

2019 ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

an analysis of the antibacterial clinical development pipeline



World Health
Organization

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2019 Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline
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Abbreviations and acronyms

ABSSSI	acute bacterial skin and skin structure infection	MIC	minimum inhibitory concentration
AWaRe	Access, Watch, and Reserve classification	MmpL3	mycobacterial membrane protein large 3
BARDA	Biomedical Advanced Research and Development Authority	MoA	mode of action
BIO	Biotechnology Innovation Organization	MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
BLI	β -lactamase inhibitor	NBTI	novel bacterial topoisomerase II inhibitor
CAP	community-acquired pneumonia	NDA	New Drug Application
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator	NDM	New Delhi metallo- β -lactamase
cIAI	complicated intra-abdominal infection	NIH/NIAID	National Institutes of Health, National Institute of Allergy and Infectious Diseases
CRAB	carbapenem-resistant <i>Acinetobacter baumannii</i>	OPP	other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority)
CRE	carbapenem-resistant <i>Enterobacteriaceae</i>	OXA	oxacillinase
CRPA	carbapenem-resistant <i>Pseudomonas aeruginosa</i>	PBP	penicillin-binding protein
cUTI	complicated urinary tract infection	PDF	peptide deformylase
DBO	diazabicyclooctane	PK/PD	pharmacokinetics/pharmacodynamics
DHFR	dihydrofolate reductase	R&D	research and development
DNA	deoxyribonucleic acid	REPAIR	Replenishing and Enabling the Pipeline for Anti-Infective Resistance
DNDi	Drugs for Neglected Diseases initiative	SME	small- or medium-sized enterprise and <i>Serratia marcescens</i> enzymes
DOI	declaration of interest	TAG	Treatment Action Group
DprE1	decaprenylphosphoryl- β -D-ribose 2-epimerase	TB	tuberculosis
EMA	European Medicines Agency	TB Alliance	Global Alliance for TB Drug Development
EML	essential medicines list	tet	tetracycline resistance encoding gene
ESBL	extended-spectrum β -lactamase	UTI	urinary tract infection
FDA	Food and Drug Administration	VAP	ventilator-associated pneumonia
GARDP	Global Antibiotic Research and Development Partnership	VIM	Verona integron-encoded metallo- β -lactamase
HAP	hospital-acquired pneumonia	VRE	vancomycin-resistant <i>Enterococci</i>
ICTRP	International Clinical Trials Registry Platform	WHO	World Health Organization
IgG	immunoglobulin G	XDR	extremely drug resistant
IgM	immunoglobulin M		
IMI	Innovative Medicines Initiative and imipenem-hydrolysing β -lactamase		
IMP	active-on-imipenem type β -lactamases		
iv	intravenous		
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance		
KPC	<i>Klebsiella pneumoniae</i> carbapenemase		
LeuRS	leucyl-tRNA synthetase		
MAA	marketing authorisation application		
MBL	metallo- β -lactamase		
MDR	multidrug-resistant		

Executive summary

This report is the World Health Organization's (WHO) third annual review of the clinical antibacterial pipeline to analyse how the pipeline responds to the WHO priority pathogens list. This report covers direct-acting small molecules and biological agents that are in development worldwide. It assesses to what extent the pipeline addresses the WHO priority pathogens, *Mycobacterium tuberculosis* and *Clostridioides difficile* and to what extent the antibacterial agents are innovative. This report is part of the WHO's efforts in global research and development (R&D) priority setting to contain antimicrobial resistance.

Key messages:

- The clinical pipeline remains insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.
- It is primarily driven by small- or medium-sized enterprises (SMEs), with large pharmaceutical companies continuing to exit the field.
- Eight new antibacterial agents have been approved since 1 July 2017, but overall, they have limited clinical benefits.
- One new anti-tuberculosis (anti-TB) agent, pretomanid, developed by a not-for-profit organization, has been approved for use within a set drug-combination treatment for MDR TB.
- The current clinical pipeline contains 50 antibiotics and combinations (with a new therapeutic entity) and 10 biologicals, of which 32 antibiotics are active against the WHO priority pathogens:
 - Six of these agents fulfil at least one of the innovation criteria; only two of these are active against the critical MDR Gram-negative bacteria.
- More than 40% of the pipeline targeting WHO priority pathogens consists of additional β -lactam and β -lactamase inhibitor (BLI) combinations, with a major gap in activity against metallo- β -lactamase (MBL) producers.
- The anti-TB and *C. difficile* antibacterial pipeline is more innovative than the WHO priority pathogens pipeline, with more than half of the antibiotics fulfilling all of the innovation criteria.

Market approvals

Since 2017 eight new antibiotics – including one for the treatment of TB – have been approved (Table 1). Two, vaborbactam + meropenem and lefamulin, were classified as meeting at least one of the innovation criteria. The other newly approved antibiotics are derivatives of known classes, such as the two tetracycline derivatives eravacycline and omadacycline. Half of the new agents target carbapenem-resistant *Enterobacteriaceae* (CRE); however, only one is of a new class. New approved antibiotics to treat carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are absent. Thus, there is a visible mismatch between the few newly approved antibiotics and the WHO priority pathogens list.

Of the two new β -lactam/BLI combinations that have been approved, vaborbactam is a first-in-class BLI that contains a cyclic boronate pharmacophore and relebactam, a diazabicyclooctane (DBO) analogue. Both are active against many CRE isolates, but not against CRE where resistance is due to MBLs such as the New Delhi metallo- β -lactamase (NDM) enzyme.

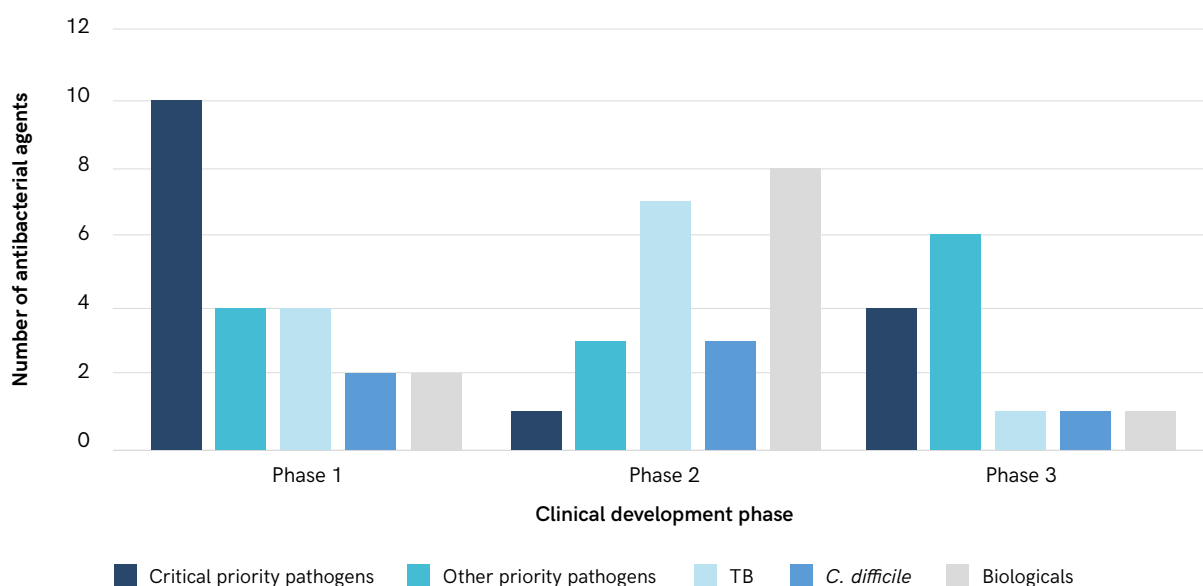
Pretomanid, which was approved by the US Food and Drug Administration (FDA) in August 2019 for use within a set drug-combination treatment for MDR TB, is the first new TB drug to be developed and registered by a not-for-profit organization, the Global Alliance for TB Drug Development (TB Alliance).

Overall, the newly approved products have limited clinical benefit over existing treatments. The lack of differentiation against existing treatments, their non-inclusion in clinical guidelines and their higher prices in comparison to existing generic treatments make it difficult to predict their place in the treatment landscape. As six of the eight are from existing classes where multiple resistance mechanisms are well established, the possibility of fast emergence of resistance to these new agents is foreseen.

Clinical antibacterial pipeline

As of 1 September 2019, there are 50 antibiotics and combinations (with a new therapeutic entity), and 10 biologicals in the clinical pipeline (Phase 1–3) targeting the WHO priority pathogens, TB and *C. difficile* (Fig. 1). Of these 50 antibiotics, 32 target the WHO priority pathogens, and 12 of those have activity against at least one of the critical Gram-negative pathogens (Table 2). There are 12 antibiotics targeting TB and six for the treatment of *C. difficile* infections.

Fig. 1. Antibacterial agents in clinical development (Phase 1–3)



Innovativeness

Of the 32 antibiotics that are being developed and that target the WHO priority pathogens, six fulfil at least one of the four criteria that were used to assess the extent to which agents in the pipeline can be classified as innovative (see criteria under section 2.3.2).

Only two of the antibiotics that meet at least one of the innovation criteria are active against the critical Gram-negative bacteria. On 17 July 2019, Polyphor terminated development of the intravenous form of murepavadin, which was the only potential treatment option against Gram-negative bacteria that fulfilled all four of the innovation criteria, due to concerns over nephrotoxicity observed in Phase 3. Seven of the 12 antibiotics under development for TB meet at least one of the innovation criteria (Table 4).

The current pipeline is dominated by β -lactam/BLI combinations ($n = 13$, 41% of products targeting WHO priority pathogens). Of the β -lactam/BLI combinations, the majority target extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae*, *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillinase-48 (OXA-48)-producing *Enterobacteriaceae*. There are only two agents (cefiderocol and

durlobactam [ETX-2514] + sulbactam) that are active against MDR *A. baumannii* and one (cefiderocol) that is active against MDR *P. aeruginosa*.

Market dynamics and funding situation

Public and philanthropic investment in developing antibacterial agents has increased in recent years, through mechanisms such as the Biomedical Advanced Research and Development Authority (BARDA), Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR) Impact Fund, and the Global Antibiotic Research and Development Partnership (GARDP). Private investment, however, has further decreased, with large pharmaceutical companies and private venture capital investors abandoning the area.¹ Recognizing the need to ensure that effective antibiotics are available to enable and secure modern medicine (e.g. for patients undergoing chemotherapy or organ transplantation), governments are testing different models to change the value and market dynamics for antibiotics. Current examples include the United States' revised hospital reimbursement system and the United Kingdom and Sweden's pilots on alternative antibiotic procurement and payment models. It is important that all these efforts focus on the most useful and innovative products in the clinical and preclinical pipeline. This assessment should help governments in making appropriate decisions in this regard.

Future changes in methodology for the 2020 update

On 1 October 2019 the advisory group agreed to expand the scope of the clinical antibacterial pipeline review to non-traditional products as well as to include inhaled products for the 2020 pipeline update.

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/en/) and will feed into the data dashboard being developed by the Global AMR R&D Hub.

In addition to this report, in 2019 WHO developed a set of target product profiles for missing antibacterial treatments and has reviewed the preclinical antibacterial drug development pipeline.² The preclinical pipeline data is available through the WHO Global Observatory on Health R&D: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products_preclinical/en.



1. Introduction

Antimicrobial resistant infections are a major threat to global health, as access to effective antibiotics underpins basic and modern medicine. Cancer chemotherapy, invasive surgeries, organ transplantations and complicated deliveries can only be performed without the risk of serious infections because of access to effective antibacterial treatments.

Mortality and morbidity from resistant infections is on the rise globally, and all countries are affected. In the United States alone, each year more than 2.8 million people get an antibiotic-resistant infection, resulting in more than 35,000 deaths.³ In Europe, antibiotic resistance is responsible for an estimated 33,000 deaths annually.⁴ Globally, children and neonates are disproportionately affected by antibiotic resistant infections, particularly in low- and middle-income countries. Pneumonia and bloodstream infections causing sepsis are among the major causes of childhood mortality under the age of 5. Approximately 30% of newborns with sepsis die due to bacterial infections resistant to first-line antibiotics.⁵

Infection prevention and control as well as the conservation of existing antibiotics through antimicrobial stewardship programmes is key to the prevention and control of antimicrobial resistance. In addition, to ensure continued effective treatment of bacterial resistant infections, there is also an urgent need for the development of new antibacterial agents.

In 2017, the Group of 20 (G20) nations committed to intensifying global collaboration on antimicrobial resistance and to further examine options for market incentives for antimicrobial resistance-related R&D. This led to the establishment of the Global AMR R&D Hub. In 2019, the G20 renewed its commitments to antibiotic R&D. The Inter-Agency Coordination Group on Antimicrobial Resistance convened by the Secretary-General of the United Nations, in its final report,⁶ also identified the need for increased investment into antibiotic R&D and to build upon existing alternative models to develop new antibiotics.

This report confirms that although there has been an increase in awareness raising and political discussion on the need to accelerate R&D of new antibiotics, the clinical antibacterial pipeline remains insufficient and further investment and policy action are needed.

In the last couple of years, the majority of the large research-based pharmaceutical companies have exited the field of antibiotic R&D. Despite commitments from the private sector through the AMR Industry Alliance, concrete action is limited. A number of SMEs remain active in R&D and have launched new antibiotics in recent years. However, it is a sobering reality that many of these SMEs are struggling to commercialize their antibiotics in the current market-driven environment.

Product development partnerships such as the Drugs for Neglected Diseases *initiative* (DNDi), which produced fexinidazole for the treatment of sleeping sickness; the Medicines for Malaria Venture, which brought forward multiple malaria medicines; and most recently the TB Alliance, which developed pretomanid, have proven that non-traditional development pathways can very effectively lead to innovative treatments targeting urgent global public health needs. However, it is essential to maintain existing antibiotic R&D and create novel market incentives to both retain and attract new private investment into antibiotic R&D in a sustainable manner.

A number of actors have also newly joined the field supporting antibiotic R&D. GARDP, a joint initiative between WHO and DNDi, supports early- to late-stage R&D and brings the products to market, while ensuring access and responsible use. BARDA, CARB-X, Innovative Medicines Initiative (IMI), Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) and the REPAIR Impact Fund are some of the current funders for antibiotic R&D. However, with the exception of BARDA and GARDP, these organizations mainly target early-stage research (up until Phase 1).

To address the challenging market dynamics of antibiotics and their present low value, a few pilot efforts are currently ongoing to explore new payment models to incentivize antibiotic development. One example is the United Kingdom National Health Service's subscription-style model, that utilizes payment for access to antibiotics as opposed to paying for volume. Initiatives are also being set up to try to revive existing old antibiotics and prevent shortages and stock-outs. A consortium of foundations and hospitals in the United States, for instance, has formed a not-for-profit company, Civica Rx, to manufacture or subcontract manufacturing of generic medicines that are affected by shortages, including generic intravenous antibiotics.⁷

This report confirms that despite increased awareness raising and political discussion on the need to accelerate R&D of new antibiotics, the clinical antibacterial pipeline remains insufficient. Additional initiatives and investments are needed to drive antibiotic R&D and innovation and to build a robust pipeline.

This report is the WHO's third annual review of the clinical antibacterial pipeline to analyse how the pipeline has responded to the WHO priority pathogens list. In addition, in 2019 for the first time WHO reviewed the preclinical antibacterial drug development pipeline and published a database: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products_preclinical/en

2. Methods

Evaluation of the antibacterial clinical development pipeline was conducted through consensus agreement by an advisory group comprising clinicians, microbiologists and experts in antibiotic R&D, pharmacokinetics/pharmacodynamics (PK/PD) and antimicrobial resistance (see Acknowledgements). The experts reviewed the quality criteria and assessed each agent against those criteria during a two-day advisory group meeting (30 September–1 October 2019). The group was assisted by members of the WHO Secretariat. Members of the advisory group who had conflicts of interest (Annex 1) with respect to a particular agent were excluded from the discussion of that agent. The draft evaluation of all antibiotics and this report were circulated to all members of the advisory group for feedback before publication.

2.1 Scope and inclusion/exclusion criteria

This review is limited to new therapeutic entities⁸ that are in Phase 1–3 clinical trials and do not have market authorization for human use anywhere in the world. It is restricted to agents that could potentially be used to treat bacterial infections caused by the WHO priority pathogens⁹ (Box 1), TB or *C. difficile* and that have a specific antibacterial effect. The analysis does not include:

- preventive interventions, such as vaccines or topical decolonizing agents;
- immunomodulating or microbiome modulating agents;
- nonspecific inorganic substances;
- biodefence agents;
- agents not developed for systemic use (injectable or oral formulations) but only for topical application (e.g. creams or eye drops);
- new formulations of existing treatments; or
- analysis of clinical effectiveness.

Fixed-dose combinations of potentiators (molecules that enhance the effectiveness of antibiotics but are not antibacterial themselves) and antibacterial agents are included if they contain a new chemical entity.

The analysis only includes agents that are in active development. Agents for which no progress or activity in clinical development has been recorded for 5 years or more are listed in a separate table. Agents that no longer appear in a company's development pipeline were excluded. One of the main sources of data is clinical trial registries, but not all trials are registered. Thus, all companies and institutions are encouraged to register clinical trials in line with the *WHO International Standards for Clinical Trial Registries*¹⁰ and through the International Clinical Trials Registry Platform (ICTRP).

2.2 Search strategy

This 2019 clinical pipeline update is based on the 2017 publication of *Antibacterial Agents in Clinical Development* and the subsequent update in 2018.¹¹ Information on agents in development was sought from a variety of sources. The cut-off point was 1 September 2019, and no agents were added or removed after that date. All agents that met the inclusion criteria were included. Publications were cross-checked by compound name and synonyms (research numbers and brand names) to remove duplicates. Some data sources reported different phases of development in different countries or the use for different indications. For these agents, the most advanced development phase was listed in this clinical pipeline update with a footnote.

The data for analysis was collected through desktop research as well as from relevant stakeholders, including different associations of pharmaceutical companies active in the area, global and regional public and private funders, and foundations (see Acknowledgements).

Sources were consulted as follows:

- Journal articles (review articles published since 1 July 2018 through 1 September 2019; search terms: antibacterial pipeline OR antibiotic pipeline) on the clinical antibacterial pipeline were retrieved from PubMed and conference abstracts and posters. For Phase 1 agents where

limited data was available, information from company websites was used and evaluated by the advisory group for credibility for inclusion.

- The lists of antibiotics in clinical development of the Pew Charitable Trusts and the Access to Medicines Foundation's *Antimicrobial Resistance Benchmark* were consulted.
- The ICTRP and ClinicalTrials.gov were searched.
- In collaboration with the European Medicines Agency (EMA), the commercial database AdisInsight was searched.
- The 2018 pipeline data was sent to various stakeholders, including alliances for pharmaceutical companies and SMEs as well as global public and private R&D funding bodies (see Acknowledgements) for submission of updates with supporting documentation.
- A targeted desktop search of products was carried out with national experts from China, Japan and the Russian Federation.
- Agents developed for use against TB were identified from published reviews of the TB pipeline, notably of the TB Alliance.

The search strategy is described in more detail in the 2017 WHO report.¹¹

2.3 Assessment of activity against priority pathogens and innovation

Evidence for activity against WHO priority pathogens and innovation was retrieved from peer-reviewed publications. For agents in the early stages of development, information from presentations and posters at scientific conferences and information published by the developers was also used. Information was considered only if it was publicly available and after an internal quality review to ensure it was scientifically sound.

2.3.1 Expected activity against priority pathogens

Both in vitro and in vivo (when available) data was reviewed for activity against WHO priority pathogens. In assessing activity, the advisory group made judgements about whether the agent was potentially clinically active against the selected bacteria based on published minimum inhibitory

concentrations (MICs) and their pharmacokinetics. When available, data on PK/PD and information on non-clinical or clinical efficacy was considered in the assessment. Drugs that have shown activity in vitro but are currently not being developed for relevant indications were not assessed against the respective pathogens.

The advisory group classified agents for which there was inconclusive data as "possibly active", represented by a question mark. For agents for which there was little or no data on their activity against specific pathogens, the advisory group classified the agents as "possibly active", if drugs of the same class are known to be active against the respective pathogen.¹²

2.3.2 Innovation

An agent was considered innovative if there was an absence of known cross-resistance to existing antibiotics. In this context, cross-resistance is defined as within-class cross-resistance that can be measured by systematic susceptibility testing in vitro of a diverse panel of genetically defined pathogens, combined with genetic characterization of mutants and molecular structural analysis. An increase in the MIC of a new derivative in strains that are resistant to a representative of the same antibacterial class compared to the wild type constitutes cross-resistance even if the MIC increase stays below the clinical breakpoint.

Surrogate predictors for the absence of cross-resistance which were also assessed include the following:¹³

- new class (new scaffold or pharmacophore);
- new target (new binding site);
- new mode of action.

These were used where sufficient information on cross-resistance was not available. All four innovation criteria were separately assessed for each agent.

If products do not meet the innovation criteria it does not necessarily mean they do not have clinical utility for specific patients. For example, a better safety profile than the standard of care, a less invasive route, or better clinical outcomes or increased activity against priority pathogens could provide improvements but need to be proven in clinical trials. These aspects were not reviewed for this report.

TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEARCH AND DEVELOPMENT

FIVE REASONS WHY



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.



Patients with multidrug-resistant TB (MDR-TB¹) 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.



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-TB²) is successful in only one in three patients at best.



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

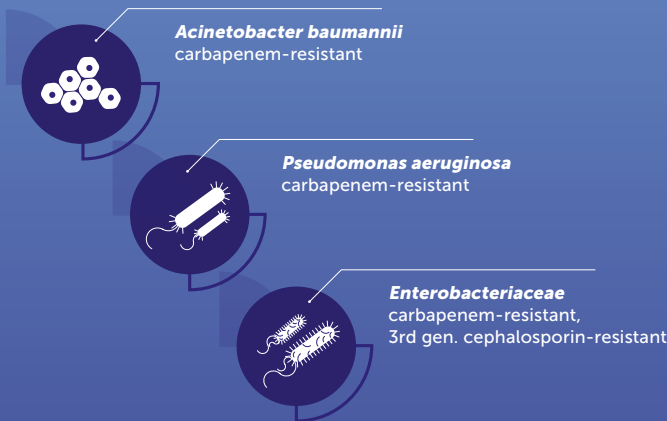


Only two new antibiotics for treatment of MDR-TB have reached the market in over 70 years. R&D investment in TB – seriously underfunded – is at its lowest level since 2008.

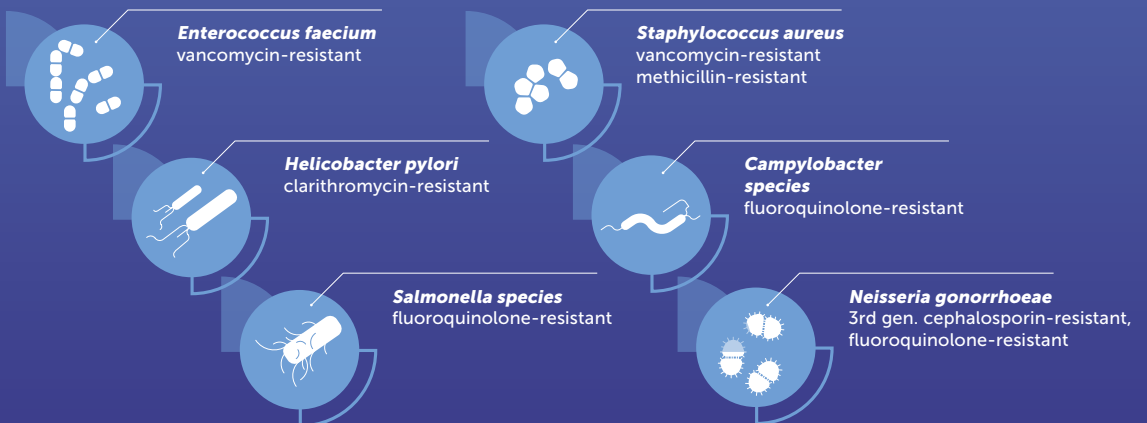
¹ MDR-TB – multidrug-resistant tuberculosis, that does not respond to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines.
² XDR-TB – extensively drug-resistant tuberculosis, defined as MDR-TB plus resistance to fluoroquinolones and injectable second-line anti-TB medicines.

OTHER PRIORITY PATHOGENS

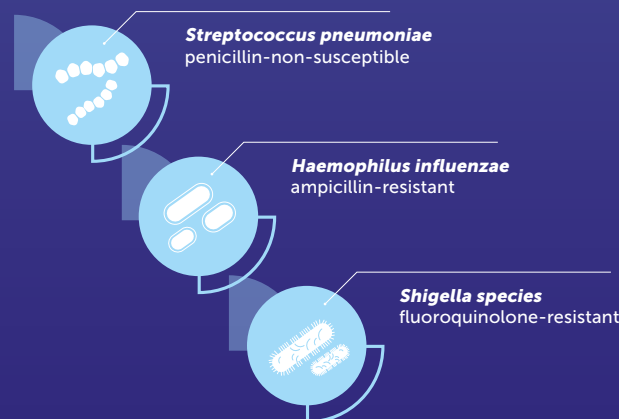
CRITICAL PRIORITY



HIGH PRIORITY



MEDIUM PRIORITY



3. Agents that obtained market authorization

Since WHO's first analysis of the clinical antibacterial pipeline in 2017, eight new antibiotics, including one for the treatment of TB, have been approved. Most of these are derivatives of known classes, such as the tetracycline derivatives eravacycline and omadacycline, as well as the majority targeting CRE (n = 4) and other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority) (OPPs) (n = 4).

Both omadacycline and eravacycline are semi-synthetic and fully synthetic tetracycline derivatives, respectively. Omadacycline (intravenous and oral) has both Gram-positive activity – including methicillin-resistant *Staphylococcus aureus* (MRSA) – and limited Gram-negative activity. It is approved for both skin infections and community-acquired pneumonia (CAP). The need for new agents for skin infections is limited, and the Gram-negative activity of omadacycline has not been studied in the clinic. Nonetheless, having an oral single agent option for CAP may prove useful for selected patients.¹⁴ Eravacycline (intravenous only) is approved for complicated intra-abdominal infections (cIAIs); it failed in trials of complicated urinary tract infections (cUTIs).¹⁵ Further work is needed to assess the clinical use and value of omadacycline and eravacycline.

Of the two newly approved β -lactam/BLI combinations, vaborbactam is the first representative of a new chemical class, a BLI that contains a cyclic boronate pharmacophore and that, in combination with meropenem, is active against KPC-producing *Enterobacteriaceae*. The other is relebactam, a DBO analogue that, in combination with imipenem/cilastatin, is active against Class A (including KPC) and Class C β -lactams. Both of these agents are intravenous only, and neither is active against MBLs nor any relevant OXA enzymes. Another visible gap in the newly approved antibiotics is agents for treating carbapenem-resistant *A. baumannii* (CRAB) and *P. aeruginosa* (CRPA) isolates.

Pretomanid, a nitroimidazo-oxazine which was developed by the not-for-profit organization TB Alliance, was approved by the US FDA. It is part of a three-drug combination (with bedaquiline and

linezolid), 6-9-month, all-oral regimen for the treatment of adult patients with extremely drug resistant (XDR) TB and treatment-intolerant or non-responsive MDR pulmonary TB. Pretomanid was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs.¹⁶

The recently approved antibiotics have mainly been approved for the treatment of cUTI and/or cIAI. Two new antibiotics target CAP, one of which is a member of the pleuromutilin class (lefamulin), which has been used topically in humans and is an established class for systemic use in veterinary medicine. Two of the newly approved antibiotics were incorporated into the *WHO Model List of Essential Medicines* in 2019: vaborbactam + meropenem and plazomicin.¹⁷ Unfortunately, Achaogen, the company which developed plazomicin, has filed for bankruptcy, highlighting the difficult market dynamics that antibiotic developers are currently facing.

In 2019, to ensure access to patients who need them while restricting irresponsible excessive use, WHO classified all new antibiotics under the AWaRe (Access, Watch, Reserve) index:

- delafloxacin (Watch);
- vaborbactam + meropenem (Reserve);
- plazomicin (Reserve);
- eravacycline (Reserve); and
- omadacycline (Reserve).

Further evidence and studies are needed regarding the added clinical value and effectiveness of these agents. So far, no post-approval usage data has been made available to evaluate the indications and adequacy of their usage in different populations and countries, nor does it seem likely that such data will be available in the near future. Based on anecdotal evidence and current sales figures, clinicians appear reluctant to use the new antibiotic agents to treat the infectious syndromes (cUTI, cIAI) that were the initial target of regulatory authority approval.

Table 1. Antibiotics that gained market authorization between July 2017 and September 2019

Name (trade name)	Market authorization holder	Approved by (date)	Antibiotic class	Route of administration	Indication/s	WHO EML & AWaRe	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela)	Melinta	FDA (6/2017 ABSSSI, 10/2019 CAP) MAA	Fluoroquinolone	iv & oral	ABSSSI, CAP	AWaRe: Watch	○	○	○	●	-	-	-	-
Vaborbactam + meropenem (Vabomere)	Melinta	FDA (8/2017) EMA (11/2018)	Boronate BLI + carbapenem	iv	cUTI	WHO EML & AWaRe: Reserve	○	○	● ¹	/	?	✓	-	-
Plazomicin (Zemdri)	Achaogen	FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML & AWaRe: Reserve	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	AWaRe: Reserve	?	○	●	/	-	-	-	-
Omadacycline (Nuzyra)	Paratek	FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSSI (iv, oral)	AWaRe: Reserve	○	○	○	●	-	-	-	-
Relebactam + imipenem/cilastatin (Recarbrio)	MSD	FDA (7/2019)	DBO-BLI + carbapenem/ degradation inhibitor	iv	cUTI, cIAI		○	?	● ¹	/	-	-	-	-
Lefamulin	Nabriva	FDA (8/2019)	Pleuromutilin	iv & oral	CAP		/	/	/	●	?	✓ ²	-	-
Pretomanid (PA-824)	TB Alliance	FDA (8/2019)	Nitroimidazole	oral	XDR TB		/	/	/	● ³	-	-	-	-

Pathogen activity: ● active; ? possibly active; / activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. The only agents assessed against OPP were those that are not active against critical priority pathogens. OPP includes the high- and medium-priority pathogens.

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data or no agreement among the advisory group; - criterion not fulfilled.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CC, new chemical class; DHFR, dihydrofolate reductase; iv, intravenous; EML, essential medicines list; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; NDA, New Drug Application (FDA); MAA, marketing authorisation application (EMA); PBP, penicillin-binding protein; T, new target.

¹ Active against *K. pneumoniae* carbapenemase (KPC), but not metallo-β-lactamase-producing *Enterobacteriaceae*.

² First systemic formulation of this class, which was previously used in animals and topically in humans.

³ Approved for the treatment of XDR TB or treatment-intolerant/non-responsive MDR-TB, in combination with bedaquiline and linezolid.

4. Agents in clinical development

The following sections describe the current antibacterial clinical development pipeline with activity against the WHO priority pathogens, TB and *C. difficile* with a specific section on biological agents in development.

4.1 Antibiotics being developed against WHO priority pathogens

There are currently 32 antibacterial agents in clinical development Phases 1–3 targeting WHO priority pathogens, of which 12 have activity against at least one of the critical Gram-negative pathogens. Murepavadin was in Phase 3 trials and had fulfilled all four of the innovation criteria in the 2018 update, including the main criteria for absence of known cross-resistance. But the agent was removed as of 17 July 2019 after Polyphor terminated its development for systemic infections due to concerns about nephrotoxicity.¹⁸ Murepavadin remains in development for inhalation therapy.

The majority of products in the clinical pipeline are derivatives of existing classes. Of the 32 agents, six fulfil at least one of the four innovation

criteria. Half of these are in Phase 3 clinical trials (taniborbactam, zoliflodacin, gepotidacin); a novel FabI inhibitor (afabicin) is in Phase 2, and a boronate BLI (VNRX-7145) and an FtsZ inhibitor (TXA-709) are in Phase 1.

Since the 2018 update, several new products have entered Phase 1 (e.g. SPR-206), which benefited from support from CARB-X, JPIAMR, BARDA and the REPAIR Impact Fund. The two novel oral topoisomerase inhibitors (zoliflodacin and gepotidacin) have successfully moved from Phase 2 to Phase 3 trials. Lefamulin (a novel pleuromutulin) and relebactam + imipenem/cilastatin (a DBO BLI) moved from Phase 3 to FDA approval; and two antibiotics (omadacycline and eravacycline) moved from New Drug Application (NDA) submission to gaining FDA approval. One additional product, cefiderocol, a β -lactam which is intrinsically more stable to a variety of β lactamases and has activity against all three critical priority pathogens, received FDA approval for cUTI after the cut-off date of this report and is thus still included in Table 2.

Table 2. Antibiotics that are being developed against WHO priority pathogens

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Lasclufloxacin	NDA ¹	Fluoroquinolone	iv & oral (Kyorin)	○	○	○	?	-	-	-	-
Cefiderocol ¹²	NDA ² MAA ²	Siderophore cephalosporin	iv (Shionogi)	●	●	●	/	?	-	-	-
Sulopenem, Sulopenem etzadroxil/probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○ ³	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate-BLI + cephalosporin	iv (VenatoRx)	○	?	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	β-lactam BLI + cephalosporin	iv (Allegra)	○	○	○ ⁴	/	-	-	-	-
Zoliflodacin	3	Topoisomerase inhibitor (spiropyrimidenetrione)	oral (Entasis/GARDP)	/	/	/	●	✓	✓	-	✓
Gepotidacin	3	Topoisomerase inhibitor (triazacenaphthylene)	iv & oral (GSK)	/	/	/	●	?	✓	-	✓
Levonadifloxacin Alalevonadifloxacin	3 ⁵	Fluoroquinolone	iv oral (Wockhardt)	○	○	○	?	-	-	-	-
Cefilavancin (TD-1792)	3 ⁶	Glycopeptide-cephalosporin conjugate	iv (Theravance/R Pharm)	/	/	/	●	-	-	-	-
Solithromycin	3 ⁷	Macrolide	iv & oral (Melinta/Fujifilm Toyama Chemical)	/	/	/	●	-	-	-	-
Contezolid Contezolid acefosamil	2/3 ⁸	Oxazolidinone	oral (MicuRx) iv & oral (MicuRx)	/	/	/	●	-	-	-	-
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
BOS-228 (LYS-228)	2	Monobactam	iv (Boston Pharmaceuticals)	○	○	●	/	-	-	-	-
Nafithromycin (WCK-4873)	2	Macrolide	oral (Wockhardt)	/	/	/	●	-	-	-	-
TNP-2092	2	Rifamycin-quinolizone hybrid	iv & oral (TenNor)	/	/	/	?	-	-	-	-
Benapenem	2 ⁹	Carbapenem	iv (Sichuan Pharmaceutical)	○	○	○	/	-	-	-	-
Zidebactam + cefepime	1	DBO-BLI/PBP2 binder + cephalosporin	iv (Wockhardt)	○	?	●	/	-	-	-	-
Nacubactam + meropenem	1	DBO-BLI/PBP2 binder + meropenem	iv (NacuGen Therapeutics)	○	○	● ¹⁰	/	-	-	-	-
ETX0282 + cefpodoxime	1	DBO-BLI/PBP2 binder + cephalosporin	oral (Entasis)	○	○	● ¹⁰	/	-	-	-	-
VNRX-7145 + ceftibuten	1	Boronate-BLI + cephalosporin	oral (VenatoRx)	○	○	●	/	?	✓	-	-
SPR-741 + β-lactam	1	Polymyxin (potentiator) + β-lactam	iv (Spero)	?	?	?	/	-	-	-	-
SPR-206	1	Polymyxin	iv (Spero)	●	●	●	/	-	-	-	-

... continued Table 2. Antibiotics that are being developed against WHO priority pathogens

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	○	○	○	●	-	-	-	-
TP-271	1	Tetracycline	iv & oral (Tetraphase)	?	○	○	●	-	-	-	-
TP-6076	1	Tetracycline	iv (Tetraphase)	●	○	?	/	-	-	-	-
EBL-10031 (apramycin)	1 ¹⁰	Aminoglycoside	iv (Juvabis)	?	-	?	/	-	-	-	-
AIC-499 + unknown BLI	1	β-lactam + BLI	iv (AiCuris)	?	?	?	/	-	-	-	-
TNP-2198	1	Rifamycin-nitroimidazole conjugate	oral (TenNor)	/	/	/	●	-	-	-	-
TXA-709	1	FtsZ inhibitor	oral & iv (Taxis)	○	○	○	●	✓	✓	✓	✓
BCM-0184	1	?	oral (Biocidium)	○	○	○	●	?	?	?	?
ARX-1796 (oral avibactam prodrug)	1	DBO-BLI + β-lactam	oral (Arixa Pharmaceuticals)	○	○	● ¹¹	/	-	-	-	-

Pathogen activity: ● active; ? possibly active; ○ not or insufficiently active; / activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. The only agents assessed against OPPs were those that are not active against critical priority pathogens. OPP includes the high- and medium-priority pathogens.

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data or no agreement among the advisory group; - criterion not fulfilled.

¹ Clinical development only for Japan; registered on 20 September 2019 for CAP in Japan (oral).

² NDA submitted in December 2018 and MAA submitted in April 2019.

³ Active against ESBL-producing cephalosporin-resistant but not carbapenem-resistant *Enterobacteriaceae*.

⁴ Active against ESBL-producing cephalosporin-resistant and some KPC-producing CRE.

⁵ Clinical development only for India.

⁶ Clinical development only for Russia.

⁷ Clinical development only for Japan.

⁸ Contezolid acefosamil: Phase 2 in the United States. Contezolid: Phase 3 in China; NDA in China expected in 2020.

⁹ Clinical development only for China.

¹⁰ Previously used in animals.

¹¹ Active against KPC but not MBL-producing *Enterobacteriaceae*.

¹² FDA approval on 14 November 2019 for cUTI, which was after the cut-off date of this report.

4.1.1 β -Lactams

β -Lactams are a well-established group of antibiotics that interrupt bacterial cell-wall formation through covalent linking to penicillin-binding proteins (PBPs) and subsequently disrupt peptidoglycan biosynthesis. The group includes penicillins, cephalosporins, carbapenems and monobactams.

The emergence of bacteria that produce enzymes (β -lactamases) that hydrolyse β -lactam antibiotics has rendered many of these agents ineffective.¹⁹ In addition, the spread of ESBLs that confer resistance to broad-spectrum cephalosporins and of carbapenemases that confer resistance to carbapenems is also a concern.

There are four structural classes²⁰ of β -lactamases, known as A, B, C and D. Only Class B enzymes are MBLs. These enzymes contain a zinc ion in their active site that activates a water molecule, which serves as the nucleophile in hydrolysing β -lactams. The remaining classes (A/C/D) use a serine nucleophile to hydrolyse β -lactams, and thus are termed serine-

β -lactamases. ESBLs belong mostly to Class A. Enzymes with carbapenemase activity are found among Class A (KPC, IMI and SME), Class B MBLs (IMP, NDM, VIM) and notably Class D (OXA).²¹

The main strategy for circumventing hydrolysis of β lactams is to combine a β -lactam antibiotic with a BLI to restore the effectiveness of the β -lactam antibiotic. Traditional BLIs (clavulanic acid, tazobactam and sulbactam) inhibit ESBLs, but do not inhibit carbapenemases of the same class.

Over the past years, some new BLI combinations with carbapenems or cephalosporins have entered the market (e.g. ceftolozane + tazobactam and ceftazidime + avibactam),²² but they do not cover all classes, namely Class B MBLs (e.g. NDM-1) and Class D enzymes produced by *Acinetobacter*. The spread of NDM-1-producing CRE has caused outbreaks with high mortality in different countries, most recently in Tuscany, Italy, where 31 out of 75 patients died of sepsis.²³ The last-line treatment options in such invasive infections are usually colistin and tigecycline.

Table 3. Expected activity of β -lactams and β -lactam/BLI combinations against common β -lactamases

	CRE				CRAB	CRPA
	A	A	D	B		
	ESBL (CTX-M)	KPC (KPC-2,-3)	OXA (OXA-48)	MBL (NDM)		
Vaborbactam + meropenem	●	●	●	-	-	-
Relebactam + imipenem/cilastatin	●	●	●	-	-	?
Cefiderocol	●	●	●	●	●	●
Sulopenem	●	-	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	-	-	-	-	●	-
Taniborbactam (VNRX-5133) + cefepime	●	●	●	●	-	?
Enmetazobactam (AAI-101) + cefepime	●	?	-	-	-	-
BOS-288	●	●	●	●	-	-
Zidebactam + cefepime	●	●	●	?	-	?
Nacubactam + meropenem	●	●	●	?	-	-
ETX-0282 + cefpodoxime	●	●	●	-	-	-
VNRX-7145 + ceftibuten	●	●	●	-	-	-
ARX-1796 (oral avibactam prodrug)	●	●	●	-	-	-

Pathogen activity: ● active; ? possibly active; - not or insufficiently active or activity not assessed.

Grey shading: Agents with market approval on the cut-off date of this report.

In the clinical pipeline, most of the BLIs (e.g. VNRX-7145) inhibit Class A, C and some D enzymes, but very few inhibit Class B enzymes. Table 3 shows the activity of different β -lactams and β -lactam/BLI combinations recently approved (since 2017) and currently in development against the most clinically relevant β -lactamases, especially carbapenemases. The table shows that the majority do not inhibit all clinically relevant β -lactamases. One notable gap is agents with the ability to inhibit all β -lactamase producers, including Class B producers (MBLs).

Cefiderocol, a siderophore cephalosporin that was recently approved by the FDA, is intrinsically more stable against β -lactamases, including ESBL and AmpC. It also has greater uptake into the periplasmic space due to its siderophore-like property. Cefiderocol is currently the agent with the broadest Gram-negative spectrum, but it still exhibits considerable cross-resistance to existing classes.

Resistance mechanisms other than β -lactamase production are not influenced by BLIs. This is important for the treatment of *P. aeruginosa* and to a certain extent *A. baumannii*, as they have developed resistance mechanisms beyond the production of β -lactamases, including decreased permeability of the outer membrane, upregulated efflux pumps and modified PBPs. Consequently, many new BLI combinations are most successful in treating CRE and have little to no benefit in treating *P. aeruginosa* and *A. baumannii*.

The DBO class of BLIs in the pipeline – such as ETX-2514, nacubactam and zidebactam, which are non- β -lactam BLIs – have intrinsic antibacterial activity based on binding to PBP2 and may result in synergistic antibacterial activity in *Enterobacteriaceae*.²⁴

Despite inhibition of β -lactamases, other resistance mechanisms may still confer resistance to β -lactam/BLI combinations.²⁵⁻²⁷

Legend: Expected activity against priority pathogens:

CRAB	CRPA	CRE	OPP
○	?	●	/

Pathogen activity: ● active; ? possibly active; ○ not or insufficiently active; / activity not assessed

Cefiderocol, iv

NDA, MAA

● ● ● /

- A cephalosporin, linked to a siderophore, that makes use of the bacterial iron transport mechanism to facilitate uptake of the agent through the outer membrane of Gram-negative bacteria.²⁸ Stable against most β -lactamases, including some MBLs, but has partly elevated MICs in CRPA and KPC overproducers.²⁹
- Susceptibility rates are comparable to those of colistin and tigecycline,³⁰ PK/PD are similar to those of other cephalosporins.
- FDA approved on 14 November 2019 in the United States for cUTI, including pyelonephritis. Submitted to the EMA in April 2019.
- Phase 3 trials for cUTI vs imipenem/cilastatin, NCT02321800), hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) vs meropenem (NCT03032380) and critical Gram-negative pathogens vs best-available therapy (NCT02714595).

Sulopenem, iv/oral

Phase 3

○ ○ ○ /

- Synthetic penem; oral prodrug sulopenem etzadroxil.
- Activity against *Enterobacteriaceae*, including ESBL producers; Gram-positive activity similar to that of carbapenems; complete cross-resistance with existing carbapenems.³¹
- Active against ESBL-producing cephalosporin-resistant but not carbapenem-resistant *Enterobacteriaceae*.
- Phase 3 trial in uncomplicated and complicated UTI (NCT03354598, NCT03357614).

Durlobactam + sulbactam, iv

Phase 3

● ○ ○ /

- Durlobactam (ETX-2514) is a DBO-type BLI with inhibitory activity of PBP2 and thus has intrinsic activity against some *Enterobacteriaceae* spp. It restores the activity of sulbactam (penicillanic acid sulfone) in *A. baumannii*; the combination is currently being developed for *A. baumannii* infections.³²
- Phase 3 trial (NCT03445195).

Taniborbactam + cefepime, iv

Phase 3

○ ? ● /

- Taniborbactam (VNRX-5133) is a boronate-based BLI with activity against Class A, C and D β -lactamases and several MBLs, especially NDM and VIM.
- Phase 3 trial (NCT03840148).

Enmetazobactam + cefepime, iv

Phase 3

○ ○ ● /

- Enmetazobactam (AAI-101) is a tazobactam derivative (β -lactam scaffold) studied in combination with cefepime.
- Similar inhibitory activity to tazobactam but optimized dosing regimen. Cefepime is easier to potentiate than piperacillin. Some activity against some KPC strains; some added benefit over cefepime alone in bacteria-producing Class A β -lactamases and ESBLs.³³
- Phase 3 trial (EudraCT 2017-004868-35).

BOS-288, iv

Phase 2

○ ○ ● /

- BOS-288 (formerly LYS-228) is a monobactam with increased stability to serine- β -lactamases.³⁴
- Phase 2 trials (NCT03377426, NCT03354754) were terminated as part of the out-licensure of the agent to Boston Pharmaceuticals.

Benapenem, iv**Phase 2**

○ ○ ○ /

- A carbapenem currently in Phase 2 trials (NCT03578588, CTR20190760, CTR20181302).
- Clinical development only for China.
- Complete cross-resistance to other carbapenems.

ETX0282 + cefpodoxime, oral**Phase 1**

○ ○ ● /

- ETX0282 is an oral BLI of the DBO type with some intrinsic antibacterial activity against *Enterobacteriaceae* spp. due to PBP2 inhibition.
- Active against ESBL, OXA-48 and KPC, but not MBL-producing *Enterobacteriaceae*.
- A Phase 1 trial is ongoing (NCT03491748).

Zidebactam + cefepime, iv**Phase 1**

○ ? ● /

- Zidebactam is a DBO-type BLI with relevant antibacterial activity against some *Enterobacteriaceae* spp. due to PBP2 inhibition.³⁵
- Synergistic activity in *Enterobacteriaceae* with Class A β -lactamases, including ESBL and KPC, but elevated MICs in MBL producers.^{36,37} Reduced susceptibility in *Pseudomonas* due to IMP or VIM Class B carbapenemases, or combinations of mechanisms (MexAB-OprM or MexXY efflux, diminished OprD function and high-level AmpC production).³⁸
- Phase 1 trials ongoing (NCT02532140, NCT02942810, NCT02707107)

VNRX-7145 + ceftibuten, oral**Phase 1**

○ ○ ● /

- Oral boronate-based BLI with activity against Class A, C and D (OXA-48) β -lactamases; restores the susceptibility of ceftibuten in almost 90% of non-susceptible *Enterobacteriaceae*.
- Not active against MBL producers.
- Phase 1 trial announced but not registered.

Nacubactam + meropenem, iv**Phase 1**

○ ○ ● /

- Nacubactam is a BLI of the DBO type with some intrinsic antibacterial activity due to PBP2 inhibition.
- Inhibits Class A and C β -lactamases.^{39,40}
- Combination partner is meropenem; synergistic activity with various partners in *Enterobacteriaceae*, including some MBL producers (elevated MICs);⁴¹ BLI activity only in *P. aeruginosa* and not carbapenem-resistant *P. aeruginosa*, and no added benefit to carbapenem-resistant *A. baumannii*.⁴²
- Phase 1 PK trial with meropenem (NCT03174795).

AIC-499 + unknown BLI, iv**Phase 1**

? ? ? /

- Limited data available: information on structure, activity or the partner BLI has not been published.
- A Phase 1 trial started in January 2017 but has not been registered.

ARX-1796, oral**Phase 1**

○ ○ ● /

- Oral form of avibactam
- Combination partner is not known; active against KPC and OXA-48 but not MBL producers.
- Phase 1 clinical trial registered (NCT03931876); not yet recruiting.

4.1.2 Tetracyclines

Tetracyclines⁴³ are broad-spectrum, essentially bacteriostatic antibiotics that were discovered in 1948 with activity against Gram-positive and Gram-negative bacteria. Tetracyclines bind to the A site of the 30S ribosomal subunit and inhibit binding of aminoacyl-tRNA, preventing synthesis of polypeptides. Following the discovery of tetracycline, chemical modifications enabled the development of numerous semi-synthetic and, later, fully synthetic tetracyclines with improved activity against emerging MDR bacteria.⁴⁴ Since their introduction, more than 1000 tetracycline resistance genes have been reported and are often associated with mobile genetic elements, including efflux pumps, ribosomal protection proteins, tetracycline-inactivating enzymes (*tet*) and mosaic genes. The semi-synthetic parenteral glycyline, tigecycline, was approved in 2005 and overcomes certain class-specific resistance mechanisms. In 2018, the FDA approved both intravenous and oral formulations of eravacycline, a fully synthetic fluorocycline, and omadacycline, a semi-synthetic aminomethylcycline derivative of minocycline. Currently, three tetracycline derivatives, two synthetic and one semi-synthetic, are in Phase 1 trials.

KBP-7072, oral

Phase 1



- An omadacycline derivative, optimized for Gram-positive respiratory pathogens.
- Limited information available.⁴⁵
- Two Phase 1 trials are completed (NCT02454361, NCT02654626).

TP-271, iv/oral

Phase 1



- Synthetic tetracycline vulnerable to *tet*(A) and *tet*(X).
- Activity similar to that of tigecycline against *Haemophilus influenzae* and Gram-positive pathogens, including vancomycin-resistant *Enterococcus faecium*.⁴⁶
- Phase 1 trials ongoing (NCT03024034, NCT02724085).

TP-6076, iv

Phase 1



- Synthetic tetracycline optimized for Gram-negative pathogens; little influence on *tet* (M, Q, K, A, B and D); elevated MICs in *A. baumannii* overexpressing *adeAB*.⁴⁷
- MICs lower than those of tigecycline in *Enterobacteriaceae* and *A. baumannii*; higher MICs in cases of carbapenem resistance, especially in tigecycline co-resistant strains.⁴⁸
- Phase 1 trial ongoing (NCT03691584).

4.1.3 Aminoglycosides

Aminoglycosides are bactericidal and active against Gram-negative bacteria such as *Pseudomonas*, *Acinetobacter* and *Enterobacter* spp. They are administered via the intravenous or intramuscular route. Commonly used aminoglycosides, such as gentamicin, netilmicin, tobramycin and amikacin, show different resistance rates globally. The most common resistance mechanism is the production of aminoglycoside-modifying enzymes. A newer resistance mechanism is the production of bacterial ribosome-modifying enzymes (16S rRNA methylases), which often occur in NDM-producing *Enterobacteriaceae*.⁴⁹ The recently approved aminoglycoside plazomicin has been optimized to address most aminoglycoside-modifying enzymes.

EBL-10031, iv

Phase 1



- EBL-10031 (apramycin) was licensed in 1980 for oral therapy in animals.
- First warning of resistance in 1986,⁵⁰ resistance described by AAC(3)-IV, acetylation of the 1-amino group.⁵¹
- Phase 1 trial is registered (NCT04105205).

4.1.4 Topoisomerase inhibitors

Topoisomerase inhibitors include quinolones, which are synthetic antibiotics discovered in the 1960s. The drugs in use today are fluoroquinolones. They target two essential type II topoisomerases: DNA gyrase and topoisomerase IV. They bind preferentially to the gyrase subunit GyrA and to the topoisomerase IV subunit ParC.⁵² New agents in clinical development, such as lascufloxacin, are optimized for Gram-positive bacteria and pathogens that

cause respiratory tract infections (*Streptococcus pneumoniae*, *H. influenzae*, *Moraxella* spp., *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumoniae*). There is usually cross-resistance among fluoroquinolones. Two new bacterial topoisomerase II inhibitors (zoliflodacin and gepotidacin), which are in development, have new chemical structures with distinct but potentially overlapping binding sites with fluoroquinolones.^{53,54} These new agents target Gram-positive pathogens, respiratory tract infection pathogens and *Neisseria gonorrhoeae*. One agent being developed against *C. difficile* infections is described in section 4.3.

Lascufloxacin, iv/oral

NDA

○ ○ ○ ?

- Fluoroquinolone optimized for Gram-positive and respiratory tract infection spectrum.⁵⁵
- Spectrum and activity similar to those of levofloxacin, except very low MICs against wild-type *S. aureus* and elevated MICs against MRSA due to cross-resistance. Depending on breakpoints, probably limited efficacy against MRSA; complete cross-resistance in Gram-negative bacteria.
- Developed in Japan; registered in September 2019 for CAP in Japan.

Zoliflodacin, oral

Phase 3

// // ●

- Novel bacterial topoisomerase II inhibitor (spiropyrimidetrione scaffold) with activity against *N. gonorrhoeae* and Gram-positive cocci; clinical development for uncomplicated gonorrhoea.
- No cross-resistance has been described.^{56,57}
- Phase 3 trials for treatment of uncomplicated gonorrhoea ongoing (NCT03959527).

Gepotidacin, iv/oral

Phase 3

// // ●

- Novel bacterial topoisomerase II inhibitor (triazacenaphthylene scaffold); active against Gram-positive and Gram-negative cocci.
- Some cross-resistance described in gonococci.⁵⁸
- Phase 3 trial registered for treatment of uncomplicated UTI (NCT04020341) and gonorrhoea (NCT04010539).

Levonadifloxacin, iv Alalevonadifloxacin, oral

Phase 3

○ ○ ○ ?

- Fluoroquinolone; oral prodrug of levonadifloxacin, which is the arginine salt of S-(-)-nadifloxacin. Nadifloxacin has been available since 1993 as a topical drug for acne.⁶⁰
- Optimized for Gram-positive activity.
- Same activity spectrum as that of lascufloxacin.
- Phase 3 trial completed in India for the treatment of ABSSSI (NCT03405064).

4.1.5 FabI inhibitor

FabI (enoyl-acyl carrier protein reductase) is critical for the final step in elongation of fatty acid biosynthesis in many bacteria. As such, it is an attractive target for drug development. FabI inhibitors have been known since the 1950s, and are represented by isoniazid and ethionamide for TB treatment and the nonspecific biocide and slow-binding FabI inhibitor triclosan. These agents have different binding characteristics.⁶¹ It is not known whether they exert selection pressure on staphylococci, which could lead to cross-resistance.^{62,63}

Afabicin, iv/oral

Phase 2

// // ●

- Afabicin (Debio-1450) is a new staphylococcus-specific antibiotic class developed for *S. aureus* infections as iv and oral form (prodrug).⁶⁴
- Activity in vitro is comparable to that of rifampicin; active against extra- and intracellular *S. aureus*, independent of resistance patterns. Slow reduction of bacterial load.⁵⁹ Risk for emergence of high-level resistance may be offset by high affinity to the target.^{63,65,66}
- Phase 2 trials in staphylococcal ABSSSI (NCT02426918) and bone or joint infections (NCT03723551).

4.1.6 FtsZ inhibitor

FtsZ is a vital cell division protein that is conserved in most bacteria. It undergoes assembly at the mid-cell, forming a dynamic membrane-attached ring structure which then recruits other division proteins to the Y-ring to form the divisome. Inhibiting FtsZ blocks cell division, and thus it is an attractive target for new antibiotics.^{67,68}

TXA-709, iv/oral

Phase 1



- The orally bioavailable methylbenzamide antibiotic TXA-709 and its active metabolite TXA-707 target FtsZ and have been tested against *S. aureus*.⁶⁹
- Phase 1 trial not registered.

4.1.7 Oxazolidinones

Oxazolidinones inhibit protein synthesis through binding at the P site of the 50S ribosomal subunit. They have been in clinical use since 2000; linezolid was the first drug approved, followed by tedizolid. Modifications of the scaffold may address class-specific resistance mechanisms. Some agents in this class have been developed for *C. difficile* infections and TB.

Contezolid, oral

Contezolid acefosamil, iv/oral

Phase 2/3



- Activity against MRSA, vancomycin-resistant *E. faecium* and resistant *S. pneumoniae*.
- Little information published, and potential differences from linezolid are unclear.^{70,71}
- A Phase 2 trial of contezolid acefosamil in patients with ABSSSI has been completed (NCT02269319) in the United States, and a Phase 3 trial of contezolid has been completed in China.

4.1.8 Macrolides and ketolides

Macrolides inhibit protein synthesis through binding to the 50S ribosomal subunit. They are bacteriostatic with activity against many Gram-positive bacteria and limited activity against Gram-negatives. Second-generation semi-synthetic derivatives of the first natural product include clarithromycin and azithromycin.⁷²

Ketolides are a subclass of the macrolides and are structural analogues of erythromycin, a 14-membered macrolide. They have higher affinity than macrolides to domains II and V of the 23S ribosomal RNA and retain activity against the main resistance mechanisms of erythromycin.

Solithromycin, iv/oral

Phase 3



- Activity in vitro similar to that of telithromycin.^{73,74}
- Cross-resistance with telithromycin not known; no cross-resistance with macrolides in pneumococci or Group A streptococci, but cross-resistance reported in staphylococci.
- An NDA was filed but rejected by the US FDA because liver toxicity had not been adequately characterized. The application to the EMA has been withdrawn. Fujifilm Toyama Chemical has acquired the rights to develop solithromycin in Japan, and submitted a new drug application in Japan in April 2019 for the treatment of ear, nose and throat infections.
- The NDA in the United States was based on two Phase 3 trials for CAP (NCT01756339, NCT01968733); and one Phase 3 trial for treatment of gonorrhoea (NCT02210325).

Nafithromycin, oral

Phase 2



- Activity in vitro similar to that of telithromycin.⁷⁵
- Active against some macrolide- and ketolide-resistant pneumococci, but cross-resistance in *ermB*-induced pneumococci, staphylococci and group A streptococci. High MICs to *H. influenzae*.
- Safety and potential liver toxicity unknown
- Phase 2 trial registered (NCT02903836).

4.1.9 Antibiotic hybrids

Antibiotic conjugates have been researched in the last few decades, with a focus on antibiotics conjugated to a range of functional moieties to create dual-acting agents. Four conjugates (including one against *C. difficile*) are in clinical development, mostly against Gram-positive bacteria.

<p>Ceflavancin, iv Phase 3 ///●</p> <ul style="list-style-type: none"> • A glycopeptide-cephalosporin conjugate. • Phase 2 trial completed (NCT00442832). • Phase 3 trial registered (CJ01003003), for development in Russia. 	<p>SPR-741+ β-lactam, iv Phase 1 ????/</p> <p>A polycationic polymyxin derivative that interacts with the negatively charged outer membrane of Gram-negative bacteria and enables penetration of antibiotics that are usually restricted to Gram-positive bacteria.⁷⁹</p> <ul style="list-style-type: none"> • Expected to be less toxic than other polymyxins. • Phase 1 pharmacokinetics trial with ceftazidime, piperacillin/tazobactam and aztreonam completed (NCT03376529).
<p>TNP-2092, iv/oral Phase 2 ///?</p> <ul style="list-style-type: none"> • Rifamycin-quinolone pharmacophore conjugate to prevent fast emergence of resistance to the rifamycin antibiotic.^{76,77} • Activity comparable to that of rifamycin; clinical development of oral form against gastrointestinal pathogens, including <i>Helicobacter pylori</i>;⁷⁸ iv form against prosthetic joint infections, including <i>S. aureus</i>. • Phase 2 trial recruiting for treatment of ABSSSI (NCT03964493). 	<p>SPR-206, iv Phase 1 ●●●/</p> <ul style="list-style-type: none"> • Polymyxin nonapeptide.⁸⁰ • It is still unclear whether lower MIC values will translate into useful activity in colistin-resistant strains and what role nephrotoxicity will play in the clinical management of patients. • Phase 1 trial recruiting (NCT03792308).
<p>TNP-2198, oral Phase 1 ///●</p> <ul style="list-style-type: none"> • Rifamycin-nitroimidazole conjugate active against anaerobes; <i>C. difficile</i>, <i>H. pylori</i> and bacterial vaginosis. • Phase 1 trial registered in China. 	

4.1.10 Polymyxins

Polymyxins are cationic polypeptides, that have been revived as a last-resort antibiotic against extensively resistant Gram-negative bacteria. Colistin and polymyxin B are increasingly used, but resistance has also emerged in response to the increased use. Two new polymyxin derivatives are in early clinical development (SPR-741 and SPR-206). One does not have intrinsic antibacterial activity but can enhance the activity of other antibiotics through permeabilization of the bacterial cell wall.

4.2 Agents in development for treating TB infections

Human TB is caused by *M. tuberculosis*. Among the estimated 10 million new TB cases occurring worldwide in 2018, an estimated 500,000 new cases (5%) were resistant to rifampicin or rifampicin and isoniazid, two of the most important first-line TB drugs.⁸¹ Innovative new treatments, particularly for drug-resistant TB, are urgently needed. Currently, 12 agents are being developed against *M. tuberculosis* of which seven meet the innovation criteria of the absence of known cross resistance. Several new targets are being pursued, including DprE1 (decaprenylphosphoryl- β -D-ribose 2-epimerase), which is important for cell wall synthesis, and leucyl-tRNA synthetase (LeuRS), which is important for protein synthesis. Among agents in development for treating TB, four target DprE1, one targets LeuRS, and one is a GyrB inhibitor. In addition, three oxazolidinones, a riminophenazine (clofazimine analogue), one imidazopyridine amide and one ethambutol derivative are in clinical development (Table 4). More information will be needed to assess the

potential role of these individual agents in future anti-TB treatment, in particular any contribution they might bring to combination regimens.

In August 2019, the FDA approved pretomanid, a nitroimidazo-oxazine, which was developed by TB Alliance. Pretomanid is part of a three-drug (in combination with bedaquiline and linezolid), 6-9-month, all-oral regimen for treating adult patients with XDR TB and treatment-intolerant or

non-responsive MDR pulmonary TB. Pretomanid was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs.⁸² Pretomanid is the first new TB drug to be successfully developed and registered by a not-for-profit organization. This demonstrates the important role played by product development partnerships in addressing unmet public health needs and working in collaboration with the pharmaceutical industry.

Table 4. Antibiotics for the treatment of TB and non-tuberculous mycobacteria in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
SQ-109	2/3	Ethambutol derivative	oral (Sequella/Infectex)	-	-	-	-
GSK-3036656 (GSK070)	2	LeuRs inhibitor (oxaborole)	oral (GSK)	✓	✓	✓	✓
Delpazolid (LCB01-0371)	2 ¹	Oxazolidinone	oral (LegoChem Biosciences/HaiHe Biopharma)	-	-	-	-
Sutezolid	2 ²	Oxazolidinone	oral (TB Alliance/Sequella)	-	-	-	-
Telacebec (Q-203)	2	Imidazopyridine amide	oral (Qurient/Infectex)	✓	✓	✓	✓
BTZ-043	2	DprE1 inhibitor (benzothiazinone)	oral (University of Munich; Hans Knöll Institute, Jena; German Center for Infection Research)	✓	✓	✓	✓
Macozinone (PBTZ-169)	2	DprE1 inhibitor (benzothiazinone)	oral (Innovative Medicines for Tuberculosis Foundation) ³	✓	✓	✓	✓
OPC-167832	1/2	DprE1 inhibitor (3,4-dihydrocarbostyryl)	oral (Otsuka)	✓	✓	✓	✓
SPR-720 ⁴	1	GyrB inhibitor (benzimidazole ethyl urea)	oral (Spero)	-	✓	-	-
TBA-7371	1	DprE1 inhibitor (azaindole)	oral (TB Alliance, Bill & Melinda Gates Medical Research Institute, Foundation for Neglected Disease Research)	✓	✓	✓	✓
TBI-166 ⁵	1	Riminophenazine (clofazimine-analogue)	oral (Institute of Materia Medica, TB Alliance, Chinese Academy of Medical Sciences & Peking Union Medical College)	-	-	-	-
TBI-223	1	Oxazolidinone	oral (TB Alliance/Institute of Materia Medica)	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.

These agents are being developed for use against TB and non-tuberculous mycobacteria. Their activity against other priority pathogens was not systematically assessed.

¹ Delpazolid also completed a Phase 1 trial as an injectable for MRSA and VRE spp. infections.

² Developed by Sequella and independently by the TB Alliance; non-exclusive patent license held by Sequella and by the Medicines Patent Pool.

³ In Russia developed by Nearmedic Plus.

⁴ The GyrB/ParE inhibitor novobiocin is no longer in clinical use.

⁵ Clofazimine is approved for leprosy and used also for TB (off-label).

SQ-109, oral**Phase 2/3**

- An ethambutol derivative.
- Ethambutol analogue, inhibits mycobacterial membrane protein large 3 (MmpL3) transporters, which are involved in exporting mycolic acids for synthesis of the mycobacterial cell wall.
- A Phase 2 trial for treatment of *H. pylori* infection (NCT01252108) was withdrawn due to lack of funding. Two Phase 2 trials for treatment of TB are completed (NCT01785186, NCT01218217). Phase 2b trial completed in the Russian Federation.⁸³

GSK-3036656, oral**Phase 2**

- GSK-3036656 (GSK070) belongs to a novel class (axoborole) with a new mechanism of action that inhibits LeuRS.
- Phase 2 bactericidal activity trial currently recruiting (NCT03557281).

Delpazolid, oral**Phase 2**

- Delpazolid (LCB01-0371), belongs to the class of oxazolidinones.
- Presently recruiting in a Phase 2 early bactericidal activity trial (NCT02836483).
- Also completed a Phase 1 trial as an injectable for MRSA and VRE (vancomycin-resistant *Enterococci*).

Sutezolid, oral**Phase 2**

- Belongs to the class of oxazolidinones.
- Phase 2 trial currently recruiting (NCT03959566).

Telacebec, oral**Phase 2**

- Telacebec (Q-203) is an imidazopyridine amide that inhibits cytochrome bc1 in the respiratory chain.
- Phase 2 trial recently completed (September 2019) (NCT03563599).

SPR-720, oral**Phase 1**

- DNA gyrase GyrB inhibitor, developed for infections caused by non-tuberculous mycobacteria.
- Phase 1 trial recently completed (October 2019) (NCT03796910).

TBI-166, oral**Phase 1**

- Derived from riminophenazine analogues (clofazimine-analogue; clofazimine has been used in leprosy since 1962); currently in development in China.
- Phase 1 trial not registered.

TBI-223, oral**Phase 1**

- Belongs to the class of oxazolidinones.
- In Phase 1 trial (NCT03758612).

4.2.1 DprE1 inhibitors

These four compounds inhibit DprE1, which is a flavoenzyme that catalyses a key step in the synthesis of the complex cell wall of *M. tuberculosis*.⁸⁴ The mechanism of action of many compounds discovered in TB phenotypic screening programmes appears to be through inhibition of this flavoenzyme.

BTZ-043, oral**Phase 2**

- DprE1 inhibitor, benzothiazinone.
- Phase 1 trial completed (March 2019) (NCT03590600).
- Phase 2 multiple ascending dose study registered to evaluate early bactericidal activity (NCT04044001).

Macozinone, oral**Phase 2**

- Macozinone (PBTZ-169) is a DprE1 inhibitor, benzothiazinone.
- Phase 1 trials ongoing (NCT03036163, NCT03776500).
- A Phase 2a trial in the Russian Federation was terminated due to slow enrolment (NCT03334734).

OPC-167832, oral **Phase 1/2**

- DprE1 inhibitor, 3,4-dihydrocarbostyl derivative.
- Phase 1/2 trial for uncomplicated pulmonary TB is recruiting (NCT03678688).

TBA-7371, oral **Phase 1**

- DprE1 inhibitor, azaindole.
- Phase 1 trial completed (NCT03199339).

4.3 Agents in development for treating *C. difficile* infections

Infections with *C. difficile* can cause severe enterocolitis and are a serious public health threat in developed countries. *C. difficile* infections are primarily managed by prevention, control and antimicrobial stewardship, and treatment options are still available. Therefore, *C. difficile* was not reviewed for inclusion in the WHO priority pathogens list for R&D. Nonetheless, agents developed for *C. difficile* infections are listed in Table 5.⁸⁵

Table 5. Antibiotics (small molecules) for the treatment of *C. difficile* infections in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
Ridinilazole	3	Bis-benzimidazole	oral, not absorbed (Summit)	✓	✓	✓	✓
OPS-2071	2	Quinolone	oral (Otsuka)	-	-	-	-
DNV-3837 (MCB-3837)	2	Oxazolidinone-quinolone hybrid	iv (Deinove)	-	-	-	-
MGB-BP-3	2	DNA minor groove binder (distamycin)	oral, not absorbed (MGB Biopharma)	✓	✓	✓	✓
ACX-362E	1	DNA polymerase III C inhibitor	oral, not absorbed (Acurx Pharmaceuticals)	✓	✓	✓	✓
CRS3123	1	Methionyl-tRNA synthetase inhibitor (MetRS)	oral (Crestone; National Institute of Allergy and Infectious Diseases)	✓	✓	✓	✓

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data or no agreement by the advisory group; - criterion not fulfilled. These agents are being developed for *C. difficile* infections; their activity against WHO priority pathogens was not assessed.

Ridinilazole, oral **Phase 3**

- Non-absorbable bis-benzimidazole, new structure with a new mode of action that is not yet clear. It might inhibit cell division by binding to the DNA minor groove.⁸⁶⁻⁸⁹
- Phase 2 trials completed (NCT02784002, NCT02092935), and a Phase 3 trial is currently recruiting (NCT03595566).

OPS-2071, oral **Phase 2**

- Quinolone, chemical structure undisclosed.
- Developed for enteric infections, including due to *C. difficile*.
- Phase 2 trials ongoing (NCT02473393, NCT03850509).

DNV-3837, iv **Phase 2**

- Prodrug, oxazolidinone-quinolone hybrid for iv treatment.⁹⁰ The activity comes from the oxazolidinone moiety.
- Phase 2 trial recruiting (NCT03988855).

MGB-BP-3, oral **Phase 2**

- Non-absorbable antibiotic with a novel chemical structure (distamycin derivative), a new target and mode of action (DNA minor groove binder). It acts on multiple binding sites and interferes with transcription.^{91,92}
- Active against Gram-positive bacteria; resistance in Gram-negative bacteria through efflux pumps.
- Phase 1 trial completed (NCT02518607)

ACX-362E, oral**Phase 1**

- New chemical class with a new target and a new mode of action: DNA polymerase III C inhibitor.
- A Phase 1 trial is under way but not registered.

CRS3123, oral**Phase 1**

- New chemical class with a new target and a new mode of action: a diaryldiamine derivative that inhibits the Met-aminoacyl-tRNA synthetase.⁹³
- Active against Gram-positive bacteria, including *C. difficile*; inhibits toxin production in vitro.
- Little information about the propensity for emergence of single-step resistance due to target mutations.
- Systemic absorption only at higher doses.
- Phase 1 trial completed (NCT01551004, NCT02106338); Phase 2 trial planned.

4.4 Biological agents

Ten biologicals are included in this report, comprising monoclonal and polyclonal antibodies, and phage endolysins (Table 6). The scope will be expanded for the 2020 update (see Discussion). Only one biological antibacterial that targets *C. difficile* toxins, bezlotoxumab, is currently approved. Hence, all these products can in principle be considered innovative, as they target new structures through new modes of action. So far, these non-traditional agents have been developed for pre-emptive or adjunctive therapy. Their potential use for single agent therapy remains to be proven,⁹⁴ and there have been several clinical failures in the past.⁹⁵

Table 6. Biological antibacterial agents in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens		
				PA	SA	CD
AR-301 (tosatoxumab, salvecin)	3	Anti- <i>S. aureus</i> immunoglobulin M (IgM) monoclonal antibody	iv (Aridis)	/	●	/
MEDI-4893 (suvratrox-umab)	2	Anti- <i>S. aureus</i> IgG monoclonal antibody	iv (MedImmune)	/	●	/
CF-301 (exebacase)	2	Phage endolysin	iv (ContraFect)	/	●	/
SAL-200 (tonabacase)	2	Phage endolysin	iv (Intron Biotechnology)	/	●	/
MEDI-3902 (gremubamab)	2	Anti- <i>P. aeruginosa</i> IgG monoclonal antibody	iv (MedImmune)	●	/	/
AR-101 (panobacumab, aerumab)	2 ¹	Anti- <i>P. aeruginosa</i> serotype O11 IgG monoclonal antibody	iv (Aridis, Shenzhen Arimab Biopharmaceuticals Co.)	●	/	/
514G3	2	Anti- <i>S. aureus</i> IgG monoclonal antibody	iv (XBiotech)	/	●	/
DSTA-4637S	1	Anti- <i>S. aureus</i> IgG monoclonal anti-body/rifamycin	iv (Genentech/Roche)	/	●	/
IMM-529	1/2	<i>C. difficile</i> polyclonal antibody	oral (Immuron)	/	/	●
PolyCab	1	<i>C. difficile</i> polyclonal antibody	iv (MicroPharm)	/	/	●

Pathogen activity ● active; / not applicable.

Abbreviations: CD, *C. difficile*; PA, *P. aeruginosa*; SA, *S. aureus*.

These biologics are not influenced by conventional resistance mechanisms, and the criterion of innovation was not applied.

¹ Clinical development only for China.

4.4.1 Activity against *S. aureus*

AR-301, iv Phase 3

- Anti-*S. aureus* immunoglobulin G1 (IgG1) monoclonal antibody targets virulence factor α -toxin.
- Phase 1 and 2 proof-of-concept trial (NCT01589185) completed.
- Phase 3 trial for the adjunctive treatment of *S. aureus* VAP currently recruiting (NCT03816956).

MEDI-4893, iv Phase 2

- Anti-*S. aureus* IgG monoclonal antibody targets virulence factors α -toxin and surface-localized clumping factor A.⁹⁶
- Long half-life, estimated to be 80–112 days.⁹⁷
- In Phase 2 trial (NCT02296320).

CF-301, iv Phase 2

- A phage endolysin similar to SAL-200.⁹⁸
- No resistance appears to emerge in serial passages.
- Similar questions about immunogenicity as for SAL-200.
- Phase 2 trial completed (NCT03163446).

SAL-200, iv Phase 2

- Recombinant form of phage endolysin SAL-1, an enzyme that destroys the peptidoglycan cell wall of a bacterium to release new virus particles.⁹⁹
- Fast killing of *S. aureus*; synergistic with antibiotics.
- Very short half-life.¹⁰⁰
- An immune response against the enzyme might limit its usefulness; antibodies were detected in 37% of volunteers, but it is not clear whether this is clinically relevant.
- Phase 2 trials (NCT03089697, NCT03446053) for treatment of persistent *S. aureus* bacteraemia.

514G3, iv Phase 2

- Anti-*S. aureus* IgG3 monoclonal antibody targets virulence factor SpA (involved in immune evasion); cloned from the B cells of a healthy human donor with pre-existing antibodies against SpA.¹⁰¹
- Phase 1 and 2 trials completed for adjunctive treatment of bacteraemia caused by *S. aureus* (NCT02357966).

DSTA-46375, iv Phase 1

- Thiomab-antibiotic conjugate, anti-*S. aureus* IgG monoclonal antibody bound to a rifamycin analogue.
- Antibody binds to surface proteins of *S. aureus* and releases rifamycin to kill intracellular *S. aureus*.¹⁰²
- Phase 1 trial on pharmacokinetics and safety in patients with *S. aureus* bacteraemia (NCT03162250).

4.4.2 Activity against *P. aeruginosa*

MEDI-3902, iv Phase 2

- Anti-*P. aeruginosa* IgG monoclonal antibody; targets virulence factors Psl and PcrV, which are involved in the secretion of multiple virulence factors.^{103,104}
- Clinical trials for the prevention of VAP caused by *P. aeruginosa* in colonized patients.
- Phase 2 trial under way for VAP (NCT02696902).

AR-101, iv Phase 2

- Anti-*P. aeruginosa* serotype O11 IgG1 monoclonal antibody binds to surface polysaccharide alginate to enhance immune response.
- Phase 2a trials completed for hospital-acquired pneumonia in 2009.
- Currently in clinical development in China.

4.4.3 Activity against *C. difficile*

IMM-529, oral

Phase 1/2

- Anti-*C. difficile* polyclonal antibody (IgG, IgA, IgM) against toxin A + B derived from vaccinated cow's colostrum.
- Also targets *C. difficile* spores and vegetative cells.
- 80% efficacy in prophylaxis and therapy in animal models.
- Phase 1/2 trial registered (NCT03065374).

PolyCab, iv

Phase 1

- *C. difficile* polyclonal antibody against *C. difficile* toxins produced in sheep.
- Phase 1 trial registered (ISRCTN80902301).

4.5 Agents that are not under active development or for which there is no recent information

In the antibiotic field, it is not uncommon for companies to suspend product development for several years, in the hope that the product may be bought by another company or that they can continue development at a later stage. Such compounds are still listed in the (online) clinical development pipelines, but typically do not move through the clinical development pathway. If such products have not shown any activity for at least 5 years, they are listed in Table 7 as agents that are not under active development or for which there is no recent information.

Table 7. Agents that are not under active development or for which there is no recent information

Name (synonym)	Phase	Antibiotic class	Developer
GT-1	1	Siderophore-cephalosporin	Geom
CB-618	1	DBO-BLI	Merck
IDP-73152	1	<u>Peptide deformylase (PDF) inhibitor</u>	ILDong
TD-1607	1	Glycopeptide-cephalosporin hybrid	Theravance
KBP-5081	1	Oxazolidinone	Xuanzhu/KBP BioSciences
KBP-0078	1	Oxazolidinone	Xuanzhu/KBP BioSciences
DS-2969	1	<u>GyrB inhibitor</u>	Daiichi Sankyo
YF-49-92.MLS	1	Nitroimidazole	C & O Pharmaceutical
GSK-3342830	1	Siderophore-cephalosporin	GSK
Ramoplanin	2	Lipodepsipeptide	Nanotherapeutics
CG400549	2	<u>FabI inhibitor</u>	CrystalGenomics
Finafloxacin	2	Fluoroquinolone	MerLion
Brilacidin	2	<u>Novel member targeting antibiotic</u>	Innovation Pharmaceuticals
Kelimycin	3	Macrolide	IMB/CAMS/Shenyang Tonglian

Underlined: New chemical class.

5. Discussion and outlook

5.1 New agents insufficiently address a global need

Of the eight new antibiotics, including one for the treatment of TB, that have been approved since 2017 (delafloxacin, vaborbactam + meropenem, eravacycline, omadacycline, relebactam + imipenem/cilastatin, lefamulin, plazomicin and pretomanid) only two – vaborbactam + meropenem and lefamulin – represent a new chemical scaffold. The other newly approved antibiotics are derivatives of known classes such as the two tetracycline derivatives eravacycline and omadacycline. Only eravacycline has activity against CRE. Omadacycline’s modification of the scaffold was focused on Gram-positive bacteria with an orally available alternative that may offer a clinical advantage in certain situations compared to existing agents.¹⁴

Vaborbactam + meropenem and plazomicin were added to the *WHO Model List of Essential Medicines* as essential antibiotics. Delafloxacin was classified as a Watch antibiotic in the WHO AWaRe classification, whereas vaborbactam + meropenem along with eravacycline, omadacycline and plazomicin were classified as Reserve antibiotics to be used as last-resort antibiotics and a key target

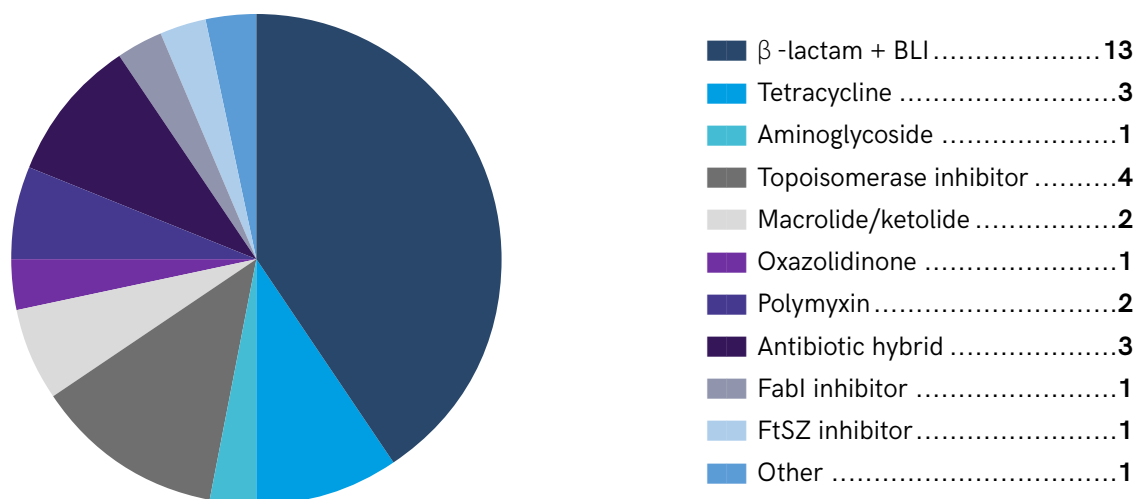
in antimicrobial stewardship activities. Pretomanid was the only antibiotic agent approved for the treatment of TB infections.

The above-listed broad-spectrum antibiotics have been mainly approved for the treatment of cUTI and/or cIAI in addition to two new antibiotics for CAP. Further evidence is needed to evaluate the true added clinical value of these agents. It is assumed that the majority of these new agents will mainly be used in tertiary health-care facilities for targeted treatment where microbiological results are available to treat infections caused by the critical and high-priority pathogens. Thus, there is also an urgent need for accessible and affordable diagnostics and the building of laboratory capacity in low-resource settings to support the responsible use of these agents.

5.2 The current clinical pipeline remains insufficient against priority pathogens

Overall there are currently 50 antibiotics and combinations (with a new therapeutic entity), and 10 biologicals in the clinical pipeline (Phase 1-3) targeting the priority pathogens, TB and *C. difficile*. A total of 32 antibiotics target the priority

Fig. 2. Summary of antibiotics in the clinical pipeline targeting the WHO priority pathogens



pathogens, 12 target TB and six target *C. difficile* infections (Fig. 2). There has been some progress in the number of antibiotics targeting the critical Gram-negative bacteria, with just over half of the 32 antibiotics targeting at least one of these bacteria. However, only two of these – cefiderocol (Phase 3) and SPR-206 (Phase 1) – have activity against all three critical priority pathogens.

The majority of antibiotics targeting the priority pathogens are β -lactam and BLI combinations (Fig. 2). The antibacterial agents in clinical development do not sufficiently address the problem of extensively or pan-drug-resistant Gram-negative bacteria. The critical priority pathogens, in particular carbapenem-resistant *A. baumannii* and *P. aeruginosa* are insufficiently addressed in the clinical pipeline. New antibacterial agents without pre-existing cross-resistance are urgently needed, especially for geographical regions with high resistance rates of Gram-negative bacteria.

5.3 More innovative approaches are required, but there are scientific and economic challenges

Six of the 32 antibiotics being developed for the treatment of priority pathogens met at least one of the innovation criteria. These include two boronate BLIs (taniborbactam + cefepime and VNRX-7145 + ceftibuten), two new topoisomerase inhibitors (zofludacin and gepotidacin) as well as a new FabI inhibitor (afabacin) and an FtsZ inhibitor (TXA709). The two novel bacterial topoisomerase II inhibitors are chemically distinct but are in the same functional class, and there is little information on potential cross-resistance, with only some cross-resistance reported for gepotidacin. The functional class of BLIs is predicted to show some cross-resistance to other BLI classes despite belonging to a new chemical class. Due to other resistance mechanisms, cross-resistance to other β -lactams and BLI combinations will be seen when they are used clinically. In addition, there are seven innovative products targeting TB of which four are DprE1 inhibitors with different chemical structures. In addition, there are four innovative products targeting *C. difficile* infections.

Of the 10 biological treatments in clinical development, six target *S. aureus* and two *P. aeruginosa*. An additional two target *C. difficile*. All of the biologicals, comprising six monoclonal

1 WHO draft AMR impact fund financial model, 2019

antibodies, two polyclonal antibodies and two phage-derived endolysins, are currently being developed as pre-emptive or adjunctive treatments. While the biologicals can be considered innovative, their potential use as alternative treatment options has yet to be proven, and it seems unlikely that they could be used to replace therapeutic antibiotics. The higher costs of monoclonal antibodies compared with regular antibiotics may also limit their potential use as alternative treatments, especially in low- and middle-income countries.¹⁰⁵

Overall, the pipeline is dominated by improvements of existing classes. While this has the advantage that the risky discovery process starts with a well-characterized, validated lead, some level of cross-resistance and fast adaptation of bacterial populations can be expected. Most searches for modified molecules of known classes focused on certain class-specific resistance mechanisms. This resulted in improvement but not in full restoration of susceptibility in a given pathogen. Ideally, R&D should result in entirely new classes, targets and modes of action to avoid cross-resistance to existing antibiotics.¹⁰⁶

Finding novel chemical structures with new binding sites and new modes of action is, however, scientifically difficult and less successful than drug discovery in other fields.¹⁰⁷ The challenges include finding compounds that have more than one binding site (in order to avoid single-step resistance) and that penetrate the outer layers of Gram-negative cell walls without being pumped out immediately by efflux pumps. Another general hurdle is toxicity due to the high concentrations required to kill bacteria.

The lack of diverse compounds suitable for bacterial treatment in the chemical libraries of pharmaceutical companies and the low specificity of screening methods represent major challenges. The absence of new, suitable chemical matter to serve as leads for drug discovery is a major bottleneck in antibiotic discovery.¹⁰⁸

5.4 Non-traditional approaches are attracting R&D interest

In addition to direct-acting small molecules ("traditional antibiotics") and large molecules (antibodies and endolysins) that have been analysed in this clinical pipeline report, some additional,

non-traditional medicines have reached the clinical phase of development. The most advanced of these in the clinic are microbiome-modulating therapeutics directed against recurrent *C. difficile* infection and include rationally selected live bacteria or synthetic microbiota (engineered live bacteria).¹⁰⁹ Other non-traditional therapies against recurrent *C. difficile* infection are an antibiotic-inactivating β -lactamase (oral cephalosporinase) and a toxin binder (activated charcoal). With a few exceptions, other types of non-traditional agents (virulence inhibitors, immunomodulators and phage/phage derived products) are not yet in clinical development. All of these agents face substantial development hurdles.¹¹⁰ They will be included in the 2020 pipeline update.

5.5 Market dynamics remain unfavourable

While public investment in the development of antibacterial agents has increased in recent years, mainly from Germany, the United Kingdom and the United States through mechanisms such as BARDA, CARB-X and GARDP, private investment has further decreased with even more big pharmaceutical companies abandoning the area over the past years. The bankruptcy of Achaogen is a prominent example of how difficult it is for small companies that develop such products to raise private funds in addition to public investment. This is linked to the economic problems that all recently approved antibiotics are facing. Sales of branded antibiotics in their main market, the United States, are very low. During the period from August 2018 to July 2019, for example, sales ranged from US\$ 0.8 million (zemdri/plazomicin) to US\$ 143.1 million (teflaro/ceftaroline fosamil).¹ This does not allow these companies to survive and sustain their R&D activities nor to fulfil their final regulatory commitments, including paediatric formulations and ongoing surveillance. One reason for the lack of financial return is that many of the new antibiotics that came to market are not innovative. Their clinical benefits or advantages over existing (cheaper) antibiotics are not clear enough and not underpinned by clinical trial outcomes. This lack of differentiation to existing treatment options makes it difficult to convince clinicians of the drugs' potential value in certain situations and to find a place in the treatment landscape, within treatment guidelines and formularies. The problem, however,

goes beyond that, as overall reimbursement for new antibiotics is often compared to generic standard of care. Governments are starting to react; the United States has revised its hospital reimbursement system, and the United Kingdom and Sweden are running pilot projects to test how to procure and pay for antibiotics differently. Other countries need to follow suit to build confidence that new, innovative antibiotics are a good investment both from a public health as well as from a business perspective. All these efforts should focus on the most useful and innovative products in the clinical and preclinical pipeline.

5.6 The pipeline outlook remains bleak

Given the average progression rates and development duration¹¹¹ (average development time from Phase 1 until approval is approximately 7 years), the current pipeline could lead to a further 11 new antibiotic approvals in the next 5 years, the majority of which are modifications of existing classes and not active against the critical MDR and XDR Gram-negative bacteria. In addition, due to limited funding for Phase 2 and 3 clinical trials, there is a risk that agents will remain stagnant in these phases due to the high cost of conducting the trials.

Of the 10 antibiotics in Phase 1 that are possibly active or active against the critical resistant Gram-negative bacteria, approximately one will be made it to the market in the next 10 years (using an attrition rate estimate of 14% for antibiotics for Phase 1 products).¹¹² This outlook has remained the same since the 2017 report.

Governments and R&D stakeholders need to collectively identify new solutions to reinvigorate funding towards antibacterial R&D and to improve the efficiency of and costs of late-stage clinical trials. The basis of all R&D activities should be innovation and the increased societal value of antibiotics to ensure a viable market as well as access to and responsible use of new and existing antibiotics. This is currently not the case for the clinical antibacterial pipeline.

6. Methodological considerations

6.1 Variable data quality

The aim of this report is to provide a complete, accurate picture of 2019 clinical development activities on the basis of publicly available data. While every effort was made to ensure that the analysis was as complete as possible, and assessments were based on peer-reviewed publications, the availability and quality of the data continue to vary.

A range of sources was used to find information about products in development. None of the public databases searched (peer-reviewed literature, patents, clinical trials) covered all the products that were finally listed in this report. Knowledge of drug development projects, especially for early-stage products, relies to a certain extent on informal information from experts in the field, including from presentations and posters given at scientific conferences and business meetings. We considered such projects only when the information about them was publicly available.

Despite WHO's position on clinical trial transparency, some of the products in the pipeline are not listed in any clinical trial registry, and the results of most trials were not disclosed within the recommended 12 months after completion. The absence of critical data from earlier phases and from randomized controlled trials complicated the assessment of some agents in advanced development phases. It is essential that any public investment in antibiotic drug development includes an obligation to adhere to clinical trial transparency standards and to publish both positive and negative results.

Data inequality impeded assessment of expected activity against priority pathogens. While peer-reviewed assessments of activity were available for some agents, for others we had to rely on publicly available company information or comparisons with other agents with a similar structure if no data was published.

Assessments of innovations were also subject to certain limitations. Lack of known cross-resistance

is the most relevant criterion of innovation in the context of antibiotic resistance. A new chemical scaffold, a new target/binding site and a new mode of action are "surrogate markers" and good predictors of lack of cross-resistance. For these reasons, the four aspects were assessed separately. There is, however, no clear definition of "surrogate markers", and a "?" in some instances indicates that the experts could not agree whether a criterion had been fulfilled. For some compounds, lack of information (e.g. structure not published) made assessment impossible. Developers should make a special effort to define and characterize the cross-resistance of their agents with existing classes. When this information was available, it allowed categorization of a compound.

6.2 Limitations

The review of the clinical antibacterial pipeline was undertaken with certain limitations, including reliance on data available in the public domain and input from the advisory group, which led to a degree of publication bias. Certain limitations were addressed through an additional effort to capture drug candidates being developed in China, Japan and the Russian Federation to ensure a more comprehensive global analysis. Further targeted efforts will be taken into consideration for future updates as well as the expansion of the geographical background of the advisory group.

All individuals and/or companies are encouraged to register clinical trials in line with the *WHO International Standards for Clinical Trial Registries* and through the ICTRP. 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 for incorporation in subsequent publications.

The membership of the advisory group has been expanded for greater geographical balance; however, the membership will be reviewed and adjusted on an annual basis, and added efforts made to increase the geographical and gender balance.

6.3 Planned changes for the 2020 update

On 1 October 2019, the advisory group reviewed the current methodology and scope and agreed on the following for the 2020 update and subsequent updates thereafter:

- expand the scope to include non-traditional products; and
- expand the route of administration to include inhaled products.

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Annex 1. 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 pipeline. The declarations of interest (DOIs) were collected and thoroughly reviewed by the WHO Antimicrobial Resistance Division following WHO standard protocol.

Prior to the advisory group meeting, all the experts submitted written disclosures of competing interests 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 update their declaration if any new conflicts had arisen in the meantime.

The experts who declared no potential conflicts of interest were Richard Alm, Mark Butler, Lloyd Czaplewski, Stephan Harbarth, Christian Lienhardt, Norio Ohmagari, Mical Paul, Ursula Theuretzbacher and Guy Thwaites. These experts were allowed full participation in the meeting. In addition, Jennie Hood participated as an observer with no conflict of interest.

The experts who disclosed potentially significant conflicts of interest were Roman Kozlov, François Franceschi, John Rex and Lynn Silver. These participants were excluded from discussions of the relevant interests listed below.

François Franceschi has been the project leader for the antimicrobial memory recovery and

exploratory programme at GARDP since April 2018 and was previously the programme officer for therapeutic development at NIAID. François was asked to recuse himself from discussion on the GARDP product zoliflodacin.

Roman Kozlov is the rector of Smolensk State Medical University and the chief specialist of the Russian Federation's Ministry of Health for Clinical Microbiology and Antimicrobial Resistance. In his DOI he disclosed that he had been awarded financial support in the past 4 years from Merck Sharp and Dohme AG. He was recused from discussion on imipenem/cilastatin + relebactam.

John Rex is chief medical officer and director of F2G Ltd, chief strategy officer of CARB-X, non-executive director and consultant of Adenium Biotech ApS, operating partner and consultant of Advent Life Sciences, expert-in-residence at the Wellcome Trust and has provided consulting services to Polyphor, Ltd., Allegra Therapeutics GmbH, Shionogi Inc. and F. Hoffmann-La Roche. He also reported having shareholdings in AstraZeneca Pharmaceuticals, F2G Ltd., Adenium Biotech ApS, Advent Life Sciences, Macrolide Pharmaceuticals and Bugworks Research Inc., but noted that no products from these companies were to be discussed in the advisory group meeting. The products discussed at the meeting from which he was recused are cefiderocol, DSTA-46375, enmetazobactam, and murepavadin.

Lynn Silver is president of LL Silver Consulting LLC. In her DOI, she reported having provided consulting services for the following companies: Achaogen, Debiopharm, Melinta, Merck Sharp and Dohme AG, Nabriva and Taxis. The products discussed at the meeting from which she was recused are afabacin, delafloxacin, imipenem/cilastatin + relebactam, lefamulin, plazomicin, solithromycin, TXA-709 and vaborbactam + meropenem.

All the reported interests were disclosed to the chair before the meeting and to other meeting participants by the technical unit in a slideshow presentation; they are also disclosed in this meeting report and will be disclosed in relevant publications.



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