisions [6].

Implementation of the AWaRe antibiotic book as a stewardship intervention is also suggested in the *Global research agenda for antimicrobial resistance in human health* that was published by WHO in 2023 [34].

Research and development and marketing of new antibiotics

Efficacy and safety data available from pre- and post- approval studies usually do not provide conclusive evidence on how to best use new antibiotics, including for which patients. The reasons for this are multiple and have been described in detail in a separate publication [10]. While some elements to improve the quality of trials for new antibiotics overlap with existing guidance (e.g., the guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections by the European Medicines Agency [35]), existing challenges are presented in more detail along with potential solutions.

Further, countries where lack of access is the main problem could benefit from strategies to incentivize access to the market for these products such as pull incentives that guarantee a fixed annual payment to manufacturers regardless of sales. Several pull incentives have been implemented in different countries and others have been proposed and researched in recent years. On the other hand, where Reserve antibiotics are accessible and available, strategies to optimize their use could benefit both from local stewardship interventions (for which more and more evidence is available) and on broader country-level government policy interventions to restrict access to specific antibiotics.

Conclusion

While the uptake of AWaRe across the health system spectrum and clinical development pipeline is encouraging, we recognize opportunities to improve the current classifications, definitions, and selection of Reserve antibiotics to the WHO EML. Our hope is to catalyze further discussion during the meeting of the 25th WHO Expert Committee on the Selection and Use of Essential Medicines and amongst the WHO Technical Advisory Group on AWaRe (TAG-AWaRe). Specifically, on what changes to the Reserve definition and potentially other AWaRe categories could be beneficial for the future development and success of the WHO EML and AWaRe classification.

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