ANTIBACTERIAL AGENTS IN PRECLINICAL DEVELOPMENT

an open access database

World Health Organization

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Executive summary

This is the World Health Organization's first comprehensive overview of the preclinical antibacterial pipeline to date based on publicly available data on each included project. This report and the respective WHO database capture 252 antibacterial agents in development targeting the pathogens on the WHO priority pathogens list (Annex I), *Mycobacterium tuberculosis* and *Clostridioides difficile*. The preclinical pipeline is dynamic and scientifically diverse, with agents being developed in many parts of the world to prevent and treat drug-resistant bacterial infections:

- 252 agents are being developed by 145 individual institutions that target the WHO priority pathogens, *M. tuberculosis* and *C. difficile*.
- The review captures research projects from institutions with a wide geographical distribution, 66 (45.5%) institutions in the European Region, 51 (35.2%) in the Region of the Americas, 22 (15.2%) in the Western Pacific Region, 5 (3.4%) in the South-East Asia Region and 1 (0.7%) in the African Region.
- 108 (42.9%) are direct-acting small molecules (single agents) and 90 (35.7%) are nontraditional products that include phages, anti-virulence agents, immunomodulators, microbiome-modifying therapies and potentiators, among others.
- 100 (39.7%) agents target a single pathogen, of which 43 target *M. tuberculosis*.
- Almost 1/3 of the agents target cell wall synthesis or act directly on the membrane.
- Approximately 2-5 direct-acting small molecules and 1 nontraditional product may make it to the market in the next 10 years.
- The preclinical pipeline is dominated by small and medium-sized enterprises (n = 104, 71% of all institutions that submitted data).
- This is the first review of the preclinical pipeline that makes all of the drug development projects and institutions available through a public database.

The WHO database of the preclinical pipeline reflects approximately 84% (252 out of 304) of preclinical pipeline projects that were published in a recent anonymized preclinical review[1] based primarily on data from confidential funding sources. The review captured 407 products from the hit to lead to CTA/IND (Clinical Trial Application/Investigational New Drug Application) enabling studies phases. Of these products, 304 had entered the lead optimization or CTA/IND-enabling studies phase (the scope of this current report).

The data at the product level is available and downloadable on the WHO Global Observatory on Health R&D (https://www.who.int/research-observatory/monitoring/processes/antibacterial_products_preclinical/en).

WHO will continue to review the preclinical and clinical antibacterial pipeline and make the data available on a regular basis to promote innovation, collaboration and transparency as well as to track evolution of the pipeline and see how the antibacterial research and development ecosystem is responding to the priority pathogens list. The ultimate aim is to collectively move forward in developing antibacterial treatments that can treat drug-resistant bacterial infections.

If you have comments or have products that should be included in this review, please contact antibacterialpipeline@who.int.

[1] Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. Nat Rev Microbiol. 2019. doi:10.1038/s41579-019-0288-0.

1. Introduction

In 2017 the WHO published the *Prioritization of bacterial pathogens to guide research and development of new antibacterial agents* (WHO priority pathogens list).[2] Since then, WHO reviews all antibacterial agents in clinical development against this list on an annual basis to evaluate how the pipeline and the research and development (R&D) ecosystem are responding to the priority pathogens list. The most recent review confirms that very few agents are in development that target critical Gram-negative bacteria. Moreover, only a handful of products fulfil the WHO criteria for an innovative new product that is likely to overcome cross resistance.[3] To complement this analysis of the clinical pipeline, in 2019 WHO undertook a review of the preclinical pipeline to identify promising projects. All of the data collected is made publicly available on the WHO Global Observatory on Health R&D. Ultimately, greater transparency will lead to stronger collaboration around potentially innovative but challenging projects, support a community of scientists and drug developers, and generate more interest in and funding of drug development for novel antibacterial agents. WHO will continue to update the preclinical and clinical pipeline data on the Global Observatory on Health R&D on a regular basis.

[2] Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017.

[3] 2019 update of antibacterial agents in clinical development. Geneva: World Health Organization; 2019.

2. Methodology

2.1 Scope and inclusion/ exclusion criteria

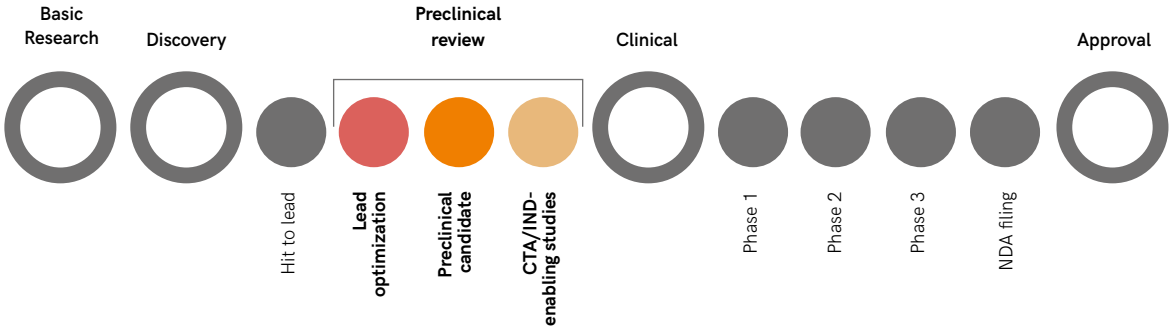
The review focuses on antibacterial agents that target the WHO priority pathogens (Annex I), *M. tuberculosis* and *C. difficile*. The scope of this preclinical pipeline review (Fig. 1) is products that are in the lead optimization phase of discovery or the preclinical candidate phase, or that are ready for a formal Investigational New Drug Application (IND) – also termed a Clinical Trial Authorization (CTA). For regulatory authorities that do not use IND/CTA, this stage indicates the commencement of human testing.

The review encompasses both traditional and nontraditional approaches, including direct- and indirect-acting antibacterials, small and large molecules, anti-virulence agents and biofilm disruptors, potentiators, microbiome-modifying agents, immunomodulators, repurposed non-antibiotics and antibiotics from animal to human use, decolonization agents and combination therapies. The review does not include vaccines, diagnostics, antifungals, antivirals or anti-parasitics. Wound care agents, nonspecific supportive treatments, medical devices, and industrial and animal use agents are also not included.

2.2 Data collection

A WHO online call held from 18 January to 18 April 2019 generated the primary data. In addition, a targeted search of products in preclinical development was undertaken in China, Japan and Russia through contractual partners who were experts in the field and conducted a desktop review in the respective languages. This data was supplemented with information from the Access to Medicine Foundation, BEAM Alliance, BIO, CARB-X, Global AMR R&D Hub, Global Antibiotic Research and Development Partnership (GARDP), IFPMA, JPIAMR, Needham & Company, NIH/ NIAID, Pew Charitable Trusts, REPAIR Impact Fund, TB Alliance, TB Union and Treatment Action Group (TAG). Data presented was primarily submitted directly by the institutions. Where possible, WHO corroborated the data through a scoping study of publications, conference abstracts or posters, institutional websites and other information in the public domain.

Fig. 1. Traditional drug development phases showing the preclinical phases included in this report



Lead optimization: iterative in vitro and in vivo screens of lead compounds to generate suitable pharmacological, safety and pharmacokinetic profiles of one or more candidates to progress into preclinical development; ***preclinical candidate:*** a lead compound that passes initial toxicology tests and demonstrates a sufficient safety profile which when combined with a suitable understanding of pharmacological efficacy warrants advancement; ***CTA/IND-enabling studies:*** studies including ADME (absorption, distribution, metabolism and excretion) and GLP (good laboratory practice) toxicology, as well as formulation and manufacturing development necessary to obtain the permission of regulatory authorities to begin human clinical testing.

3. Agents in preclinical development

3.1 Geographical distribution

The review captures 252 preclinical projects that are affiliated with 145 institutions having a wide geographical distribution (Fig. 2). Most of data was collected from the European Region (n=66, 45.5%) and the Region of the Americas (n=51, 35.2%). This is approximately 84% (252 out of 304) of preclinical pipeline projects that were published in a recent anonymized preclinical review[1] based primarily on data from confidential funding sources. The review captured 407 products from the hit to lead to CTA/IND-enabling studies phases, of which 304 products were in the lead optimization to CTA/IND-enabling studies phases (the scope of this current report).

Most institutions are commercial institutions (n=114, 78.6%), followed by academic institutions (n=27, 18.6%) and foundations (n=4, 2.8%) (Fig. 3). The majority of the 114 commercial institutions are small and medium-sized enterprises (n=106/114, 93%), of which 96 are small enterprises. This is indicative of the number of large pharmaceuticals that have exited the antibacterial discovery area.

Fig. 3. Categorization of institutions with preclinical pipeline projects

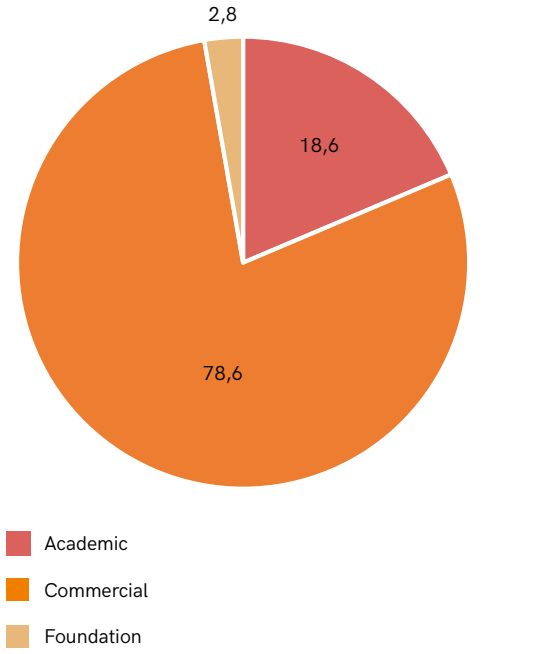
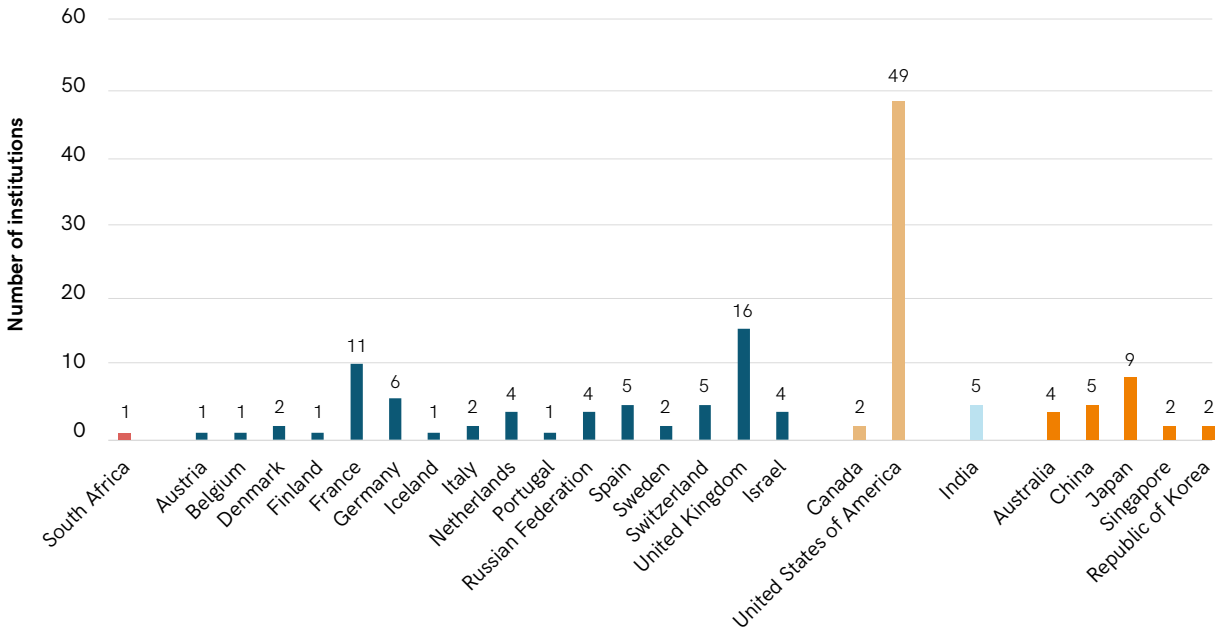


Fig. 2. The geographical distribution of the 145 institutions with preclinical pipeline projects



3.2 Categorization of preclinical agents

The review reveals a large range of different agents in preclinical development. The majority (n = 209, 83%) are direct-acting curative treatment agents comprising 144 small and 65 large molecules. This category is complemented by 37 indirect-acting adjuvant treatment options and 6 preventative agents. WHO further categorized the agents based on their treatment modality (Table 1) and by their self-declared preclinical development stage following a consensus-based approach to defining the categorization through expert consultation and building on existing categorization by the Pew Charitable Trusts and recent publications in the field.[1,4]

The majority are direct-acting small molecules (n = 108, 42.9%), followed by nontraditional approaches (n = 90, 35.7%) and antimicrobial peptides (n = 27, 10.7%) (Fig. 4). Taking a closer look at the nontraditional products[4] in the pipeline, 28 are classified as phage or phage products, and 18 as anti-virulence agents, closely followed by potentiators.

Table 1. Distribution of preclinical programmes by antibacterial agent category and preclinical development stage

Treatment modality	Total (%)	Development stage		
		LO	PCC	CTA/IND
Direct-acting small molecules	**108 (42.9)**	**51**	**44**	**13**
Antimicrobial peptides	**27 (10.7)**	**12**	**12**	**3**
Novel combinations	**9 (3.6)**	**2**	**4**	**3**
Repurposed agents	**18 (7.1)**	**3**	**9**	**6**
Animal to human	2	-	2	-
Formulation	11	-	5	6
Non-antibiotics	5	3	2	-
Nontraditional approaches	**90 (35.7)**	**40**	**39**	**11**
Anti-virulence agents (small and large molecules)	18	13	2	3
Biologics	9	4	5	-
Decolonization agents	3	-	3	-
Immunomodulators	11	5	4	2
Microbiome-modifying agents	1	1	-	-
Phage/phage-derived peptides	28	10	17	1
Potentiators/enablers (resistance-modulating, penetration-enabling)[a]	17	6	6	5
Other	3	1	2	-
Total	**252 (100)**	**108**	**108**	**36**

LO, lead optimization; PCC, preclinical candidate; IND, IND-enabling studies.

[a] Such as novel β-lactamase inhibitors, biofilm-disrupting agents and cell membrane perturbation agents.

[4] Theuretzbacher U, Piddock LJV. Non-traditional antibacterial therapeutic options and challenges. Cell Host Microbe. 2019; 26:61–72.

Table 2 shows the 252 products categorized according to their antibacterial mode of action and preclinical development stage. Overall, most of the products target cell wall synthesis (50) of which 11 are β-lactam/ β-lactamase inhibitor combinations. Thirty-six products have direct membrane effect, and these are primarily in the lead optimization or preclinical candidate phase. There are forty products that have other modes of action from the traditional categories showing the diversity in the preclinical pipeline. This includes biofilm, efflux pump and toxin inhibitors, CRISPR/Cas9 gene targeting and other anti-virulence modes of action amongst others. For 33 (13.1%) products, no information on the mode of action was available (either not known or not disclosed).

Fig. 4. Distribution of treatment modality main groups by preclinical pipeline stage

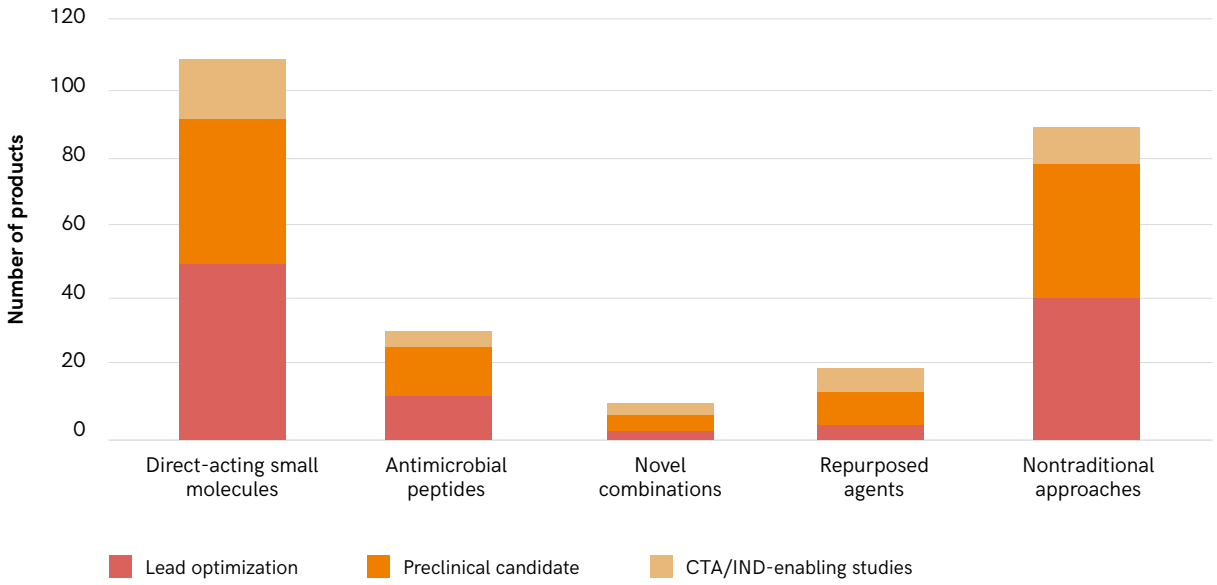
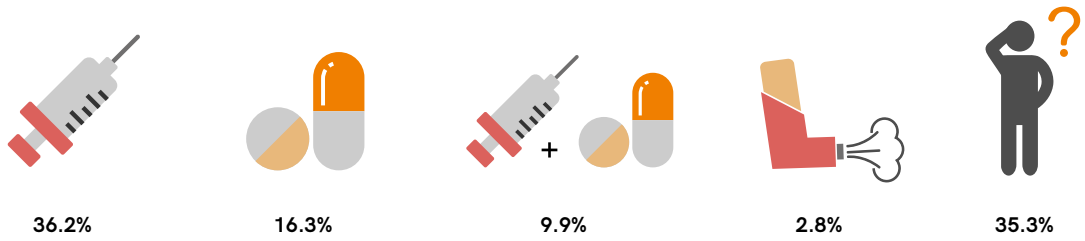


Table 2. Distribution of programmes by mode of action and preclinical development stage

Mode of action	Total (%)	Development stage		
		LO	PCC	CTA/IND
Cell wall synthesis	**50 (19.8)**	**12**	**22**	**16**
Cell membrane	**36 (14.3)**	**13**	**19**	**4**
DNA replication	**8 (3.2)**	**3**	**4**	**1**
Protein synthesis	**21 (8.3)**	**12**	**7**	**2**
Cell metabolism	**18 (7.2)**	**8**	**8**	**2**
Immunomodulation	**11 (4.4)**	**5**	**4**	**2**
Bacteriophage	**28 (11.1)**	**10**	**17**	**1**
Other	**47 (18.7)**	**26**	**15**	**6**
Not disclosed	**33 (13.1)**	**19**	**12**	**2**
Total	**252 (100)**	**108**	**108**	**36**

A total of 89 (35.3%) programmes had an "undefined or unreported" route of administration, which is to be expected for programmes at this early development stage (Fig. 5). The majority are injectables (36.2%), followed by oral treatments (16.3%). A further 9.9% target both IV and oral formulations. Inhalation is targeted by 2.8% of the products as a delivery route.

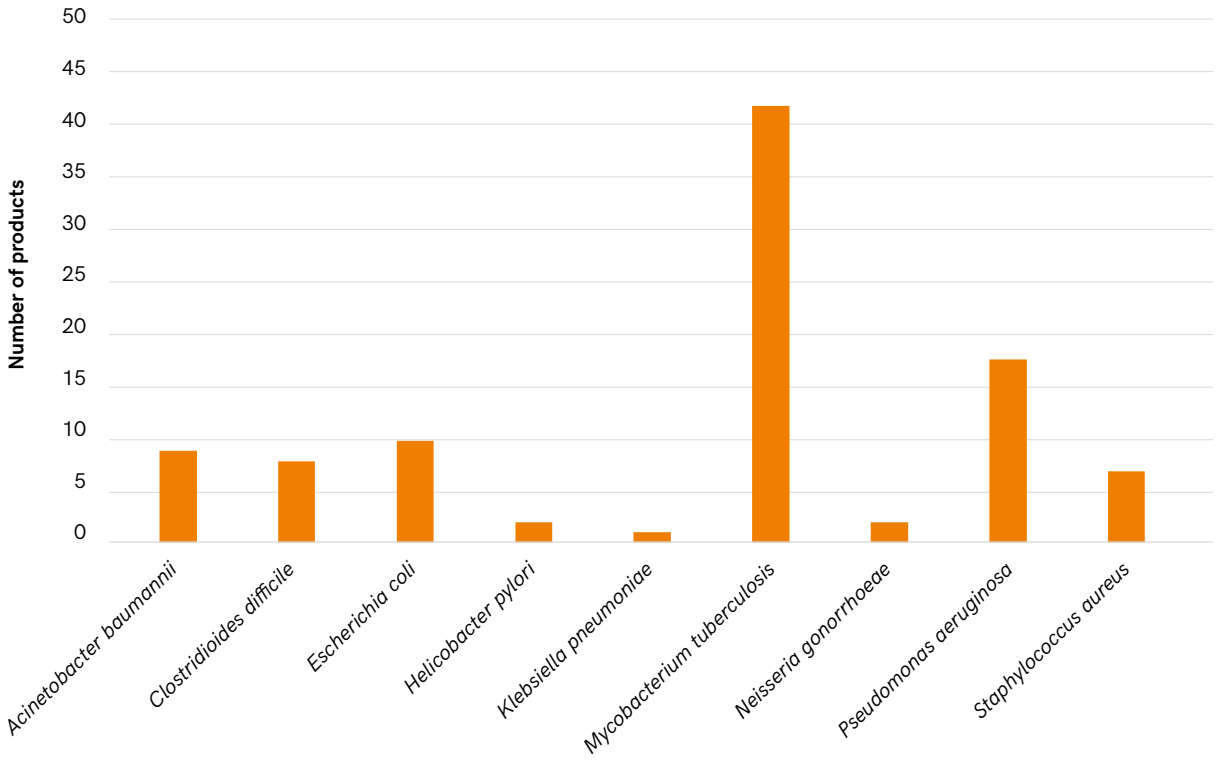
Fig. 5. Categorization of preclinical products by route of administration



3.3 Antibacterial spectrum of agents in the preclinical pipeline

The 2017 WHO priority pathogens list identified pathogens that cause antibiotic-resistant infections for which there is an urgent global need for new antibacterial treatments. Examination of the preclinical pipeline projects indicates that a significant number of products (n = 100, 40%) were focused on a single pathogenic species, which represents a strong shift towards pathogen-focused therapies rather than broader spectrum agents that can also be used empirically. A total of 43 products target *M. tuberculosis*, and a further 38 products target the WHO critical Gram-negative priority pathogens (Fig. 6).

Fig. 6. Pathogens targeted by single pathogen target products



4. Discussion and conclusions

This is WHO's first global analysis of the preclinical antibacterial pipeline based on information from individual projects which are all publicly available in the new WHO database on the Global Observatory on Health R&D. The analysis complements reviews of the preclinical pipeline based on anonymous data by providing institutional and product-level data from the preclinical pipeline projects which captures over 80% of the anonymized review. The data suggests several trends:

Overall there is a broad geographical distribution of preclinical pipeline projects as well as a large diversity of antibacterial strategies and modes of action. Given the high expected attrition rate of preclinical pipeline products, large numbers of candidates are needed in the preclinical phases to ensure that a few eventually come to market. It is predicted that of the products in the preclinical pipeline in this review, approximately two to five direct-acting small molecules and one nontraditional product may make it to the market in 10 years. More projects and consequently more funding are required to ensure a robust preclinical pipeline that brings forward some successful candidates into clinical development.

The main focus of the current preclinical pipeline is Gram-negative pathogens combined with a shift towards pathogen-specific agents. This shift likely reflects an influence of the WHO priority pathogens list, which emphasizes resistant Gram-negatives as the most critical priority and seems to have been interpreted as a suggestion to focus on individual pathogens rather than on infections. The pathogen-specific focus may face challenges for clinical use and development, as it would probably require complementary diagnostics which do not necessarily exist yet – at least not outside highly specialized hospitals – and thus will be an additional challenge for use in low-resource settings.

The preclinical pipeline is innovative in the sense that it is not dominated only by direct-acting small molecules, but also includes many projects that pursue nontraditional approaches, in particular phages, and antimicrobial peptides. This is a significant difference to the clinical pipeline, which is still dominated by derivatives of existing classes of antibacterials, in particular β-lactam/β-lactamase inhibitor combinations and tetracyclines.[3] The challenge for the way forward will be that for some of these new nontraditional approaches, there is no clear pathway for regulatory approval and clinical use.[3] The failure rate of such new approaches is expected to be considerably higher than that of proven pathways for new agents of existing antibiotic classes.

It is very encouraging to see a wide variety of new innovative approaches in the preclinical pipeline. Nonetheless, many scientific challenges are yet to be overcome. Scaling up the use of phage therapy, for example, will require moving away from individual phage cocktails to fixed phage cocktails that can be used routinely for certain indications. Other nontraditional products will not replace existing antibiotics, but rather will restore or enhance their efficacy, and thus will be used in conjunction with them. The added value of decolonizing agents also still needs to be further assessed. The recent review by Theuretzbacher and Piddock[4] provides an in-depth discussion of the opportunities and challenges of the various nontraditional approaches. Only new approaches that do not fall in the category of personalized medicines and that do not require advanced clinical settings, diagnostics and expertise are likely to make a significant impact on the global antimicrobial resistance situation.

With respect to the drug developing institutions, the preclinical antibacterial pipeline is driven by small and medium-sized entities and academic institutions. As these entities and institutions generally rely on external funding and development partnerships, the current market dynamics and investment into antibiotic R&D do not provide for a supportive environment to progress successful products beyond clinical Phase 1.

The diverse preclinical pipeline has been influenced by recent efforts to stimulate the research into the development of new antibacterial agents. It is

encouraging to see the different approaches being pursued in different regions of the world. As is the case in general with new innovative approaches, most projects are likely to fail before they reach the final clinical stages. The size of the preclinical pipeline thus is still likely to be insufficient to generate the needed innovative therapeutics that are urgently required. It is essential to continue to invest in the discovery and preclinical phases to find and progress new antibacterial treatments to address the challenge of drug-resistant bacterial infections.

All of the data contained in this report can be downloaded from the WHO Global Observatory on Health R&D: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products_preclinical/en

5. Limitations and disclaimer

The analysis and assessment of the preclinical pipeline relies largely on data submitted by the respective developers through the open WHO data call. A thorough data cleaning was undertaken, and where available, other sources were used for additional information or the developer was contacted to clarify or fill gaps in the submission. In the absence of clinical data as well as detailed data on the different molecules in development, no independent assessment was undertaken with respect to the antibacterial strategy, risks of development or innovation of the individual projects. This review should be considered as a snapshot and not an analysis. A comparison with other assessments of the preclinical pipeline based on anonymized data[1] suggests that this review reflects over 80% of the preclinical projects. The WHO Secretariat welcomes any additional information and/or feedback on the data presented in this document, which should be sent to antibacterialpipeline@who.int. WHO will hold another open data call for the next preclinical pipeline review and encourages wide participation.

Annex I: WHO priority pathogens list

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, 3rd gen. cephalosporin-resistant

Priority 2: HIGH

- *Enterococcus faecium,* vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and -resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter spp.*, fluoroquinolone-resistant
- *Salmonella species*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, 3rd gen. cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

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

Source: Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis.
Geneva: World Health Organization; 2017.
https://www.who.int/medicines/areas/rational_use/prioritization-of-pathogens/en/

World Health Organization
Antimicrobial Resistance Division
20 Avenue Appia
1211 Geneva 27
Switzerland
https://www.who.int/antimicrobial-resistance/en/