Antibacterial pipeline trends and recommendations to enhance research and development

Policy brief

World Health Organization
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Acknowledgments

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The advisory group consisted of:

- Cesar A. Arias, Professor and Chief, Division of Infectious Diseases, Houston Methodist Hospital and Houston Methodist Research Institute, Houston, TX; Department of Medicine, Weill Cornell Medical College, New York, NY, United States of America; Founder and Scientific Advisor, Molecular Genetics and Antimicrobial Resistance Unit/International Center for Microbial Genomics, Universidad El Bosque, Bogotá, Colombia
- Lloyd Czaplewska, Director, Chemical Biology Ventures, United Kingdom of Great Britain and Northern Ireland
- Prabavathi Fernandes, retired pharmaceutical and biotechnology executive; former Chair of the National Biodefense Science Board for the Government of the United States; and former Chair of the Global Antibiotic Research and Development Partnership (GARDP) Scientific Advisory Board
- Stephan Harbarth, Full Professor, Division of Infectious Diseases and Infection Control Programme, Geneva University Hospitals, WHO Collaborating Centre, Switzerland
- Roman Kozlov, Rector, Smolensk State Medical University, and Chief Specialist of the Ministry of Health for Clinical Microbiology and AMR, Russian Federation
- Christian Lienhardt, Research Director, Institute for Research on Sustainable Development and University of Montpellier, France
- Norio Ohmagari, Director, Disease Control and Prevention Center, National Center for Global Health and Medicine, Japan
- Mical Paul, Director, Infectious Diseases Institute, Rambam Health Care Campus, and Professor, The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Israel
- John H. Rex, Editor-in-Chief, AMR Solutions and Adjunct Professor of Medicine, McGovern Medical School, Houston, TX, USA
- Lynn Silver, Owner, LL Silver Consulting, USA.
WHO also acknowledges the contribution of the observers of the advisory group:

- Radu Botgros, Senior Scientific Officer, European Medicines Agency (EMA), Netherlands (Kingdom of the)
- Joseph Campbell, Program Officer, Research Resources Section, Office of Biodefense, Research Resources and Translational Research/Division of Microbiology and Infectious Diseases/National Institute of Allergy and Infectious Diseases, USA
- Erin Duffy, Chief of R&D CARB-X, USA
- Francois Franceschi, Head of Asset Evaluation and Development, GARDP, Switzerland
- Ramya Gopinath, Medical Officer, Division of Anti-Infectives, Food and Drug Administration (FDA), USA
- Martin Heidecker, Chief Investment Officer, AMR Action Fund, Switzerland
- Lesley Ogilvie, Secretariat Director, Global AMR R&D Hub, Germany
- Jean-Baptiste Perrin, Policy Officer, Health Emergency Preparedness and Response Authority (HERA), Belgium
- Raquel Rodriguez, Policy Officer, HERA, Belgium
- Mike Sharland, Chair of the WHO Antibiotic Working Group of the Essential Medicines List (EML) and Essential Medicines List for Children, and St George’s University, United Kingdom
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Feedback and additional information for future editions are welcomed. Please send any comments to: antibacterialpipeline@who.int.

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### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMR</td>
<td>antimicrobial resistance</td>
</tr>
<tr>
<td>BEAM Alliance</td>
<td>Biotech companies from Europe innovating in Anti-Microbial resistance research Alliance</td>
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<tr>
<td>BIO</td>
<td>Biotechnology Innovation Organization</td>
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<tr>
<td>BPPL</td>
<td>bacterial priority pathogens list</td>
</tr>
<tr>
<td>CRE</td>
<td>carbapenem-resistant Enterobacterales</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ESBL</td>
<td>extended-spectrum β-lactamase</td>
</tr>
<tr>
<td>GARDP</td>
<td>Global Antibiotic Research and Development Partnership</td>
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<tr>
<td>HERA</td>
<td>Health Emergency Preparedness and Response Authority</td>
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<tr>
<td>HIC</td>
<td>high-income country</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers and Associations</td>
</tr>
<tr>
<td>LMICs</td>
<td>low- and middle-income countries</td>
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<tr>
<td>MCMs</td>
<td>medical countermeasures</td>
</tr>
<tr>
<td>PIP</td>
<td>paediatric investigation plan</td>
</tr>
<tr>
<td>PSP</td>
<td>paediatric study plan</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>research and development</td>
</tr>
<tr>
<td>SME</td>
<td>small and medium-sized enterprises</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>UMIC</td>
<td>upper-middle-income country</td>
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<tr>
<td>US FDA</td>
<td>United States Food and Drug Administration</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Key points

- **Antimicrobial resistance (AMR) is one of the leading causes of death worldwide** and one of the top 10 global health threats identified by the World Health Organization (WHO) (1). Bacterial AMR is estimated to have caused 1.27 million deaths in 2019 and to have been associated with 4.95 million deaths (2).

- **The number of antibacterial agents approved and in development is insufficient to tackle the global threat posed by the emergence and spread of drug-resistant infections.** Of 128 total clinical programmes in the WHO antibacterial pipeline over the past 6 years, only 16 new antibacterials have received market approval by any stringent regulatory authority or WHO-listed authority.

- **The antibacterial pipeline is highly fragile.** Ninety-three per cent of developers active in the clinical space are small biotechnology companies, while in the preclinical stage the vast majority (86.7%) of developers are very small, privately funded organizations (11–50 employees) with limited resources.

- **There is a continued need for innovative new drugs to combat extensively resistant Gram-negative bacteria, i.e., critical priority pathogens, and the evolving mechanisms of drug resistance.** This ongoing need is especially crucial for oral formulations.

- Despite children having the highest AMR disease burden, especially in low- and middle-income countries (LMICs), only six out of 14 late-stage antibiotics in the pipeline have an approved paediatric investigation/study plan (PIP/PSP).

- **Over 90% of clinical antibacterial product development takes place in high-income (84%) and upper-middle income (12%) settings,** which benefit from more funding opportunities and connections to R&D initiatives in other therapeutic areas.

- **More data on the clinical use of newly approved antibacterial agents is urgently needed to understand their effectiveness in different contexts**
Introduction

The AMR pandemic has caused a rapid decline in the effectiveness and range of available antibacterials. In human health, the consequences of AMR continue to be devastating, especially for LMICs. In 2019, AMR was associated with 4.95 million deaths, with patients in LMICs being 1.5 times more likely to die of it compared to those in high-income countries (HICs). One out of every five deaths associated with AMR occurred in children under the age of 5, with almost all of these (99.65%) occurring in LMICs, particularly in sub-Saharan Africa.

Health system recovery post-COVID-19 has presented a significant challenge. Moreover, COVID-19 exposed rampant antibiotic overuse, insufficient human resource preparedness and a high incidence of health-care-associated bacterial infections. To support efficient AMR pandemic preparedness and response, health systems must focus on infection prevention and control measures and invest in capacity-building initiatives on AMR (stewardship, surveillance, monitoring and awareness raising).

Developing better vaccines, diagnostics and antimicrobials, also called medical countermeasures (MCMs), against drug-resistant pathogens is urgently needed alongside measures to ensure equitable access to new and existing medicines. As a part of a multisectoral response to AMR, WHO called for increased R&D in AMR and has been tracking progress in the antibacterial development pipeline. Since 2017, as part of the implementation of the Global Action Plan on AMR, WHO has analysed the clinical and (since 2019) the preclinical development pipeline of antibacterial agents. The scope is to assess to what extent the pipeline addresses the most threatening pathogens for AMR according to the WHO bacterial priority pathogens list (BPPL), as well as Mycobacterium tuberculosis, Clostridioides difficile and Helicobacter pylori. Following five annual reviews of the antibacterial pipeline, WHO confirms that the pace of R&D still lags behind the swift and continuous evolution of pathogens, driven by the widespread use of antimicrobials.

At the most recent meeting of the WHO Strategic and Technical Advisory Group for Antimicrobial Resistance, in 2023, experts and technical leaders recommended working with funders to prioritize funding for R&D, addressing the BPPL and the fungal priority pathogens list. The leaders emphasized that setting sound targets in addressing AMR is a crucial step in anticipation of the United Nations General Assembly High-Level Meeting on AMR to be held in September 2024. The Global Leaders Group has declared a crisis in antibiotic access and R&D, calling for sustained funding to drive innovation, and collaboration between public and private sectors to navigate challenges and establish global access to antibiotics. WHO and the Quadripartite Joint Secretariat are actively working to fortify these partnerships, while also advocating for the inclusion of AMR in the WHO convention on pandemic prevention, preparedness and response.

Purpose of this document

This policy brief provides a summary of the trends observed in the antibacterial pipeline and discusses areas that require immediate attention. It calls for policymakers, funders and global public health organizations to collaboratively recognize, prioritize and act to enable development of novel approaches to curb AMR.
### Key challenges and recommendations

#### 1. A robust clinical pipeline is needed to combat drug resistance

- In the past 6 years, only six antibiotics have been authorized to treat critical bacterial pathogens that cause drug-resistant infections with the highest rates of mortality and morbidity.
- Drug resistance is rapidly increasing for authorized antibiotics and for those still under development.
- Antibacterial agents in clinical development do not sufficiently address the problem of extensively or pan-drug-resistant Gram-negative bacteria. In particular, carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa* continue to be insufficiently addressed. New antibiotics are urgently needed on the market to offer patients alternative options when first-line treatments start to fail.

**Recommendation 1.** As part of a comprehensive response, ensure adequate resources – including push and pull incentives (10) – for R&D and equitable and global access of essential and priority health products.

#### 2. Small and medium-sized enterprises (SMEs) that drive the antibacterial pipeline experience high turnover rates in preclinical development; only a few programmes advance to clinical trials.

- The current crisis in antibiotic development is due to high R&D costs and lack of incentives (7). The delayed and uncertain return on investment has made many profit-oriented companies and investors cautious about continuing in this field (7, 10).
- Most developers in the preclinical stages (n = 97, 86.7%) are SMEs with extremely limited financial, scientific and technical resources. They have fewer than 50 employees, and over half of these (n = 62, 55.4%) have fewer than 10 employees (micro-sized).
- From 2019 to 2023, only 19% (n = 51 of 269) of programmes advanced successfully through the preclinical development stages. SMEs have reported facing scientific hurdles and ongoing challenges related to COVID-19, such as staff shortages and delayed funding, resulting in an unstable pipeline.

**Recommendation 2.** Focus on addressing the specific needs and stimulate support of SMEs that are driving innovation in this sector through significant public-private or private partnerships such as accelerators.

#### 3. More innovative medicines are needed to combat drug-resistant Gram-negative bacteria, especially against critical priority pathogens.

- Some progress has been made in developing antibiotics to combat priority pathogens; however, innovative products against resistant Gram-negative bacteria are still scarce for both authorized and pipeline agents.
- Only two of the agents approved since 2017 met the WHO criteria for innovation (i.e., having no known cross-resistance, a new target, new mode of action or a new drug class).
- Only 34% (n = 11 of 32) of antibiotics in development are considered innovative; of these, only three are intended against critical Gram-negative bacteria.

**Recommendation 3.** Foster innovation in new drugs to combat drug-resistant Gram-negative bacteria. Catalyse efforts and incentives to promote development of innovative antibacterial agents against the most pressing priorities. Funders and developers are encouraged to prioritize options for this group of bacteria and explore projects that circumvent resistance, such as considering new modes of action and new targets or new classes.
More antibacterial oral formulation options are needed.

- The proportion and number of oral medications in the pipeline have remained relatively stable, from 37% ($n = 16$ of 43) in 2017 to 34% ($n = 21$ of 62) in 2023. However, the 2023 pipeline lacks oral antibiotic treatment options for extended-spectrum β-lactamase (ESBL)-producing bacteria and for carbapenem-resistant Enterobacterales (CRE).
- Oral treatments for these infections are crucial for outpatient care, reducing complications and costs compared to in-hospital parenteral treatment. Particularly for oral medicines, it remains essential to implement effective antimicrobial stewardship strategies that encourage proper prescribing practices and deter antibiotic misuse.

**Recommendation 4.** Greater emphasis should be placed on the development of oral formulations to support outpatient and step-down treatments, especially for ESBL-producing bacteria and CRE.

Despite children having the highest AMR disease burden, especially in LMICs, an imbalance exists in the development of antibacterial agents with paediatric indications and/or formulations compared to adults.

- The high burden of disease in children under 5 due to AMR (2) highlights the need for new paediatric antibacterial treatments.
- Paediatric antibacterial development is lacking globally; only six out of 14 late-stage antibiotics in the pipeline have an approved paediatric investigation/study plan (PIP/PSP).
- PIPs/PSPs are essential for collecting crucial data through clinical studies to authorize medications for children (11).

**Recommendation 5.** Prioritize the needs of vulnerable and fragile populations who suffer the highest burden of AMR. This includes timely investigation of new treatment options in paediatric and neonatal patients and developing age-appropriate formulations to enable their administration.

The development of antibacterial drugs takes place predominantly in HICs, despite the disproportionately higher disease burden of AMR in LMICs.

- In the current pipeline, over 90% of clinical programmes are led by developers in high-income and upper-middle-income countries.
- LMICs face challenges in antibacterial R&D due to economic constraints limiting expertise and training (12).
- Reliable post-approval usage data are also urgently needed for newly approved antibiotics to evaluate real-life pathogen-specific indications and the relevance of their use in different countries and populations, particularly in LMICs, where negative outcomes are amplified (2, 13).

**Recommendation 6.** Through global leadership, partnership and funding, encourage AMR R&D in LMICs. Foster collaboration to strengthen the scientific and drug development community in LMICs to spark scientific interest for the development of novel antibacterial agents that respond to the needs of these populations and to increase access.

More support is needed in developing non-traditional agents.

- Traditional measurements of drug efficacy may not be reliable indicators of clinical outcomes for non-traditional agents in the pipeline (14).
- To fully harness their clinical potential and improve funding opportunities for non-traditional programmes, further support is necessary for policy development which entails post-approval, marketing and prescriber use data.

**Recommendation 7:** Regulators should cooperate with developers to explore how current clinical trials can support the development of non-traditional agents in the pipeline to ensure their safe, effective and timely deployment and market availability.
Conclusion

Existing antibacterial agents are inadequate against the escalating challenge of drug-resistant infections. Immediate global coordination and cooperation is essential to enhance innovative R&D, improve AMR data collection and sharing, and implement investment strategies that are focused on addressing the needs of vulnerable patients, particularly in LMICs, which lack equitable access to medicines, vaccines and diagnostics despite bearing the greater burden of AMR.

Further reading

• WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: World Health Organization; 2024.
References


Annex. Declaration of interests of advisory group members

Management of conflicts of interest was a priority throughout the analysis and decision-making for the antibacterial clinical and preclinical pipeline. The declarations of interest (DOIs) were collected and thoroughly reviewed by the WHO AMR Division following WHO standard operating procedures.

Prior to the advisory group meeting, all the experts submitted written disclosures of competing interests that had arisen during a period of 4 years preceding the WHO advisory work and that were relevant for consideration before their confirmation as participants in the meeting, including employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants (including contracted research, patents received or pending, royalties, stock ownership or options), other personal financial interests, as well as whether the institution or employer had a financial relationship with a commercial entity that had an interest in antibacterial products evaluated by the advisory group.

Experts were also asked to disclose academic or scientific activities that included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about an antibacterial product. In addition, at the start of the meeting, all members were asked to provide updates about their declaration if any new conflicts had arisen in the meantime.

The experts who declared no potential conflicts of interest were Prabha Fernandes, Stephan Harbarth, Christian Lienhardt, Mical Paul and Norio Ohmagari. These experts were allowed full participation in the meeting.

Lloyd Czaplewski disclosed in his DOI that he provided consultancies and had been awarded financial support in the previous 4 years from Clarametyx, Novo Repair Impact Fund, Novo Holdings, Chemical Biology Ventures Ltd and Curza.

Roman Kozlov disclosed in his DOI that his research unit had been awarded financial support in the previous 4 years from Merck Sharp and Dohme, Pfizer and Astellas Pharma.

John H. Rex disclosed in his DOI having provided consulting services, received research grants/support, held shares or commercial interest in the previous 4 years from Basilea Pharmaceutica (SAB), Novo Holdings, Bugworks Research, Forge Therapeutics, Sumitovant, GlaxoSmithKline, AstraZeneca Pharmaceuticals, F2G, Advent Life Sciences, Iterum Therapeutics and Pfizer.

Lynn Silver reported in her DOI having provided consultancy, reviewed programmes or grants in the previous 4 years for Appili, Debiopharm, Forge, CDD-SPARK, Novo-Repair Fund and Dartmouth.

Following assessment of the DOIs, Cesar Arias, Lloyd Czaplewski, Roman Kozlov, John Rex and Lynn Silver were excluded from discussions involving products from commercial entities or other organizations listed above.

All reported interests were disclosed to the meeting participants by the technical unit in a slide show presentation; the interests are also disclosed in this report and in relevant publications.

Cesar Arias disclosed in his DOI that his former institution was awarded financial support more than 3 years previously from Merck Sharp and Dohme and Entasis Therapeutics.