A Technical Guide to Implementing the World Health Organization's AWaRe Antibiotic Classification in MTaPS Program Countries

Background

Ensuring access to and appropriate use of good-quality antimicrobials is a key priority of global strategies to combat antimicrobial resistance (AMR). A majority of countries have developed national action plans based on the 2015 World Health Organization (WHO) Global Action Plan for Antimicrobial Resistance.[1] In an effort to address the major component of the International Health Regulations related to containing AMR and to guide countries' implementation of antimicrobial stewardship (AMS) programs, WHO released a set of recommendations to help global, regional, and national policy makers develop guidelines on which antibiotics (ATB) to use and when.[2] The resulting AWaRe (Access, Watch, Reserve) classification tool[3] is meant to be applied to a country's essential medicines lists (EMLs) with the ATB placed in one of three primary categories:

ACCESS: These are the ATB of choice for each of the 25 most common infections. They should be available at all times, affordable, and of assured quality. This group will include first-choice antibiotics (sensitive, narrow-spectrum ATB with low toxicity and propensity to develop resistance) and second-choice antibiotics (sensitive, broader-spectrum ATB with both increased risk of toxicity and potential to develop resistance).

WATCH: This group includes most of the "highest-priority, critically important antimicrobials" for human medicine[4] and veterinary use.[5] These ATB are recommended only for specific, limited indications. They include sensitive ATB with either higher toxicity concerns or a higher potential to develop resistance. They should not be used for prophylaxis in animals or in agricultural production. The use of these ATB must be actively monitored through point-prevalence surveys.

RESERVE: These antibiotics should only be used as a last resort, when all other antibiotics have failed or cannot be used due to contraindications. Newer-generation ATB are placed in this category. Their use is strictly limited to very specific patients and clinical settings, but they must always be available

[1] WHO. 2015. Global Action Plan on Antimicrobial Resistance. Geneva: World Health Organization.
[2] WHO. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2017. Available at: https://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf
[3] WHO. AWaRe – a new WHO tool to help countries improve antibiotic treatment, increase access and reduce resistance. WHO/MVP/EMP/IAU/2019.04. Geneva: World Health Organization.
[4] WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). Critically important antimicrobials for human medicine. 5th revision 2016. Available at: http://www.who.int/foodsafety/publications/antimicrobials-fifth/en/
[5] World Organization for Animal Health. List of Antimicrobial Agents of Veterinary Importance. May 2015. Available at: https://www.oie.int/doc/ged/D9840.PDF

when needed. Reserve antibiotics are protected and prioritized as targets of strict AMS activities, including monitoring and reporting.

Discouraged Antibiotics: In its most recent policy briefs,[6] WHO included a fourth category that is technically not part of the AWaRe categorization but is important to know for those who are selecting medicines for EMLs. This fourth category—mostly including antibiotic combinations—was included in WHO's 2019 EML update. Some antibiotics, such as certain fixed-dose combinations (e.g., azithromycin+cefixime, ofloxacin+ornidazole, cefpodoxime+levofloxacin), do not have any reasonable indications for the treatment of infectious diseases in humans and may negatively affect AMR control and patient safety. Consequently, WHO recommends that these combination antibiotics be excluded from national EMLs.

Goals of AWaRe Categorization: The overall goal is to reduce the use of antibiotics in the Watch and Reserve groups (the antibiotics most crucial for human medicine and at higher risk of resistance) and to increase the use of Access antibiotics where availability is low. The first goal of AWaRe is to have all countries report antibiotic use, through the Antimicrobial Resistance Surveillance System (GLASS), by 2023, and the second is for 60% of global antibiotic consumption to come from medicines in the Access category.[7] Currently, 65 countries track antibiotic use but only 29 meet the 60% Access national consumption goal.[8] Evidence shows that meeting the 60% goal will result in not only better use of antibiotics but also reduced costs and increased access. Reaching this threshold by 2023 will contribute to countries' achievement of the health-related Sustainable Development Goals.

To support countries in tracking and reporting antibiotic consumption, the AWaRe categorization provides a suitable framework for target setting, especially in the use of Access antibiotics, and can be included as a monitoring and evaluation indicator. To improve coordination, the Global Antimicrobial Resistance Surveillance System (GLASS) platform will incorporate the global monitoring of ATB consumption in 2019;[9] countries implementing AMR activities will be expected to report antibiotic consumption using the platform.

Other advantages to adopting the AWaRe categorization include:

- Increased access, reduced costs—many of the antibiotics on the Access list are among the most affordable
- Better therapeutic results—the AWaRe categories specify which antibiotics to use for specific syndromes, including when a laboratory diagnosis is not available
- Public health gains—antibiotics, one of the biggest advancements in modern medicine, will maintain their life-saving effectiveness by increasing the use of medicines on the Access list and reducing the use of those on Watch and Reserve lists

[6] WHO. Access to medicines, vaccines and pharmaceuticals: AWaRe Policy Brief, April 2019.
[7] WHO. Adopt AWaRe: Handle antibiotics with care. Available at: https://adoptaware.org/
[8] WHO. AWaRe Factsheet.
[9] WHO. Report on Surveillance of Antibiotic Consumption 2016 – 2018: Early implementation. Available at: https://www.who.int/medicines/areas/rational_use/who-amr-amc-report-20181109.pdf?ua=1&ua=1

Purpose of this Implementation Guideline

Revising an EML entails complex decisions that assess health outcomes while accounting for ease of access and use, monitoring, registration, and cost of listed medications.[10] This document is intended to guide experts tasked with revising a national EML to apply the AWaRe classifications to ATB used to treat infectious diseases.

Integrating the AWaRe Categorization into the Essential Medicines List

The WHO Model List of Essential Medicines, which serves to guide the development of national and institutional EMLs, is updated every two years. The current versions of the EML are the 21st WHO Essential Medicines List and the 7th WHO Essential Medicines List for Children, both published in June 2019.[11] These versions are also the second to use the AWaRe categorization criteria for ATB.

Experts involved in revising country EMLs should consult the antibacterial section (pages 73–152) of the WHO technical guidelines on the selection and use of essential medicines.[12]

Following are key steps to consider when integrating the AWaRe categorization into the EML:

Two scenarios to consider:

- If the country is revising the EML as a part of a revision cycle, integrate the AWaRe component into the revision process
- If the national EML has recently been revised without AWaRe groupings, embark on the AWaRe categorization process separately and add the guidance as an addendum once it has been approved/authorized
- Review the current national essential antibiotics list against the WHO AWaRe database of 180 antibiotics, and the list of 37 antibiotics (19 Access, 11 Watch and 7 Reserve) included individually in the WHO model Essential Medicines List[13]. Identify antibiotics in the national list that are not captured by the AWaRe list and antibiotics in the AWaRe list that are absent from the national list. This is a desk review exercise.
- Gather evidence about local epidemiology of infectious diseases. Study the major infectious syndromes in the country and list the key microorganisms involved. This will entail a review of published and unpublished data from various sources in the country, including ministry of health (national public health laboratory) and university research institutes, and other external research, such as from WHO surveys.

[10] Magrini N, Robertson J, Forte G, et al. Tough decisions on essential medicines in 2015. Bull World Health Organ 2015; 93: 283–84.
[11] WHO Model Lists of Essential Medicines. Available at: http://www.who.int/medicines/publications/essentialmedicines/en/
[12] WHO. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2017. Available at: https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf;jsessionid=C3118A8FEB2CDFBCBBB96EF130FE71DC?sequence=1
[13] WHO releases the 2019 AWaRe Classification Antibiotics. https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotics/en/

- Establish the antibiotic resistance profile of the causal microorganisms of prevalent local syndromes. This will entail gathering data from national reference laboratories and other accredited laboratories that conduct antibiotic sensitivity testing in either standalone laboratories or public and private hospitals and clinics. Note that for results of such a compilation to reflect the national resistance profile accurately, there needs to be a certain level of standardization of testing protocols across the selected laboratories. The data must also be fairly recent and representative of all areas of the country.
    - *Note that several countries in low and medium income countries may not have adequate and reliable data on germs and resistance profiles. In these cases, countries could adopt the antibiotics in the WHO model list, until the country is able to gather reliable, country-specific data (see England approach)*[14].
- Identify and list the sensitive and accessible antibiotics that will comprise the first and second treatment choices for prevalent syndromes. These will go into the Access category (defined above). Be sure that these antibiotics are authorized for use in the country.
- Review the country's antibiotic supply chain to establish availability of different classes of antibiotics that will potentially be listed in the EML or the ability to procure and adequately distribute them.
- List the sensitive and easy-access antibiotics that can be used as alternatives if the first- and second-choice antibiotics fail. These ATB will go into the Watch category, which also includes any antibiotic that is not in the Access group but is commonly used in the animal and agricultural food production sectors. List antibiotics that require more active pharmacovigilance surveillance, as determined by the national pharmacovigilance committee, even if they are commonly used antibiotics.
- Identify easy-access antibiotics that are used to treat the syndromes only in very special cases to put in the Reserve category. These include the more expensive antibiotics, newer-generation antibiotics, and the most toxic classes that require close pharmacovigilance monitoring during treatment.
- Establish strategies to implement AMS programs (national and peripheral) that will strengthen adherence to EML guidelines in the country. Stewardship programs should be considered in the Watch and Reserve categories. Develop strict guidelines and procedures for use at the facility level and implement tools to monitor and report use and misuse.
- Establish a CQI mechanism within health facilities (drug and therapeutics committee) to continuously support adherence to guidelines and EML antibiotics selection to ensure that providers don't continue to prescribe antibiotics that are not on the EML.
- Establish a robust monitoring system that involves central-level participation as well as peripheral data collection and reporting. Monitoring should include tracer commodities from the Access, Watch, and Reserve categories.
- Establish intermediate milestones with a goal to reach 60% of antibiotic consumption coming from the Access group by 2023.
- Enroll the country in the GLASS platform and ensure regular data reporting on antibiotic consumption using the platform.

[14] Budd, E,mma et al. We have adapted the WHO AWaRe index to create a specific index for England. Being AWaRe. Journal of Antimicrobial Chemotherapy, dkz321, July 2019. Available at: https://doi.org/10.1093/jac/dkz321.

Annex 1 shows a proposed Excel spreadsheet to guide the collection of information needed for AWaRe categorization, track actions taken, and provide recommendations for managers and prescribers.

Practical Considerations for Sustainability of AWaRe

- Countries should include AWaRe categorization prominently in their AMS action plans
- Infectious diseases experts should systematically integrate AWaRe in all future standard treatment guideline revisions
- Supply chain and logistics management systems should integrate AWaRe categorization in their procurement policies and should measure absolute and relative antibiotic consumption per AWaRe category
- Supply chain monitoring systems should ensure availability, at all times, of different classes of ATB at a particular level if they are in the standard treatment guidelines for that level
- Training programs should integrate AWaRe approaches into pre- and in-service training programs as much as possible to ensure that health workers are informed
- Countries should consider some potential managerial/restrictive/regulatory approaches for those in the Watch and Reserve categories to ensure rational use and longer-term effectiveness
- At the facility level, drug and therapeutics committees/AMS committees should play a strong role in advocating for, promoting, training, and monitoring adherence to AWaRe
- Monitoring systems should provide feedback to the district and facility levels regarding their compliance with the AWaRe usage recommendations
- Facility leadership should institutionalize systematic mentorship of managers and prescribers to increase adherence

Conclusion

Adopting the AWaRe categorization in the EML revision process makes the process less complex. It also gives the country an opportunity to set targets for measuring and reporting progress. The steps proposed to carry out this categorization are suggestive and not prescriptive. Each country will work with experts to adopt the best approach to complete this exercise.

Annexes

Annex 1: Illustrative Template for Managing AWaRe Classification

		AWaRe Classification for LMICs							
	Template to be used by countruy staff or consultant to collect information and guide AWaRe Classification in the countries								
	* Reference: Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. www.thelancet.com/infection Vol 18 January 2018. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30724-7/fulltext								
				ACESS GROUP		**WATCH GROUP**	**RESERVE GROUP**		
				Which indicates the antibiotic of choice for each of the 25 most common infections. These antibiotics should be available at all times, affordable and quality-assured.		**Which includes most of the "highest-priority critically important antimicrobials" for human medicine and veterinary use. These antibiotics are recommended only for specific, limited indications**	**Antibiotics that should only be used as a last resort when all other antibiotics have failed.**		
		Local Country germs mostly responsible (national data aggregate)	**Sensitivity/Resistance profile of indexed germs in country (national data aggregate)**	**1st Choice Antibiotic (sensitive narrow spectrum ATB with low toxicity)**	**2nd Choice Antibiotic (sensitive broader spectrum ATB; increased risk of toxicit or resistance selection)**	**Sensitive ATB with higher toxicity concerns or resistance potential; highest priority agents/critically important ATB for human medicine; should not be used for prophylaxis in animal/agricultural production. Active monitor of use by point-prevalence surveys***	**Last resort option ATB; accessible when needed; use tailored to very specific patients and clinical settings in case of treatment failure or contraindications; protected and prioritized as key targets of strict AMS; Newer generation ATB. Central monitoring and reporting**	**Note to program managers**	**Note to Prescribers**
	Infectious Syndrome (Most common or severe affections)	**Most Common causal agents (groups or syndromic classification)**		**Key Monitoring Indicator: Proportion of all antibiotics in the country placed in this category**	**Key Monitoring Indicator: Proportion of all antibiotics in the country placed in this category**	**Key Monitoring Indicators: 1) proportion of tracer commodities of this class not uesd in animal and agricultural production; 2) proportion of antibiotics in this class used as first or second line treatment**	**Key Monitoring Indicators: 1) proportion of tracer commodities of this class availabe at key service sites; 2) proportion of times antibiotics in this category were used without comforming to indication criteria**	**Note here mainly concerning monitoring and tracking**	**Notes here are guideline recommendations**
1	Community-acquired pneumonia (children) (CAP)								
2	Pharyngitis								

Annex 2: Illustrative Checklist for AWaRe Actions Completion

	☑=Y
■ Review the current national essential antibiotics list against the WHO AWaRe list of 54 antibiotics	O Done O In progress O Not done
■ Gather evidence about local epidemiology of infectious diseases and infectious syndromes in the country and list the key microorganisms involved	O Done O In progress O Not done
■ Establish the antibiotic resistance profile of the causal microorganisms of prevalent local syndromes	O Done O In progress O Not done
■ Identify and list the sensitive and accessible antibiotics that will comprise the first and second treatment choices for prevalent syndromes (Access)	O Done O In progress O Not done
■ Review the country's antibiotic supply chain to establish availability and accessibility of different classes of antibiotics that will potentially be listed in the EML	O Done O In progress O Not done
■ List the sensitive and easy-access antibiotics that can be used as alternatives if the first- and second-choice antibiotics fail (Watch)	O Done O In progress O Not done
■ Identify easy-access antibiotics that are used to treat the syndromes only in very special cases (Reserve)	O Done O In progress O Not done
■ Establish strategies to integrate and implement the AWaRe categorization into AMS programs that will strengthen adherence to EML guidelines in the country	O Done O In progress O Not done
■ Establish a CQI mechanism within health facilities to continuously support adherence	O Done O In progress O Not done
■ Establish a robust monitoring system that involves central-level participation and peripheral data collection and reporting	O Done O In progress O Not done
■ Establish intermediate milestones with a goal to reach 60% of antibiotic consumption coming from the Access group by 2023	O Done O In progress O Not done
■ Enroll the country in the GLASS platform and ensure regular data reporting on antibiotic consumption	O Done O In progress O Not done