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Comment

Classifying Antibiotics in the WHO Essential Medicines List to Promote optimal use – be AWaRe!

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Background

Optimising the use of antimicrobials is a key priority of the global strategy to combat antimicrobial resistance (AMR).[1] Antibiotic guidance should be developed to meet the aims of Sustainable Development Goal 3 - achieving universal access to safe, effective, quality and affordable medicines.[2] Improving global prescribing is a complex issue which requires pragmatic short-term targets, ambitious long-term goals and realistic expectations. In low and middle-income countries (LMIC) settings, there are difficulties in identifying specific targets for intervention.[3] Furthermore, sustained, reliable availability of antibiotics at an affordable cost and adequate quality remains a major concern for both high-income countries (HICs) and LMICs.[4] Regular shortages and high cost of older off patent antibiotics are an increasing threat to their optimal use.[5] Defining which antibiotics should be the focus of different levels of stewardship intervention is a global priority.[6]

Revision of the Essential Medicines List (EML) also entails complex decisions assessing health outcomes while accounting for feasibility, monitoring, registration, and cost of listed medications.[7] The last complete revision of antibiotics was conducted in 2001.[8] For the 2017 EML update, comprehensive reviews on antibiotic use for specific clinical infections were commissioned by the WHO.[9] After assessing the evidence on the most frequent and severe bacterial infections, the Expert Committee has identified a limited number of options as first and second choice antibiotics for each of them and finally categorised antibiotics into three groups with the goal of improving access and clinical outcomes, reduce the potential for development of AMR and preserve the effectiveness of 'last resort' antibiotics (Figure).

New WHO EML/EMLc Antibiotic Groups – Access, Watch, Reserve – AWaRe

Access Group

To improve access to effective therapy, the Committee designated specific 'Access' antibiotics. Antibiotics selected for the Access group were those listed as first and second choice for the empiric treatment of 21 common or severe clinical syndromes. First choices were generally narrow spectrum agents with a lower toxicity risk. Second choices for specific syndromes were broader spectrum antibiotics that may have an increased risk of toxicity or resistance selection. This access designation for 29 antibiotics emphasises their role as the core set of antibiotics that should be consistently available everywhere at an appropriate quality, dose, duration, formulation and price.

Watch Group

The Watch group includes antibiotic classes that were considered generally to have higher toxicity concerns or resistance potential. This group is also substantially overlapping with the highest priority agents on the list of Critically Important Antimicrobials (CIA) for Human Medicine.[10] That means the antibiotics that should not be used for prophylactic uses in food producing animals and agriculture. A small number of antibiotics from the Watch group were also recommended as first or second choice treatments only for a limited number of specific indications. Antibiotics were designated to the Watch group to assist the development of tools for stewardship at local, national, and global levels. Active monitoring of the Watch antibiotics is encouraged through point-prevalence surveys to ensure use aligns with guidance.

Reserve Group

The Reserve group includes antibiotics which should be treated as 'last-resort' options. These should be accessible when needed, but use should be tailored to highly specific patients and clinical

settings, when other alternatives have failed or cannot be used (e.g., serious or life-threatening infections due to multi-drug resistant bacteria). These medicines should be protected and prioritized as key targets of high-intensity national and international stewardship programs involving central monitoring and reporting, to preserve their effectiveness. The Reserve group also includes newer antibiotics.

Scope and Limitations

Several major limitations to this type of new broad categorisation remain. Not all classes of antibiotics are included in the list. There is a weak evidence base for recommending specific antibiotics or classes into the different categories though the relation between use of specific classes and propensity for resistance selection seemed sufficient to recommend this categorisation to facilitate stewardship. It is recognised that the List will need local adaptation and further revision over time.

Future Directions

A standing EML Working Group has been established to review additional syndromes, adapt current synopsis into short structured documents, coordinate the development of a guidance document on optimal dose and duration of antibiotic treatments and to improve methods for communicating the stewardship messages associated with these new Access, Watch, and Reserve (AWaRe) groups. An *AWaRe Index*, a novel metric for stewardship, could be introduced, to help estimate the relative use of narrow and broad spectrum antibiotics. This could enable relevant stakeholders to track progress in optimising use, evaluate impact of interventions and define ambitions for quality improvement. WHO member states would need to be supported as the clinical guidance is contextualised and implemented in their settings.

Conflict of Interest

Drs. Gandra, Magrini, Mathur, and Zeng have nothing to disclose. Profs. Harbarth, Pulcini, and Sharland receive institutional non-personal industry support for academic studies not related to the EML. They have no relevant financial or individual conflicts of interest to declare.

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Figure

Figure 1 Classification of antibiotics into AWaRe groups: Access (green), Watch (yellow), and Reserve (red)