

## AWaRe Policy Brief

### Background and size of the problem

Improving the use of antibiotics, often referred to as antibiotic stewardship, is one of the key interventions necessary to curb the further emergence and spread of antimicrobial resistance (AMR). This means that antibiotics should only be used when needed in situations where they can provide large benefits to patients; furthermore, when antibiotics are recommended, prescribers should opt for those antibiotics that combine optimal efficacy for the suspected causative pathogens for a given bacterial infection with a low propensity to further worsen the AMR problem. Unfortunately, currently a large proportion (>50% in many settings) of antibiotic prescriptions (several million prescriptions every year) are inappropriate because prescribers use antibiotics “just in case” even if they are not indicated and / or because they use antibiotics with unnecessarily large spectrum, thus contributing to the spread of AMR.

On the other hand, in many parts of the world there is not only overuse and misuse of antibiotics but also underuse. Childhood deaths due to pneumonia (estimated globally at over 2million per year) because of lack of access to antibiotics remains for example frequent in many parts of the world. Promoting **access** to this life-saving class of medicines for those who may benefit from them therefore also needs to be a priority.

Antibiotic stewardship tries to narrow the gap between excess (too many antibiotics for people who do not need them, and too large spectrum antibiotics used as first choice) and access (not enough antibiotics for people with severe infections). Balancing these contrasting forces is obviously a big challenge, especially if this problem is to be tackled on a global level and new approaches are urgently needed.

### Factors underlying the problem

The factors underlying the problem of suboptimal antibiotic use are complex, but include, among others, lack of knowledge and awareness of the problem by prescribers and the public, diagnostic uncertainty due to limitations of actual diagnostic tests and insufficient diagnostic capacities, lack of access to evidence-based treatment guidelines taking into account local epidemiology, lack of access to data reflecting the quality of antibiotic prescribing and use, preference for dispensing large spectrum antibiotics even when narrow spectrum alternatives are available).

### The AWaRe classification as a tool to support effective policy options

With the 2017 update of the Model List of Essential Medicines, WHO proposed a new classification

of antibiotics, the AWaRe classification (**A**ccess, **W**atch, **R**eserve), in the context of a comprehensive review of the optimal antibiotic choices for many common infectious syndromes in adults and children. The AWaRe classification aims to help prescribers, pharmacists, antibiotic stewards and policy makers to address the AMR challenge. In 2019, the classification was further reviewed and expanded to the most available antibiotics and to reflect experiences collected between 2017 and 2019.

The AWaRe classification groups antibiotics into the following categories:

**Access** – antibiotics that represent first or second-line for empirical treatment of common infectious syndromes based on a systematic assessment of the available evidence and that have a favorable safety profile with a low propensity to further aggravate AMR. All Access antibiotics are part of the EML core list, meaning that these antibiotics should be widely available in all settings (while still making efforts to ensure their appropriate use). Many penicillins belong to this class.

**Watch** – antibiotics that present a higher potential to negatively impact AMR. Some Watch group antibiotics are also included in the EML core list since they are the most effective options for a limited group of well-defined clinical syndromes, but their use should be tightly monitored and restricted to the limited indications. Fluoroquinolones, which are unfortunately commonly used in many settings, belong to the Watch group as their use should be avoided for indications for which they are no longer first or second choice.

**Reserve** – “last-resort” antibiotics, that have activity against multi (MDR)- or extensively (XDR) resistant bacteria, and therefore represent a valuable, non-renewable resource that should be used as sparingly as possible. Some of the newly approved antibiotics (e.g. ceftazidime-avibactam) fall into this class, as do some of the older “rediscovered” antibiotics (e.g. polymyxins).

**Discouraged antibiotics** – this fourth category – mostly including antibiotic combinations - was developed in the 2019 EML update. Some antibiotics, such as certain fixed dose combinations of antibiotics, do not have any reasonable indications for the treatment of infectious diseases in humans and may negatively impact AMR and patient safety.

### Three policy options

How can the AWaRe categories be used to monitor antibiotic consumption, optimize antibiotic use and be useful as an additional tool for antibiotic stewardship at national level? Countries can adopt policies to use AWaRe in the following three areas in order to optimize antibiotic use and strengthen stewardship actions:

#### 1. AWaRe for monitoring of antibiotic consumption

Measuring antibiotic use is a key component of antibiotic stewardship. However, many commonly used metrics such as “Defined Daily Doses (DDD) per 1000 inhabitants per day” are difficult to interpret since they contain

only limited information about the quality of antibiotic use. Furthermore, denominator data are not always available. Measuring antibiotic consumption, e.g. by quantifying the use of antibiotics in each of the AWaRe categories (relative or absolute) allows some inference about the overall quality of antibiotic use in a given country. Countries should first compare and benchmark national / regional antibiotic use using absolute consumption data, and then relative use according to AWaRe categories. The combination of both absolute and relative consumption by category allows simple benchmarking (e.g. an overuse of Watch antibiotics can become immediately apparent and a reduction in Watch antibiotics can be identified as a target for antibiotic stewardship interventions) and assessment of trends over time (to evaluate the impact of interventions). Certain countries, such as the United Kingdom, Germany and Switzerland, have already adopted AWaRe for antibiotic use surveillance and the first WHO report released in October 2018 has used AWaRe to evaluate antibiotic use in several countries.

**Target:** The WHO General Program of Work 2019-2023 has adopted a new indicator based on AWaRe: Access >60% (the proportion of Access antibiotics should be more than 60% of overall antibiotic use) that will become a common global target to reduce AMR (by favoring the use of ACCESS narrow spectrum antibiotics in comparison to WATCH and RESERVE ones).

**Likely impact:** Using AWaRe for monitoring antibiotic consumption should be highly feasible even in low- and middle-income setting, as illustrated by the WHO report on surveillance of antibiotic use. The assessment of antibiotic use according to AWaRe categories should allow countries to identify potential problems and key targets for interventions; this will be further facilitated by the clear target postulated by WHO.

## 2. Align the national Essential Medicines List (NEML) with the WHO Model EML

NEMLs should be aligned with the WHO Model List. Many countries list in their NEML or in hospital therapeutic formularies antibiotics that are not part of the WHO List or too many antibiotics of the same class. Antibiotics on the WHO EML should be prioritized for procurement, access, and distribution to different levels of the healthcare system. Deviations from the WHO EML should be justified (e.g. by documented differences in the epidemiology of pathogens causing infections and their resistance profile).

**Likely impact:** By aligning the national EML with the WHO EML, the antibiotic stewardship concepts underlying the EML WHO List should be incorporated at the country level. This should help to make first-line antibiotics with low resistance potential (e.g. nitrofurantoin for the treatment of lower urinary tract infections) available, while reducing the use of broader spectrum medicines (e.g. ciprofloxacin, a fluoroquinolone that easily spreads AMR).

## 3. Update or establish national / regional treatment guidelines for infectious syndromes using AWaRe

National treatment guidelines should reflect the AWaRe categories by specifying the recommended clinical indications for each antibiotic and the AWaRe category corresponding to each antibiotic. This will help to achieve full consistency between guidelines and appropriateness monitoring. Watch group antibiotics should for example only be

recommended for the syndromes for which they are listed as first or second choice options in the WHO EML. Within each syndrome, use of 1<sup>st</sup> choice antibiotics should be prevalent. Reserve antibiotics should still be strongly recommended as they represent a valid (and sometimes the only) alternative for a number of highly selected conditions. Restricting access to these life-saving medicines would make do patients more harm than good.

**Likely impact:** The lack of high-quality treatment guidelines is a key obstacle to improving the use of antibiotics. Aligning the guidelines with the WHO EML and its underlying stewardship principles should increase the use of access antibiotics.

Based on AWaRe, an instrument designed using rigorous evidence-based criteria, these policy options are feasible, can easily be included in a robust delivery roadmap, and provide space for adjustment in response to changing epidemiological circumstances.