GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

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Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics

The World Health Organization was requested by Member States to develop a global priority pathogens list (global PPL) of antibiotic-resistant bacteria to help in prioritizing the research and development (R&D) of new and effective antibiotic treatments. To date, the selection of pathogens for R&D activities has been largely guided by small and large pharmaceutical companies according to a variety of parameters, such as perceived/unmet medical need, pressure of investors, market size, scientific discovery potential, and availability of specific technologies. Previous PPLs, issued by the Centers for Disease Control and Prevention (CDC, Antibiotic Resistance Threats in the United States, 2013; http://www.cdc.gov/drugresistance/threat-report-2013/) and the Public Health Agency of Canada (PLoS One. 2015;10(4):1-11), focused on national public health priorities to increase scientific, political and public awareness without including specific R&D criteria.

> The major objective of the global PPL is to guide the prioritization of incentives and funding, help align R&D priorities with public health needs and support global coordination in the fight against antibiotic-resistant bacteria. The WHO PPL targets policy initiatives to incentivize basic science and advanced R&D by both public funding agencies and the private sector investing in new antibiotics.

METHODOLOGY

A coordinating group of eight experts in infectious diseases, clinical microbiology, R&D, public health and infection control were selected to define the protocol. The global WHO-PPL was developed applying a multi-criteria decision analysis (MCDA) technique, which allows the evaluation of different alternatives according to multiple criteria. The MCDA method incorporates both **expert opinion** and **evidence-based data** in a transparent, explicit, and deliberative fashion. The main strength of this approach is the relatively high weight given to the evidence retrieved and summarised for each criterion in order to reduce the impact of individual perceptions and beliefs. The prioritization exercise has been performed through the following steps: 1. Selection of antibiotic-resistant bacteria to be prioritized; 2. Selection of criteria for prioritization; 3. Data extraction and synthesis; 4. Scoring of alternatives and weighting of criteria by experts; and 5. Finalization of the ranking of pathogens.

SELECTION OF ANTIBIOTIC-RESISTANT BACTERIA TO BE PRIORITIZED

Twenty bacteria were selected in line with current burden of diseases and previous prioritization exercises. Since the focus of this prioritization exercise was R&D for new antibiotics, it did not address prioritization for mycobacteria, fungi, protozoa, helminthes and viruses, which therefore were not considered for inclusion.

SELECTION OF CRITERIA FOR PRIORITIZATION

The following ten criteria were selected by the coordinating group of experts on the basis of their experience and previous prioritization exercises, reflecting the principles of MCDA (completeness, non-redundancy, non-overlap and preference independence): all-cause mortality, healthcare and community burden, prevalence of resistance, 10-year trend of resistance, transmissibility, preventability in hospital and community settings, treatability and current pipeline. For each criterion estimates based on best available evidence were summarised to inform each pairwise comparison.

DATA EXTRACTION AND SYNTHESIS

Evidence for each criterion was extracted from multiple sources, including: databases of European-financed projects running at the Infectious Diseases, Tübingen University (WP1-DRIVE-AB, EPI-Net-COMBACTE-Magnet, ESCMID guidelines) [1]; systematic reviews of published literature; 23 national and international surveillance systems of antibiotic resistant-bacteria; and international guidelines focusing on treatment and prevention of infections due to antibiotic-resistant bacteria (search stopped on 30.09.2016). Data synthesis was performed through meta-analysis of quantitative criteria (all-cause mortality, healthcare burden, prevalence and trend of resistance) and index score for semi-quantitative criteria (community burden, transmissibility, treatability, current pipeline). Data were stratified by the six WHO regions whenever possible.

SCORING OF ALTERNATIVES AND WEIGHTING OF CRITERIA BY EXPERTS

Each antibiotic-resistant bacterium was scored according to the available evidence and criteria definitions. A group of 70 experts with different backgrounds (infectious diseases, clinical microbiology, R&D, public health, paediatric and intensive medicine) and geographical origin were involved in the criteria weighting process. The relative importance of criteria was assessed by the experts via a preference-based survey, based on pairwise comparison and supported by 1000Minds software (https://www.1000minds.com). The weights of the criteria were derived by the software using mathematical methods based on linear programming and a final ranking was computed for each

[1] DRIVE-AB (number 115618; coordinator S. Harbarth, WP leader: Y. Carmeli); COMBACTE-MAGNET (number 115737-2; coordinator M. Bonten; WP leader: E. Tacconelli, A. Sifakis); ESCMID guidelines to reduce the spread of multi-drug-resistant gram negative; chair: E. Tacconelli, PID 24929732)

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participant and averaged across the whole group. Full protocol and results will be published on the World Health Organization website by the end of May 2017.

FINALIZATION OF THE RANKING OF PATHOGENS

The PPL was reviewed by the coordinating group and the advisory board in collaboration with WHO during a meeting held in Geneva 25-27 January 2017. The advisory board was composed of eight experts in the field not involved in the first two steps to act as a panel of external experts. The methodology used for the prioritization of pathogens showed a high stability of the list. No changes in the ranking were noted after stratifying the experts according to their background and geographical origin. A sensitivity analysis was performed, excluding the experts who were less consistent with their preferences with no major changes in the list. The results of the MCDA ranking and the sensitivity analysis were compared during the meeting; all differences between the lists were discussed and adjudicated.

The experts agreed on clustering the pathogens according to the type of resistance and then stratifying the results in three priority tiers: critical, high and medium.

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

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RECOMMENDATIONS BY THE PANEL

- Future R&D strategies should focus on the discovery and development of new antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria.

- The panel stressed the importance of new antibiotics for the paediatric population and for oral formulations for community diseases with a high morbidity burden such as drug-resistant *Neisseria gonorrhoeae*, *Salmonella typhi* and ESBL-producing *Enterobacteriaeceae.*

- This prioritization exercise did not cover all the possible patterns of resistance and co-resistance or other antibacterial medicines in R&D pipelines. However, considering the most important priorities expressed by the PPL, the panel agreed that development of new classes of antibiotics without cross- and co-resistance to existing classes should be supported.

- The WHO global PPL provides indications for priorities to be addressed by the R&D for new antibiotics active against priority pathogens and characteristics of the diseases they cause. It was not developed to identify public health threats. R&D needs are driven by current availability of treatment options as well as by public health threats. Moreover, public health threats may be addressed by other interventions that could significantly reduce the burden of infections due to antibiotic-resistant bacteria, such as increased vaccination coverage, improved sanitation or sustained implementation of infection control measures that are not directly connected to the development of new antibiotics.

REMARKS

- The evaluation of the evidence-based data underlines the essential role of infection control measures in reducing the spread of antibiotic-resistant bacteria and the large heterogeneity among the WHO regions in terms of implementation. A program focusing on how to increase and standardise infection control implementation would be compelling.

- Antibiotic stewardship programmes, including education, should be implemented at global level and target stakeholders in hospital and community settings and be combined with public awareness campaigns. Long-lasting investments in educational activities and innovative tools to support appropriate use of antibiotics and adequate long-term planning are urgently required.

- Analyses of the treatability criterion assumed that all existing antibiotics are equally available in different WHO regions. Measures to guarantee equal access to existing antibiotics, particularly those on the WHO Essential Medicines List, need to be implemented.

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STRENGTHS AND LIMITATIONS OF THE GLOBAL PPL

- The MCDA methodology used to develop the global PPL showed high stability of the final ranking and can be easily adopted for regular updates of the priority list or when new evidence appears or new resistance threats are identified.

- The panel found significant limitations of the current evidence for infections due to antibiotic-resistant bacteria in community and healthcare settings, in particular with respect to the frequency and burden of infections. High-quality data are missing, especially for community-acquired infections and from low-income countries.

- The panel underlines the lack of surveillance data on livestock and food, highlighting the need for coordination between human and animal surveillance systems. Inaccurate or incomplete surveillance data delay translational research on the antibiotic resistance threat and reduce the effectiveness of the "One Health" approach to limit the spread of resistance.

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