Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

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Summary

Background The spread of antibiotic-resistant bacteria poses a substantial threat to morbidity and mortality worldwide. Due to its large public health and societal implications, multidrug-resistant tuberculosis has been long regarded by WHO as a global priority for investment in new drugs. In 2016, WHO was requested by member states to create a priority list of other antibiotic-resistant bacteria to support research and development of effective drugs.

Methods We used a multicriteria decision analysis method to prioritise antibiotic-resistant bacteria; this method involved the identification of relevant criteria to assess priority against which each antibiotic-resistant bacterium was rated. The final priority ranking of the antibiotic-resistant bacteria was established after a preference-based survey was used to obtain expert weighting of criteria.

Findings We selected 20 bacterial species with 25 patterns of acquired resistance and ten criteria to assess priority: mortality, health-care burden, community burden, prevalence of resistance, 10-year trend of resistance, transmissibility, preventability in the community setting, preventability in the health-care setting, treatability, and pipeline. We stratified the priority list into three tiers (critical, high, and medium priority), using the 33rd percentile of the bacterium's total scores as the cutoff. Critical-priority bacteria included carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacteriaceae. The highest ranked Gram-positive bacteria (high priority) were vancomycin-resistant *Enterococcus faecium* and meticillin-resistant *Staphylococcus aureus*. Of the bacteria typically responsible for community-acquired infections, clarithromycin-resistant *Helicobacter pylori*, and fluoroquinolone-resistant *Campylobacter* spp, *Neisseria gonorrhoeae*, and *Salmonella typhi* were included in the high-priority tier.

Interpretation Future development strategies should focus on antibiotics that are active against multidrug-resistant tuberculosis and Gram-negative bacteria. The global strategy should include antibiotic-resistant bacteria responsible for community-acquired infections such as *Salmonella* spp, *Campylobacter* spp, *N gonorrhoeae*, and *H pylori*.

Funding World Health Organization.

Introduction

Despite the fact that the spread of antibiotic-resistant bacteria poses a substantial threat to morbidity and mortality worldwide, pharmaceutical research and development has failed to meet the clinical need for new antibiotics.[1,2] In particular, the need for investments in research and development of new anti-tuberculosis drugs has been highlighted by WHO for several years[3] with dedicated and prioritised programmes.[4,5] As for other antibiotic-resistant bacteria, in the past 20 years, only two new antibiotic classes (lipopeptides and oxazolidinones) have been developed and approved by international drug agencies (US Food and Drug Administration and European Medicines Agency)—both of which provide coverage against Gram-positive bacteria.[6] The quinolones, discovered in 1962, was the last novel drug class identified to be active against Gram-negative bacteria. Of the 44 new antibiotics in the pipeline for clinical intravenous use, only 15 show some activity against Gram-negative bacteria and only five (all modified agents of known antibiotic classes) have progressed to phase 3 testing.[7]

The decreased interest in antibiotic research and development of pharmaceutical companies in the past few decades is probably related to difficulties in clinical development and scientific, regulatory, and economic issues. The discovery of new antibiotic classes that are highly active, have acceptable pharmacokinetic properties, and are reasonably safe is complex. Clinical antibiotic trials evaluating the efficacy of new antibiotics can be difficult and expensive, especially when targeting multidrug-resistant Gram-negative bacteria, because of the near absence of rapid diagnostic tests to facilitate patient recruitment, and *Mycobacterium tuberculosis*, because of the complex combination therapy and prolonged patients' follow-up. When widely used, modified agents of old drug classes might face the challenge of rapid development

Research in context

Evidence before the study

We searched PubMed and Google scholar for publications from Jan 1, 1960, to July 1, 2017, that aimed to develop a priority list of human infectious diseases due to antibiotic-resistant bacteria, and reported the method and criteria used to determine priorities. The search terms included ("priority AND list AND infections" OR "priority list AND resistance" OR "research and development AND priority AND bacteria") and ("antibiotic AND priority AND infections OR bacteria"). Reference lists of retrieved studies were also screened for relevant publications. No restriction on publication type or language was applied. Seven publications were reviewed; one report dealt with risk of spread of infectious diseases during mass gathering, and three considered antibiotic resistance an emerging issue, but the prioritisation of pathogens was assessed together for resistant and susceptible strains. In 2011, the Public Health Agency of Sweden prioritised pathogens according to national public health relevance; using a Delphi process, five experts scored the pathogens on ten variables. Two antibiotic-resistant bacteria were evaluated: meticillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamase-producing Enterobacteriaceae. Only two publications focused on antibiotic-resistant bacteria. To define the national need for monitoring and prevention activities, the 2013 priority list from the US Centers for Disease Control and Prevention prioritised antibiotic-resistant bacteria and drug-resistant *Candida* spp, according to expert opinion, into three levels of threat (urgent, serious, and concerning). In 2015, using multicriteria analysis and expert review, the Public Health Agency of Canada prioritised antibiotic-resistant bacteria to assess the magnitude of national antimicrobial resistance and the state of surveillance.

Added value of this study

All previous priority lists focused on single-country data, and none focused on research and development needs for new antibiotics. The WHO priority list is the first international, global effort to prioritise research and development of new antibiotics according to bacterial drug resistance. The list combines evidence in ten criteria and expert opinion via a multicriteria decision analysis method, and will be regularly updated.

Implications of the available evidence

We recommend pharmaceutical companies and research centres working on the research and development of new antibiotics include multidrug-resistant and extensively resistant Gram-negative bacteria and bacteria common in the community—eg, antibiotic-resistant *Mycobacterium tuberculosis*, *Salmonella* spp, *Campylobacter* spp, *Neisseria gonorrhoeae*, and *Helicobacter pylori*—in their long-term plans. The priority list is a new tool to be included in a global, multifaceted strategy to increase awareness of antibiotic resistance and favourably affect patient outcome.

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of antibiotic resistance, and could run the risk of co-selecting resistance through use of new molecules.[8,9]

The stimulation of antibiotic research and development has a pivotal role in the development of strategies to address the global threat of antibiotic-resistant bacteria.[10,11] In support of the Global Action Plan for Antimicrobial Resistance,[12] WHO—in collaboration with the Drugs for Neglected Diseases initiative—launched the Global Antibiotic Research and Development Partnership to develop new antibiotic treatments addressing antimicrobial resistance, and to promote the responsible use of these treatments for optimal conservation.[13] The US Biomedical Advanced Research and Development Authority's Broad Spectrum Antimicrobial and Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator programmes (co-sponsored by the Wellcome Trust), and the Innovative Medicine Initiative's New Drugs for Bad Bugs programme are new models of collaboration between pharmaceutical companies and academia that promote innovation in the research and development of new antibiotics.[14–17] In parallel, regulatory agencies, such as the US Food and Drug Administration and the European Medicines Agency, are actively working on the simplification of the approval pathway for antibiotics for selected unmet medical needs.

In 2016, in the wake of the increasing global awareness of the need for new antibiotics, WHO's member states mandated that WHO create a priority list of antibiotic-resistant bacteria to direct research and development of new and effective drugs. The mandate also followed recommendations of the 2016 UN report of a high-level panel on the global response to health crises, which emphasised the threat posed to humanity from a number of under-researched antibiotic-resistant bacteria that urgently require enhanced and focused research and development investments.[18] The major goal of the WHO priority list is to prioritise funding and facilitate global coordination of research and development strategies for the discovery of new active agents against bacteria with acquired resistance to antibiotics that are also responsible for acute infections and multidrug-resistant tuberculosis. The list is aimed at pharmaceutical companies likely to invest in the research and development of new antibiotics, and at universities, public research institutions, and public–private partnerships that are becoming increasingly involved in antibiotic research and development.

Methods

Study design

Multicriteria decision analysis was used to prioritise antibiotic-resistant bacteria. This method consisted of four

steps. First, selection of the antibiotic-resistant bacteria and identification of relevant criteria, against which the antibiotic-resistant bacteria were rated in the prioritisation exercise according to predefined levels of performance, determined using available evidence.[19] Second, extraction and synthesis of evidence to support the rating of each selected bacterium. Third, after rating the antibiotic-resistant bacteria, the stakeholders (ie, the survey participants) weighted the criteria and quantified the importance of each criterion on the basis of their expertise. A final score for each bacterium was determined by summing the weights attributed by the experts to each evidence-based criterion. Finally, we undertook stability assessment of the ranking using subgroup and sensitivity analyses.

Selection of antibiotic-resistant bacteria and criteria for the prioritisation of antibiotic-resistant bacteria

The coordinating group (consisting of WHO staff and ten international experts in infectious diseases, clinical microbiology, public health, and pharmaceutical research and development) was selected through open tender launched by WHO in August, 2016. This group selected 20 bacterial species with 25 patterns of acquired resistance based on WHO's mandate, the WHO 2014 surveillance report on antibiotic-resistant bacteria of international concern,[2] the two previously published priority lists,[20,21] and experts' discussion (the selection process is detailed in the appendix). Bacteria that cause chronic infections and require extended treatment courses, such as drug-resistant *M tuberculosis*, could not be included in the prioritisation exercise. To address the need for research and development into new therapies for chronic infections, a priority exercise that includes specific criteria related to the long duration of therapy and long-term outcomes would be required. Viruses, fungi, parasites, protozoa, and helminths were outside the scope of this list. Consistent with multicriteria decision analysis best practice (completeness, no redundancy, no overlap, and preference independence),[22] we selected ten criteria to assess priority: mortality, health-care burden, community burden, prevalence of resistance, 10-year trend of resistance, transmissibility, preventability in the community setting, preventability in the health-care setting, treatability, and pipeline. The table provides the definitions and levels of the criteria.

See Online for appendix

Evidence extraction and data synthesis

For each antibiotic-resistant bacterium, the evidence to support each criterion was extracted from data sources in accordance with an a priori protocol (appendix). The main data sources were: existing databases of two projects running at Tübingen University, Germany (DRIVE-AB, 115618; COMBACTE-Magnet, EPI-Net, 115737-2; appendix); three systematic reviews (up to Sept 30, 2016; appendix); 23 national and international surveillance systems (appendix); and, 77 international guidelines on treatment and prevention of infections and colonisation due to antibiotic-resistant bacteria (appendix). Data were entered into standardised computer databases, verified for consistency (by EC and AS), and stratified by the six WHO regions (appendix). Synthesis for quantitative variables was done with meta-analyses, pooling the estimates of outcomes with random-effects models with Freeman-Tukey (double arcsine) transformation for variance stability. Protocols of the meta-analyses were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[23] Subgroup analysis was done to evaluate modification of the pooled estimates according to categorical variables. Random-effects univariate meta-regression was applied to assess significant changes of prevalence of resistance in the past 10 years. We did statistical analyses using STATA, version 14.0. A p value of less than 0·05 was considered significant. Qualitative criteria to assess priority were defined using multiple indicators based on literature and expert review (table).

Expert rating of antibiotic-resistant bacteria and weighting of criteria to assess priority

The experts participating in the survey were selected by the coordinating group through consultation with WHO and linked networks from all WHO regions. The International Affairs Subcommittee of the European Society of Clinical Microbiology and Infectious Diseases contributed a list of relevant experts from the western Pacific region, South America, and southeast Asia. Goals of the selection process included balance of geographical origin, gender, and expertise. 74 (75%) of the 99 international experts who were contacted agreed to participate in the survey. Before starting, participants received the definitions of the criteria and detailed study methods, and members of the coordinating group were available to answer questions for 2 weeks before the launch of the survey.

The evidence for each alternative was extracted from sources (in the evidence extraction and data synthesis section) according to the definitions of the criteria to assess priority and included in the dedicated database in the 1000Minds (Dunedin, New Zealand) decision-making software.[24] The weights of the criteria were determined using a preferences survey based on the PAPRIKA (Potentially All Pairwise RanKings of all possible Alternatives) method.[24] To reduce confounding factors, each survey participant was asked to rank, as higher priority, a series of pairs of hypothetical bacteria, each of which were defined by two criteria at a time in a trade-off manner consistent with the PAPRIKA method (appendix).[24] Each time the participant ranked a pair of hypothetical bacteria. All other hypothetical bacteria that could then be ranked pairwise, via the logical property of transitivity, were identified and eliminated from the participant's survey. For each participant,

	Definition	Source	Criteria level
Mortality	Pooled prevalence of all-cause mortality in patients with infections due to antibiotic-resistant bacteria	Systematic reviews and meta-analysis of studies assessing mortality in patients infected with antibiotic-resistant bacteria compared with patients infected with susceptible strains; no restriction for patient population, infection type, and setting	Low: <10% Medium: 10–20% High: 21–40% Very high: >40%
Health-care burden	Need for hospitalisation and increase in LOS in patients with infections due to antibiotic-resistant bacteria compared with patients infected with susceptible strains	Systematic review and meta-analysis of studies assessing hospitalisation and total LOS in patients infected with antibiotic-resistant bacteria compared with patients infected with susceptible strains; no restriction for patient populations, infection type, and setting	Low: hospitalisation not usually required Medium: hospitalisation usually required and LOS not significantly increased High: hospitalisation usually required and LOS significantly increased Very high: hospitalisation usually required and LOS in intensive care unit significantly increased (as measured by p value)
Community burden	Prevalence of resistance and type of infections in community setting	Review of cohort and surveillance studies evaluating the prevalence of antibiotic resistance and type of infections in community; no restriction for patient populations	Low: resistance in community rarely reported, non-systemic infections Moderate: resistance in community well reported, non-systemic infections, or resistance in community rarely reported, non-systemic and systemic infections High: resistance in community well reported, non-systemic and systemic infections
Transmissibility	Isolation and transmission among four compartments: animal–human beings, food–human beings, environment–human beings and human beings–human beings in community and hospitals	Review of studies assessing the isolation and transmission of antibiotic-resistant bacteria among four compartments (human beings, animals, food, and environment)	Low: outbreaks rare or not reported, isolation in human beings, animals, food, and environment uncommon, transmission not reported Moderate: outbreaks well reported, isolation in human beings, animals, food, and environment common, low zoonotic potential transmission High: outbreaks well reported (high attack rate) or outbreaks well reported (low attack rate), isolation in human beings, animals, food, and environment common, high zoonotic potential transmission
Prevalence of resistance	Pooled prevalence of resistance in clinically significant isolates, stratified by WHO region	Data extraction from 23 national and international surveillance systems reporting data on antibiotic-resistant bacteria (last available data reported); national data from the WHO report on antimicrobial resistance 2014	Low: <15% in most WHO regions Moderate: 15–30% in most WHO regions Moderate to high: >30% in one WHO region (others ≤30%) High: >30% in two WHO regions (others ≤30%) Very high: >30% in most WHO regions
10-year trend of resistance	Linear increment in 10-year prevalence of resistance in clinically significant isolates, stratified by WHO region	Data extraction from the same dataset searched for the prevalence criteria (reported in the past 10 years)	Decreasing: significant decrease of resistance in all WHO regions Stable: stable resistance in all WHO regions Low increase: significant increase of resistance in one WHO region Moderate increase: significant increase of resistance in two WHO regions High increase: significant increase of resistance in most WHO regions
Preventability in community and health-care setting	Availability and effectiveness of preventive measures in community and health-care settings	Review of 30 national and international guidelines assessing preventability of transmission of antibiotic-resistant bacteria in health-care and community settings (past 15 years); review of randomised trials, interrupted time series, large cohort studies assessing efficacy of preventive measures published after last published guidelines	High: preventive measures available (moderate-quality or high-quality evidence) and effective Low: preventive measures not well defined (low-quality evidence) or partly effective
Treatability	Availability of effective treatment (number of antibiotic classes, residual activity of antibiotics, oral and paediatric formulations)	Review of 47 international guidelines for treatment of infections due to antibiotic-resistant bacteria (past 15 years), European Committee on Antimicrobial Susceptibility Testing antibiotics evaluation forms, case reports and cohort studies of last-resort antibiotics (past 5 years), list of forgotten antibiotics, surveillance postmarketing data	Sufficient: at least two classes (first-line therapy) with high residual activity (>80%) and availability of oral and paediatric formulation Limited: one class (first-line therapy) with high residual activity (>80%) or at least two classes (first-line therapy) with reduced residual activity (<80%) and availability of oral or paediatric formulation or guidelines requiring combination treatment as a first-line treatment due to resistance or pathogen-related factors Absent: one class (first-line therapy) with reduced residual activity (<80%) or last-resort antibiotics, or both
Pipeline	Likelihood of development in the future (5–7 years) of new antibiotics according to the current pipeline	Review of scientific and commercial presentations, clinical trials registries, partnering meetings, scientific abstracts, company websites, selected patents, clinical phase analysis (Pew Trust) and other non-confidential material and information regarding drugs included in the current pipeline; all the included variables are summarised in a pipeline index	Likely included (>8 points): antibiotics to treat a resistant bacterium included in future registered indications (unlikely [1 point], possibly [2 points], very likely [3 points]) Possibly included (7–8 points): antibiotics to treat resistant bacterium included in clinical pipeline (no drug [1], at least one drug [2], several drugs [3]), or in preclinical projects (no project [1], insufficient number [2], sufficient number [3]) Unlikely included (<7 points): challenges in discovery (high [1], medium [2], least [3]), or challenges in clinical development (high [1], medium [2], least [3])

Rarely reported=<ten studies, surveillance, or reports. Well reported=≥ten studies, surveillance, or reports. Uncommon=<15 studies. Common=≥15 studies. High attack rate=>10% (number of new cases in the population at risk/number of persons at risk in the population). Low zoonotic potential=reports of possible transmissions between animals and human beings. High zoonotic potential=transmission between animal and human beings proved with molecular methods. Clinically significant isolates=resistance rates from invasive isolates (blood and cerebrospinal fluid) were preferably extracted for bacteria commonly causing invasive infections or other samples were specifically included (ie, faeces for *Campylobacter* or swabs for *Neisseria gonorrhoeae*) according to the most common clinical diseases. Residual activity=rate of resistance to a first-line antibiotic detected in surveys or postmarketing studies. Details of surveillance systems, reports, and guidelines are in the appendix. LOS=length of hospital stay.

Table: **Definitions and levels of criteria**

three questions were repeated twice to serve as an internal consistency check. The software recorded the number of questions answered and seconds taken to answer each question, and these results were reported as medians and IQR. The software used mathematical methods based on linear programming to derive the

weights of the criteria for each level from each participant's individual ranking.

Each bacterium's total score (derived by summing its weights across the criteria according to its performance) was established on a scale from 0 to 100%, where 100% corresponded to a hypothetical bacterium reaching the highest level on all criteria, and 0% represented a hypothetical bacterium reaching the lowest level on all criteria. Mean values of the bacteria's total scores were computed with relative SD. The final priority list was based on the mean total score for each antibiotic-resistant bacterium.

Ranking stability assessment

A sensitivity analysis was done by stratifying experts' contribution according to their consistency in answers to the three repeated questions, their area of scientific expertise (confirmed by the expert at the time of their enrolment in the survey), and geographical origin to detect potential variations in ranking. Significant changes in the mean weights of the criteria ($p<0·05$) were assessed through a one-way analysis of variance for normally distributed variables, and the Kruskal-Wallis rank test when the assumption of normality was not met. The final ranking was computed across the whole panel of experts participating in the survey and grouped according to WHO regions.

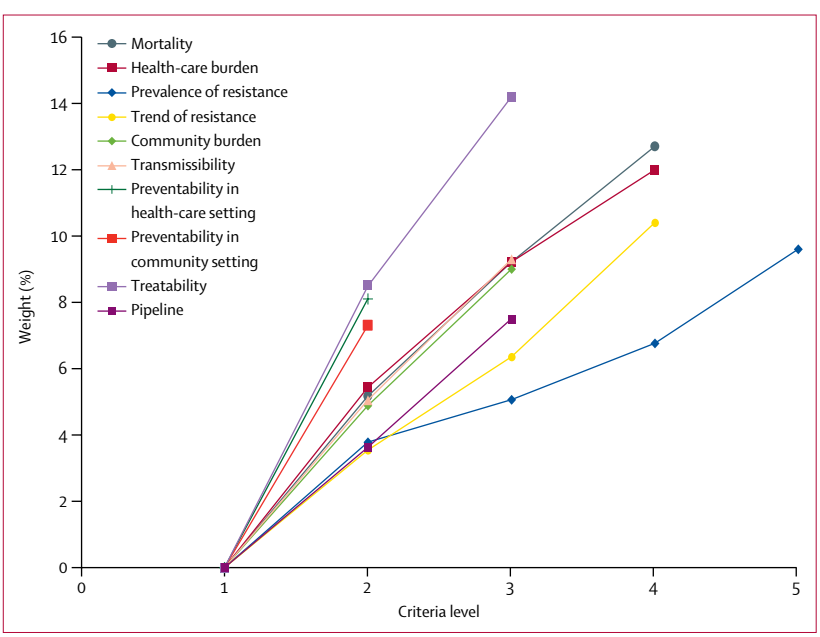

Figure 1: **Criteria value functions**
The weights of the ten criteria, computed by the survey software, according to the value of the criteria. The characteristics of the level for each criterion are detailed in the table. Five criteria (ie, 10-year trend of resistance, community burden, transmissibility, treatability, and pipeline) showed a linear increase in the weight per level, meaning the survey participants considered the shift from one level to the next as of equal importance. Three criteria (ie, mortality, health-care burden, and prevalence of resistance) showed a greater increase in their intra-level weight when there was a shift from a low to a medium level compared with a shift from a medium to a high level.

Role of the funding source

WHO supported the systematic reviews and data analysis, and WHO employees (NM, LM, MS-M, and MP-K) contributed to study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had access to all data and had final responsibility for the decision to submit for publication.

Results

The survey was launched on Dec 19, 2016, and ran for 26 days. Of the 74 experts who agreed to participate, 70 completed the survey; the four who provided incomplete responses were excluded from the final analysis. Each participant answered a median of 62 questions (IQR 44–84). The consistency check revealed that most of the participants consistently answered the three repeated questions (65 answered at least one and 46 at least two of the three repeated questions consistently); 20 answered all three repeated questions consistently. Figure 1 shows the mean weights attributed to the criteria from the survey. The four most important criteria for determining research and development priorities, together representing 49·7% of the total weight, were treatability, mortality, health-care burden, and 10-year trend of resistance.

The final ranking of the 20 bacteria and related 25 patterns of acquired resistance was computed by averaging each bacterium's total score across the entire group of participants. These scores ranged from 91·0% (SD 5·2) for the top-ranked bacterium (carbapenem-resistant *Acinetobacter baumannii*) to 22·1% (6·7) for the bottom-ranked bacterium (vancomycin-resistant *Staphylococcus aureus*). Antibiotic-resistant Gram-negative bacteria rated at the highest level on the four most heavily weighted criteria. The highest-ranked Gram-positive bacteria were vancomycin-resistant *Enterococcus faecium* at 54·5% (7·2) and meticillin-resistant *S aureus* at 52·7% (11·2). Among bacteria typically responsible for community-acquired infections, the highest ranked were clarithromycin-resistant *Helicobacter pylori* at 44·8% (10·1) and fluoroquinolone-resistant *Campylobacter* spp at 41·0% (7·8), *Neisseria gonorrhoeae* at 35·8% (8·9), and *Salmonella typhi* at 37·6% (9·2). Figure 2 shows the mean weight (SD) for each antibiotic-resistant bacterium.

The weights of the criteria were stratified by participants' expertise and geographical origin. The only criterion showing a significant change was community burden, with a mean value of 14·6% for survey participants from the African region and 5·9% for survey participants from the Americas region ($p=0·0046$; figure 3). No other significant differences were shown after stratifying for survey participants' scientific background. The final ranking of bacteria, computed after excluding the results of the 20 survey participants who consistently answered fewer than two repeated questions, did not show significant differences.

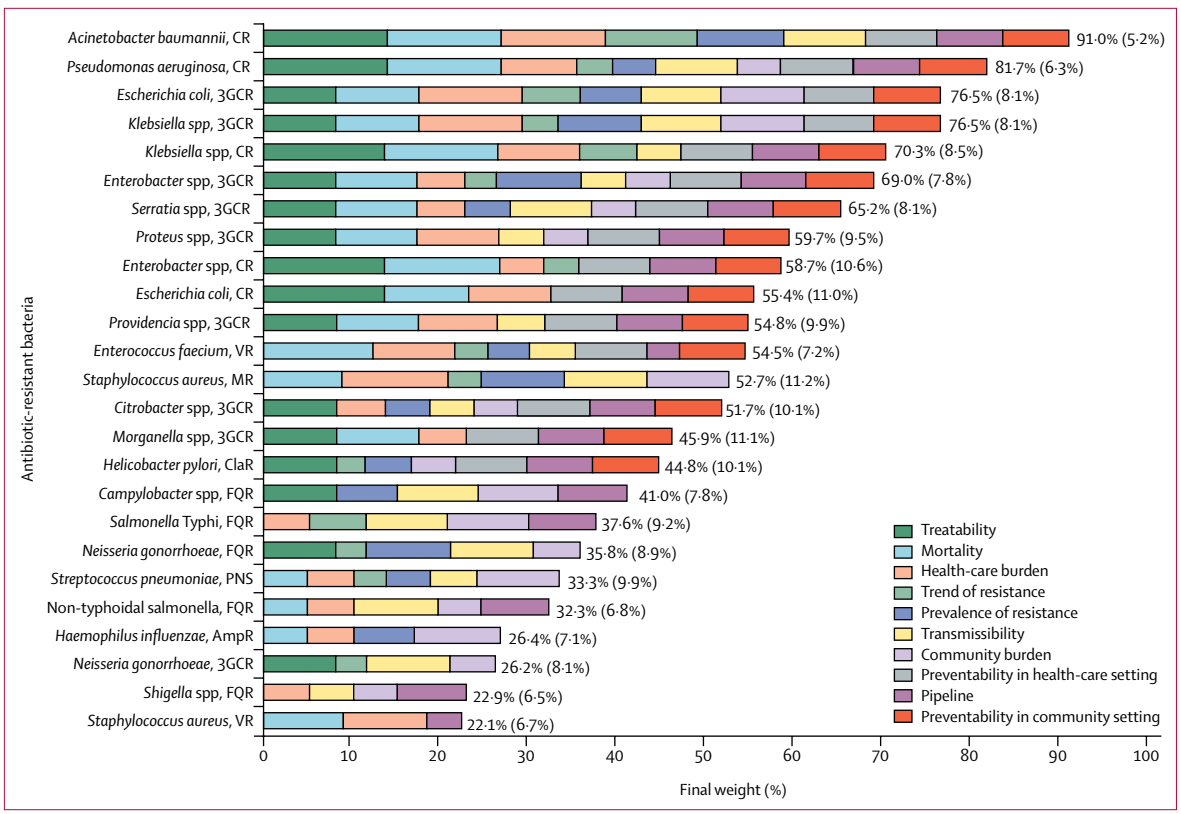

Figure 2: **Final ranking of antibiotic-resistant bacteria**
Mean (SD) pathogen weights were derived by the software from the survey participants' preferences. The segments represent the contribution of each criterion to each pathogen's final weight. CR=carbapenem resistant. 3GCR=third-generation cephalosporin resistant. VR=vancomycin resistant. MR=meticillin resistant. ClaR=clarithromycin resistant. FQR=fluoroquinolone resistant. PNS=penicillin non-susceptible. AmpR=ampicillin resistant.

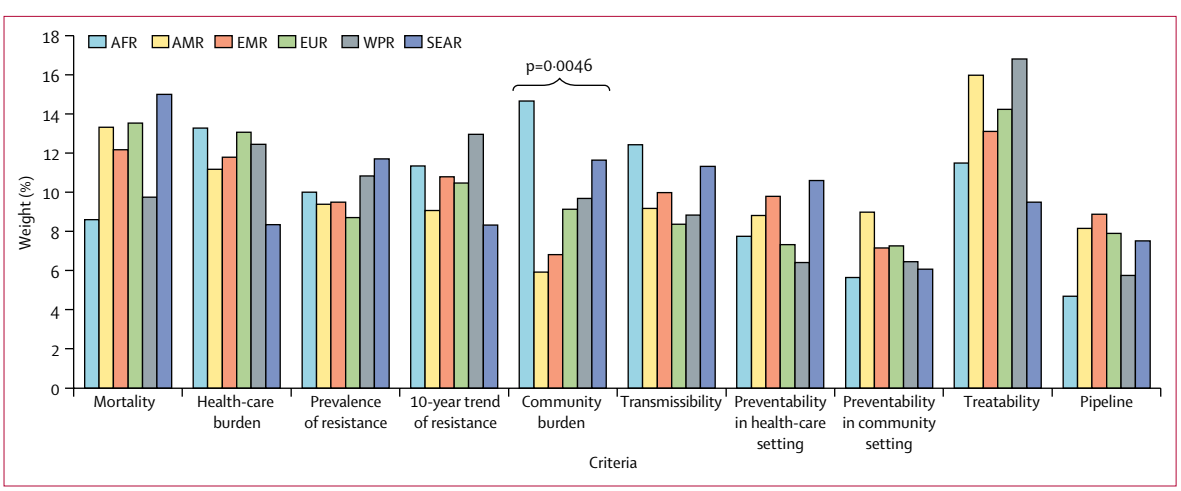

Figure 3: **Subgroup analysis of criteria by geographical origin of the experts**
The weights of the ten criteria from the survey participants, stratified according to the geographical origin of the survey participants. There was no significant difference in the weights given to the ten criteria among the WHO regions, with the exception of community burden, which had been attributed a higher importance for research and development of new antibiotics from the survey participants working in Africa. AFR=African region. AMR=Americas region. EMR=eastern Mediterranean region. EUR=European region. WPR=western Pacific region. SEAR=southeast Asian region.

The survey ranking was reviewed by the coordinating group and an external advisory board of experts to evaluate the results and the sensitivity analyses, and to plan dissemination of the results. To simplify the presentation of the results, and comply with the research and development focus, bacteria of the same species with

multiple resistance patterns were clustered by the highest position in the ranking. The priority list was then stratified into three tiers (critical, high, and medium priority), with a cutoff set at the 33rd percentile of the bacterium's total scores (panel). The critical-priority tier included the bacteria that scored more than 66·0%: carbapenem-resistant *A baumannii*, *P aeruginosa*, and Enterobacteriaceae, and third-generation cephalosporin-resistant Enterobacteriaceae. The high-priority tier included bacteria that scored between 66·0% and 34·0%: vancomycin-resistant *E faecium;* meticillin-resistant and vancomycin-resistant *S aureus*; clarithromycin-resistant *H pylori*; fluoroquinolone-resistant *Campylobacter* spp and *Salmonella* spp, and fluoroquinolone-resistant and third-generation cephalosporin-resistant *N gonorrhoeae*. The medium-priority tier included bacteria that scored less than 34·0%: penicillin-non-susceptible *Streptococcus pneumoniae*; ampicillin-resistant *Haemophilus influenza,* and fluoroquinolone-resistant *Shigella* spp.

Discussion

The WHO priority list is an innovative example of an international effort to prioritise research and development of new antibiotics, which combines evidence and expert opinion via a multicriteria decision analysis method. Aside from multidrug-resistant tuberculosis as a global priority for research and development, the results of the prioritisation exercise for other pathogens suggest that research and development strategies should focus on new antibiotics that are specifically active against multidrug-resistant and extensively drug-resistant Gram-negative bacteria that cause acute infections in both hospital and community settings. Overall mortality, availability of effective therapy, health-care burden, and the increase in drug resistance were weighted as the most important criteria to assess priority. The highest ranked Gram-positive bacteria were resistant *S aureus* and *E faecium*, which were both included in the high-priority tier. Although these Gram-positive bacteria are responsible for high clinical and epidemiological global burden, sufficient available treatment options are more likely to be successful than the drugs available to treat Gram-negative bacterial infections.

The PAPRIKA method was used for the prioritisation of antibiotic-resistant bacteria; this method has two major advantages over most other methods. First, the PAPRIKA method generates a set of weights for each individual participant in the preferences survey, which is by contrast with methods that produce aggregated data across the group of participants only. Individual-level data allowed us to investigate the heterogeneity of the experts' preferences, and the extent to which these differences were related to demographic and background characteristics. Second, pairwise ranking is cognitively less difficult for decision makers than choosing between more than two alternatives (bacteria), or between alternatives defined by more than two criteria at a time.

***Panel:* WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria**

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*[25]

Other priority bacteria

Priority 1: critical

- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high

- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

Priority 3: medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant

There are some differences between the WHO priority list and previous efforts, such as the 2013 list from the US Centers for Disease Control and Prevention (CDC) and the 2015 list from the Public Health Agency of Canada.[20,21] First, the WHO list has a research and development focus; the intent of this list is not to prioritise public health interventions or surveillance activities. This distinction is important because prioritisation for public health must consider whether investments and interventions in vaccination, sanitation, health management, and infection control measures can reduce the burden of diseases more rapidly than development of new antibiotics, which is a slow and uncertain process. Second, the WHO priority list includes the analysis of the current pipeline for antibiotics, and provides a multicomponent definition of therapeutic options. The effectiveness of treatment includes the number of classes of antibiotics considered as first-line treatment in evidence-based guidelines and their residual activity (ie, the resistance to a first-line antibiotic detected in surveys or postmarketing studies). The assumption is that a first-line antibiotic for which there is a prevalence of resistance greater than 20·0% should not be considered to be as effective as another first-line agent with minimal resistance and only a few case reports of clinical resistance. In the evaluation, we included the availability of paediatric and oral formulations, which would have a substantial effect on quality of life in young patients and patients treated in the community. In addition, because antibiotic resistance

is a global issue affecting both animal and human health, data on transmission potential among human beings, animals, food, and environment were collected, and included in the transmissibility criterion, in accordance with the One Health approach.[26]

The WHO priority list we present has a few limitations. First, because of the evidence-based method used to develop the list, we did not assess incidence or estimate future burden of diseases. There are no active global surveillance systems that could be used to calculate the real burden and mortality associated with resistant infections. Antibiotic resistance was assessed through the use of prevalence data from 23 national and international surveillance systems, and included only pathogens that are generally highly prevalent in the six WHO regions.[2] To define the global prevalence of resistance more precisely, we included only clinically relevant samples (ie, blood and cerebrospinal fluid for severe infections, swabs for *N gonorrhoeae*, and stools for *Shigella* spp and *Campylobacter* spp). Incidence data could have substantially increased the precision of the list, but they are limited to only a few countries, focused on health-care-associated infections, and mainly derived through complex estimates.[27,28]

The CDC estimated that in 2013 more than 2 million people in the USA acquired a serious health-care-associated infection due to the bacteria included in the WHO list, and at least 22 000 people died as a consequence of these infections.[20] Similar estimates of the annual number of deaths attributable to antibiotic-resistant bacteria have been reported from Europe and Thailand, and India estimated 56 500 deaths among neonates were attributable to infections by bacteria resistant to first-line antibiotics.[29–31] These estimates were based on the national resistance proportions in blood cultures from hospitals and extrapolated from bloodstream infections to infections at other body sites or calculated through the application of a ratio between each one and the estimated national numbers of resistant bloodstream infections. This method is associated with several biases and has been criticised.[32]

Another limitation was the inability to estimate the absolute numbers of deaths at the global level, which would have increased the precision of the mortality criterion. Such an estimate was not possible due to insufficient data from most of the WHO regions. Additionally, the priority list does not include all possible patterns of resistance. The aim of the priority list is to drive research and development of new antibiotics with no cross-resistance and co-resistance with existing classes, which could be achieved if the focus was on new chemical scaffolds, novel multimolecular targets, and associated novel mode of action. For example, carbapenem resistance was chosen as a suitable marker for extensively resistant and pan-resistant bacteria. Because carbapenem resistance usually also involves a broad range of co-resistance to unrelated antibiotic classes, a research and development effort targeting carbapenem-resistant Gram-negatives should deliver a new antibiotic without cross-resistance and co-resistance to other classes and thus cover colistin-resistant strains.

Our assessment of the evidence was also limited by the available surveillance and clinical data. Although colistin resistance is increasingly reported as a cause of mortality in immunocompromised patients, epidemiological data are missing for most countries. However, the multicriteria decision analysis method allows for the list to be updated frequently, as soon as new evidence is available. The scarcity of surveillance data is particularly evident for community-acquired infections and for low-to-middle-income countries. To reduce this bias in our calculation, we considered not only the prevalence of resistance among community isolates, whenever available, but also the type and frequency of infections. The critical-priority tier includes third-generation cephalosporin-resistant *Escherichia coli*, which causes not only health-care-associated infections but also urinary tract infections, among others in the community. The high-priority tier includes fluoroquinolone-resistant *N gonorrhoeae*, *Campylobacter* spp, and *Salmonella* spp, which, although not associated with a high mortality, have high prevalence in the community and few treatment options.

The research and development for new antibiotics cannot be limited to antibiotic-resistant bacteria. The burden of health-care-associated infections is also associated with bacteria with no acquired resistance to antibiotics—eg, *Clostridium difficile*. The 2013 priority list developed by the CDC[20] includes *C difficile* as an urgent threat but underlined that the cause of the burden is not related to resistance to antibiotics. Efforts to reduce the burden of non-resistant bacteria should also focus on new strategies, such as host defence peptides, bacteriophages, and vaccines.

The data analysis for the development of the WHO priority list also points out areas where urgent interventions are needed at global level. The little available evidence particularly affected the global analysis of surveillance data in different compartments. Because antibiotic resistance is a multifaceted and cross-sectorial issue, affecting human beings, animals, food, and environment, an interconnected and integrated One Health surveillance framework across these compartments is essential. High heterogeneity in implementation of infection prevention and control measures was observed, and the need for interventions focusing on how to increase standardisation of infection prevention and control is compelling. The absence of microbiology laboratory capacity in low-income and middle-income countries further complicates patient-specific treatment. The unbalanced supply of antibiotics across WHO regions, and the few coordinated, standardised controls on generic drugs also contributes

to the burden of resistant infections, in particular for community and paediatric infections.[33,34]

The WHO priority list suggests that the prioritisation of research and development of new antibiotics against multidrug-resistant tuberculosis and Gram-negative bacteria is urgently needed. Global research and development strategies should also include antibiotics active against more common community bacteria, such as antibiotic-resistant *Salmonella* spp, *Campylobacter* spp, and *H pylori*. Further efforts should address how to provide incentives for the development of oral formulations for community infections with a high morbidity burden in both low-income and middle-income countries and high-income countries—eg, drug-resistant *N gonorrhoeae* and third-generation cephalosporin-resistant Enterobacteriaceae. To drive the long-term plans of pharmaceutical companies and research centres involved in research and development of new antibiotics, and to reduce the burden of resistant infections, the WHO priority list of antibiotic-resistant bacteria must be allied to an increased political awareness in a global, multifaceted strategy.

Contributors

ET and EC designed the study protocol. AS, SH, MM, CP, GK, JK, YC, NS, and UT reviewed the study protocol. EC and AS extracted and managed the data. PH provided assistance with the software and statistical analysis. EC did the statistical analysis. ET, EC, AS, SH, MM, CP, GK, JK, YC, NS, UT, DLM, MO, KO, JP, MC, EMC, CRH, MLG, and NM reviewed and discussed the survey results. ET, EC, and AS wrote the first draft of the Article. All authors provided feedback, commented on, and reviewed the manuscript. Several members of the working group (FRB, SM-K, DK, and LM) contributed to data extraction or analysis.

Declaration of interests

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