PRIORITIZATION OF PATHOGENS TO GUIDE DISCOVERY, RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS FOR DRUG-RESISTANT BACTERIAL INFECTIONS, INCLUDING TUBERCULOSIS

World Health Organization

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Foreword

Infectious diseases are among the top 10 causes of death and the leading cause of disability-adjusted life years worldwide. Among these, acute lower respiratory tract infections, diarrhoeal diseases and tuberculosis (TB) are responsible for significant global morbidity and mortality. The overall burden of communicable diseases is strongly linked to poverty and, as a result, the African continent still suffers from the highest mortality from infectious diseases.

The reasons for the emergence and re-emergence of infectious diseases worldwide include a breakdown of public health measures in the face of epidemic transitions, increasing international travel, immigration for political, social and economic reasons, microbe adaptation and ability to change, and transmission of several pathogens between animals and humans. Of great concern is the global emergence of resistance of infectious pathogens to many first-line medicines.

Equitable access to medicines is another major concern in many low- and middle-income countries where common, treatable infections like pneumonia and TB are still associated with high numbers of deaths, often in children. The emergence of pathogenic microbes with drug resistance, not only to the most commonly used antibiotics but also to second-line, "reserve" medicines,

further increases the burden of infectious diseases. Low-income countries are particularly vulnerable because of conditions that enable the spread of these diseases, such as poor sanitation, lack of control of and guidance on antibiotic use, inadequate health-care services and systems, and limited or inadequate infection control measures.

Middle- and upper-middle-income countries are not free of the burden of drug resistance, however. BRICS countries (Brazil, Russian Federation, India, China and South Africa) and several European countries face major epidemics of multidrug-resistant infections caused by common Gram-negative bacteria and multidrug-resistant-TB (MDR-TB), with devastating public health and economic consequences. Sadly, the pipeline for new antibiotics currently includes only a small number of novel compounds in development. In the past 20 years, only two new antibiotic classes, both active only against Gram-positive bacteria, have received global regulatory approval by international regulatory agencies. In the same time period, no new antibiotics against Gram-negative bacteria have been approved. In addition, only two completely new drugs for MDR-TB treatment (bedaquiline and delamanid) have reached the market in over 70 years.

In 2016, at the high-level meeting of the UN General Assembly on antimicrobial resistance, Heads of State directed an unprecedented level of attention to curbing the spread of infections that are resistant to antimicrobial medicines. They reaffirmed their commitment to stopping the misuse of antimicrobial medicines in human health, animal health and agriculture, and recognized the need for stronger systems to monitor drug-resistant infections and the amounts of antimicrobials used in humans and animals. In the wake of the increasing global awareness of the need for new antibiotics, Member States highlighted market failures, and called for new incentives for investment in research and development of new, effective and affordable medicines, rapid diagnostic tests, and other important therapies to replace those that are losing their effectiveness. In response to this and in line with the Global Action Plan on Antimicrobial Resistance to support the identification of pathogens of greatest concern, WHO developed a priority list of antibiotic-resistant bacteria to underpin renewed efforts for the research and development of new antibiotics.

2016 was also the first year of implementation of the WHO End TB Strategy, which was adopted by the World Health Assembly in 2014 and aimed at attaining universal access to TB prevention, diagnosis and treatment. Global TB care and control measures saved an estimated 49 million lives between 2000 and 2015, yet widespread MDR-TB threatens to reverse the gains made from decades of effort to contain the TB epidemic. MDR-TB was declared a global crisis by WHO in 2014, 21 years after TB had been declared a global emergency (in 1993) and despite greatly improved cure rates in patients with drug-susceptible TB. The TB emergency prompted the establishment of new financing mechanisms to support countries in tackling the TB epidemic, most notably the Global Fund and Unitaid. However, investment in research and development for TB has major gaps in the funding needed to develop new tools that would help achieve the targets of the WHO End TB Strategy.

The overall goal of the following report is to present the priority pathogens to be targeted for research and development of new antibiotics to treat drug-resistant bacterial infections and TB. It is acknowledged that viral, fungal and parasitic infections may well need a similar strategy in the near future. The development of new antibiotics to tackle the serious problem of drug-resistant infections needs to be prioritized in the global political agenda of world leaders and health policy-makers. It also needs to be linked to the development of appropriate health-care delivery services and to proper stewardship to safeguard the use of current and future medicines. This challenge cannot be simplified in a "one size fits all" approach. The only possible defence against the threat of antimicrobial resistance and the (very real) possibility of a post-antibiotic era is a global and coordinated effort by all stakeholders. This document reflects the commitment and contribution of WHO and its partners to help establish priorities for critically needed research and development on new antibiotics against drug-resistant bacterial infections and TB, in line with our mission of ensuring health for all.

Dr Tedros Adhanom Ghebreyesus
WHO Director-General

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Acknowledgements

Executive summary

Antimicrobial resistance is one of the most complex global health challenges today. The world has long ignored warnings that antibiotics and other medicines are losing their effectiveness after decades of overuse and misuse in human medicine, animal health and agriculture. Common illnesses like pneumonia, post-operative infections, diarrhoeal and sexually transmitted diseases, as well as the world's largest infectious disease killers – tuberculosis (TB), HIV and malaria – are increasingly becoming untreatable because of the emergence and spread of drug resistance.

Worsening antimicrobial resistance could have serious public health, economic and social implications. The threat of antimicrobial resistance is also becoming a key consideration for programmes addressing maternal and child health, sexual and reproductive health, foodborne diseases, water and sanitation, and infection prevention and control. The World Bank has warned that antimicrobial resistance could cause more economic damage than the 2008 financial crisis. And although the 21st century is being shaped by technology and innovation, humans could soon find themselves in an era where simple infections once again kill millions every year.

The past three years have seen unprecedented global political momentum to address antimicrobial resistance: in 2015, governments adopted a global action plan at the World Health Assembly and in 2016 passed a political declaration at the United Nations General Assembly. Antimicrobial resistance has made it onto the agendas of the G7 and G20 groups and is a core component of the Global Health Security Agenda.

WHO is working closely with the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health in leading global efforts against antimicrobial resistance and ensuring that the necessary momentum is consolidated and sustained. These efforts are guided by an ad-hoc interagency coordination group established in 2017. A global development and stewardship framework to combat antimicrobial resistance is being drafted to support the development of new antimicrobial medicines, diagnostics, vaccines and other tools.

One of the gravest global concerns about antimicrobial resistance currently is that antibiotic resistance has emerged in so many pathogens, including TB. In 2016, in the wake of the increasing global awareness of the need for new antibiotics, and to support the implementation of the Global Action Plan on Antimicrobial Resistance, WHO developed a priority pathogens list (PPL) of antibiotic-resistant bacteria to support research and development into new and effective drugs. This action also followed recommendations in the 2016 United Nations report of a high-level panel on the global response to health crises, which emphasized the threat posed to humanity from a number of under-researched antibiotic-resistant bacteria that urgently require enhanced and focused investment in research and development.

2016 was also the first year of implementation of the WHO End TB strategy, which was adopted by the World Health Assembly in 2014. The End TB Strategy serves as the core strategic document for all WHO Member States on TB prevention, control and elimination, including the prevention and management of TB drug resistance. The End TB strategy is an evolution of the 2006 WHO Stop TB Strategy and its predecessor, the 1995 WHO DOTS Strategy, which Member States started to implement after WHO declared TB a global health emergency in 1993. Twenty-one years later, in 2014, multidrug-resistant TB (MDR-TB) was declared a global public health crisis by WHO, with a call urging increased investment in research and development, especially for new drugs and diagnostics.

Prioritization of pathogens for research and development is highly challenging given the absence of established criteria defining the impact of pathogens on human health. As a result, no consensus exists on the most effective methodology to develop prioritization in infectious diseases. Ranking antibiotic-resistant organisms to direct future research and development requires a detailed identification and integration of extensive information that defines the burden of antimicrobial resistance (microbiological, epidemiological, and clinical). Moreover, communicable diseases differ in clinical presentation and duration (e.g. acute versus chronic), treatment approaches (e.g. multidrug versus single drug therapy), and etiology (e.g. bacterial, viral, fungal).

The diversity of communicable diseases is a major challenge for prioritization of pathogens. As a result, the scope and focus of the work underlying this document was agreed beforehand to allow the deliverables requested by Member States to be

achieved within a realistic timeframe. Pathogens were considered separately, according to their natural history in terms of acute or chronic course of the diseases. It was not possible to apply the same framework to both TB and to other bacterial pathogens, thus they were considered and are reported separately. Several criteria applicable to resistant bacteria do not apply to MDR-TB, e.g. the treatment approach (combinations of drugs are needed for TB and drug-resistant TB while one antibiotic could suffice for several other bacteria) and modes of transmission (TB is almost exclusively airborne while transmission of the other bacteria is by food, animal and human interactions, such as the hands of health-care workers).

This document therefore addresses *Mycobacterium tuberculosis*, a prioritized programme of WHO, and other antibiotic-resistant bacteria, which have been overlooked until recently despite their considerable health and economic burden. It is acknowledged that similar assessments would be useful for communicable diseases caused by viral and fungal pathogens (e.g. following the recent publication of the WHO HIV drug resistance report[1]). Pesticide, parasitic and vector resistance fall outside of the scope of this document.

The priority of TB for research and development has been previously articulated by WHO and is reiterated here. The rationale for TB – and multidrug-resistant forms of the disease – being a global priority for research and development is illustrated in the figure below.

Section 1 of this report therefore focuses on TB and *Mycobacterium tuberculosis* as a priority pathogen.

Section 2 reports the priority list of other antibiotic-resistant bacteria developed through a multicriteria decision analysis.

This report recommends the following:

- Drug discovery and development strategies should focus urgently on new antibiotics specifically active against *Mycobacterium tuberculosis* (including multi- and extensively drug-resistant strains) and against multi- and extensively drug-resistant Gram-negative bacteria that cause acute clinical infections in both hospital and community settings worldwide.

- Global research and development strategies should include antibiotics active against more common community bacteria, such as antibiotic-resistant *Salmonella* spp., *Campylobacter* spp., *Helicobacter pylori, Neisseria gonorrhoeae*, and third-generation cephalosporin-resistant Enterobacteriaceae.

- Discovery and development of new antibiotic classes with novel targets and mechanisms of action without cross-resistance to existing classes is of the utmost priority.

- Development strategies should include the important need for new antibiotics for paediatric use and user-friendly (e.g. oral) formulations.

- Specific attention should be paid to the implementation of antibiotic stewardship initiatives at the global level, especially in combination with educational activities and public awareness campaigns.

- Long-term plans of pharmaceutical and research agencies involved in the development of new antibiotics must be aligned with increased political awareness in a global, multifaceted strategy to reduce the burden of resistant infections.

- Improved coordination and governance between different initiatives against antimicrobial resistance and communities should be explored to exploit synergies and create a basis of mutual understanding and collaboration.

There is very little treatment

Acinetobacter baumannii, CR
Enterobacteriaceae, CR
Pseudomonas aeruginosa, CR

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[1]   http://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf

TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEARCH AND DEVELOPMENT

FIVE REASONS WHY

1

Tuberculosis (TB) is the number one global infectious disease killer today, causing 1.8 million deaths per year. Drug-resistant TB is the most common and lethal airborne AMR disease worldwide today, responsible for 250 000 deaths each year.

2

Patients with multidrug-resistant TB (MDR-TB[1]) need complex and prolonged multidrug treatment with costly, highly toxic, and much less effective second-line medicines. There is a limited number of second-line medicines to treat MDR-TB and only 52% of patients are successfully treated globally.

3

In about 50% of MDR-TB patients worldwide, treatment regimens are already compromised by second-line drug resistance. Treatment of extensively drug-resistant disease (XDR-TB[2]) is successful in only one in three patients at best.

4

Patients with M/XDR-TB face agonising, prolonged suffering and often permanent disability while on treatment, compounded by devastating economic hardship, stigma and discrimination.

5

Only two new antibiotics for treatment of MDR-TB have reached the market in over 70 years. R&D investment in TB — seriously underfunded - is at its lowest level since 2008.

[1] MDR-TB — multidrug-resistant tuberculosis, that does not respond to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines.
[2] XDR-TB — extensively drug-resistant tuberculosis, defined as MDR-TB plus resistance to fluoroquinolones and injectable second-line anti-TB medicines.

OTHER PRIORITY PATHOGENS

CRITICAL PRIORITY

Acinetobacter baumannii
carbapenem-resistant

Pseudomonas aeruginosa
carbapenem-resistant

Enterobacteriaceae
carbapenem-resistant,
3rd gen. cephalosporin-resistant

HIGH PRIORITY

Enterococcus faecium
vancomycin-resistant

Staphylococcus aureus
vancomycin-resistant
methicillin-resistant

Helicobacter pylori
clarithromycin-resistant

Campylobacter species
fluoroquinolone-resistant

Salmonella species
fluoroquinolone-resistant

Neisseria gonorrhoeae
3rd gen. cephalosporin-resistant,
fluoroquinolone-resistant

MEDIUM PRIORITY

Streptococcus pneumoniae
penicillin-non-susceptible

Haemophilus influenzae
ampicillin-resistant

Shigella species
fluoroquinolone-resistant

Introduction

Aim

The main aims of prioritizing pathogens are to allow for priority setting in research and development, to catalyse public and private funding for research and development, and to accelerate global research and development strategies for the discovery of new antibacterial agents to treat multidrug-resistant tuberculosis (MDR-TB) and other drug-resistant bacterial infections.

Target audience

The target audience includes pharmaceutical companies, universities, public research institutions and public-private partnerships likely to invest in the research and development of new antibacterial agents.

Approach

Prioritization of pathogens for research and development is highly challenging given the absence of established criteria that define the impact of pathogens on human health (1). As a result, no consensus exists on the most effective methodology to develop prioritization of infectious diseases. Ranking antibiotic-resistant organisms in order to direct future research and development requires a detailed identification and integration of extensive information that defines the burden of antimicrobial resistance (microbiological, epidemiological and clinical). Moreover, communicable diseases differ in clinical presentation and duration (e.g. acute versus chronic), treatment approaches (e.g. multidrug versus single drug therapy), and in etiology (e.g. bacterial, viral, fungal).

While in some instances, such as chemical hazards (2), food safety (3) and noncommunicable diseases (4), a number of tools and guidelines have been developed, the diversity of communicable diseases presents major challenges for prioritization of pathogens. As a result, the scope and focus of the work underlying this document were agreed beforehand to allow the deliverables requested by Member States to be achieved within a realistic timeframe. This document therefore addresses prioritization of pathogens responsible for MDR-TB and other drug-resistant bacterial infections. It is acknowledged that similar assessments would be useful for communicable diseases caused by viral and fungal pathogens as well.

The diversity of communicable diseases presents major challenges for prioritization of pathogens. Pathogens were therefore considered separately. Mycobacterium tuberculosis, the etiological agent of TB, differs to a great extent from the other diseases/bacteria considered. In particular, several of the criteria suitable for other bacteria do not apply to MDR-TB, for example duration of illness (TB tends to be more chronic in nature compared with the acute diseases caused by most of the other bacteria), the treatment approach (combinations of medicines are needed for both drug-susceptible and drug-resistant TB while one antibiotic can be used for most other bacteria) and modes of transmission (TB is almost exclusively airborne while transmission of the other bacteria is by food, animal and direct human interactions, such as the hands of health-care workers).

Thus, Section 1 deals with TB separately describing the current situation and the urgent need for new TB treatments and reiterating the priority of TB for research and development as has been articulated by WHO previously.

Sections 2 reports the methodology and results of the multi-criteria decision analysis used to prioritize other antibiotic-resistant bacteria.

Section 1: Tuberculosis

1.1 A top infectious disease killer

Tuberculosis (TB) is one of the top 10 causes of death worldwide (5). Caused by *Mycobacterium tuberculosis* – an obligate pathogenic bacterial species in the family Mycobacteriaceae - and spread exclusively by airborne transmission - TB is the top global infectious disease killer from a single infectious pathogen (Fig. 1). TB caused an estimated 1.8 million deaths in 2015, including 0.4 million deaths associated with HIV co-infection (6).

Fig 1. Top ten causes of death in 2015
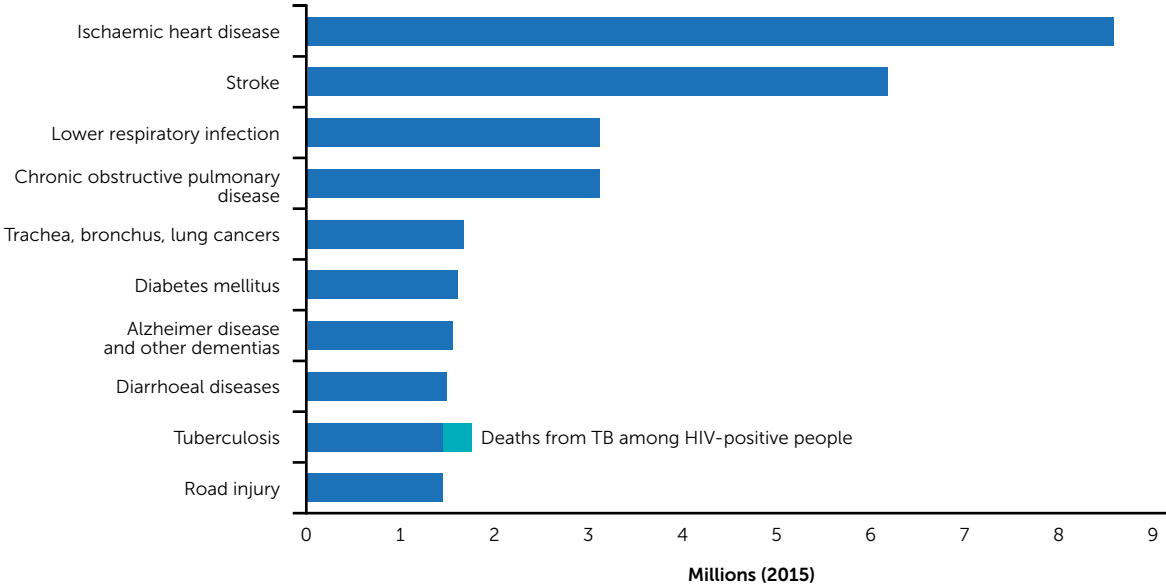
Ending the TB epidemic is one of the targets of the Sustainable Development Goals and requires the implementation of a mix of biomedical, public health and socioeconomic interventions, often beyond the health sector, as well as major breakthroughs in research and innovation.

Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015 (Fig. 2). This needs to accelerate to a 4–5% annual decline by 2020 in order to reach the first milestone of the WHO End TB Strategy (7).

Fig 2. Projected global trajectory of TB incidence rate 2015-2035 required to reach 2035 targets of END TB Strategy
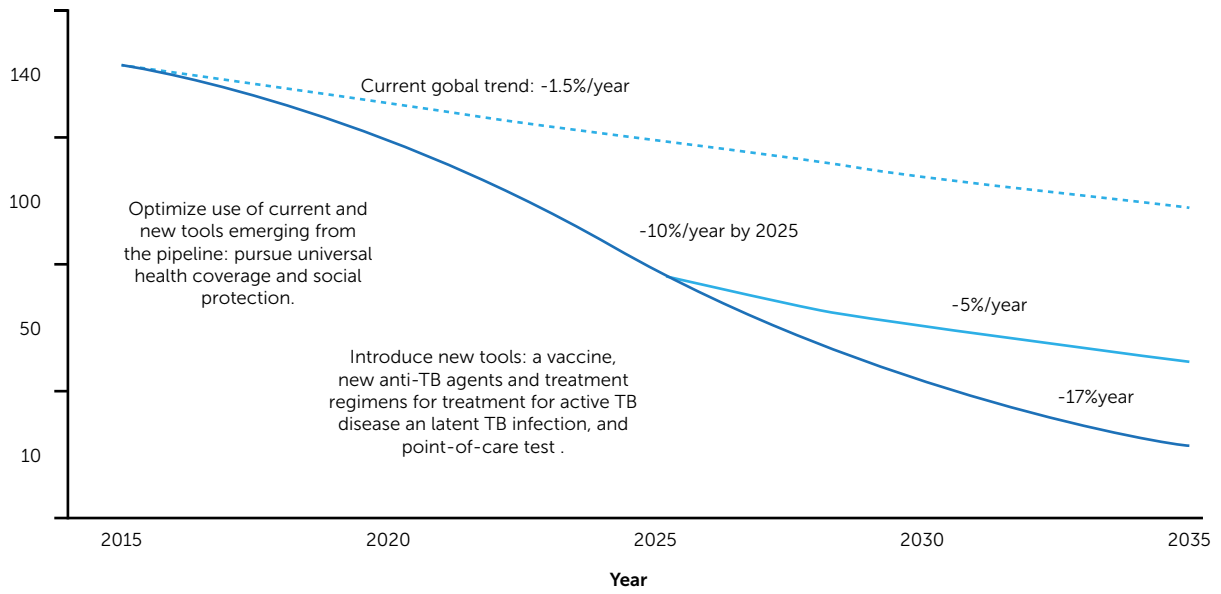
Intensified research and innovation is therefore one of the three pillars of the WHO End TB Strategy, which, together with the other two pillars of patient-centred care and bold policies, are founded on four underlying principles (Fig. 3) (7).

Fig 3. The WHO End TB Strategy: three pillars based on four underlining principles
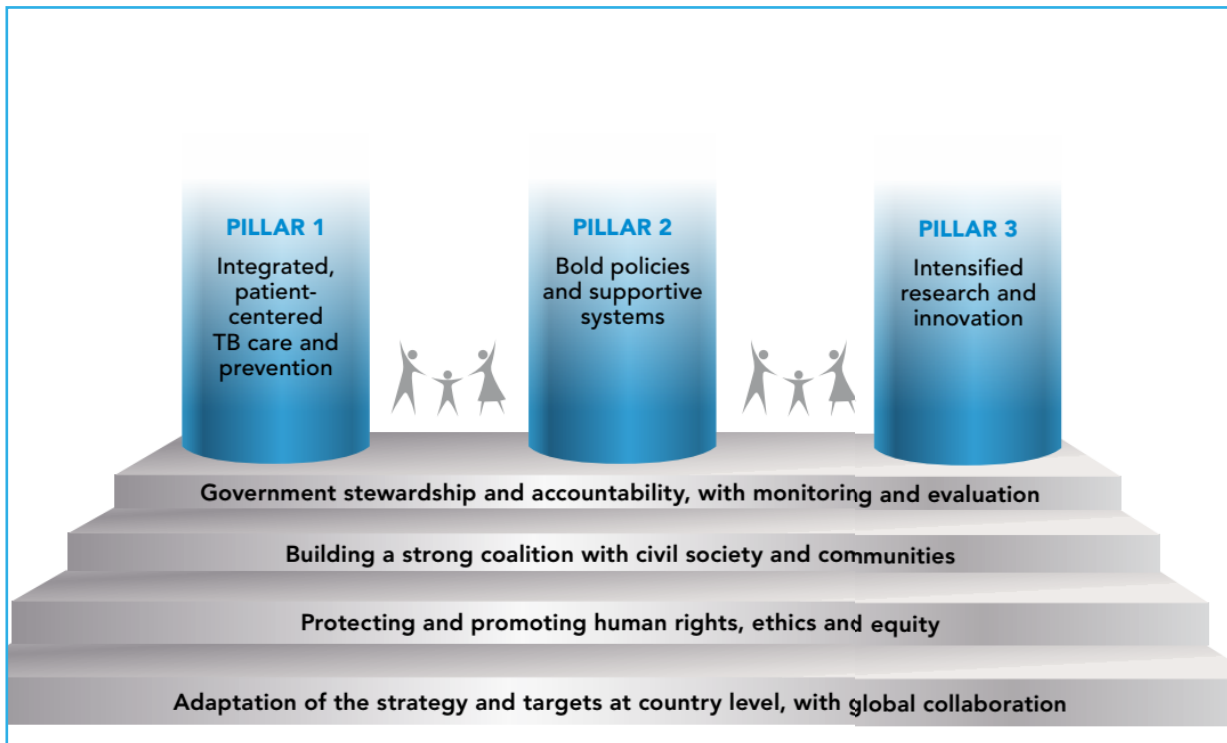
According to the 2016 WHO Global Tuberculosis Report, six countries accounted for 60% of new TB cases globally in 2015: China, India, Indonesia, Nigeria, Pakistan and South Africa (6). G20 nations accounted for 54% of all global cases of TB (5.6 million in 2015) and 46% of deaths (816 000 in 2015). Global progress against TB depends on major advances in TB prevention and care in these countries.

Treatment of TB disease requires multidrug therapy for extended periods. Drug-susceptible TB is treated with a combination of four first-line medicines (rifampicin, isoniazid, pyrazinamide and ethambutol). When rifampicin is compromised by resistance - often associated with concurrent resistance to isoniazid, and defined as multidrug-resistance (MDR[2]) - treatment options become much more complicated.

Patients with rifampicin-resistant TB (RR-TB) or MDR-TB need prolonged treatment (often up to two years) with costly, highly toxic, and much less effective second-line medicines, of which there are only a limited number. Inadequate treatment of MDR-TB and RR-TB (hereafter collectively called "MDR-TB" as treatment for both conditions requires second-line medicines) often leads to increased resistance. Extensively drug-resistant TB (XDR-TB)[3] − occurring when fluoroquinolones and other injectable TB drugs (kanamycin, amikacin, capreomycin) are compromised by resistance − makes further treatment very difficult or even impossible in many patients. WHO declared MDR-TB a global public health emergency in 2014 (8).

1.2 MDR-TB: a global public health crisis and health security threat

The 2016 WHO Global TB Report indicated that there were 580 000 (range: 520 000 - 640 000) new cases of MDR-TB in 2015 (6). Of these, an estimated 250 000 (160 000 - 340 000) patients died in 2015, making MDR-TB the most common and deadly disease caused by antimicrobial resistance worldwide.

Most of the burden of MDR-TB in the world is concentrated in populous countries with a large burden of TB, although several small countries have high MDR-TB incidence rates per population number. Thirty countries account for about 90% of the global disease burden of MDR-TB (Fig. 4) based on data reported to WHO (6).

Fig 4.   Top 30 countries with a high-burden of TB, multidrug-resistant TB (MDR-TB) and HIV-associated TB

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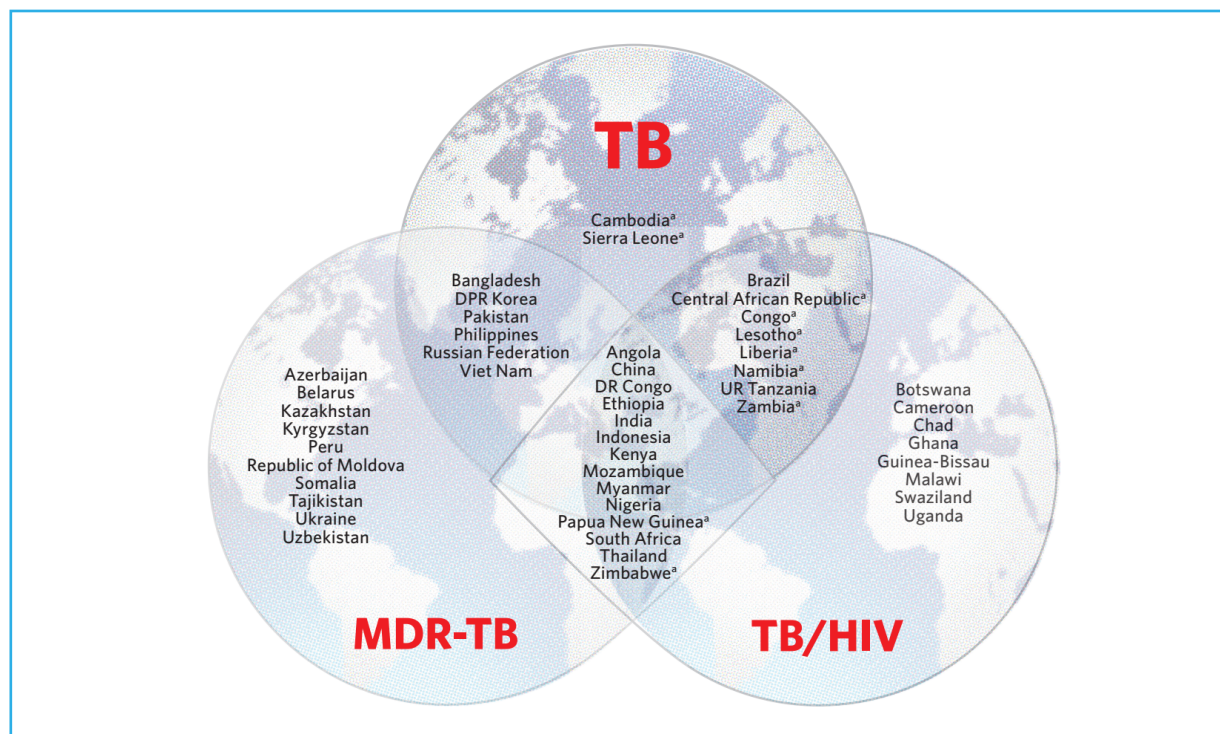
[2]   MDR-TB is defined as resistance to rifampicin and isoniazid.
[3]   XDR-TB defined as MDR plus resistance to fluoroquinolones and injectables (kanamycin, amikacin, capreomycin).

Unlike drug-susceptible TB epidemics, MDR-TB is often an epidemic of more affluent countries. Wide geographical and country variations occur, with China, India, Indonesia, Nigeria, Pakistan and the Russian Federation, together accounting for 60% of the global MDR-TB burden (6). G20 nations have 55% of the total burden of MDR-TB (322 000 estimated cases in 2015). These countries also have most of the deaths and future costs from MDR-TB. As TB predominantly affects people of working age, the human, social and economic impact will continue to be profound. WHO drug resistance surveillance data (since 1994) show that almost no country has escaped the threat of MDR-TB (9). Globally, 3.9% (2.7 - 5.1%) of new and 21% (15 - 28%) of previously treated TB cases had MDR-TB in 2015 (Fig. 5) (6).

Fig 5. Estimated incidence of multidrug-resistant TB in 2015 (for countries with at least 1 000 incident cases)
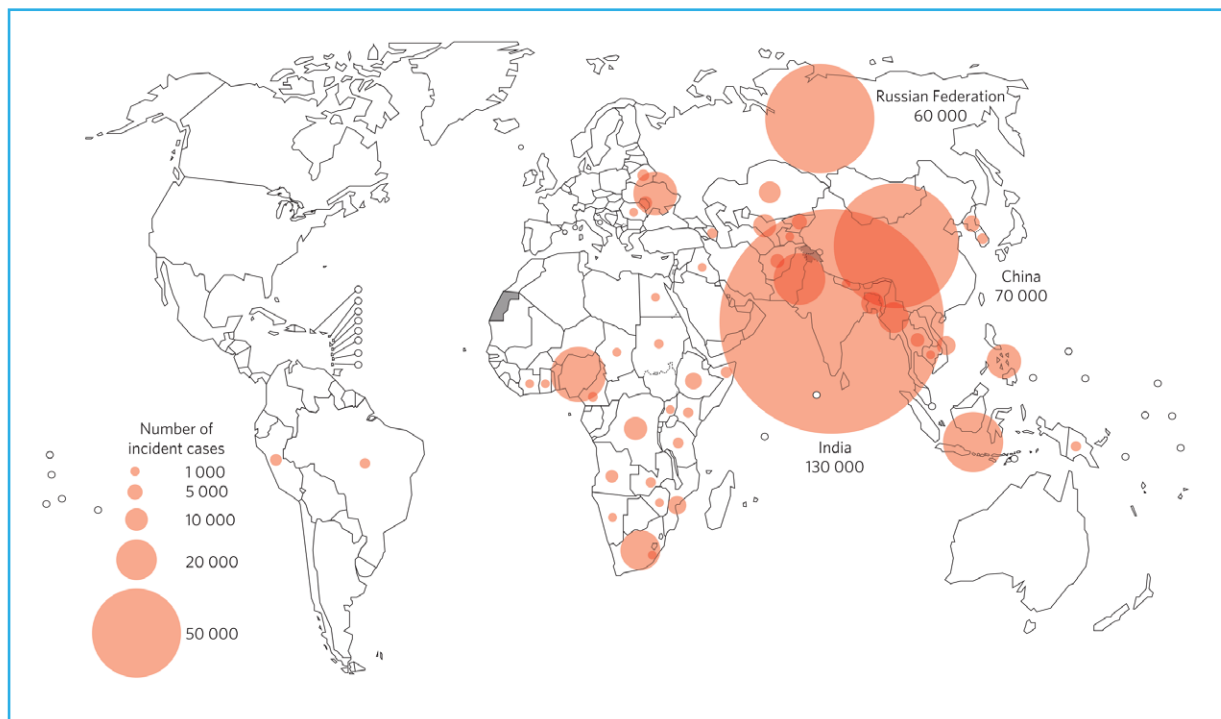
Among countries with representative data for at least three years, the burden of MDR-TB is either increasing faster or decreasing more slowly than the overall TB burden (6).

Only 52% of the MDR-TB patient cohorts reported to WHO in 2015 were successfully treated, while 17% of patients died, 22% were lost to follow up or not evaluated, and treatment failed in 9% of patients (Fig. 6) (6).

Fig 6. Outcomes of treatment of multidrug-resistant TB, annual cohorts by WHO region and globally, 2007-2013

Furthermore, second-line treatment regimens are already compromised – in 2015, over half of the patients with MDR-TB had additional resistance to either a fluoroquinolone or a second-line injectable agent or both (6). Pooled surveillance data show that in 2015, 9.5% (7.0-12.1%) of MDR-TB cases globally had XDR-TB, with data reported from 118 countries. Levels of XDR-TB are much higher than the global average in several countries of Eastern Europe. The numbers of XDR-TB cases

reported were highest in Europe (Russian Federation and Kazakhstan) while nearly all of the cases in Africa were from South Africa.

Among 4 086 XDR-TB patients in 47 countries for whom outcomes were reported to WHO in 2015 (Fig. 7), 28% successfully completed treatment, 27% died, 21% had treatment failure and 24% were lost to follow up or were not evaluated (6).

Fig 7. Treatment outcomes for patients with extensively drug-resistant TB, globally and by WHO region, 2013
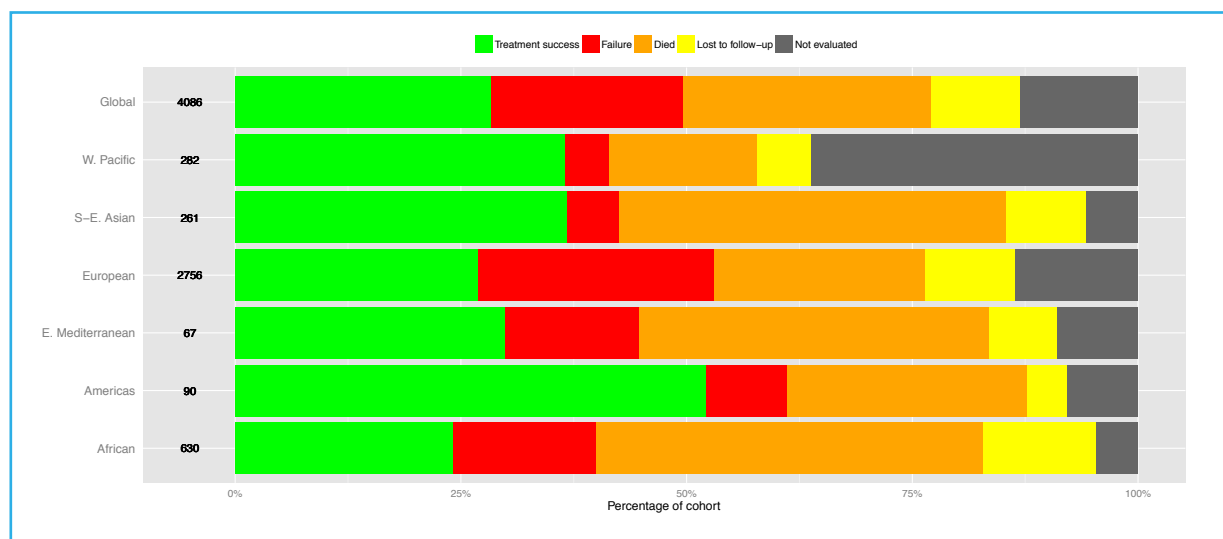
Treatment outcomes for patients with multi and extensively drug-resistant TB (M/XDR-TB) have remained static for many years despite improvements in the coverage of treatment and availability of more effective (later generation fluoroquinolones) or new medicines (bedaquiline and delamanid). Cases with resistance to most (if not all) available anti-TB medications have been reported in several settings over the past 10 years (10-12).

M/XDR-TB threatens years of progress made in global TB control and is a threat to global health security. Transmission occurs almost exclusively by the air to close contacts of M/XDR-TB cases, often in congregate settings and in vulnerable groups, such as those with HIV co-infection, migrants, health-care workers, prisoners and miners, or in children. Contrary to earlier assumptions, acquisition of drug resistance does not lower the transmissibility or virulence of TB strains (13-15).

Explosive outbreaks of M/XDR-TB have been reported in the literature (16-18). Moreover, modelling studies and recent publications from several countries clearly show that transmission is a much more important driver of outbreaks or undetected epidemics than previously thought (17,19,20). Furthermore, the 2016 WHO global TB report showed that over 50% of the estimated global burden of M/XDR-TB now occurs in previously untreated TB patients, reflecting ongoing high levels of community and household transmission. M/XDR-TB outbreaks with high mortality have resulted in public health emergencies in several countries. The risk of MDR-TB replacing drug-susceptible TB epidemics has been flagged in modelling studies and is not implausible (21,22). The persistent lack of effective treatment for latent MDR-TB infection further compounds the problem (23-25).

1.3 Arduous, toxic and limited treatment options

The frequency and severity of adverse drug reactions are much higher in patients on regimens for MDR-TB than in those on treatment for drug-susceptible TB. Several of the second-line medicines used in MDR-TB treatment are old drugs which are often associated with severe or serious harm, at times leading to permanent disabilities such as deafness and chronic neuropathy, depression and suicidal tendencies.

Recommended second-line regimens need to contain at least five medicines - including an injectable drug usually given intramuscularly every day for several months. These medicines have well-known adverse effects and they often need to be stopped temporarily, or even replaced. Some of the most common and troublesome effects are nausea and vomiting, hearing loss (irreversible), peripheral neuropathy, depression, allergic reactions, rashes, visual disturbances, seizures, psychosis, and kidney and liver failure.

Prolongation of the QT interval in patients on new TB medicines (bedaquiline and delamanid) may predispose to serious heart dysrhythmias (26,27). This risk may increase when fluoroquinolones and clofazimine - repurposed drugs commonly used in MDR-TB regimens – are used at the same time. Close monitoring of patients, including special testing (e.g. audiometry, electrocardiography, biochemistry), at regular intervals is therefore necessary to ensure that adverse drug reactions are detected and managed quickly.

Hospitalization of patients with MDR-TB is still the main model of care in many countries despite WHO recommendations for a decentralized approach to treatment. Hospitalization cost is one of the main contributors (together with medicines) to the overall cost per patient treated in countries with a high-burden of MDR-TB. The cost of medicines can range from US$ 2 000 to more than US$ 20 000 per patient depending on the regimen that has to be used based on drug-resistance profiles, compared with US$ 50 to US$ 100 per patient for first-line TB medicines (28).

1.4 Profound human suffering and health service dilemmas

Patients with M/XDR-TB face agonizing, prolonged suffering and often permanent disability while on treatment, as well as devastating economic hardship, stigma and discrimination. Health services are confronted by numerous ethical, legal and human rights challenges, given the ongoing airborne transmission of the bacteria, with explosive outbreaks described in congregate settings such as prisons and health-care facilities.

The adverse drug reactions from medicines used to treat M/XDR-TB greatly increase the suffering of patients and negatively affect their quality of life. They also add substantial costs to the health system because of the need to monitor and manage adverse effects.

The clinical and programmatic management of MDR-TB also raises ethical challenges because of the limited therapeutic options. The lack of sufficient effective medicines frequently induces doctors to adopt practices that, although probably well-intentioned, are often ethically unacceptable. Unethical practices that have been observed in the field include (but are not limited to) involuntary isolation of patients, denial of diagnosis because of limited treatment options, a lack of patient-centred approaches to support delivery of treatment, a lack of informed patient consent, and a lack of support to patients who reach the end of their treatment pathway without any further prospects of cure.

1.5 Critical gaps in investment in research and development

Investment in research to develop new and better interventions for TB (including drug-resistant forms of the disease) is insufficient. Funding for TB research is at its lowest level since 2011, according to the US-based Treatment Action Group (TAG), which tracks research and development funding annually. In 2015, only US$ 620 million was invested in TB research, against the estimated global annual need of at least US$ 2 billion per year (26). Funding during 2005–2014 never exceeded US$ 0.7 billion per year (Fig. 8), which resulted in modest development pipelines, especially for medicines and vaccines (29,30).

Fig 8. TB research funding targets of the Annual Global Plan and actual funding, 2015 (29) (reproduced with permission)
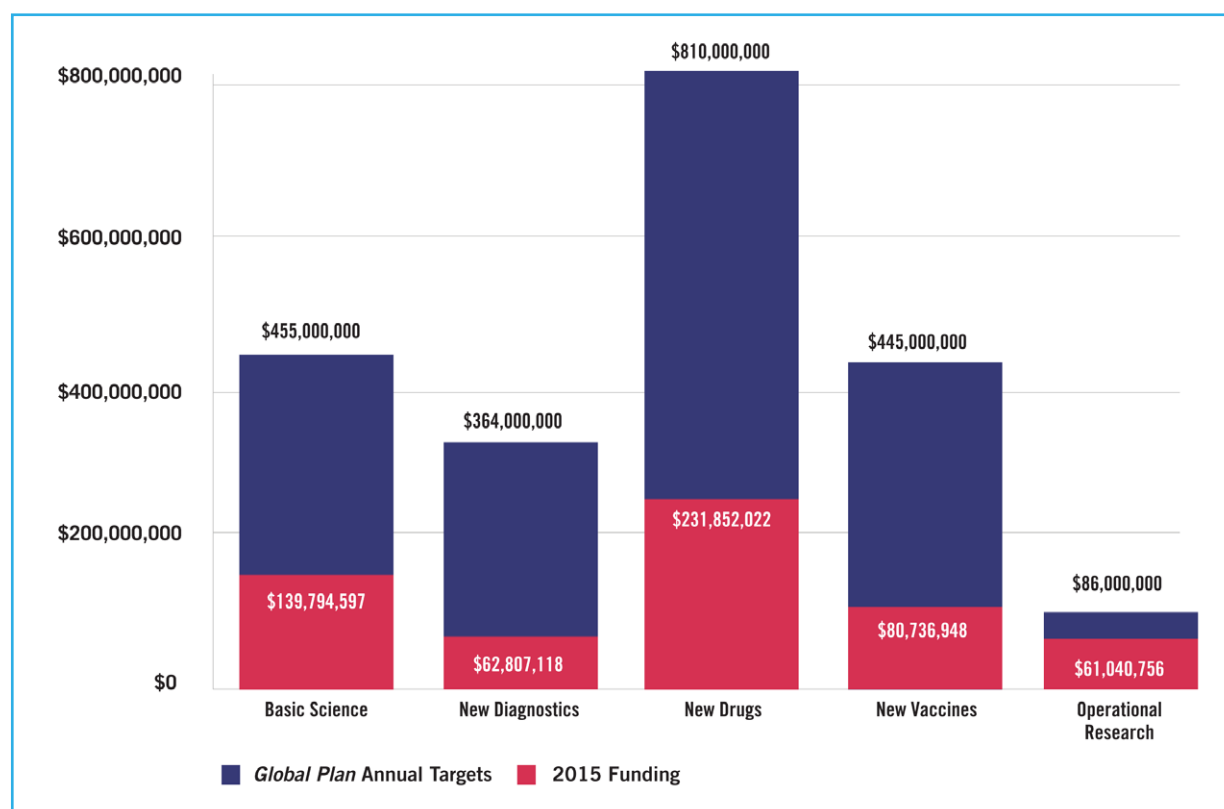
Based on research category, the 2016 TAG report indicated that TB research funders invested as follows:

- Drug research and development: US$ 231.9 million
- Basic science: US$ 139.8 million
- Vaccine research and development: US$ 80.7 million
- Diagnostics: US$ 62.8 million
- Operational research: US$ 61.0 million
- Infrastructure/unspecified: US$ 44.4 million

Every category of research saw a decline in spending compared with 2014, with the exception of operational research, where funding increased by a modest US$ 8.2 million. The drop in funding for drug research and development was the second consecutive year of declining funding, with funding at its lowest level since 2010. Changing the course of the TB epidemic requires major technological breakthroughs – including short and effective treatment for latent TB infection, and completely new, universal, short treatment regimens that would be effective despite the presence of drug

resistance. However, the greatest innovations in TB drug development over the past five years have come from optimizing and repurposing existing drugs rather than discovering and advancing new compounds through the early stages of clinical development (Fig. 9) (6). Research and development for TB – as with other forms of antimicrobial resistance – is hampered by the lack of commercial incentives to develop new medicines. This market failure is compounded by the fact that combinations of drugs are required to treat M/XDR-TB successfully, which further dilutes already weak commercial incentives.

Fig 9. Pipeline of TB drug development (repurposed and new drugs)

Discovery		Preclinical development		Clinical development		
Lead optimization	**Early stage development**	**Good Laboratory Practice toxicity**	**Phase I**	**Phase II**	**Phase III**	
Cyclopeptides	TBI-166	**BTZ-043***	**Q203***	**Sutezolid (PNU-100480)**	**Rifapentine**-**Moxifloxacin** for Drug Sensitive TB	
Diarylquinolines	CPZEN-45*	TBA-7371*	**PBTZ169***	**Linezolid EBA[c]**	**Delamanid (OPC-67683)** with OBR[b] for MDR-TB	
DprE Inhibitors	SQ609*	GSK-070*		**High Dose Rifampicin** for DS-TB	**Pretomanid**-**Moxifloxacin**-Pyrazinamide Regimen (STAND)	
InhA Inhibitor, Ureas	1599*			**Bedaquiline (TMC207)**-**Pretomanid (PA-824)**-Pyolive greenrazinamide Regimen	**Bedaquiline**-**Pretomanid**-**Linezolid** NiX-TB Regimen	
Macrolides, Azaindoles						
Mycobacterial Gyrase Inhibitors				**Levofloxacin** with OBR[b] for MDR-TB	**Bedaquiline**-STREAM MDR-TB Trial Stage 2 with oral OBR[b] (9 mo) or OBR[b] with injectables (6 mo)	
Pyrazinamide Analogs						
Ruthenium(II)Complexes					**Bedaquiline**-**Linezolid** with OBR for MDR-TB (NExT Trial)	
Spectinamides						
Translocase-1 Inhibitors, Clp, Mmp13, **Oxazolidinones**, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides						

Chemical classes: **fluoroquinolone**, **rifamycin**, **oxazolidinone**, **nitroimidazole**, **diarylquinoline**, **benzothiazinone**, **imidazopyridine amide**.
* New chemical class

[a] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php
[b] OBR = Optimized Background Regimen
[c] EBA = Early Bactericidal Activity
Source: Working Group on New TB Drugs, 2016 – www.newtbdrugs.org

At the end of 2015, the pipeline of TB drugs had only five new compounds in the active phase of clinical development. These included bedaquiline and delamanid, the first completely new MDR-TB drugs ever developed (6), which were marketed after accelerated or conditional regulatory approval (based on Phase IIb data). As of May 2017, four additional new compounds have entered the clinical development pipeline (30).

The very modest pipeline for TB drugs is a major concern. In 2010, there were three compounds in phase I trials. In the targets for drug research and development in the 2011–2015 Stop TB Partnership Global Plan, this number was predicted to increase to 21 by 2015, if given full funding (Fig. 10) (29). However, in reality, by January 2016 the pipeline had regressed to only two candidates in phase I trials (31). Although several new regimens are in phase III trials, the 2011 targets for completely new regimens (for drug-susceptible and drug-resistant TB) have also not been reached. Expectations that these new regimens will reach the market before 2025 (32), the first milestone for measuring progress in the WHO End TB Strategy, are tempered.

Fig 10. TB drug R&D progress report. Research targets of the 2011–2015 Stop TB Partnership Global Plan compared with actual products developed by 2015 (29) (reproduced with permission)

2011-2015 Global Plan indicators of success	Target (2015)	Reality (2015)
Number of new and/or re-purposed drugs in phase I trials	21	2
Number of single or combination phase II trials investigating new and/or repurposed drugs	34	17
Number of new regimens for DR-TB in phase III trials	3	8
Number of new regimens for DR-TB in phase III trials	2	5
Duration of treatment of LTBI	2-3 months	3 months

Section 2: Ranking of other drug-resistant bacterial infections

2.1 Background

Antibiotic resistance is a growing threat to public health and to the provision of health care worldwide. Infections caused by antibiotic-resistant pathogens substantially increase the burden of both health-care-associated infections and community-acquired infections (33,34). Several factors can contribute to the emergence and spread of antibiotic resistance worldwide; these include inappropriate antibiotic use and prescriptions in health-care settings and the community, extensive use in agricultural and veterinary sectors, ageing populations, increasing numbers of immunocompromised individuals, growing global travel and migration from countries that have higher levels of antibiotic-resistant pathogens, and an inadequate number of new antibiotics in the development pipeline (35).

Although differences in the distribution of risk factors between countries are evident, gaps in surveillance, and a lack of standards for methodology and data sharing particularly affect the assessment of the antibiotic resistance burden (36). The current knowledge of the burden of antibiotic resistance is based on prevalence data mainly of health-care infections. Incidence data are limited to a few high- and middle-income countries,

are focused on nosocomial infections and are derived through complex estimations. In the United States of America (USA), the National Healthcare Safety Network reported high levels of resistance to several antibiotic classes in both Gram-positive and Gram-negative bacteria responsible for health-care infections between 2011 and 2014. Methicillin resistance was detected in more than 50% of staphylococcal isolates; carbapenem resistance was reported in 45-65% of *Acinetobacter baumannii* isolates and vancomycin resistance among enterococci was higher than 80% in all the surveyed years (37) (Table 1). When compared to the US data, the European Centre for Disease Prevention and Control (ECDC) surveillance network showed overall lower rates of resistance in Gram-positive bacteria (although with large differences between countries), and the same worrying rates among Gram-negative bacteria (38) (Table 1). In 2014, WHO published the results of an extensive effort that aimed to summarize the global prevalence of seven antibiotic-resistant bacteria of international concern (Table 1). Although substantial differences in reporting were noted, very high rates of resistance were observed in both community-acquired and health-care-associated infections in all WHO regions (39).

Table I. Antibiotic-resistant bacteria in the United States of America, Europe and the world

USA 2011–2014: health-care-associated infections (CLABSI, CAUTI, SSI, VAP) (37)
Staphylococcus aureus: >50% methicillin resistance
Enterococcus faecium: 80-85% vancomycin resistance
Klebsiella pneumoniae: 10% carbapenem resistance
Escherichia coli: 16-36% third-generation cephalosporin resistance
Pseudomonas aeruginosa: 25% carbapenem resistance
Acinetobacter baumannii: 45-65% carbapenem resistance, 40-70% multidrug resistance

Europe 2015: invasive isolates (blood and cerebrospinal fluids) (38)
Staphylococcus aureus: 17% methicillin resistance
Enterococcus faecium: 8% vancomycin resistance
Klebsiella pneumoniae: 31% third-generation cephalosporin resistance, 8% carbapenem resistance
Escherichia coli: 12% third-generation cephalosporin resistance
Pseudomonas aeruginosa: 19% carbapenem resistance
Acinetobacter baumannii: 56% carbapenem resistance

Worldwide 2013: all isolates (39)
Staphylococcus aureus: 12-80% (AFR), 4-84% (WPR) methicillin resistance
Escherichia coli: 2-70% (AFR), 16-68% (SEAR), 0-77% (WPR) third-generation cephalosporin resistance
Klebsiella pneumoniae: 8-77% (AFR), 34-81% (SEAR), 1-72% (WPR), 0-54% (EMR) third-generation cephalosporin-resistance
Non-typhoidal Salmonella: 2-49% (EMR) fluoroquinolone-resistance
Neisseria gonorrhoeae: 0-36% (EUR), 0-31% (WPR), 0-31% (AMR) third-generation cephalosporin resistance
Shigella spp.: 3-28% (WPR) fluoroquinolone-resistance
Streptococcus pneumoniae: 57-60% (AFR) penicillin non-susceptible

CLABSI: central line associated bloodstream infection; CAUTI: catheter associated urinary tract infection; SSI: surgical site Infection; VAP: ventilator associated pneumonia.

WHO regions - AFR: Africa Region, EMR: Eastern Mediterranean Region, EUR: European Region, SEAR: South-East Asia Region, WPR: Western Pacific Region.

An accurate definition of mortality associated with antibiotic-resistant infections is difficult to formulate and the absolute number of deaths globally is also difficult to define because of the lack of national data and the difficulty of controlling for confounding factors such as comorbidities, access to and availability of antibiotics, and proper hospital care (40). Among the few incidence data available, the Centers for Disease Control and Prevention (CDC) estimated that in 2013 more than 2 million people in the USA acquired a serious infection from an antibiotic-resistant pathogen and at least 22 000 died from these infections (41) (Fig. 11). Similar yearly figures for cases and deaths were reported from Europe and Thailand in 2007 and 2012 respectively (42,43) (Fig. 11). An estimated 56 500 neonates in India and 19 400 in Nigeria died in 2012 from sepsis caused by bacteria resistant to first-line antibiotics (44) (Fig. 11).

Fig. 11. Number of infections and deaths associated with antibiotic-resistant bacteria in selected countries

USA: Centers for Disease Control and Prevention, 2013 (41)

Population: **300 million**

Bacteria: CR Enterobacteriaceae, DR Neisseria gonhorroeae, MDR Acinetobacter, DR Campylobacter, ESBL Enterobacteriaceae, VRE & MDR Pseudomonas spp., DR non-typhoidal Salmonella, FQR Salmonella Typhi, DR Shigella spp., MRSA & DR Streptococcus pneumoniae, VRSA

No. cases: **20 36100**

No. deaths: **22 618**

Thailand: Thailand Antimicrobial Resistance Containment and Prevention Program, 2012 (43)

Population: **70 million**

Bacteria (nosocomial infections): MDR Escherichia coli, MDR Klebsiella pneumoniae, MDR Acinetobacter baumannii, MDR Pseudomonas aeruginosa, MRSA

No. cases: **87 751**

No. deaths: **38 481**

Europe: European Centre for Disease Prevention and Control, 2007 (42)

Population: **500 million**

Bacteria: MRSA, VRE, Pen-R Streptococcus pneumoniae, 3GCR Escherichia coli, 3GCR Klebsiella pneumoniae, CR Pseudomonas aeruginosa

No. cases: **386 100**

No. deaths: **25 100**

China, Democratic Republic of the Congo, India, Nigeria, Pakistan (44)

Population: **3 billion**

Bacteria: Gram-negative and Gram-positive bacteria resistant to first-line treatment

No. cases: **214 457** (uncertainty range: 139 130-3 318 379) global estimate of neonatal sepsis caused by bacteria resistant to first-line treatment (ampicillin/gentamicin)

No. of neonatal deaths:
China **7 128** (uncertainty range 5 702-8 554)
Dem. Rep. Congo **23 497** (18 798-28 196)
India **121 395** (97 116-145 674)
Nigeria **62 221** (49 777-74 665)
Pakistan **56 337** (45 070-67 604)

CR: carbapenem-resistant; DR: drug-resistant; ESBL: extended-spectrum beta-lactamases; FQR: fluoroquinolone-resistant; MDR: multidrug-resistant; MRSA: methicillin-resistant Staphylococcus aureus; Pen-R: penicillin-resistant; 3GCR: third-generation cephalosporin-resistant; VRE: vancomycin-resistant enterococci, VRSA: vancomycin-resistant Staphylococcus aureus

The impaired effectiveness of antibiotics due to resistance is not only compromising the clinical outcome of infections, but could also affect the efficacy of standard antibiotic prophylaxis. For example, it has been recently estimated that between 39% and 51% of bacteria causing surgical site infections and 27% of those causing infections after chemotherapy are resistant to standard prophylactic antibiotics in the USA. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120 000 additional surgical site infections and infections after chemotherapy per year in the USA and 6 300 infection-related deaths (45).

Estimates of the total number of infections caused by antibiotic-resistant bacteria are usually derived from the proportion of resistant isolates in blood cultures, which is more easily defined and more likely to have a clinical impact, and then generalized to infections at other sites. In the O'Neill report (46), to overcome this problem, the number of resistant strains from other culture sites was calculated by applying a ratio between each one and the estimated national numbers of resistant bloodstream infections. This methodology has several biases and has been criticized (47).

Although the spread of antibiotic-resistant bacteria poses a significant threat to patient health worldwide, pharmaceutical research and development has failed to meet the clinical need for the development of new antibiotics. Indeed, only a few classes of new molecules are currently in development (30,36,39). In the past 20 years, only two new antibiotic classes (lipopeptides and oxazolidinones), both against Gram-positive bacteria, have been developed and approved (48). The last new drug class against Gram-negative bacteria was discovered in 1962.

Currently, of 42 new therapeutic agents in the pipeline for clinical use, only 12 antibiotics show some activity against Gram-negative priority bacteria - Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae - and five of them, all modified agents of known antibiotic classes, have progressed to Phase III testing (30).

The decline in interest in antibiotic research and development in the past few decades is because of difficulties in clinical development and several scientific, regulatory and economic issues. It is very difficult to discover new antibiotic classes that are highly active, have acceptable pharmacokinetic properties and are reasonably safe. Clinical antibiotic trials to evaluate the efficacy of new antibiotics can be difficult and expensive to conduct, especially when targeting multidrug-resistant Gram-negative bacteria, and time-consuming because of the lack of rapid diagnostic tests to facilitate patient recruitment. One of the main challenges of modified agents of old classes of antibiotics is the potential for the rapid development of resistance when widely used, including the risk of co-selecting resistance through the use of other agents.

Stimulating antibacterial drug research and development plays a pivotal role in strategies to address the global threat of antibiotic-resistant bacteria.

Recently, in support of the global action plan on antimicrobial resistance, WHO, in collaboration with the Drugs for Neglected Diseases initiative, launched the Global Antibiotic Research and Development Partnership to develop new antibiotic treatments and promote their responsible use for optimal conservation. The Broad Spectrum Antimicrobial (BSA) and Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) programmes of the US Biomedical Advanced Research and Development Authority, co-sponsored by the Wellcome Trust, and the Innovative Medicine Initiative's New Drugs for Bad Bugs (ND4BB) are new models of collaboration between pharmaceutical companies and academia to promote innovation in the research and development of new antibiotics. In parallel, regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency are working on simplification of the approval pathway for antibiotics for selected unmet medical needs.

2.2 Selection of prioritization methodology

Ranking antibiotic-resistant bacteria to direct future research and development requires a detailed identification and integration of extensive information to define the burden of the hazard (microbiological, epidemiological and clinical). In some settings, such as chemical hazards (2), food safety (3) and noncommunicable diseases (4), several tools and guidelines are available; however, for communicable diseases, the process can be very challenging because established criteria to define the effect of pathogens on human health are lacking (1). No consensus has been reached on the most effective methodology to prioritize infectious diseases.

In 2015 the ECDC made a qualitative assessment of the methodologies used in existing prioritization exercises in communicable diseases (49). Searches were made of biomedical databases (Medline, Embase, Cochrane Library and Centre for Reviews and Dissemination), grey literature (official documents, non-peer-reviewed reports) and specialist databases (Google Advanced search, WHO, World Bank). The references of relevant articles were also checked to find other related publications for inclusion. The criteria for inclusion in the ECDC review were: description of a method of prioritization/ranking; published in a peer-reviewed journal or by a government or a national/supra-national charity, nongovernmental organization or other authoritative institutions; and published in English from January 2000 to December 2014. A total of 17 studies that undertook a ranking of emerging infectious diseases were included, using five different prioritization methods [bibliometric index, Delphi, multi-criteria decision analysis (MCDA), qualitative algorithms and questionnaires]. The ECDC report concluded that, on the basis of current evidence, a single, definitive approach could not be recommended.

In order to select the best methodology to be used in this prioritization exercise, the ECDC systematic review was updated and studies published after January 2015 up to September 2016 were evaluated. Only studies dealing with human infectious diseases and specifying precisely the methodology and criteria for determining priorities were considered.

In total, 80 publications (63 from the new search, 17 from the ECDC publication) were reviewed in detail and eight were included in the final evaluation (1,41,50-55). Four studies used MCDA, two a Delphi method, one a questionnaire-based survey and one based the prioritization on expert opinion but without a scoring system to assess criteria value. The prioritization studies we included aimed mainly to assess national priorities for improving surveillance, raise public/government awareness, or identify areas where further research is most needed. Two studies were conducted at the international level, mainly with the aim of drawing public and political attention to the problem of resistant pathogens or directing new investments (51,52). None of the selected prioritizations studies specifically aimed to identify priorities for the development of new drugs.

Only two of the studies referred specifically to antibiotic-resistant bacteria (41,50) while in the remaining six antimicrobial resistance was considered an emerging issue (1,51-55), but the prioritization of pathogens was assessed for resistant and susceptible strains together (with the exception of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci). Table 2 summarizes the methodologies of previous prioritization exercises in human infectious diseases in the publications selected.

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases

Public Health Agency of Canada (PHAC), 2015 (50)

Study aim	To provide a picture of the magnitude of antimicrobial resistance and the current state of surveillance in Canada.
Methodology	Multi-criteria analysis: pathogen selection for ranking, criteria selection and definition, weighting of criteria, data capture and pathogen scoring, data quality review, sensitivity analysis of the criteria weighting, and expert review.
Criteria selection	10 criteria selected: 7 were developed based on work of PHAC, Robert Koch Institute, and CDC; 3 criteria were based on the CDC Threat Report criteria and cut-off points were modified for the Canadian context.
Criteria scoring	Criteria were scored by one of the five working group members according to national data and available literature. Scoring was on a three-point scale: 0 = nil or low; 1 = moderate; 2 = high. Each score was verified by a second working group member, with discussion when scoring differed. The larger working group came to a consensus decision on remaining issues after the verification stage.

Criteria included	Definition of criteria thresholds for scoring
Incidence	• <100 cases/year • 100-1000 cases/year • >1000 cases/year
Mortality	• <10 deaths/year • 10-100 deaths/year • >100 deaths/year
Case fatality	• <5% • 5-25% • >25%
Communicability (ability of resistant pathogens to spread between people and cause new infections)	• little to no spread between people • can spread readily in health-care settings, but rarely in the community • can spread readily in health-care and community settings
Treatability (effective treatment currently available)	• medical treatment rarely necessary or available treatment successful • 1-2 classes of antimicrobial agents available to treat infections, but therapy is usually successful • no effective antimicrobial agents exist
Public/political attention	• public perception/political awareness low • public perception/political awareness moderate • demands international actions and political attention
Preventability	• no preventive measures • preventive measures exist, but are difficult to implement • spread is easily preventable
Clinical impact of untreated infection (morbidity/attributable mortality)	• mild disease that may require an outpatient visit • rarely life-threatening but can require hospitalization • can cause life-threatening infections

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

European Centre for Disease Prevention and Control (ECDC), 2014 (51)

Study aim	To prioritize, with regard to Europe, the infectious diseases occurring worldwide that represent a risk to public health during mass gatherings.
Methodology	Delphi consensus method and development of a qualitative risk matrix (3 separate teams with different backgrounds, total of 56 ECDC experts).
Criteria selection	Literature review and expert opinion.
Criteria scoring	Infectious diseases were scored on the matrix against two main parameters: likelihood of occurring during a mass gathering and public health impact (1-5 points for each criterion). According to the output of the matrix, pathogens were ranked qualitatively as: highest, high, medium, low and lower risk.

Criteria included for public health impact	Criteria included for likelihood of occurring	Definition of criteria thresholds for scoring
Morbidity	Incidence	
Case fatality rate	Geographical distribution	
Potential for sequelae	Seasonal trend	No further definition of criteria or thresholds for scoring from 1 to 5
Existence of disease-specific treatment	Mode of transmission	
Potential to cause outbreaks	Incubation period	
Potential media interest		

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

Centers for Disease Control and Prevention (CDC), 2013 (41)

Study aim	To prioritize antimicrobial-resistant pathogens according to their need for monitoring and prevention activities in the USA.
Methodology	Expert opinion: antimicrobial-resistant pathogens were ranked by experts into three levels of threat: urgent, serious, concerning.
Criteria selection	Consultation with nongovernmental experts in antibiotic resistance who serve on the Antimicrobial Resistance Working Group of the CDC Office of Infectious Diseases Board of Scientific Counselors, National Institute of Health and Food and Drug Administration.

Criteria included	Definition of criteria / thresholds for scoring	Comments
Mortality (estimate of number of deaths in the USA per year)	Not required (expert opinion)	Number of deaths if the disease is notifiable and/or national tracking available (*Clostridium*. difficile, methicillin-resistant *Staphylococcus aureus*, *Salmonella* spp.). Estimation of deaths or cases attributed to antimicrobial resistance (using % of resistances tested from the national laboratory and number of deaths in hospital due to antimicrobial-susceptible pathogens)
Economic impact (cost attributable to all cases of disease caused by antimicrobial resistance in 1 year)	Not required (expert opinion)	US$/year (national data)
Incidence (estimate of number of cases in the USA per year)	Not required (expert opinion)	Number of diseases if the disease is notifiable/national tracking available. Estimation of number of cases attributed to antimicrobial resistance (using % of resistances tested from national laboratory, and number of in-hospital infections caused by antimicrobial susceptible pathogens)
10-year projection of incidence	Not required (expert opinion)	-
Transmissibility	Not required (expert opinion)	-
Availability of effective antibiotics	Not required (expert opinion)	-
Barriers to prevention	Not required (expert opinion)	-

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

Public Health Agency of Sweden and ECDC, 2015 (52)

Study aim	To prioritize pathogens according to their public health importance in Sweden.
Methodology	A Delphi process with five experts scoring pathogens on 10 variables.
Criteria selection	The same criteria used by the Robert Koch Institute 2011.
Criteria scoring	Same as the Robert Koch Institute 2011.

Criteria included	Definition of criteria thresholds for scoring
Incidence (symptomatic and asymptomatic, no colonization)	• <1/100 000 population • 1-20/100 000 population • >20/100 000 population
Severity (proportion of work/school absenteeism due to infectious diseases)	• negligible • small–moderate • large
Healthcare utilization (primary health care and hospitalization)	• negligible • small–moderate • large
Chronic illnesses or sequelae	• negligible • moderate • large
Case fatality rate	• <0.01% • 0.01-1% • >1%
Proportion of events requiring public health action	• small (<25%) • moderate (25-75%) • large (>75%)
Trend	• diminishing • stable • increasing
Public attention (including political agenda and public perception)	• low • moderate • high
Preventability (need for prevention improvement, including vaccines)	• low • moderate • high
Treatability (treatment possibility and needs)	• rarely necessary or available treatment effective • available but needing improvement • no effective treatment available or treatment severely limited for resistant pathogens

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

Robert Koch Institute, Berlin, 2011 (53)	
Study aim	To develop a rational system for prioritizing infectious diseases in Germany according to their importance for national surveillance and epidemiological research.
Study method	Delphi consensus method including 10 senior external experts and 10 internal experts from the Robert Koch Institute and multi-criteria decision analysis.
Criteria selection	10 modified from a previous prioritization process and reviewed by the panel.
Criteria scoring	Quantitative and qualitative criteria were scored by experts as -1, 0, 1.

Criteria included and definition	Definition of criteria thresholds for scoring
Incidence (illness and symptomatic infection)	• <1/100 000 population • 1-20/100 000 population • >20/100 000 population
Severity (work loss/school absenteeism assessed against the total burden of infectious diseases)	• negligible-small • moderate • large
Health-care utilization (primary health care and hospitalization)	• negligible • small-moderate • large
Chronicity (illness or sequelae)	• negligible • moderate • large
Case fatality rate	• <0.01% • 0.01-1% • >1%
Proportion of events requiring public health action(	• small (<25%) • moderate (25-75%) • large (>75%)
Trend	• diminishing • stable • increasing
Public attention (including political agenda and public perception)	• low • moderate • high
Preventability (prevention possibilities needs, including vaccines)	• few possibilities for prevention, or there is no need • established prevention measures but need to be improved • preventive measure are needed but not effective
Treatability	• treatment is rarely necessary, or effective treatments are available • established treatments but need to be improved • no effective treatment available or treatment severely limited for antimicrobial resistant pathogens

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

Robert Koch Institute, Berlin, 2008 (1)

Study aim	To prioritize infectious diseases to inform resource allocation for research, surveillance and other activities in Germany.
Study method	Expert consensus and multi-criteria decision analysis.
Criteria selection	Selected to represent all relevant areas (epidemiology, clinical burden, etc.)
Criteria scoring	A working group of 11 epidemiologists and infectious disease specialists scored the diseases (-1, 0, +1) according to criteria.

Criteria included	Definition of criteria thresholds for scoring
Incidence (illness and symptomatic infection)	• <1/100 000 • 1-20/100 000 • >20/100 000
Severity	• Hospitalization rare/work loss <2 days, no persisting handicaps • Hospitalization rare/work loss >5 rare, few persisting handicaps • Hospitalization frequent/work loss >5 frequent, persisting handicaps
Mortality	• <50 deaths/year in Germany • 50-500 deaths/year in Germany • >500 deaths/year in Germany
Outbreak potential (probability of outbreaks occurrence)	• rare • outbreaks with >5 cases are rare • outbreaks with >5 cases are frequent
Trend	• diminishing • stable • increasing
Emerging potential	• endemic - unlikely to be introduced to Germany • potential to be introduced to Germany sporadically • likely to emerge in Germany as a public health threat
Evidence for risk factors/groups	• risk factors/groups have been identified based on scientific evidence • risk factors/groups are known but scientific evidence is missing • risk factors/groups are unknown
Validity of epidemiological information	• epidemiological situation well known and scientifically valid • information exists but is not scientifically valid • information insufficient
International action and public attention	• no international action or political agenda, little public attention • no international action but informal political expectations, moderate public attention • international action or explicit political agendas, high public attention

Evidence for pathogenesis	• information on pathogenesis and transmission route is available and well supported by scientific evidence • information is available but not well supported by scientific evidence • information rarely available
Preventability	• few possibilities for prevention, or there is no need • prevention measures are available but there is a need for further research • strong need for further research on preventive measures
Treatability	• medical treatment is rarely necessary, or effective treatments are available to positively affect the burden of the disease or the prognosis • medical treatments are frequently indicated but have a limited effect on the burden of the disease or the prognosis • medical treatment is needed but currently there is no treatment available that positively affects the burden of the disease or the prognosis

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

World Health Organization, 2003 (54)	
Study aim	To prioritize areas for investment in infectious diseases, including antimicrobial resistance and nosocomial infections.
Study method	Modified 1-round Delphi.
Criteria selection	Not specified.
Criteria scoring	24 workshop participants ranked the diseases according to eight criteria on a 1-5 scale. Overall mean score was used for final ranking.

Criteria included	Definition of criteria thresholds for scoring
Disease impact	1-5 according to importance
Present burden of ill health	1-5 according to importance
Potential threat (5–10 years)	1-5 according to importance
Necessity for immediate public health response	1-5 according to importance
Low incidence only maintained by current public health activities	1-5 according to importance
Long-term effects on communicable diseases	1-5 according to importance
Social and economic impact	1-5 according to importance
Opportunity for health gains	1-5 according to importance
Public concern	1-5 according to importance

Table 2. Summary of the methodologies of previous prioritization exercises for human infectious diseases (cont.)

Public Health Laboratory Service United Kingdom, 2001 (55)

Study aim	To assess the relative priority of communicable diseases and identify priority areas for work.
Study method	Survey questionnaire: 1 130 questionnaires were distributed to professionals in communicable diseases control (518 were returned).
Criteria selection	Not specified.
Criteria scoring	Respondents scored each disease against four criteria on a 1-5 scale (low to high importance). A mean score for each criterion was calculated by summing the scores (range 1-5) and dividing by the number of respondents who gave a score (blank entries were disregarded). Diseases were ranked for each criterion based on the mean score.

Criteria included	Definition of criteria thresholds for scoring
Present burden of ill-health	Assessed according to age and sex-related morbidity and mortality and data on quality-adjusted life years
Health, social and economic impact	Assessed by considering the cost of infection to individuals and health-care providers
Opportunity for health gains	Assessed by considering specific activities or areas for further work that could improve the present and future burden of disease
Public concern and confidence	Assessed by considering media and public attention

2.3 Multi-criteria decision analysis: methodology for the prioritization exercise

MCDA was used to prioritize pathogens as it is a systematic approach to integrate information from a range of sources, and a structured method for comparing and ranking alternative decisions. Relevant criteria were identified against which each alternative (the antibiotic-resistant bacterium) was rated according to predefined levels of performance, based on the available evidence (56). In the past decade, MCDA has been increasingly used for decision-making in environmental and health-care-related processes (allocation of limited resources, prioritization of research ideas and management of risk) (57,58).

In order not to influence the output of the process, the selection of the criteria should follow the established MCDA best practice requirements (completeness, non-redundancy, non-overlap and preference independence) (59). In the scoring process, the criteria are rated by the designated participants, who quantify their relative importance based on their expertise. A total score for each option is determined by adding the weights given by the participants to each evidence-based criterion level, which represents both its relative importance and its degree of achievement on a particular performance dimension (59). Therefore, one of the main strengths of MCDA is its ability to incorporate both expert opinion and evidence-based data.

Several methods for scoring and weighting are available, using specially designed software (60). The most traditional approaches of MCDA applied to infectious diseases are based on value models where each criterion is divided into mutually exclusive categories. The simplest way to make such measurements is weighted linear combination, which requires the creation of a scale with identical ranges, capable of incorporating the entire criteria value model. After the weighting process, normalized values of criteria weights are used in order to incorporate the relative importance and to reach final values (1,50). Since traditional scoring requires that the same change in the value score for each criterion corresponds to the same change in the degree of the alternative desirable option, central to most of these methodologies are ratio or interval scale measurements established by decision-makers. This method assumes that all the criteria can be represented on a homogenous and universal value scale. This assumption may not hold when including both quantitative and qualitative criteria, when criteria do not have a linear relationship (i.e. odds ratios) or when there is a lack of homogeneous evidence-based data (such as, in this case, differences in surveillance systems or patient data) (59). Moreover, the weighting process in the more traditional methodologies requires the expression of the relative importance of the criteria through arbitrary ranking or attribution of values that are practically meaningless and difficult to assess.

The methodology selected for our prioritization exercise overcomes both above-mentioned limitations, because it does not require an arbitrarily predefined assumption about the scoring and the weighting process. The ranking in our prioritization is based on pairwise comparison of alternatives (i.e. choosing one alternative from two) and uses the PAPRIKA method (potentially all pairwise rankings of all possible alternatives), supported by an on-line survey software (www.1000minds.com).

In the PAPRIKA method, each survey participant is asked to rank a series of pairs of hypothetical bacteria defined on only two criteria at a time (61). Each time the participant ranks a pair of bacteria, all other hypothetical bacteria that can be ranked pairwise, by transitivity, are identified and removed from the participant's survey. For example, if an expert ranks bacterium A over bacterium B and then ranks B over bacterium C, then logically (by transitivity), A is ranked over C (and so a question on this third pair of pathogens would not be asked). The number of questions and the two criteria in each question are different for each participant, as the questions asked depend on the answer given to the preceding questions (i.e. the software adapts as each question is answered). From each participant's individual ranking, criteria weights for each level are calculated by the software using a mathematical method based on linear programming. Thus, the calculation of criteria weights is based on the preferences expressed in pairwise ranking and not on the arbitrary attribution of relative values to the criteria nor on the assumption of an a priori linear relationship within each criterion or a universal scale expressing all criteria values.

In this specific prioritization exercise, criteria levels were defined a priori, according to the available evidence. However, their numerical values (i.e. the intra-criterion relative importance) were based on the answers of individual participants. Another advantage of this methodology is that pairwise comparison is a natural type of decision that everyone experiences in daily life. Furthermore, differentiating the two hypothetical pathogens in each question based on just two criteria – in contrast to full-profile methods which involve all criteria together at once – greatly reduces the cognitive burden on participants.

Previous research-focused applications of 1000Minds software include prioritization of health technology (62), prioritizing patients for elective surgery in New Zealand (63) and access to health-care services in Canada (64), disease classification for rheumatoid arthritis (65) and systemic sclerosis (66), measuring clinical trial responses for gout patients (67), and testing physical function for hip or knee replacement patients (68). In a previous prioritization by WHO of vaccines research and development, the PAPRIKA method and the more traditional weighted summation model were used together and provided reliable results (69).

The methodology has five steps:

- Expert group selection

- Selection of the antibiotic-resistant bacteria to be prioritized

- Selection of criteria for prioritization

- Data extraction and criteria synthesis into an MCDA model

- Ranking of bacteria using dedicated software (i.e. 1000 minds)

2.3.1 Expert group selection

Experts in infectious diseases, clinical microbiology, epidemiology, public health and pharmaceutical research and development were selected to discuss and validate the steps of the project to reduce the potential uncertainty of the available evidence.

Three groups of experts were selected: a coordinating group, that was involved in all the main steps of the project; a wider advisory group, whose involvement was limited to the survey and review of the results; and a WHO working group with experts directly involved in the survey. All the experts were internationally recognized leaders in antibiotic resistance and had published widely in top-ranked, peer-reviewed journals. All coordinating group members have made major contributions to the antibiotic resistance field, which have influenced health policy-making.

The survey participants were selected through consultation with WHO representatives, the coordinating and advisory groups and the international affairs committee of ESCMID (European Society of Clinical Microbiology and Infectious Diseases). The selection process aimed to achieve a balance of participants from different geographic regions, genders and expertise.

2.3.2 Selection of antibiotic-resistant bacteria to be prioritized

The coordinating group and WHO representatives selected 20 bacteria with 25 patterns of resistance for prioritization based on WHO surveillance reports on antibiotic resistant bacteria of international concern (39), previous prioritization exercises and their knowledge in disease surveillance and burden. Table 3 shows the bacteria included for prioritization and the health burden they represent.

Table 3. Bacteria included for prioritization

Bacteria	Health burden
Acinetobacter baumannii *carbapenem-resistant*	**HIGH HEALTH-CARE BURDEN** • Great capacity to spread within hospital and to colonize environmental surfaces • Leading cause of ventilator-associated pneumonia, and bloodstream and wound infections • Intrinsically resistant to several classes of antibiotics and readily capable of acquiring resistance • High mortality in invasive infections, especially in carbapenem-resistant strain Serious threat for CDC and medium-high priority for PHAC
Campylobacter spp. *fluoroquinolone-resistant*	**MAJOR CAUSE OF ACUTE DIARROHEA** • Foodborne disease • *Campylobacter coli* and *Campylobacter jejuni* are the most important species causing acute diarrhoea in humans • Resistance increasing in both high-income and low-and middle-income countries, particularly in the WHO South-East Asia region • Estimated annual cases: 4.4-9.3/1 000 patients in high-income countries Serious threat for CDC and medium-high priority for PHAC
Enterococcus faecium *vancomycin-resistant*	**FREQUENT CAUSE OF SEVERE INFECTION IN IMMUNOCOMPROMISED POPULATIONS** • High propensity for persistence in the hospital environment • Frequent cause of hospital-acquired infections (bloodstream and urinary tract infections) in patients with underlying conditions • Limited treatment options Serious threat for CDC and medium-high priority for PHAC
Enterobacteriaceae *carbapenem-resistant* *Escherichia coli* *Enterobacter spp.* *Klebsiella spp.*	**HIGH HEALTH-CARE BURDEN** • Global spread of carbapenem resistance, mainly due to the production of carbapenemase enzymes • Increasing rates of resistance reported in most countries • High mortality rates • Very limited treatment options Urgent threat for CDC and high priority for PHAC
Enterobacteriaceae *third-generation cephalosporin-resistant* *Escherichia coli* *Klebsiella spp.* *Enterobacter spp.* *Citrobacter spp.* *Morganella spp.* *Providencia spp.* *Proteus spp.* *Serratia spp.*	**HIGH COMMUNITY AND HEALTH-CARE BURDEN** • Resistance to third-generation cephalosporins is conferred through extended-spectrum beta-lactamase or Amp-C beta-lactamase production (plasmid or chromosomally transmitted) • Community- and hospital-acquired extended-spectrum beta-lactamase-producing Enterobacteriaceae are widespread • Responsible for community-acquired (urinary tract infections) and hospital-acquired (urinary tract and bloodstream infections, ventilator-associated pneumonia) infections • The presence of chromosomally determined AmpC is associated with clinical failure with third-generation cephalosporin therapy despite in vitro susceptibility Serious threat for CDC and high priority for PHAC

Haemophilus influenzae *ampicillin-resistant*	**CAUSE OF SEVERE INFECTION IN PAEDRIATIC POPULATIONS** • Before the routine use of Haemophilus influenzae type b (Hib) conjugate vaccines in infants, invasive Hib was the leading cause of bacterial meningitis in children under five years of age • High morbidity in low-income countries with limited vaccine coverage • Ampicillin resistance is a well-documented globally. Two resistance mechanisms have been described: production of beta lactamases (beta-lactamase-positive ampicillin resistance) and alterations in penicillin binding protein 3, resulting in decreased affinity for beta-lactams (beta-lactamase-negative ampicillin resistance) • The beta-lactamase-negative ampicillin resistance phenotype could lead to clinical failure with empirical antibiotic treatment Not ranked by CDC and low priority tier for PHAC
Helicobacter pylori *clarithromycin-resistant*	**VERY COMMON INFECTION IN ALL-INCOME COUNTRIES ASSOCIATED WITH NON-CARDIA GASTRIC CANCER** • Very common infection in countries of all income levels and affecting both adults and children • Because of the increase of antibiotic resistance, the eradication rate has fallen to inadequate levels: current guidelines do not recommend standard triple therapy if the regional level of clarithromycin resistance is >20% and the eradication rate is <85% • The effectiveness of the remaining treatments for clarithromycin-resistant infection is debated • The treatment options in the paediatric population are limited Not ranked by CDC and medium-low priority for PHAC
Neisseria gonorrhoeae *fluoroquinolone-resistant* *third-generation* *cephalosporin-resistant*	**HIGH COMMUNITY BURDEN** • Common sexually transmitted infection: 78 million cases of gonorrhoea estimated globally in 2012 • Estimated 2012 global incidence of 19/1000 females and 24/1000 males • Incidence is underestimated because of the lack of diagnostic capability in some parts of the world • Resistance reported to all drugs recommended for empirical monotherapy • Current recommended dual empirical treatment (fluoroquinolone-free) does not guarantee clinical efficacy, will not entirely prevent the development of resistance and is used in only a few parts of the world Urgent threat for CDC and medium-high priority for PHAC
Non-typhoidal *Salmonella* *fluoroquinolone-resistant*	**FREQUENT CAUSE OF MORBIDITY AND MORTALITY IN LOW- AND MIDDLE-INCOME COUNTRIES** • Responsible for most of the deaths caused by a bacterial foodborne agent in 2010 (over 59 000) • Estimated global incidence of invasive infections in 2010: 49 cases/100 000 people; burden greatest in Africa: 227 cases/100 000 people, especially in children under five years • Increasing fluoroquinolone resistance detected in many countries Serious threat for CDC and medium-low priority for PHAC
Pseudomonas aeruginosa *carbapenem-resistant*	**HIGH HEALTH-CARE BURDEN** • Primarily opportunistic nosocomial pathogen: one of the commonest causes of pneumonia in immunocompromised patients and those with lung diseases • Carbapenem resistance increases the risk of mortality among patients with bloodstream infections • Very limited treatment options Serious threat for CDC and medium-low priority for PHAC

Salmonella Typhi *fluoroquinolone-resistant*	**FREQUENT CAUSE OF DEATH IN LOW- AND MIDDLE-INCOME COUNTRIES** • Most prevalent in low- and middle-income countries with poor access to sanitation • 17.8 million cases of enteric fever estimated each year in low- and middle-income countries (mainly central Africa and Asia) • 1 488 000 deaths estimated worldwide in 2015 • After the development of resistance to the first-line recommended treatments (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) in the mid-1980s, resistance to cephalosporin and fluoroquinolones has been increasingly reported Serious threat for CDC and low priority for PHAC
Shigella spp. *fluoroquinolone-resistant*	**FREQUENT CAUSE OF MORBIDITY AND MORTALITY IN LOW- AND MIDDLE-INCOME COUNTRIES** • Major cause of morbidity and mortality worldwide, especially in developing countries: 165 million cases estimated to occur annually worldwide • One million estimated deaths • Resistance to traditional first-line medicines (ampicillin, sulfonamides, nalidixic acid) is high globally and resistance to fluoroquinolones is increasingly reported worldwide Serious threat for CDC and low priority for PHAC
Staphylococcus aureus *methicillin-resistant* *vancomycin-resistant[a]*	**MAJOR CAUSE OF MORBIDITY AND MORTALITY WORLDWIDE** • Methicillin-resistant Staphylococcus aureus (MRSA) is a frequent cause of hospital-acquired infections, especially in patients with risk factors or underlying conditions • Methicillin-susceptible Staphylococcus aureus (MSSA) infections are also reported in community settings, especially community-acquired infections, and skin and soft tissue infections; also in individuals with no risk factors • Infections caused by MRSA increase morbidity, mortality, length of hospital stay and costs compared with infections caused by MSSA • Heterogeneous vancomycin-intermediate Staphylococcus aureus and vancomycin-intermediate Staphylococcus aureus, which are associated with poor outcomes, especially in invasive infections, are still rarely reported MRSA: Serious threat for CDC and high priority for PHAC Vancomycin-resistant *Staphylococcus aureus*: Concerning threat for CDC and medium-low priority for PHAC
Streptococcus pneumoniae *penicillin non-susceptible[b]*	**HIGH COMMUNITY BURDEN** • Leading cause of pneumonia in children under 5 years of age • Before widespread pneumococcal vaccination, pneumococcus caused an estimated 826 000 deaths worldwide in 2000 and 541 000 deaths among children under 5 years in 2008 • Low grade penicillin non-susceptibility associated with increased mortality when meningitis is treated with benzylpenicillin • It remains a major public health problem in low- and middle-income countries because of the vaccine cost Serious threat for CDC and medium-low priority for PHAC

CDC: Centers for Diseae Control and Prevention; PHAC: Public Health Agency of Canada.
[a] EUCAST (European Committee on Antimicrobial Susceptibility) breakpoint (minimum inhibitory concentration >2 mg/L);
[b] EUCAST breakpoint (minimum inhibitory concentration >0.06 mg/L).
References: (70-94).

2.3.3 Selection of criteria for prioritization

The selection of criteria definition was based on the research and development focus of the priority list and followed MCDA best-practice (completeness, non-redundancy, non-overlap and preference independence).

The experts also considered it essential to include a global view and One Health approach (www.who.int/features/qa/one-health/en/). Criteria included in previous prioritization were evaluated (Table 4). The final criteria selected for the prioritization exercise are shown in Table 5.

Table 4. Most relevant criteria in previous prioritization exercises

Criterion	Previous priority pathogens lists (PPLs)	Comments
Incidence	Reported in 6/8 PPLs; as number of cases/year in 4/8	Lack of incidence data for most pathogens in the lists
Future trend	Reported in 3/8 PPLs	Based on assumptions on incidence rates over period of times
Potential outbreaks	Reported in 2/8 PPLs as probability of outbreaks occurring	Limited data available
Mortality	Reported in 3/8 PPLs as mortality rate (not specified if attributable or overall mortality) Reported in 4/8 PPLs as case fatality rate Reported in 2/8 PPLs as estimated number of deaths	No global data available to assess incidence of mortality or real number of deaths
Severity	Reported in 3/8 PPLs as work absenteeism or need for hospitalization Reported in 3/8 PPLs as potential for sequelae Reported in 1/8 PPLs as morbidity (clinical impact of untreated infection) Reported in 2/8 PPLs as health-care utilization Reported in 2/8 PPLs as events requiring public health action	No evidence data available. Qualitative review in all PPLs. Difficult to select a measure valid for all the included antibiotic-resistant pathogens because of the heterogeneity of their clinical manifestations
Risk factors	Reported in 1/8 PPL as evidence of risk factors/populations at risk	Emphasizes the importance of the burden in selected populations
Transmissibility	Reported in 2/8 PPLs as ability of the diseases to spread among humans Reported in 2/8 PPLs as level of awareness/knowledge about transmission	Allows inclusion of animal, food and environment sectors to assess the likelihood of transmission between them
Preventability	Reported in 5/8 PPLs as presence or absence of preventive measures	Presence of effective preventive measures can draw attention to the need for public health interventions
Treatment	Reported in 6/8 PPLs as presence or absence of effective available treatment	

Table 5. Criteria selected for the prioritization exercise

Criterion	Definition
Mortality	Pooled prevalence of all-cause mortality in patients with infections caused by antibiotic-resistant bacteria
Health-care burden	Need for hospitalization and increase in length of stay in patients with infections caused by antibiotic-resistant bacteria compared to patients infected by susceptible strains
Community burden	Prevalence of resistance and type of infections in community settings
Transmissibility	Isolation and transmission among three sectors: animal-human, food-human, and human-human in community and hospital settings
Prevalence of resistance	Pooled prevalence of resistance in clinically significant isolates[a], stratified by WHO region
10-year trend of resistance	Linear increase in 10-year prevalence of resistance in clinically significant isolates[a], stratified by WHO region
Preventability in community and health-care setting	Availability and effectiveness of preventive measures in community and health-care settings
Treatability	Availability of effective treatments (number of antibiotic classes, residual activity of antibiotics, and oral and paediatric formulations)
Pipeline	Likelihood of future development (5-7 years) of new antibiotics based on the current drug development pipeline

[a] Clinically significant isolates: isolates from blood and cerebrospinal fluid for bacteria commonly causing invasive infections; other samples were included (i.e. stools for Campylobacter spp. or swabs for Neisseria gonorrhoeae) depending on the most common clinical diseases.

2.3.4 Data extraction and criteria synthesis into the MCDA model

Mortality

Methods

Systematic review

- Inclusion criteria: published studies reporting data on mortality in patients infected with antibiotic-resistant bacteria and including a comparison group (either patient population with infections due to susceptible bacteria or non-infected control population). No restrictions on patient characteristics and study settings

- Exclusion criteria: non-English language publications, studies evaluating colonization, study protocols, diagnostic studies, reviews, non-clinical studies, and abstracts presented at conferences

Main outcome

All-cause mortality: pooled prevalence of mortality (percentage) and 95% confidence intervals in patients with infections caused by antibiotic-resistant bacteria.

Data sources

- PubMed and OvidSP databases

- Databases of the Workpackage 1B of the DRIVE-AB-IMI project (DRIVE-AB, contract number 115618; coordinator S. Harbarth, WP leader: Y. Carmeli).

- Study period: no time restriction, last update in September 2016.

- Search terms (example for Staphylococcus aureus, methicillin-resistant): (mortality[MeSH term] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw]) AND (methicillin resistant[tw] OR methicillin resistance[tw] OR "methicillin resistance"[MeSH term] OR meticillin resistant[tw] OR meticillin resistance[tw] OR MRSA[tw] OR "methicillin-resistant staphylococcus aureus"[MeSH term]) AND ("staphylococcus aureus"[MeSH term] OR Staphylococcus aureus[tw] OR S. aureus[tw]).

Data extraction

The following data were extracted: author, title, journal, country and year of study, study population, study setting, study design, related variables, type of comparison group, number of patients in each arm who completed the follow up, antibiotic-resistant bacterium, type of infection, outcome reported (definition, value, unadjusted and adjusted effect measures, adjusting variables). For each outcome, the values for both the arms and its precision measures (standard deviation, standard error, 95% confidence intervals) and the number of patients who contributed to the measurement were collected for a pooled estimate of the data.

The full text of the eligible articles was carefully read by two reviewers to extract and enter the data into a standardized data sheet. The databases were cross-checked for any discrepancies, and inconsistencies were discussed among the study team and resolved by consensus. All major decisions were documented and differences of opinion within the research team about the extracted variables were resolved by discussion with the senior researcher. Authors of the articles included were contacted about missing data.

Data synthesis into MCDA model

Quantitative variables were reported as mean and standard deviation or median and interquartile range. Qualitative (categorical) variables were reported as relative frequencies. Pooled estimates of the prevalence of all-cause mortality were computed by meta-analysis based on a random effect model with Freeman−Tukey double arcsine transformation for variance stability using the metaprop command of STATA (Statacorp LLC, Texas).

All-cause mortality rate (30-day and in-hospital) with 95% confidence intervals was selected as the best measure for scoring the bacteria against the mortality criterion because of data availability. Four levels were defined for rating antibiotic-resistant pathogens for the mortality criterion.

Criterion	Criterion levels	Level definition
	LOW	<10%
Mortality	MEDIUM	10-20%
	HIGH	21-40%
	VERY HIGH	>40%

Summary of sources of data on mortality

- Number of studies: 292 (105 Americas Region, 104 European Region, 58 Western Pacific Region, 17 South-East Asia Region, 4 Eastern Mediterranean Region, 4 African Region)

- 80% of the studies were carried out in high-income countries

- Number of patients: 21 127

- Infection type (studies): 155 bloodstream infections, 45 pneumonia, 92 other types of infections

- Study setting (studies): 37 intensive care unit, 11 onco-haematology wards, 9 surgical wards, 235 all hospital

- Patient populations (studies): 29 paediatric populations

Pooled data were reviewed in detail and the final scoring was validated through discussion among the coordinating group. No studies were found on mortality in patients infected with antibiotic-resistant strains of *Helicobacter pylori* and *Neisseria gonorrhoeae*. These pathogens were rated in the low level of all-cause mortality, based on available data on susceptible strains and expert opinion.

Figure 12 shows the antibiotic-resistant bacteria with very high and high mortality.

Fig. 12. Antibiotic-resistant bacteria with very high and high mortality
CR: carbapenem-resistant, MR: methicillin-resistant, 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant

Mortality

VERY HIGH

Acinetobacter baumannii, CR
Enterobacter spp., CR
Enterococcus faecium, VR
Klebsiella spp., CR
Pseudomonas aeruginosa, CR

HIGH

Enterobacter spp., 3GCR
Escherichia coli, 3GCR
Escherichia coli, CR
Klebsiella spp., 3GCR
Morganella spp., 3GCR

Proteus spp., 3GCR
Providencia spp., 3GCR
Serratia spp., 3GCR
Staphylococcus aureus, MR
Staphylococcus aureus, VR

Health-care burden

Methods

Systematic review

- Inclusion criteria: published studies reporting data on length of hospital stay in patients infected with antibiotic-resistant bacteria and including a comparison group (either patient population with infections due to susceptible bacteria or non-infected control population). No restrictions for patient characteristics and study setting.

- Exclusion criteria: non-English language publications, studies evaluating colonization, study protocols, diagnostic studies, reviews, non-clinical studies and abstracts presented at conferences

Main outcome

Increase in length of stay in hospital and in the intensive care unit in patients with infections caused by antibiotic-resistant bacteria compared with patients infected with susceptible strains, expressed as weighted mean difference and standard deviation.

Data sources

- Pubmed and OvidSP databases.

- Databases of the Workpackage 1B (WP2) of the DRIVE-AB-IMI project (DRIVE-AB, contract number 115618; coordinator S. Harbarth, WP leader: Y. Carmeli).

- Study period: no time restriction, last update in September 2016.

- Search terms: (length of stay[MeSH term] OR (hospitalization[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] OR duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw]))) AND targeted bacterium/resistance pattern(s).

Data extraction

The following data were extracted: author, title, journal, country and year of study, study population, study setting, study design related variables, type of comparison group, number of patients in each arm who completed the follow up, antibiotic-resistant bacterium, type of infection, outcome reported (definition, value, unadjusted and adjusted effect measures, adjusting variables). For each outcome, the values for both the arms and its precision measures (standard deviation, standard error, 95% confidence intervals) and the number of patients who contributed to the measurement were collected in order to allow a pooled estimate of the data.

The full text of the eligible articles was carefully read by two reviewers to extract and enter the data into a standardized data sheet. The databases were cross-checked for discrepancies, and inconsistencies were discussed among the study team and resolved consensus. All major decisions were documented and differences of opinion within the research team about the extracted variables were resolved by discussion with the senior researcher. Authors were contacted about missing data.

Data synthesis into MCDA model

Quantitative variables were reported as mean and standard deviation or median and interquartile range. Qualitative (categorical) variables were reported as relative frequencies and percentages. Pooled estimates of the weighted mean difference in length of stay were computed through meta-analysis based on a random effect model using the metaprop command of STATA (Statacorp LLC, Texas).

Four levels were defined for rating antibiotic-resistant pathogens for the health-care burden criterion.

Criterion	Criterion levels	Level definition
Health-care burden	LOW	Hospitalization is not usually required
	MEDIUM	Hospitalization is usually required and length of stay is not significantly increased
	HIGH	Hospitalization is usually required and length of stay is significantly increased
	VERY HIGH	Hospitalization is usually required and length of stay in the intensive care unit is significantly increased

Summary of sources of data on health-care burden

- Number of studies: 119 (57 Americas Region, 31 European Region , 23 Western Pacific Region, 7 South-East Asia Region, 1 African Region and 0 Eastern Mediterranean Region)

- 86% of the studies were in high-income countries

- Number of patients: 6 813 cases, 15 862 comparison group

- Infection type (studies): 66 bloodstream infections, 13 pneumonia, 40 other infection types.

- Study setting (studies): 13 intensive care unit , 3 onco-haematology wards, 4 surgical wards; 99 all hospital

- Patient populations (studies): 14 paediatric populations

Length of stay data were available for 16 out of the 25 antibiotic-resistant pathogens, seven also had information on length of stay in the intensive care unit. When data were not available, rating was done based on available data on susceptible strains and expert opinion.

Figure 13 shows the shows the antibiotic-resistant bacteria with very high and high health-care burden.

Fig. 13. Antibiotic-resistant bacteria with very high and high health-care burden
CR: carbapenem-resistant, MR: methicillin-resistant, 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant

Health-care burden

VERY HIGH

Acinetobacter baumannii, CR
Escherichia coli, 3GCR
Klebsiella spp., 3GCR
Staphylococcus aureus, MR

HIGH

Enterococcus faecium, VR, VR
Escherichia coli, CR
Klebsiella spp., CR
Proteus spp., 3GCR

Providencia spp., 3GCR
Pseudomonas aeruginosa, CR
Staphylococcus aureus, VR

Community burden

Methods

Literature review

- Inclusion criteria: published studies reporting data on the incidence and/or prevalence of infections and/or colonization caused by the selected antibiotic-resistant bacteria in community settings

Main outcome

Incidence and/or prevalence of infections and/or colonization caused by antibiotic-resistant bacteria in the community.

Data sources

- PubMed and OvidSP databases

- Study period: 2006 to September 2016

Data extraction

The following data were extracted: author, title, journal, country and year of study, study population, time of data collection, study setting, study design, number of patients/individuals, type of infections, number and type of sampling, antibiotic-resistant bacteria, definition of outcomes.

Data synthesis into MCDA model

A qualitative assessment of the literature was done and three levels were defined for rating antibiotic-resistant pathogens for community burden.

Criterion	Criterion levels	Level definition
Community burden	LOW	Resistance in the community: rarely reported and Type of infection: non-systemic
	MODERATE	Resistance in the community: well reported and Type of infection: non-systemic OR Resistance in the community: rarely reported and Type of infection: non-systemic and systemic
	HIGH	Resistance in the community: well reported and Type of infection: non-systemic and systemic

Well reported: ≥10 studies/surveillance/reports; rarely reported: <10 studies/surveillance/reports.

Summary of sources of data on community burden

- Number of studies: 266

Figure 14 shows the antibiotic-resistant bacteria with a high community burden

Fig. 14. Antibiotic-resistant bacteria with a high community burden
CR: carbapenem-resistant, MR: methicillin-resistant, 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant

Community burden

HIGH

Campylobacter spp., FQR
Escherichia coli, 3GCR
Haemophilus influenzae, Amp-R
Klebsiella spp., 3GCR

Salmonella Typhi, FQR
Staphylococcus aureus, MR
Streptococcus pneumoniae, PNS

Prevalence and 10-year trend of resistance

Methods

Review of surveillance systems and the literature

- Mapping of national and international surveillance systems reporting data on prevalence of resistance (number of resistant isolates/all tested isolates)

- Extraction of prevalence data in dedicated datasets

- Systematic review and meta-analysis of published literature reporting prevalence data for the bacteria not included in any surveillance systems

Main outcome

- Prevalence of resistance in clinically significant isolates

- 10-year trend of resistance (2005-2015)

Data sources

Existing databases: European surveillance systems mapped from the SUSPIRE project (IMI project; COMBACTE Magnet-EPI-Net: COMBACTE-MAGNET (contract number 115737-2; coordinator M. Bonten; WP leader: E. Tacconelli, A. Sifakis). No time and language restriction. Last update: September 2016.

Websites of international stakeholders promoting active surveillance on antibiotic-resistant bacteria: WHO, ECDC, CDC, Centre for Disease Dynamics Control and Policy, and national and international surveillance systems. All were searched across the six WHO regions. When no information was retrieved, representatives of a country's public health authority, infectious diseases/clinical microbiology societies and national agencies collecting epidemiological data were contacted by email.

For countries with no data available or partly available on the above-mentioned sources, national data reported in the WHO Global Report on Surveillance (39) were used.

For the two bacteria not surveyed through the surveillance systems network, data were extracted from the literature.

Helicobacter pylori, clarithromycin-resistant

- A systematic review of the literature was done including the following data sources: PubMed and OvidSP databases.

- Study period: 2005 to September 2016.

- Inclusion criteria: primary studies and systematic reviews, published and reporting data on resistance of *Helicobacter pylori* to the main antibiotics in use (clarithromycin, metronidazole and levofloxacin, amoxicillin, and tetracycline). Studies analysing at least 50 isolates and reporting results at regular time intervals, up to two years, to allow secular trend analyses. Both primary and secondary resistance was considered. No language restriction.

- Search terms: *Helicobacter pylori* resistance, antibiotic, clarithromycin, metronidazole, amoxicillin, levofloxacin, ciprofloxacin, quinolones, and tetracycline. Boolean operators (NOT, AND, OR) were also used to narrow and widen the search.

Staphylococcus aureus, vancomycin-resistant

- Prevalence data were extracted from an already published systematic review and meta-analysis reporting data on prevalence worldwide (95).

Data extraction

The following information was extracted from surveillance data: surveillance systems information and characteristics (period surveyed and country, type of samples, population coverage); type and numbers of laboratories included; number of tested and resistant clinically significant isolates in the study period, when available. To reduce an overestimation of prevalence, especially for bacteria causing frequent colonization, only clinically significant samples relevant to the selected bacterium were considered (blood, cerebrospinal fluid, stools and swabs), when available. Resistance data were extracted according to the breakpoint guidelines followed by each surveillance system.

For the literature search, information was extracted on: author, title, journal, country and year of publication, study population, time of data collection, study setting, study design, number of patients/individuals, sampling, name of the bacterium and pattern(s) of resistance.

Data synthesis into MCDA model

For each bacterium, both prevalence and trend results were grouped by WHO region. The most recent point prevalence value from each country was used for calculating the pooled estimate of prevalence for each WHO region. Only the countries providing prevalence data for at least three time points in the study period were included for the trend analysis.

Pooled prevalence was expressed as percentage of resistance with 95% confidence intervals for each WHO region providing data and computed through a meta-analysis based on a random effects model.

Linear regression was used to assess the 10-year trend of resistance (2005-2016) and the beta coefficient to calculate the yearly change. Both positive and negative coefficients with a *P*-value < 0.05 were considered statistically significant.

Criterion	Criterion levels	Level definition
Prevalence of resistance	LOW	<15% in the majority of WHO regions
	MODERATE	15-30% in the majority of WHO regions
	MODERATE-HIGH	>30% in one WHO region (with the others ≤30%)
	HIGH	> 30% in two WHO regions (with the others ≤ 30%)
	VERY HIGH	> 30% in the majority of WHO regions
10-year trend of resistance	DECREASING	Significant decrease of resistance rate in all WHO regions
	STABLE	Stable resistance rate in all WHO regions
	LOW increase	Significant increase of resistance rate in one WHO region
	MODERATE increase	Significant increase of resistance rate in two WHO regions
	HIGH increase	Significant increase of resistance rate in in the majority of WHO regions

Summary of sources of data on prevalence and 10-year trend of resistance

- 23 surveillance systems were retrieved from the search, providing resistance data for 66 countries worldwide (supplementary Table 1: surveillance systems).

- Prevalence data extracted from the WHO surveillance report on antimicrobial resistance.

- No data were available from surveillance systems for *Helicobacter pylori*, clarithromycin-resistant and *Staphylococcus aureus*, vancomycin-resistant. Prevalence of resistance in these two bacteria was derived from systematic reviews of the literature.

- For the Eastern Mediterranean and Africa regions very few surveillance data were available. The data included for the Eastern Mediterranean Region were obtained from the WHO report on antibiotic resistance (39). For the Africa Region, South Africa and Kenya had active surveillance activities. The Europe and America regions had good coverage by surveillance systems (36 out of 53 and 22 out of 35 countries provided data, respectively).

WHO region	Countries providing prevalence data	Numbers of countries
Africa	Benin, Botswana, Burkina Faso, Burundi, Central Africa Republic, Congo, Ethiopia, Ghana, Guinea, Guinea Bissau, Lesotho, Malawi, Mauritania, Mauritius, Namibia, Swaziland, Uganda, Zambia, Zimbabwe	19
Americas	0	0
Eastern Mediterranean	Bahrain, Iran (Islamic Republic of), Jordan, Morocco, Oman, United Arab Emirates	6
Europe	Albania, Georgia, Moldova (Republic of), Russian Federation[a]	4
South-East Asia	Bhutan, Myanmar, Nepal, Sri Lanka	4
Western Pacific	Brunei, Cambodia, China, Kiribati, Fiji, Lao People´s Democratic Republic; Micronesia, New Caledonia, Papua New Guinea, Samoa, Singapore, Solomon Island, Tonga	13

[a] Except for *Neisseria gonorrhoeae* (data available through the Russian Gonococcal Antimicrobial Surveillance Programme), isolates were collected between 2009 and 2013, depending on the type of bacterium

Transmissibility

Methods

Review of the literature

- Inclusion criteria: studies published between 2007 and December 2016 on humans and animals, reporting data on transmission.

Main outcomes

- Percentage of antibiotic-resistant bacteria isolated in the environment, food and animals (food-producing animals and companion animals)

- Number of reported animal-human transmissions (zoonotic potential or proven zoonosis/ foodborne transmission)

- Number of environment-human transmission (suspected or proven)

- Transmission among humans in community and health-care settings in terms of outbreak capability (attack rate or outcome measure reported by the study's authors).

Data sources

- MEDLINE and OvidSP databases

- Study period: 2006 to December 2016. No language restriction

- The systematic review protocol EpideMiology and control measures of outBreaks due to Antibiotic-Resistant orGanisms in EurOpe (EMBARGO) (unpublished data) was used to obtain the number of nosocomial outbreaks up to December 2014 and the attack rate, when available

Data extraction

The following information was extracted: author, title, journal, country and year of study, study population variables, time of data collection, study setting, study design, number of subjects and sampling, antibiotic-resistant bacteria, type and setting of transmission.

Data synthesis into MCDA model

A qualitative assessment of the literature was done for data synthesis and three levels were defined for rating antibiotic-resistant pathogens.

Criterion	Criterion levels	Level definitions
	LOW	Outbreaks: rarely or not reported/Isolation in HAFE: uncommon/Transmission: not reported
	MODERATE	Outbreaks: commonly reported/Isolation in HAFE: common/Transmission: low zoonotic potential[a]
Transmissibility	HIGH	Outbreaks: commonly reported (high attack rate[b])/Isolation in HAFE: uncommon/Transmission: not reported OR Outbreaks: commonly reported/Isolation in HAFE: common/Transmission: high zoonotic potential[c]

HAFE: humans, animals, food and the environment.

[a] Low zoonotic potential: reports of possible transmissions between animals and humans.

[b] High attack rate: >10% (number of new cases in the population at risk/number of persons at risk in the population).

[c] High zoonotic potential: transmission between animal and humans proven by molecular methods.

Summary of sources of data on transmissibility

- Number of studies: 181

Figure 15 shows the antibiotic-resistant bacteria with high transmissibility

Fig. 15. Antibiotic-resistant bacteria with high transmissibility
CR: carbapenem-resistant, FQR: fluoroquinolone-resistant, MR: methicillin-resistant, 3GCR: third-generation cephalosporin-resistant

Transmissibility
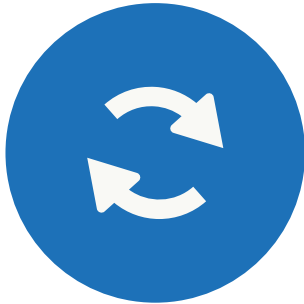
HIGH

Acinetobacter baumannii, CR
Campylobacter spp., FQR
Escherichia coli, 3GCR
Klebsiella spp., 3GCR
Neisseria gonorrhoeae, 3GCR
Neisseria gonorrhoeae, FQR

Pseudomonas aeruginosa, CR
Salmonella Typhi, FQR
Non-typhoidal Salmonella, FQR
Serratia spp., 3GCR
Staphylococcus aureus, MR

Preventability in community and health-care settings

Methods

Review of the literature

- Inclusion criteria: guidelines and guidance documents published in English between 2004 and October 2016.

Main outcome

- Availability and effectiveness of preventive measures aimed at reducing the spread of antibiotic-resistant bacteria in both community and health-care settings.

Data sources

- PubMed, Cochrane Library and Centre for Reviews and Dissemination, specialist databases (Google Advanced search, WHO, World Bank, Tripdatabase) and websites of international stakeholders (including the European Society of Clinical Microbiology and Infectious Diseases, ECDC, WHO, Society for Healthcare Epidemiology of America)

- Study period: 2006 to September 2016

Data extraction

The following information was extracted: author/ society, title, journal, country and year of publication, study setting, population profile/relevant population for the guideline, specific characteristics of the antibiotic-resistant bacterium, setting where the intervention is recommended/carried out (community/hospital), epidemiological situation where the intervention is recommended/carried out (endemic/outbreaks), outcome of the intervention reported (definition, value, unadjusted and adjusted effect measures, adjusting variables), strength of recommendation in the guidelines and level of evidence for the selected recommendation (if reported).

Data synthesis into MCDA model

Data synthesis was done through a qualitative assessment of guidelines and published literature. Two levels were defined for rating antibiotic-resistant pathogens.

Criterion	Criterion levels	Level definitions
Preventability in community and health-care settings	HIGH	Preventive measures available (moderate/high-quality evidence) and effective
	LOW	Preventive measures not well defined (low-quality evidence) or only partly effective

Summary of sources of data on preventability in community and health-care settings

- 34 guidelines on preventive measures to reduce transmission of the selected antibiotic-resistant bacteria (Supplementary Table 2)

- 13 systematic reviews and 22 primary studies (mainly interrupted time series and randomized controlled trials)

- The recommended measures varied widely from infection control measures in hospital and in the community, to recommendations on vaccination or public health interventions

Figure 16 shows the antibiotic-resistant bacteria for which preventive measures are not available or are only partly effective.

Fig. 16. Antibiotic-resistant bacteria for which preventive measures are not available or are only partly effective
CR: carbapenem-resistant, ClaR: clarithromycin-resistant, 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant

Preventability in healthcare and community setting

NOT AVAILABLE OR PARTLY EFFECTIVE

Acinetobacter baumannii, CR	*Enterococcus faecium*, VR
Enterobacteriaceae, 3GCR	*Helicobacter pylori*, ClaR
Enterobacteriaceae, CR	*Pseudomonas aeruginosa*, CR

Treatability

Methods

Review of the literature

- Inclusion criteria: guidelines and literature studies reporting data on available treatment options of infections caused by the selected antibiotic-resistant bacteria.

Main outcomes

- Number of classes of antibiotics recommended as first-line treatment in the most recent guidelines

- Resistance to the first-line antibiotics reported in post-marketing and cohort studies (expressed as percentage of residual activity)

- Availability of oral formulations

- Registration for paediatric use

- Recommendation on combination treatment in the most recent guidelines.

Data sources

Published guidelines and guidance: review of guidelines and guidance documents published between 2005 and November 2016 proposing antibiotic therapy for infections caused by antibiotic-resistant bacteria in both community and health-care settings. The literature search was limited to English language publications on humans. In case of multiple documents from the same group, the most recent update was included. PubMed, Cochrane Library and Centre for Reviews and Dissemination, specialist databases (Google Advanced search, WHO, World Bank, Tripdatabase) and websites of international stakeholders (including the European Society of Clinical Microbiology and Infectious Diseases, ECDC, and the Infectious Diseases Society of America were searched.

Update of published guidelines: review of randomized controlled trials for antibiotics approved after the guideline development or for new indications/combinations of antibiotics already included in guidelines. The literature search was limited to English language publications on humans. MEDLINE and OvidSP databases, clinicaltrial.org, Cochrane Library and Centre for Reviews and Dissemination, specialist databases (Google Advanced search, WHO, World Bank, Trip database) were searched.

When guidelines were not available, systematic reviews and reviews published between 2005 and November 2016 were examined, adopting the same eligibility criteria.

Review of publications reporting data on old antibiotics with potential effectiveness against antibiotic resistant bacteria: List of forgotten antibiotics (96).

Review of case reports reporting data on effectiveness of antibiotic(s) against the antibiotic-resistant bacteria: the same sources as the published guidelines were searched, adopting the same eligibility criteria.

Assessment of antibiotic sensitivity in vitro: Breakpoints and phenotypic in vitro antimicrobial susceptibility testing provided by the Clinical and Laboratory Standard Institute and the European Committee on Antimicrobial Susceptibility.

Review of publications reporting data on resistance: review of cohort, surveillance, prevalence studies published between 2007 and November 2016, reporting resistance rate to the selected antibiotics.

Data extraction

The following information was extracted: author/society, title, journal, country and year of publication, study population, study setting, population profile/relevant population for the guideline, name of antibiotic, route of administration, level of indication and of strength of recommendation according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (97) or similar approaches, when available, treatment registration/indications (for randomized controlled trials), percentage of the antibiotic-resistant bacterium resistant to the current treatments available, availability of oral formulations, registration for the paediatric population.

Data synthesis into MCDA model

Data synthesis was performed through a qualitative assessment of guidelines and published literature. Three levels were defined for rating antibiotic-resistant pathogens.

Criterion	Criterion levels	Level definitions
Treatability	SUFFICIENT	At least 2 classes of antibiotics (first-line therapy) with high residual activity[a] (>80%) and availability of oral and paediatric formulations
	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 and/or paediatric formulations OR Guidelines requiring combination treatment as first-line treatment because of resistance or pathogen-related factors
	ABSENT	One class (first-line therapy) with reduced residual activity (<80%) and/or last resort antibiotics

[a] Residual activity: rate of resistance to a first-line antibiotic detected in surveys or post-marketing-studies.

Summary of sources of data on treatability

- Literature review retrieved a total of 43 guidelines (Supplementary Tables 3 and 4), 38 randomized controlled trials, 43 systematic reviews, 54 reviews, 30 primary studies (including retrospective or prospective studies, case series or case reports).

- A total of 60 studies were also retrieved for evaluation of the residual susceptibility.

- Availability and effectiveness of old antibiotics was based on one specific review on the topic (96).

Figure 17 shows the antibiotic-resistant bacteria for which treatments are not available or are limited.

Fig. 17. Antibiotic-resistant bacteria for which preventive measures are not available or are only partly effective
CR: carbapenem-resistant, ClaR: clarithromycin-resistant, 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant

Treatability

ABSENT

Acinetobacter baumannii, CR
Enterobacteriaceae, CR
Pseudomonas aeruginosa, CR

LIMITED

Campylobacter spp., FQR
Enterobacteriaceae, 3GCR
Neisseria gonorrhoeae, FQR
Neisseria gonorrhoeae, 3GCR

Pipeline

Methods

Review of currently available information on antibiotics in the pipeline (in clinical development and pre-clinical projects).

Main outcome

Likelihood of the development in the future (5-7 years) of new antibiotics potentially targeting the selected antibiotic-resistant bacteria based on the current pipeline

Data sources

Review of scientific and commercial presentations, clinical trial registries, partnering meetings, scientific abstracts, company websites, selected patents, clinical phase analysis and other unrestricted material and information on drugs in the current pipeline.

Data extraction

The following information was extracted on new molecules currently in development: likelihood of inclusion in future registered indication, number of molecules with a potential coverage included in current clinical pipeline and pre-clinical projects, challenges in discovery and development of new molecules for the selected antibiotic-resistant bacteria.

Data synthesis into MCDA model

Data synthesis was done by expert scoring of the following:

- Likelihood of selected antibiotic resistant bacteria to be a future drug target: unlikely (1 point); possibly (2 points); very likely (3 points)

- No. of drugs included in clinical pipeline: no drugs (1 point); at least one drug (2 points); several drugs (3 points)

- No. of pre-clinical projects: no projects (1 point); insufficient number (2 points); sufficient number (3 points)

- Challenges in discovery: very few (3 points); several (2 points); many (1 point)

- Challenges in clinical development: very few (3 points); several (2 points); many (1 point).

Three levels were defined for rating the antibiotic-resistant pathogens.

Criterion	Criterion levels	Level definitions
	LIKELY TO BE INCLUDED	>8 points
Pipeline	WILL POSSIBLY BE INCLUDED	7-8 points
	UNLIKELY TO BE INCLUDED	< 7 points

Figure 18 shows the antibiotic-resistant bacteria for which there are very few antibiotics in the development pipeline.

Fig. 18. Antibiotic-resistant bacteria for which there are very few antibiotics in the development pipeline

There are very few antibiotics in the pipeline for

Acinetobacter baumannii, CR
Campylobacter spp., FQR
Citrobacter spp., 3GCR
Enterobacter spp., 3GCR
Enterobacteriaceae, CR
Helicobacter pylori, CR
Morganella spp., 3GCR
Proteus spp., 3GCR
Providencia spp., 3GCR
Pseudomonas aeruginosa, CR
Salmonella spp, FQR
Serratia spp., 3GCR
Shigella spp., FQR

CR: carbapenem-resistant, FQR: fluoroquinolone-resistant, 3GCR: third-generation cephalosporin-resistant

2.3.5 Summary of the evidence assessment methods: strengths and limitations

A summary of the methodologies for the evidence assessment of the criteria and their strengths and limitations are shown in Table 6.

Table 6. Summary of the methodologies for the evidence assessment of the criteria

Criterion	Methodology	Strengths and limitations
Mortality	Systematic reviews and meta-analyses of studies assessing mortality in patients infected with antibiotic-resistant bacteria compared to patients infected with susceptible strains. No restriction for patient population, infection type and setting	• Allows the rating of antibiotic-resistant pathogens according to the severity of the disease. • Does not take into account the total number of deaths among patients infected by antibiotic-resistant pathogens. • Adjusted analysis could not be done because of the scarcity of information on specific populations for all the pathogens included. • Overall crude mortality was calculated instead of infection-attributable mortality because of lack of data. • 80% of the studies were conducted in high-income countries.
Health-care burden	Systematic reviews and meta-analyses of studies assessing hospitalization and total length of stay in patients infected with antibiotic-resistant bacteria compared to patients infected with susceptible strains. No restriction for patient population, infection type and setting	• Expresses the severity of infections by antibiotic-resistant pathogens, especially for pathogens that may not cause death. • Reflects the excess burden due to antibiotic resistance. • Does not take into account the total number of hospitalizations. • 80% of the studies were conducted in high-income countries. • Does not consider the differences in determinants of hospitalization for different national health plans and economies.
Community burden	Review of cohort and surveillance studies evaluating the prevalence of antibiotic resistance and type of infections in the community. No restriction for patient population	• Summarizes qualitatively the importance of the burden of antimicrobial resistance in the community in terms of frequency of infections and clinical severity. • Data were extracted mainly from observational studies with good representativeness of almost all the WHO regions for most of the pathogens included. • National and international surveillance in the community or high-quality, multicentre studies were only available for a few pathogens.

Transmissibility	Review of studies assessing the isolation and transmission of antibiotic-resistant bacteria between four sectors (humans, animals, food, environment)	• Qualitative assessment of antibiotic resistance in the community, hospital setting, the environment, food and animals based on the One Health approach. • Very limited data for precise assessment of the potential for outbreaks and calculation of the attack rate.
Prevalence of resistance	Data extraction from 23 national and international surveillance systems reporting data on antibiotic-resistant bacteria (last available data reported); and national data from the 2014 WHO report (39)	• Prevalence data were extracted from national and international surveillance systems with good and precise representativeness of the surveyed countries. • Coverage range was wide in some WHO regions (EUR, AMR, WPR), but limited in others (AFR, EMR). • Final values were pooled through meta-analysis, attributing more weight to countries reporting greater sample size. • Only clinically significant samples were considered (i.e. blood and cerebrospinal fluid for pathogens causing severe infections; stools for Campylobacter spp., Shigella spp. and Salmonella spp.; and swabs for Neisseria gonorrhoeae), which provided a more precise assessment of the prevalence of resistance in infected patients, rather than colonized individuals.
10-year trend of resistance	Data extraction from the same dataset searched for prevalence of resistance (reported in the past 10 years)	• Provides a dynamic picture of the threat of emerging resistance. • Both clinical significance and statistical power for the increasing/decreasing trend were considered for each WHO region. • Pooled prevalence allows weighting according to the sample size of the available isolates. • Not all the countries contributing to the prevalence analysis provided enough data to calculate trend (especially in EMR and AFR).
Preventability in community and health-care settings	Review of: 34 national and international guidelines assessing preventability of transmission of antibiotic-resistant bacteria in health-care and community settings; randomized controlled trials; interrupted time series; and large cohort studies assessing effectiveness of preventive measures after last published guidelines	• Qualitative assessment was necessary because of the difficulty in determining actual efficacy and availability of preventive measures. • The quality of the studies was poor and there was great variation in the preventive measures available in different parts of the world. • Availability of preventive measures does not necessarily equate to their universal implementation.

Treatability	Review of: 47 international guidelines for treatment of infections caused by antibiotic-resistant bacteria; antibiotics evaluation forms of the European Committee on Antimicrobial Susceptibility; case reports and cohort studies of last resort antibiotics (past 5 years); list of forgotten antibiotics (96); and post-marketing surveillance data	• Only a qualitative assessment of current treatments available was possible because of the difficulty in defining a single outcome in such diverse infections. • Assessment of guidelines assumed equal availability of each antibiotic worldwide. Adjustment for unequal supply of each antibiotic in the WHO regions was not possible. • Data on residual activity were available mainly from studies on post-marketed drugs and they may not be representative of the global distribution of concomitant resistance to other classes in the selected antibiotic-resistant strains. • No account was taken of side-effects and toxicity of the antibiotics.
Pipeline	Review of: scientific and pharmaceutical company presentations; clinical trial registries; partnering meetings; scientific abstracts; pharmaceutical company websites; selected patents; clinical trial phase analysis (98); and other unrestricted material and information on drugs in the current pipeline. All the variables included were summarized in a pipeline index	• Expert opinion of the current pipeline. • Data on drug development are rarely made publicly available. • The pipeline is continuously and rapidly changing and this evaluation represents only a snapshot of the current pipeline.

AFR: African Region, AMR: Americas Region, EMR: Eastern Mediterranean Region, EUR: European Region, WPR: Western Pacific Region.

2.3.6 Summary of the evidence

The following graphics summarize the prevalence and trend evidence, and other criteria l, for each antibiotic-resistant bacterium. The world map shows five ranges in prevalence of resistance indicated by different colours.

The 10-year trend of resistance is represented by arrows indicating the direction of the trend across different WHO regions. Mortality, health-care and community burden, preventability, transmissibility, pipeline, and treatability are scored according to their criteria levels.

Acinetobacter baumannii, carbapenem-resistant (CR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

| Americas ↗ | Europe ↗ | Eastern Mediterranean — | Africa ↗ | South-East Asia ↗ | Western Pacific ↗ |

Mortality ● ● ● ●	**Transmissibilty** ● ● ● ○
Treatability ● ○ ○	**Preventability** ○ in the community
Healthcare burden ● ● ● ●	**Community burden** ● ○ ○ ○
Pipeline ● ○ ○	**Preventability** ○ in healthcare setting

Campylobacter spp., fluoroquinolone-resistant (FQR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

| Americas ↗ | Europe — | Eastern Mediterranean — | Africa — | South-East Asia — | Western Pacific ↘ |

Mortality ● ○ ○ ○	**Transmissibilty** ● ● ●
Treatability ● ● ○	**Preventability** ● in the community
Healthcare burden ● ○ ○ ○	**Community burden** ● ● ●
Pipeline ● ○ ○	**Preventability** ● in healthcare setting

Enterobacter spp., third generation cephalosporin-resistant (3GCR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

Americas ↗   Europe —   Eastern Mediterranean —   Africa —   South-East Asia ↗   Western Pacific →

Mortality ● ● ● ○

Transmissibilty ● ● ○

Treatability ● ● ○

Preventability ○ in the community

Healthcare burden ● ● ○ ○

Community burden ● ● ● ○

Pipeline ● ○ ○

Preventability ○ in healthcare setting

Enterobacter spp., carbapenem-resistant (CR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↗   Europe —   Eastern Mediterranean —   Africa —   South-East Asia ↗   Western Pacific →

Mortality ● ● ● ●

Transmissibilty ● ○ ○

Treatability ● ○ ○

Preventability ○ in the community

Healthcare burden ● ● ○ ○

Community burden ● ○ ○

Pipeline ● ○ ○

Preventability ○ in healthcare setting

Enterococcus faecium, vancomycin-resistant (VR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↗   Europe ↗   Eastern Mediterranean —   Africa —   South-East Asia ↗   Western Pacific ↗

Mortality ● ● ● ●

Transmissibilty ● ● ○

Treatability ● ● ○

Preventability ○ in the community

Healthcare burden ● ● ● ○

Community burden ● ○ ○

Pipeline ● ○ ○

Preventability ○ in healthcare setting

Escherichia coli, third generation cephalosporin-resistant (3GCR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↗   Europe ↗   Eastern Mediterranean —   Africa ↗   South-East Asia ↗   Western Pacific ↗

Mortality ● ● ● ○

Transmissibilty ● ● ●

Treatability ● ● ○

Preventability ○ in the community

Healthcare burden ● ● ● ●

Community burden ● ● ●

Pipeline ● ● ●

Preventability ○ in healthcare setting
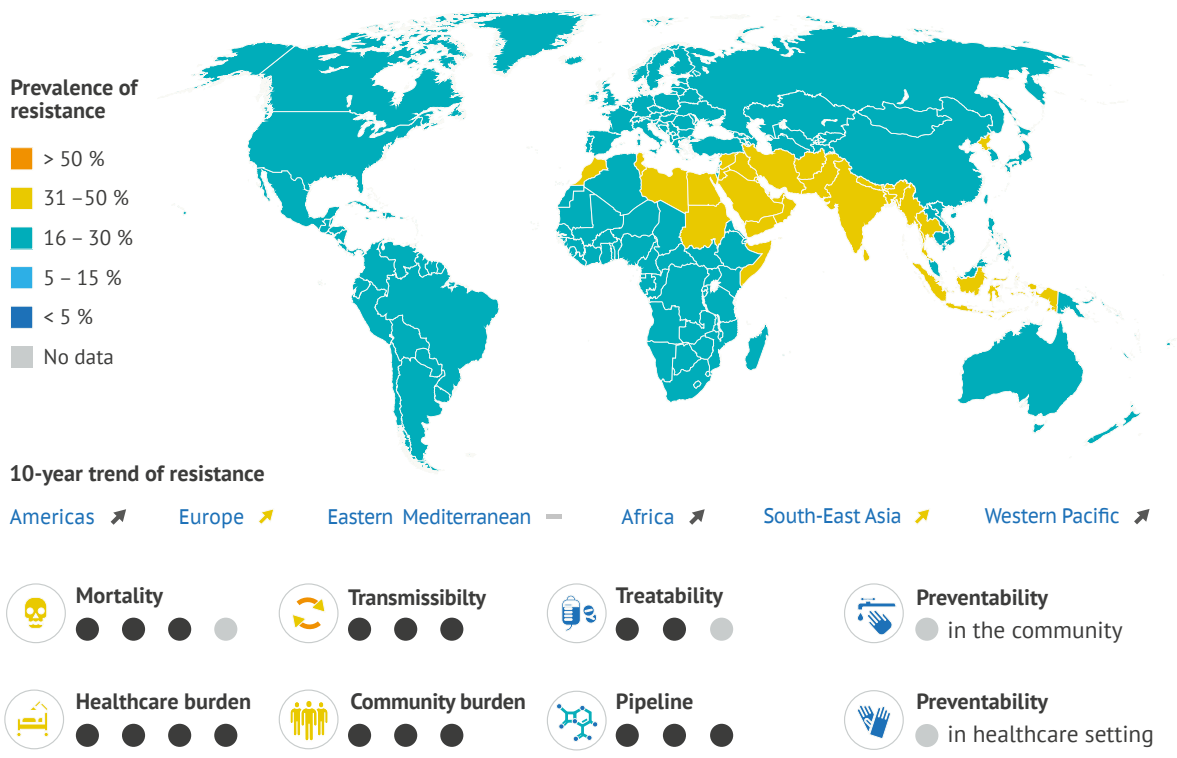
Escherichia coli, carbapenem-resistant (CR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ➡   Europe ➡   Eastern Mediterranean —   Africa —   South-East Asia ↗   Western Pacific ↗

Mortality ●●●○

Transmissibilty ●○○

Treatability ●○○

Preventability ○ in the community

Healthcare burden ●●●○

Community burden ●○○

Pipeline ●○○

Preventability ○ in healthcare setting

Haemophilus influenzae, ampicillin-resistant (AmpR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↗   Europe —   Eastern Mediterranean —   Africa —   South-East Asia —   Western Pacific ↗

Mortality ●●○○

Transmissibilty ●○○

Treatability ●●●

Preventability ● in the community

Healthcare burden ●●○○

Community burden ●●●

Pipeline ●●●

Preventability ● in healthcare setting

Helicobacter pylori, clarithromycin-resistant (ClaR)

Prevalence of resistance

- 🟧 > 50 %
- 🟨 31 – 50 %
- 🟦 16 – 30 %
- 🟦 5 – 15 %
- 🟦 < 5 %
- ⬜ No data

10-year trend of resistance

Americas ↘   Europe ↘   Eastern Mediterranean ↗   Africa ↘   South-East Asia ↗   Western Pacific ↗

| Mortality | ● ○ ○ ○ | Transmissibilty | ● ○ ○ | Treatability | ● ● ○ | Preventability ○ in the community |
| Healthcare burden | ● ○ ○ ○ | Community burden | ● ● ○ | Pipeline | ● ○ ○ | Preventability ○ in healthcare setting |

Klebsiella spp., third generation cephalosporin-resistant (3GCR)

Prevalence of resistance

- 🟧 > 50 %
- 🟨 31 – 50 %
- 🟦 16 – 30 %
- 🟦 5 – 15 %
- 🟦 < 5 %
- ⬜ No data

10-year trend of resistance

Americas ↘   Europe ↗   Eastern Mediterranean —   Africa ↗   South-East Asia ↗   Western Pacific ↗

| Mortality | ● ● ● ○ | Transmissibilty | ● ● ○ | Treatability | ● ● ○ | Preventability ○ in the community |
| Healthcare burden | ● ● ● ● | Community burden | ● ● ● | Pipeline | ● ● ● | Preventability ○ in healthcare setting |

Klebsiella spp., carbapenem-resistant (CR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

| Americas ↗ | Europe ↗ | Eastern Mediterranean — | Africa ↗ | South-East Asia ↗ | Western Pacific ↗ |

Mortality ● ● ● ●

Transmissibilty ● ● ○

Treatability ● ○ ○

Preventability ○ in the community

Healthcare burden ● ● ● ○

Community burden ● ○ ○

Pipeline ● ○ ○

Preventability ○ in healthcare setting

Neisseria gonorrhoeae, third generation cephalosporin-resistant (3GCR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

| Americas ↗ | Europe ↘ | Eastern Mediterranean — | Africa — | South-East Asia — | Western Pacific ↗ |

Mortality ● ○ ○ ○

Transmissibilty ● ● ●

Treatability ● ● ○

Preventability ● in the community

Healthcare burden ● ○ ○ ○

Community burden ● ● ○

Pipeline ● ● ●

Preventability ● in healthcare setting

Non-typhoidal Salmonella, fluoroquinolone-resistant (FQR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

| Americas ↗ | Europe ↗ | Eastern Mediterranean — | Africa ↗ | South-East Asia ↗ | Western Pacific ↗ |

Mortality ● ● ○ ○

Transmissibilty ● ● ●

Treatability ● ● ●

Preventability ● in the community

Healthcare burden ● ● ○ ○

Community burden ● ● ○

Pipeline ● ○ ○

Preventability ● in healthcare setting

Pseudomonas aeruginosa, carbapenem-resistant (CR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

| Americas ↗ | Europe ↗ | Eastern Mediterranean — | Africa — | South-East Asia ↗ | Western Pacific ↗ |

Mortality ● ● ● ●

Transmissibilty ● ● ●

Treatability ● ○ ○

Preventability ○ in the community

Healthcare burden ● ● ● ○

Community burden ● ● ○

Pipeline ● ○ ○

Preventability ○ in healthcare setting

Salmonella Typhi, fluoroquinolone-resistant (FQR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↗   Europe —   Eastern Mediterranean —   Africa —   South-East Asia ↗   Western Pacific ↗

Mortality ● ● ○ ○

Transmissibilty ● ● ●

Treatability ● ● ●

Preventability ● in the community

Healthcare burden ● ● ● ○

Community burden ● ● ●

Pipeline ● ○ ○

Preventability ● in healthcare setting

Shigella spp., fluoroquinolone-resistant (FQR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↗   Europe —   Eastern Mediterranean —   Africa →   South-East Asia —   Western Pacific —

Mortality ● ○ ○ ○

Transmissibilty ● ● ●

Treatability ● ● ●

Preventability ● in the community

Healthcare burden ● ● ○

Community burden ● ● ○

Pipeline ● ○ ○

Preventability ● in healthcare setting

Staphylococcus aureus, methicillin-resistant (MR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ↘   Europe ↘   Eastern Mediterranean —   Africa ↘   South-East Asia ↗   Western Pacific ↗

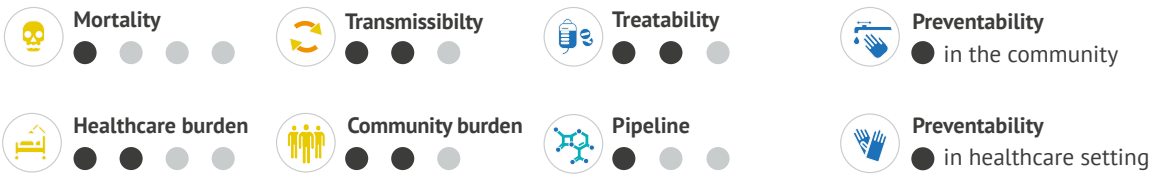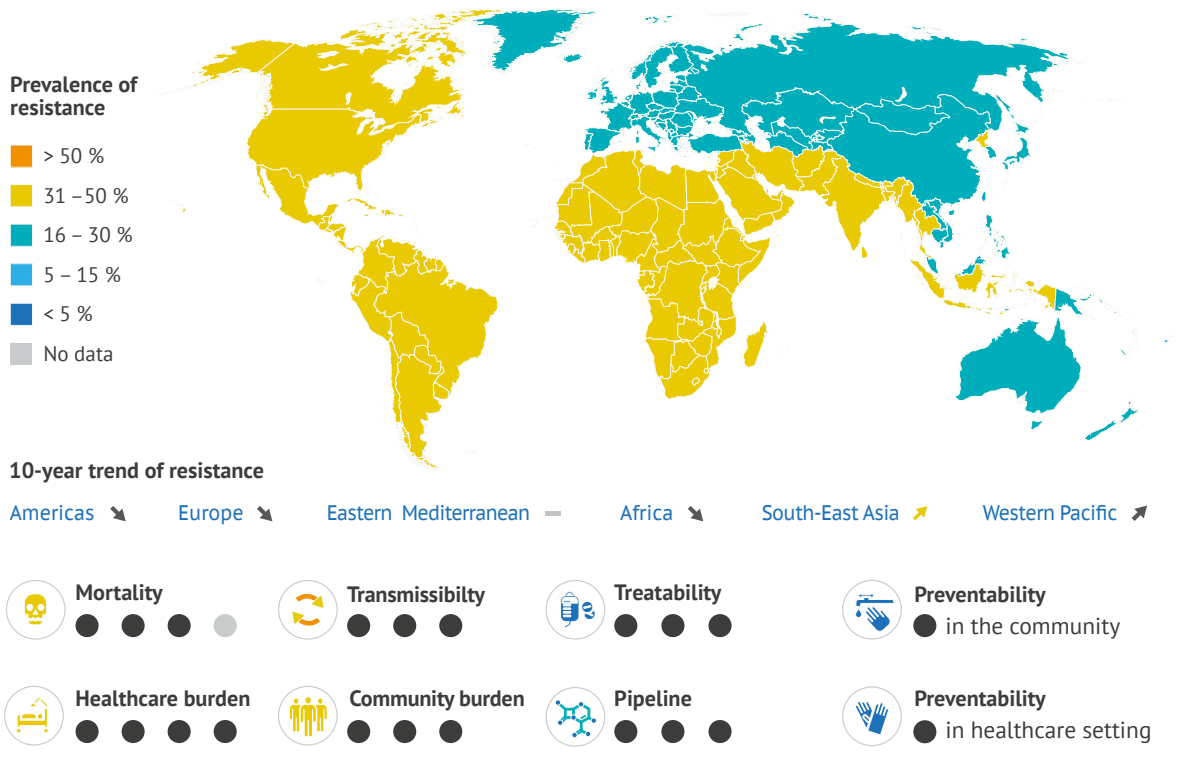|	
Mortality ● ● ● ○	**Transmissibilty** ● ● ●
Treatability ● ● ●	**Preventability** ● in the community
Healthcare burden ● ● ● ●	**Community burden** ● ● ●
Pipeline ● ● ●	**Preventability** ● in healthcare setting

Staphylococcus aureus, vancomycin-resistant (VR)

Prevalence of resistance

- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas —   Europe —   Eastern Mediterranean —   Africa —   South-East Asia —   Western Pacific —

Mortality ● ● ● ○	**Transmissibilty** ● ● ○
Treatability ● ● ●	**Preventability** ● in the community
Healthcare burden ● ● ● ○	**Community burden** ● ● ○
Pipeline ● ● ○	**Preventability** ● in healthcare setting

Streptococcus pneumoniae, penicillin-non-susceptible (PNS)

Prevalence of resistance
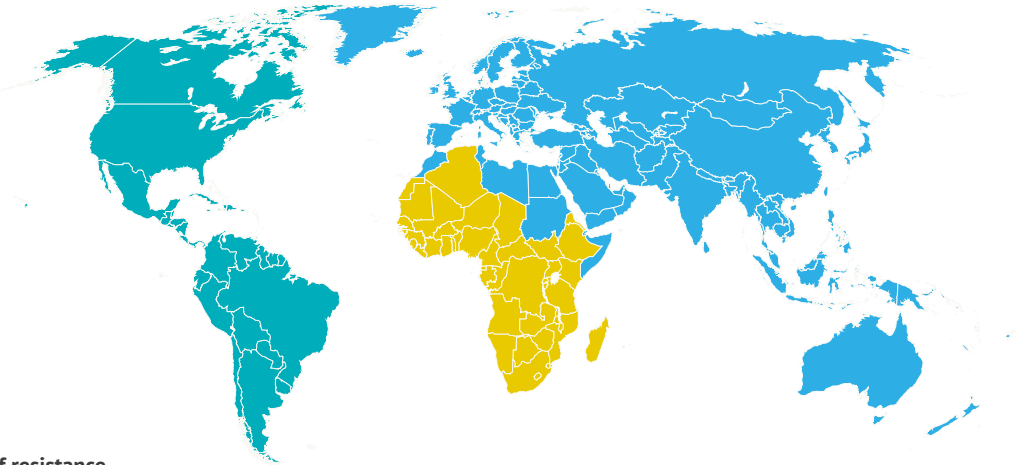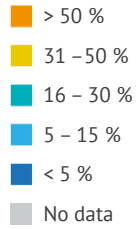
- > 50 %
- 31 – 50 %
- 16 – 30 %
- 5 – 15 %
- < 5 %
- No data

10-year trend of resistance

Americas ⬊   Europe ⬈   Eastern Mediterranean —   Africa —   South-East Asia —   Western Pacific ⬊

💀 **Mortality** ● ● ○ ○

🔄 **Transmissibilty** ● ● ○

🧪 **Treatability** ● ● ●

🚰 **Preventability** ● in the community

🛏 **Healthcare burden** ● ● ○ ○
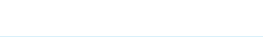
👥 **Community burden** ● ● ●

⚗ **Pipeline** ● ● ●

🧤 **Preventability** ● in healthcare setting

2.3.7 Ranking

After rating the pathogens into the evidence-based priority matrix and following MCDA methodology, criteria weighting was assessed by expert opinion of the relative importance of the selected criteria. In this prioritization exercise, many international experts completed a preference-based survey based on the PAPRIKA method and supported by 1000 minds software (www.1000minds.com/). Details of the methodology are provided in Section 3.2.

The survey-software elicits the participants´ preferences between two options, defined on two criteria at the time. For the purpose of this specific prioritization exercise, each expert was iteratively asked which one of two hypothetical bacteria was more antibiotic-resistant and should be targeted first for future research and development of new antibiotics. To check internal consistency, the experts were presented with three pairs of identical questions in random order during the survey.

The number of questions and time taken to answer each question were recorded by the software and reported as medians and interquartile range. From each participant´s individual ranking, criteria weights for each level were calculated by the software. Each bacterium's total score – calculated by summing their weights for the different criteria – was established on a scale of 0 to 100%, where 100% corresponds to a hypothetical bacterium reaching the worst levels on all the criteria and 0% to reaching the best levels on all the criteria. Mean values and relative standard deviations of the bacteria's total scores were calculated. The final priority list was based on the mean total score for each antibiotic-resistant bacterium.

Ranking stability assessment

The ordinal association between the participant´s final ranking was assessed by the Kendall rank correlation coefficient.

The final weights and rankings of the criteria were stratified according to the participants' scientific expertise (infectious diseases, clinical microbiology, epidemiology, public health and pharmaceutical research and development) and geographical origin (WHO region) in order to assess variations in the relative importance of the criteria and the bacteria ranking because of differences in background. Significant changes in criteria mean weights ($P < 0•05$) were assessed by one-way ANOVA and the Kruskal-Wallis rank test for normally and non-normally distributed variables, respectively. The final ranking was calculated for the whole panel of experts and grouped according to WHO region.

A sensitivity analysis was done after excluding the responses of the experts who gave a different answer in more than one repeated question. The hypothesis that the final ranking could have been influenced by the unbalanced geographic distribution of the experts was assessed by re-running the prioritization and attributing the same weights to each WHO region.

2.4 Survey results

The survey began on 19 December 2016 and ran for 26 days. Of the 74 experts who agreed to participate, 70 completed the survey; four who gave incomplete responses were excluded from the final analysis. Each expert answered a median of 62 questions (interquartile range: 44-84). The majority of the experts answered the three repeated questions consistently (93% answered at least one of the three repeated questions consistently, 71% answered two consistently and 28% answered all three consistently).

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 (Fig. 19).

Fig 19. Criteria value functions computed by the survey software
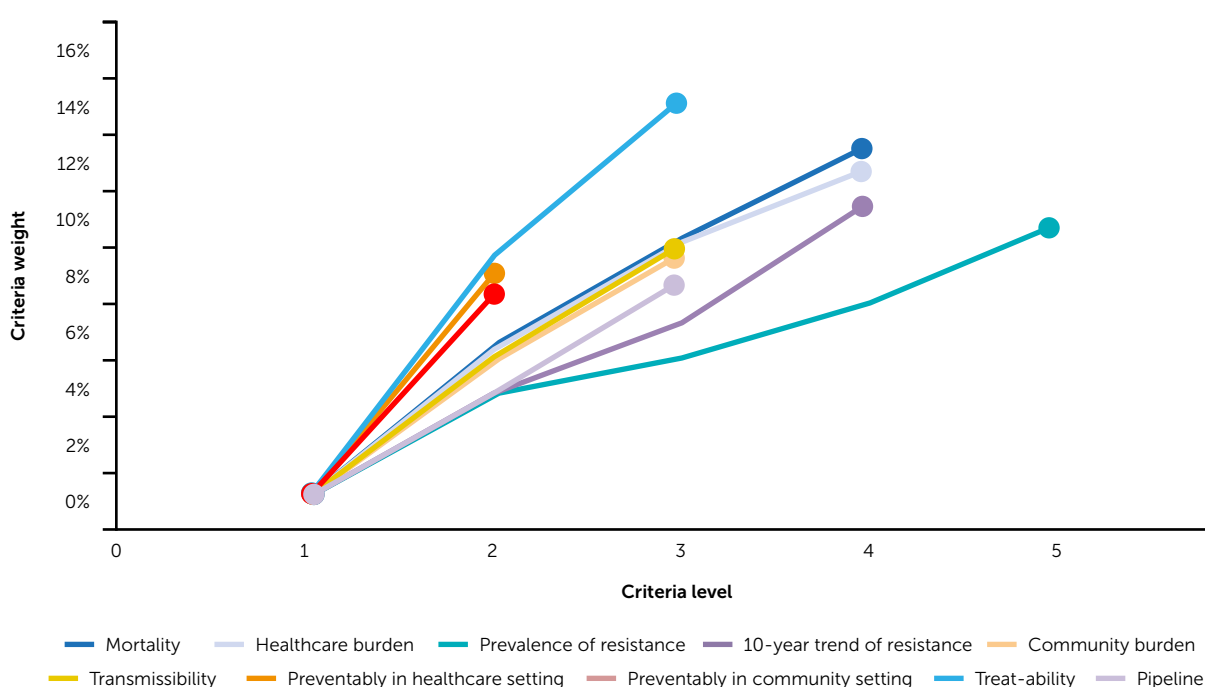
Each criterion is represented by a linear function, reflecting how much a shift towards a higher level determines an increase in the total attributed weight. For some criteria the function is almost linear (each shift of level has the same effect on the total weight), for some other criteria, shifts in the lower levels are weighted more than shifts in the highest levels. The weight attributed to the highest level corresponds to the total criterion weight. The criteria weights sum to 100%. Five criteria – 10-year trend of resistance, community burden, transmissibility, treatability and pipeline – showed a linear increase in the weight by level, meaning that the shift from each level to the next was considered by the experts to be of equal importance. Three criteria – 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. For example, the shift from low to medium health-care burden gave an increase of 5.4% in the weight, while a shift from high to very high gave a 2.8% increase in weight. For the prevalence of resistance, a shift from the first to the second level (from prevalence <15% in all WHO regions to 15-30% in all the WHO regions) gave an increase of 3.8% in the weight, whereas a shift from the third to the fourth level (>30% in one WHO region and >30% in two WHO regions) gave an increase of just 1.7%.The final ranking of the 25 antibiotic-resistant bacteria was computed by averaging each bacterium's total score for all the survey participants. These mean (standard deviation) scores ranged from 91.0%

(5.2%) for the top-ranked bacterium (*Acinetobacter baumannii,* carbapenem-resistant) to 22.1% (6.7%) for the bottom-ranked one (*Staphylococcus aureus,* vancomycin-resistant). Antibiotic-resistant Gram-negative bacteria were rated at the highest level on the four most heavily weighted criteria. The highest ranked Gram-positive bacteria were vancomycin-resistant Enterococcus faecium [54.5% (7.2%)] and methicillin-resistant *Staphylococcus aureus* [52.7% (11.2%)]. Among bacteria typically responsible for community-acquired infections, the highest ranked were clarithromycin-resistant *Helicobacter pylori* [44.8% (10.1%)], fluoroquinolone-resistant *Campylobacter* spp. [41.0% (7.8%)], fluoroquinolone-resistant *Neisseria gonorrhoeae* [35.8% (8.9%)] and fluoroquinolone-resistant *Salmonella* Typhi [37.6% (9•2%)] (Fig. 20).

Fig 20. Final ranking of other antibiotic-resistant bacteria (mean weight and standard deviation)

AmpR: ampicillin-resistant, CR: carbapenem-resistant, ClaR: clarithromycin-resistant, FQR: fluoroquinolone-resistant, MR: methicillin-resistant, PNS: penicillin non susceptible 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant
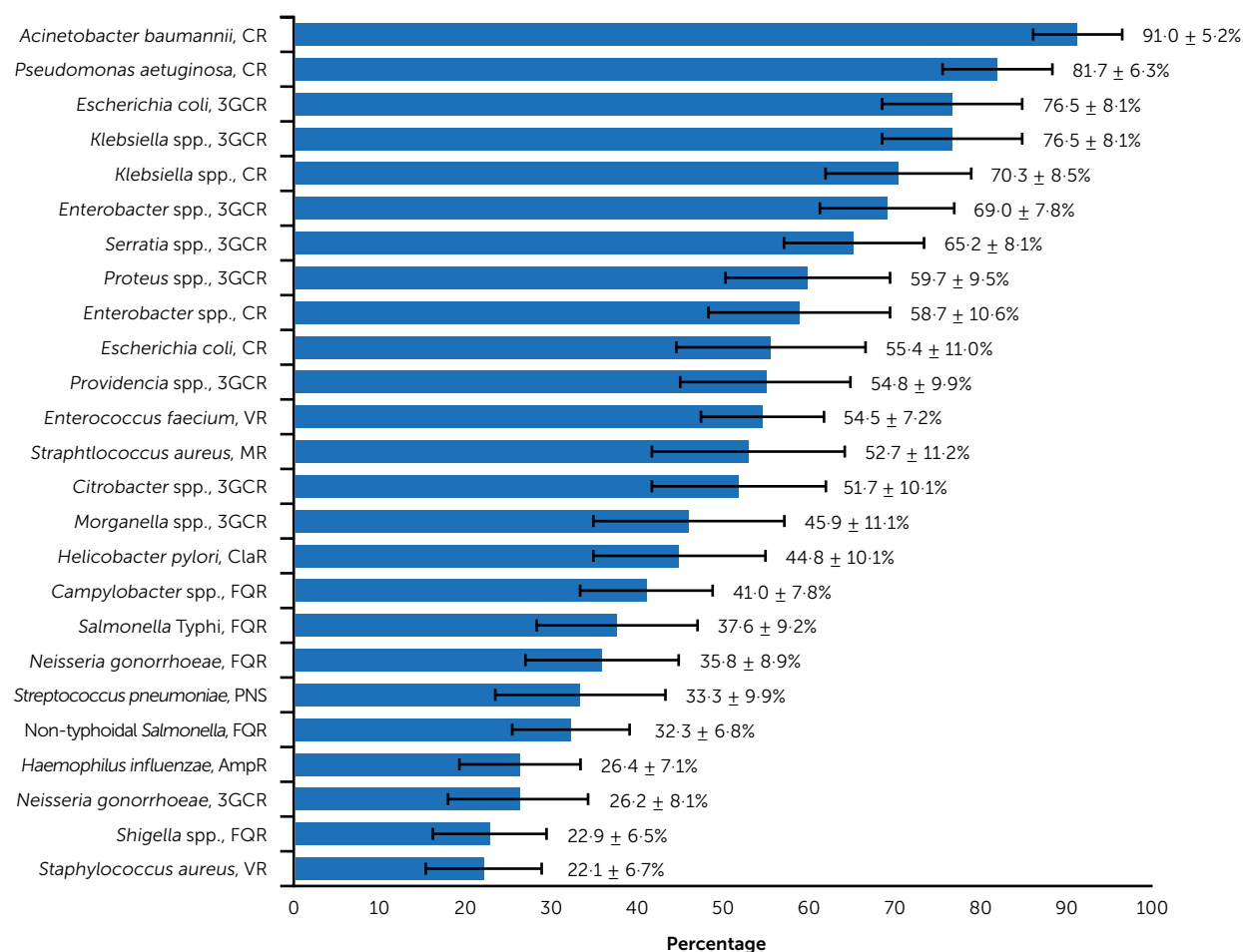

Criteria weights attributed by the experts were stratified according to WHO region and compared to identify any significant changes in relative importance. The only criterion that showed a significant change was community burden with a mean value of 14•6% for experts from the Africa region and 5•9% for experts from the Americas region (P = 0•0046) (Fig. 21). No significant differences in criteria ranking were found after stratifying by the scientific background of the experts.

Fig 21. Subgroup analysis of criteria weights by geographic region

AFR: African region, AMR: Americas region, EMR: Eastern Mediterranean region, EUR: European region, SEAR: South-East Asian region, WPR: Western Pacific region
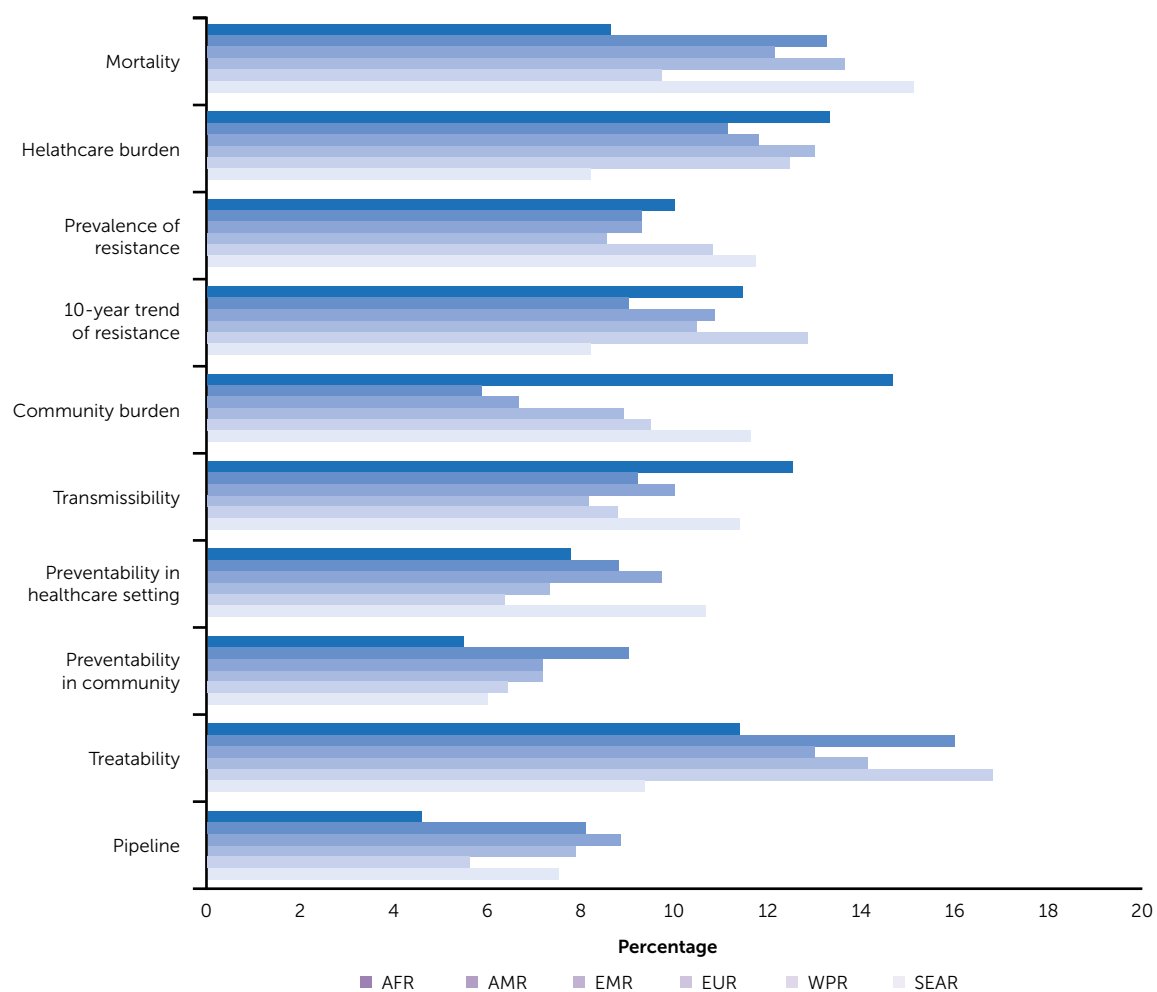
Source: WHO

AFR: African region, AMR: Americas region, EMR: Eastern Mediterranean region, EUR: European region, SEAR: South-East Asian region, WPR: Western Pacific region

Ranking by region was relatively stable compared with the overall final ranking. The only statistically significant difference was in the priority list of experts from Africa, who gave an additional 8.1% of the total weight to *Staphylococcus aureus*, methicillin-resistant compared to the overall ranking.

The final ranking of pathogens after excluding the results of the 20 experts who consistently answered fewer than two repeated questions did not show significant differences. An additional sensitivity analysis was done assuming an equal number of participants from each WHO region, with no significant changes to the final ranking order.

The final ranking computed through the software showed a high level of agreement between the whole group of participants (Kendall coefficient of concordance 0.869).

2.5 Ranking of other drug-resistant bacterial infections: overall results

(Note: Mycobacterium tuberculosis is covered in Section 1)

The survey ranking was reviewed by the coordinating group and an expert panel to evaluate the results and the sensitivity analyses and to develop the dissemination plan. To simplify the presentation of results and comply with the research and development focus, bacteria of the same species with multiple resistance patterns were grouped together in the highest ranked position (Fig. 23)". For example, if different carbapenem-resistant Enterobacteriaceae were ranked in 3rd, 5th and 6th position, they were grouped and ranked in the 3rd position. The priority pathogen list was then stratified into three tiers using a cut-off at the 33rd percentile of the pathogen total scores. The critical priority tier included the bacteria that scored over 66%: *Acinetobacter baumannii, Pseudomonas aeruginosa,* and

Enterobacter spp., carbapenem-resistant and *Enterobacter* spp., third-generation cephalosporin-resistant. The high priority tier included bacteria scoring between 65% and 34%: *Enterococcus faecium,* vancomycin-resistant; *Staphylococcus aureus,* methicillin-resistant and vancomycin-resistant; *Helicobacter pylori,* clarithromycin-resistant; *Campylobacter* spp., *Salmonella* spp., and *Neisseria gonorrhoeae,* fluoroquinolone-resistant; and *Neisseria gonorrhoeae,* third-generation cephalosporin-resistant. The medium priority tier included bacteria scoring less than 33%: *Streptococcus pneumoniae,* penicillin-non-susceptible; *Haemophilus influenzae,* ampicillin-resistant and *Shigella* spp., fluoroquinolone-resistant.

Fig 23. Priority pathogens for R&D of new antibiotics
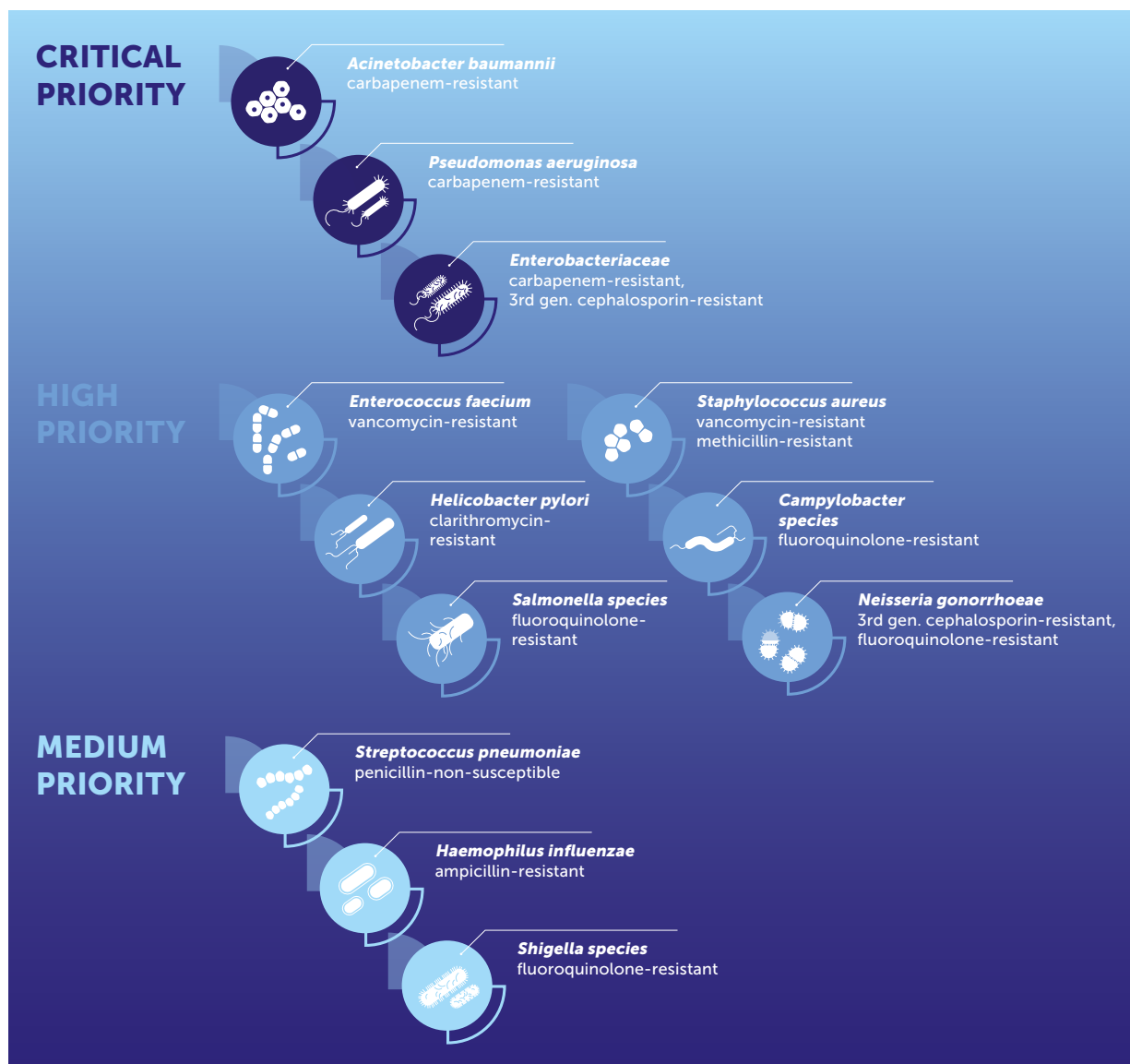
2.6 Conclusions

- The WHO prioritization exercise suggests that drug research and development strategies should focus urgently on new antibiotics specifically active against tuberculosis and multi- and extensively drug-resistant Gram-negative bacteria that cause acute infections in both hospital and community settings.

- Global research and development strategies should also include antibiotics active against more common community bacteria, such as antibiotic-resistant *Salmonella* spp., *Campylobacter* spp. and *Helicobacter pylori.*

- Further efforts should address how to incentivize the development of oral formulations for community infections caused by antibiotic-resistant bacteria with a high morbidity burden, such as drug-resistant *Neisseria gonorrhoeae* and third-generation cephalosporin-resistant Enterobacteriaceae.

- To drive long-term plans of pharmaceutical and research centres working in research and development of new antibiotics, the WHO list must be aligned with increased political awareness in a global, multifaceted strategy to reduce the burden of resistant infections.

- Although this prioritization exercise does not cover all the possible patterns of resistance and co-resistance, the results clearly support prioritization in the development of new antibiotic classes with new targets and mechanisms of action without cross-resistance to existing classes.

- The WHO Priority Pathogens List underlines the important need for new antibiotics for the paediatric population and for user-friendly (e.g.

oral) formulations for diseases caused by drug-resistant bacteria with high morbidity in both high-income and low- and middle-income countries, such as multidrug- and extensively drug-resistant *Mycobacterium tuberculosis,* drug-resistant *Neisseria gonorrhoeae,* fluoroquinolone-resistant *Campylobacter* spp. and *Salmonella* spp., clarithromycin-resistant *Helicobacter pylori,* and third-generation cephalosporin-resistant Enterobacteriaceae.

- The expert working group acknowledges that the availability of prevention measures does not necessarily equate with their universal implementation and that dedicated efforts should be made to increase public health prevention interventions when their effectiveness is proven. A dedicated programme led by WHO should be responsible for increasing and standardizing the implementation of infection control strategies.

- Specific attention should be paid to the implementation of antibiotic stewardship initiatives globally, especially in combination with educational activities and public awareness campaigns. The rational and sustainable use of existing antibiotics is essential to preserve their residual efficacy. Moreover, extensive promotion of different and responsible prescribing behaviour would protect new drugs from the rapid development of new bacterial resistance. Long-term investment in educational activities and innovative tools to support appropriate use, and adequate financing plans for projects are therefore urgently needed globally.

Strengths of the prioritization exercise

- The prioritization of pathogens is an innovative international effort to standardize and prioritize research and development for new medicines for tuberculosis and other drug-resistant bacterial infections. It includes a multi-component definition of treatability as available therapeutic options and an analysis of the current clinical pipeline for antibacterial agents.

- Assessment of the current treatments available included a detailed evaluation of the evidence, coupled with data on residual susceptibility of existing drugs (i.e. the rate of resistance to a first-line antibiotics in surveys or post-marketing studies), and availability of oral and paediatric formulations. An assessment by experts of antibiotics in development highlighted that, for the majority of the priority pathogens, new drugs will not be available in the short term.

- The list of pathogens can be updated by either including other resistant bacteria or defining new criteria. Because of the flexibility of the methodology, it would be possible to re-run the analyses including more experts, new bacteria or new criteria levels, whenever updated or better quality data become available or new resistance threats are identified.

- Data on transmission potential between humans, animals, food and the environment were collected and included in the transmissibility criterion, following the One Health approach. Antibiotics are widely used in human medicine, livestock production and aquaculture (for disease prevention and treatment, and growth promotion). *Mycobacterium tuberculosis* is almost exclusively found in humans, although human-to-animal transmission has been described in the scientific literature. Resistant bacteria are reported in humans, animals, food and the environment, and one of the main drivers of the spread of resistance is the overuse of antibiotics in one or more of these sectors. The One Health approach recognizes that the health of humans, animals and ecosystems are interconnected and interdependent. Animals and the environment could represent a reservoir for pathogens, facilitate the exchange and spread of resistance, and lead to infectious diseases driven by highly varied and dynamic human-animal and human-environment interactions.

- The results of the modelling showed that the final ranking was stable, even after stratifying the data by WHO region, and analysing the consistency and sensitivity.

- The development of the priority criteria used the PAPRIKA method, which has two main advantages. First, the method generates a set of weights for each individual participant in the preferences survey, in contrast to most other methods which produce aggregated data across a group of participants only. Individual-level data allowed us to investigate differences in the experts' preferences, and the extent to which they were associated with demographic and background characteristics. Second, pairwise ranking is less difficult for decision-makers than choosing between more than two alternatives (in this instance, the bacteria) or between alternatives defined on more than two criteria at a time. Prioritization exercises based only on consensus have several drawbacks: they can lead to a diluted version of the best opinion with the result representing the lowest common denominator; disagreement is difficult to explore and could result in artificial consensus; the facilitator's opinion may dominate; and the success of the method depends mainly on the quality of the participants.

Limitations

- Incidence rates and future burden of diseases were not estimated. With the exception of TB, for which strong surveillance and monitoring systems have been in place since 1994, there are almost no global routine surveillance systems for other bacteria. These could be used to calculate the true mortality burden associated with resistant infections in the future. To define the global prevalence of resistance more precisely, only clinically relevant samples (blood and cerebrospinal fluid for severe infections, swabs for *Neisseria gonorrhoeae*, and stools for *Shigella* spp. and *Campylobacter* spp.) were included. Incidence data could have significantly increased the precision of the modelling but these are limited to a few countries, focus on health facility-associated infections and are mainly derived through complex estimations.

- With the exception of TB, absolute numbers of deaths globally, which would have increased the precision of the mortality criterion, were not available from most WHO regions. Available estimates have been criticized mainly for the same reasons as estimates of the number of cases. The choice of overall crude mortality instead of the preferred infection-attributable mortality was also because of a lack of available data.

- The economic costs of infections caused by resistant bacteria were not included because of the lack of global data (TB excluded); what estimations there were, were mainly from high-income countries. These costs are difficult to extrapolate to lower income regions because of the very different health-care systems.

Gaps in understanding the burden of antibiotic resistance

- With the exception of TB, there is a large gap in the current evidence on infections caused by antibiotic-resistant bacteria in community and health-care settings, in particular for data on the frequency and burden of infections. High-quality data were missing, especially for community-acquired infections and from middle- and low-income countries.

- Major data gaps in surveillance (except TB) are evident, especially in the African and Eastern Mediterranean regions. Gaps in prevalence estimations are not only due to the lack of surveillance systems but also to scarce or low-quality diagnostic tools in many low-income countries. International surveillance programmes, such as those promoted by WHO, the Center for Disease Dynamics, Economics & Policy and ReAct, are trying to fill these gaps, but results from these initiatives are not yet available and were not included in this prioritization process. The value of surveillance data is clearly seen in the case of TB, which has greatly facilitated the prioritization of *Mycobacterium tuberculosis* as a target pathogen for research and development.

- As antibiotic resistance is a multifaceted and cross-sectoral issue affecting humans, animals, food and the environment, much more integrated surveillance is needed through an interconnected and integrated One Health surveillance framework across these four compartments.

- Great differences in the implementation of infection prevention and control measures were seen and interventions to increase the implementation of standardized infection prevention and control measures are urgently needed. The lack of microbiology laboratory capacity in low- and middle-income countries further complicates patient-specific treatment. For some microorganisms such as *Neisseria gonorrhoeae* the absence of a network of laboratories means that routine testing is difficult and the infection is often misdiagnosed. The infection might be not treated even though effective treatments are available.

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