2021 ANTIBACTERIAL AGENTS IN CLINICAL AND PRECLINICAL DEVELOPMENT:

an overview and analysis

World Health Organization

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Abbreviations and acronyms

ABC	*Acinetobacter baumannii*-calcoaceticus complex
ABSSSI	acute bacterial skin and skin structure infection
Abx MCP	antibiotic macrocyclic peptide
AMR	antimicrobial resistance
AP	acute pyelonephritis
AWaRe	Access, Watch, and Reserve (WHO classification)
BARDA	Biomedical Advanced Research and Development Authority
bid	*bis in die* or twice a day
BLI	β-lactamase inhibitor
BPaL	bedaquiline, pretomanid and linezolid
BSI	bloodstream infections
CABP	community-acquired bacterial pneumonia
CAP	community-acquired pneumonia
CDAD	*Clostridioides difficile*-associated diarrhoea
CDI	*Clostridioides difficile* infections
CDSCO	Central Drugs Standard Control Organization of the Government of India
CF	cystic fibrosis
CHAI	Clinton Health Access Initiative
cIAI	complicated intra-abdominal infection
COVID-19	coronavirus disease
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRABC	carbapenem-resistance *Acinetobacter baumannii* complex
CRE	carbapenem-resistant *Enterobacterales*
CRISPR	clustered regularly interspaced short palindromic repeats
CRPA	carbapenem-resistant *Pseudomonas aeruginosa*
cSSTI	complicated skin and soft tissue infection
CTA	Clinical Trial Application
cUTI	complicated urinary tract infection
CYP	cytochrome P450
DBO	diazabicyclooctane
DOI	declaration of interest
DprE1	decaprenylphosphoryl-β-D-ribose 2-epimerase
EIND	Emergency Investigational New Drug
EMA	European Medicines Agency
EML	WHO essential medicines list
EMLc	WHO essential medicines list for children
EOT	end of treatment
ESBL	extended-spectrum β-lactamase
FabI	enoyl-acyl carrier protein reductase
FimH	type 1 fimbrin D-mannose specific adhesin
FtsZ	filamenting temperature-sensitive Z
GARDP	Global Antibiotic Research and Development Partnership
GIT	gastrointestinal tract
G-ve	Gram-negative
G+ve	Gram-positive
G7	Group of Seven intergovernmental organization
GyrA	DNA gyrase subunit A
GyrB	DNA gyrase subunit B
HABP	hospital-acquired bacterial pneumonia
HAP	hospital-acquired pneumonia
IAI	intra-abdominal infection
ICTRP	International Clinical Trials Registry Platform
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IMI	imipenem-hydrolysing β-lactamase
IMP	active-on-imipenem type β-lactamases
IND	Investigational New Drug
iv	intravenous

KPC	*Klebsiella pneumoniae* carbapenemase
LeuRS	leucyl-tRNA synthetase
m-MITT	microbiologic-modified intent-to-treat
m-MITTR	microbiologic-modified intent-to-treat resistant
m-MITTS	microbiologic-modified intent-to-treat susceptible
MAA	marketing authorisation application
MBL	metallo-β-lactamase
MDR	multidrug-resistant
MDR/RR-TB TB	multidrug- or rifampicin-resistant
MIC	minimum inhibitory concentration
MoA	mode of action
MRSA	methicillin-resistant *Staphylococcus aureus*
NAAT	nucleic acid amplification test
NDA	New Drug Application
NDM	New Delhi metallo-β-lactamase
NIAID	National Institute of Allergy and Infectious Diseases
OmpA	outer membrane porin A
OPP	other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority)
ORR	overall response rate
OUCRU	Oxford University Clinical Research Unit
OXA	oxacillinase
PBP	penicillin-binding protein
PDMA	Pharmaceuticals and Medical Devices Agency (Japan)
PK/PD	pharmacokinetics/ pharmacodynamics
PO	*per os* or oral administration
qid	*quater in die* or four times a day
R&D	research and development
RCT	randomized controlled trial
Rhu-pGSN	rhu-plasma gelsolin
rRNA	ribosomal RNA
SBL	serine-β-lactamase
spp	*species pluralis* or multiple species
T3SS	type III secretion system
TB	tuberculosis
TBP	tebipenem
TBP-PI	tebipenem pivoxil
TEAE	treatment-emergent adverse effect
tet	tetracycline resistance encoding gene
TOC	test of cure
tRNA	transfer RNA
US FDA	US Food and Drug Administration
UTI	urinary tract infection
uUTI	uncomplicated urinary tract infection
VABP	ventilator-associated bacterial pneumonia
VAP	ventilator-associated pneumonia
VIM	Verona integron-encoded metallo-β-lactamase
VRE	vancomycin-resistant enterococci
WHO	World Health Organization
XDR	extensively drug resistant

Executive summary

This report presents an analysis of antibacterial agents in preclinical (third annual review) and clinical (fifth annual review) development. The analysis covers traditional (direct-acting small molecules) and non-traditional antibacterial agents in development worldwide. It evaluates to what extent the present pipeline addresses infections caused by WHO bacterial priority pathogens *(1)*, *Mycobacterium tuberculosis* and *Clostridioides difficile*. The report also provides an assessment of traditional agents with respect to whether they meet a set of predefined criteria for innovation, namely absence of known cross-resistance, new target, mode of action (MoA) and/or class.

KEY FACTS ABOUT THE CLINICAL PIPELINE:

- The current clinical antibacterial pipeline contains 77 antibiotics and/or combinations that include at least one new therapeutic entity. Of these, 45 are traditional antibacterial agents and 32 are non-traditional. In addition, there are three more antibiotics in NDA/MAA stages.
- Of the 45 traditional antibiotics, 27 (60%) are reported to be active against the WHO bacterial priority pathogens, 13 (28%) against *M. tuberculosis* and five (11%) exclusively against *C. difficile.*
- Analysis of the 27 antibiotics under development against WHO bacterial priority pathogens found that:
  - six fulfil at least one of the WHO innovation criteria;
  - of these six "innovative compounds", only two are active against at least one multidrug-resistant (MDR) Gram-negative bacterium from the "critical" category (i.e. CRAB, CRPA, CRE); and over 40% (13/27) are β-lactam and β-lactamase inhibitor (BLI) combinations, with a major gap in activity against metallo-β-lactamase (MBL) producers.
- Of the 45 traditional antibacterials, seven new products entered the clinical pipeline since the last report, and six were either discontinued or there was no recent available information about them (see section 3.5).
- Analysis of the 32 non-traditional antibacterials shows that:
  - six of these antibacterials are antibodies, nine are bacteriophages or phage-derived enzymes, 10 are microbiome-modulating agents, one is a immunomodulating agent and six are grouped as miscellaneous agents.
- Analysis of the newly approved antibacterials shows that:
  - Twelve new antibiotics have been approved by either the US Food and Drug Administration (US FDA) or the European Medicines Agency (EMA) or both since 1 July 2017.
  - With some exceptions, all newly approved agents have limited clinical benefit over existing treatment.
  - Over 80% (10/12) of the newly approved antibiotics belong to existing antibiotic classes where resistance mechanisms are established.
  - Since the last report, one new antibacterial, cefiderocol, was approved that is effective against all three critical Gram-negative bacteria, including isolates carrying a variety of β-lactamases, among them ESBL and AmpC.
- Overall, the clinical pipeline and the recently approved antibacterial agents are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance (AMR) *(2).*

KEY FACTS ABOUT THE PRECLINICAL PIPELINE

- There are 121 commercial and non-commercial entities developing 217 antibacterial agents/programs that are in the preclinical stage.
- The annual analysis of the preclinical pipeline shows that from one year to the other, one third of the development programmes are discontinued.
- In the preclinical pipeline against WHO critical pathogens, many of the agents show activity against more than one pathogen. A total of 69 agents (31.8%) have activity against *Pseudomonas aeruginosa* and 50 agents (23%) have activity against *Acinetobacter baumannii.* In addition, approximately 28% of the agents target key *Enterobacterales*.
- A total of 95 agents (43.8%) have been classified by the product developers as species specific. Of these, 44 agents target WHO critical Gram-negative bacteria: 21 target *P. aeruginosa*, eight target *A. baumannii* and 15 target *Enterobacterales*. In addition, 19 species-specific agents are directed against *Staphylococcus aureus* and 20 against *M. tuberculosis*.
- The preclinical pipeline contains 90 (41.5%) direct-acting small molecules, 33 antimicrobial peptides (15.2%) and 92 (42.4%) non-traditional products, including bacteriophages (*n* = 28; 12.9%), antibody (*n* = 8; 3.7%) and immunomodulatory compounds (*n* = 7; 3.2%) (Table 8).
- A total of 152 agents (70%) were being developed as single agents, whereas 39 compounds (18%) were in development in combination with a second agent. In 26 programmes (12%) this information was not provided.
- In terms of MoA of the agents in preclinical development, 56 (25.8%) act directly on the cell membrane, 37 (17.1%) target cell wall synthesis, 24 (11.1%) target virulence factors, 18 (8.3%) target protein synthesis and 10 (4.6%) act through immunomodulation.
- The majority (50.4%) of preclinical developmental research projects are being conducted in the European Region, followed by 37.2% in the Region of the Americas (mostly the USA and Canada), 9.3% in the Western Pacific Region and 4.1% in the South-East Asia Region.
- The preclinical pipeline continues to be dominated by companies (*n* = 103; 85.1%). Most (*n* = 84; 81.6%) of these commercial entities are privately owned companies, and a significant proportion of all companies have < 50 employees.

Recent marketing approvals

Since 2017 and until 1 November 2021 (the cut-off date of this publication), 12 new antibacterial drugs have been approved (Table 1).

Innovation

Antibacterial agents are evaluated against the four WHO innovation criteria: new chemical class, new target, new MoA and absence of known cross-resistance. Recently approved antibacterial agents show a limited degree of innovation. Most newly approved agents are derivatives of existing classes, and only two compounds (lefamulin and vaborbactam in combination with meropenem) meet one innovation criteria representing a new chemical class. When evaluating the absence of cross-resistance, inconclusive data are associated with three compounds: the vaborbactam and meropenem combination, lefamulin, and cefiderocol.

Evaluation against WHO priority pathogens list

Evaluation of how well the newly approved products address global public health priorities revealed that only one agent targets carbapenem-resistant *A. baumannii* (CRAB), P. *aeruginosa* (CRPA) and some carbapenem-resistant *Enterobacterales* (CRE); five agents target CRE; and seven target other priority pathogens (OPP) that are "high" or "medium" priority on the WHO priority pathogens list. For treatment of resistant *M. tuberculosis*, one agent, pretomanid, was approved, in combination with two other antibacterial agents (bedaquiline and linezolid), for the treatment of extensively drug resistant tuberculosis (XDR-TB) and drug-intolerant or non-responsive multidrug-resistant tuberculosis (MDR-TB). Having only one agent targeting the critical pathogens (CRAB, CRPA, CRE) highlights the urgency for new products to treat infections caused by these pathogens. This urgency is striking when considering that resistance might arise with use and that there is a need to preserve effective new agents to ensure their longevity.

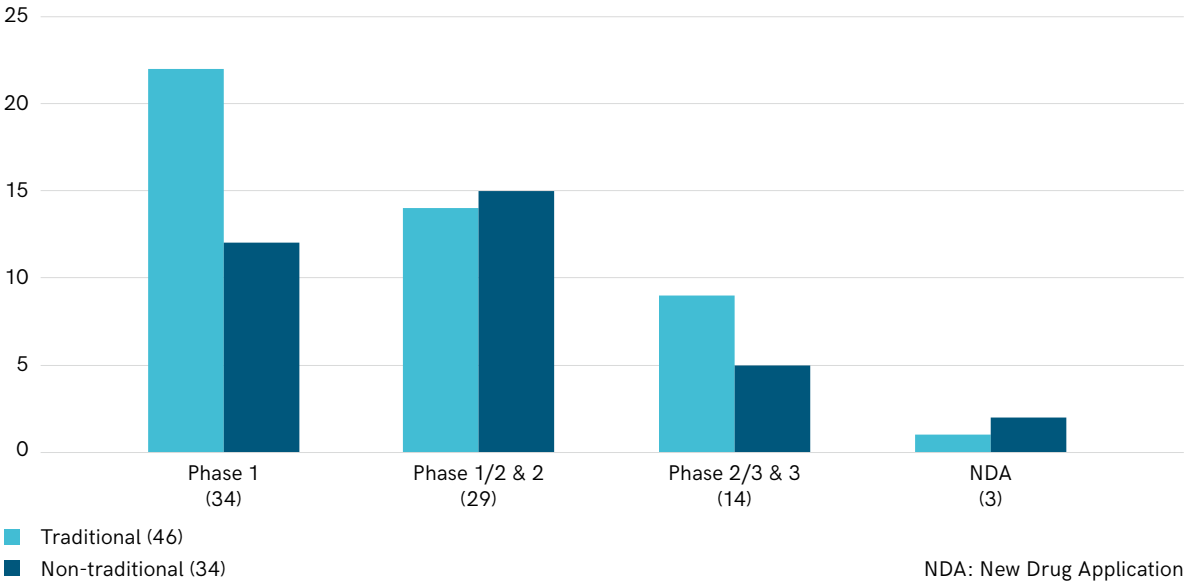
Traditional antibacterial pipeline in clinical development

As of 1 November 2021, 45 antibiotics with new therapeutic entities targeting WHO priority pathogens, *M. tuberculosis* and *C. difficile* were in different phases of clinical development (Phases 1–3) (Fig. 1). A new therapeutic entity is defined as any antibiotic that has a new substance, a new chemical entity, a new biological entity and/or a new molecular entity *(3).*

Of the 45 antibiotics in clinical development, 27 target WHO bacterial priority pathogens (Fig. 2). More than 50% of these (*n* = 17) are active against at least one of the critical Gram-negative pathogens: seven target CRAB, five target CRPA and 11 target CRE.

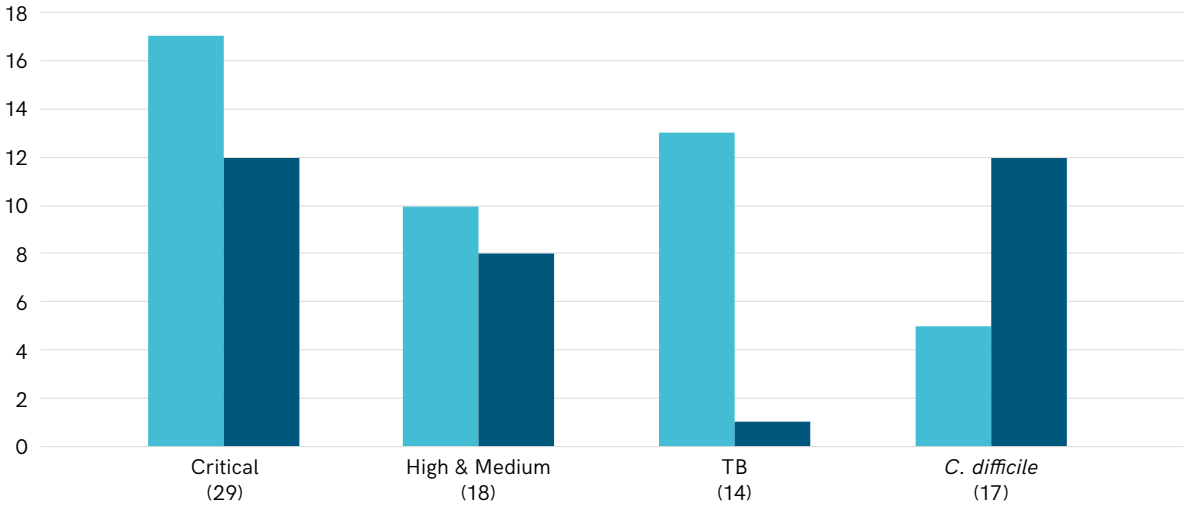
Thirteen of the 45 antibiotics identified are in development for TB and five for the treatment of *C. difficile* infections (CDIs).

Fig. 1. Traditional and non-traditional antibacterials by clinical development phase (Phases 1–3 and NDAs)



NDA: New Drug Application

Fig. 2. Traditional and non-traditional antibacterials in clinical development (Phases 1–3 and NDAs) by intended target



Total counts may not equal 80 since some antibacterials have activity for several pathogens and other have not confirmed activity against the WHO BPPL for which are tested.

NDA: New Drug Application

Innovation

Of the 27 traditional antibiotics under development against WHO priority pathogens, six meet at least one of the four WHO innovation criteria. Only two (taniborbactam and VNRX-7145 in combination with ceftibuten) target at least one of the critical Gram-negative bacteria. The current antibiotic pipeline continues to be dominated by β-lactam/BLI combinations (*n* = 13, 50% of antibiotics targeting WHO priority pathogens) that poorly respond to the innovation criteria. Of the 13 agents being developed against *M. tuberculosis*, six meet the innovation criteria "absence of known cross-resistance" and seven represent a new chemical class. Regarding CDIs, there are overall five products in the pipeline and four innovative agents with two agents that address all four innovation criteria.

Meeting one or more of the innovation criteria is indicative of a product's potential to overcome existing mechanisms of antibacterial resistance and is a crucial part of the WHO evaluation of new antibacterial compounds.

Potential for clinical utility of Phase 3 antibacterials

The potential for clinical utility for each of the Phase 3 traditional antibacterials is in Annex 2. The information draws from published information. The scope is to highlight certain drug attributes that are relevant for their potential clinical use and, when relevant, clinical trial study design and results. Since the last report in 2020, nafithromycin (previously WCK 4873) clinical utility table has been added.

Non-traditional antibacterials in the clinical pipeline

The analysis of the clinical pipeline included 32 non-traditional antibacterials (in addition to two antibacterials in NDA/MAA stages) (Fig.1).

- Twelve target critical Gram-negative bacteria (five *P. aeruginosa*, three *Escherichia coli*, and one *Campylobacter jejuni/E. coli*, and three have broad-spectrum activity against Gram-positive and Gram-negative bacteria).
- Eight target high and medium priority Gram-negative bacteria (seven target *S. aureus* and one *Helicobacter pylori*).
- One agent targets TB, and 12 are intended against *C. difficile*.

These non-traditional approaches are diverse: they include six antibodies, nine bacteriophages and phage-derived enzymes, 11 microbiome-modulating agents, two immunomodulating agents and six miscellaneous agents that include anti-virulence agents. Most of these products are not intended for treatment as single agents but as a complement to traditional agents.

Preclinical antibacterial pipeline

The preclinical pipeline database captures 217 antibacterial agents targeting WHO priority pathogens, *M. tuberculosis* and *C. difficile*. The data were collected through a WHO data call and were complemented through a desk review that covered product information available in the public domain. The interactive database includes preclinical drug candidates from lead optimization to Clinical Trial Application (CTA)/ Investigational New Drug (IND)-enabling studies covering traditional antibiotics, as well as biological agents and non-traditional approaches such as bacteriophages that are being developed by commercial and non-commercial entities worldwide. The preclinical pipeline is dynamic and innovative, with agents being developed in many parts of the world to prevent and treat drug-resistant bacterial infections.

Gaps and constraints in the current clinical R&D landscape

The 2021 review and analysis of antibacterial pipelines concluded that recently approved antibacterial agents, and those in the different stages of clinical development, are still insufficient to address antimicrobial-resistant infection emergence and spread. In addition, the review found that:

- Among the recently authorized antibacterial agents, only one compound, cefiderocol, is intended for use against the WHO critical pathogens CRAB and CRAP (in addition to CRE).
- Most of the 27 products in Phases 1–3 are combinations of β-lactams with BLIs. Most of the BLIs inhibit Class A, C and some D enzymes, but only three agents inhibit Class B enzymes (MBLs), leaving *MDR A. baumannii* and *P. aeruginosa* infections extremely poorly addressed.

- Since 2017 only twelve products have been authorized, reflecting the considerable time associated with traditional R&D models and also reflecting the small size of the overall clinical pipeline.
- There are 27 traditional products in different stages of the clinical pipeline against bacteria listed by WHO as priority pathogens. However, this number should be interpreted considering the estimated failure rate *(4)* or voluntary product discontinuation; several obstacles make it challenging to reach and maintain marketing authorization, including investment and reimbursement schemes.
- Most of the products in Phase 3 are developed as intravenous (iv) formulations; only two are developed as oral formulations. Oral antibiotics are needed and could provide options for step-down from iv therapy or for outpatient treatment of infections. In addition to limiting side effects associated with prolonged iv therapy, new oral antibiotic options against priority pathogens could reduce hospitalizations and their associated cost, lower hospital-acquired infection risk and help in optimizing antibiotic treatments.
- In general, there is a delay both in the global availability of newly authorized agents and in development of paediatric indications among authorized products.

Editorial note: in this report the terms *antibacterial agents* and *antibiotics* are used somewhat interchangeably. In this context, the *antibiotics* under analysis are those that kill or prevent bacterial growth. Also in this report the order *Enterobacterales* instead of the family *Enterobacteriaceae* was used; the same applies to *Clostridioides difficile*, which replaces the former nomenclature *Clostridium difficile*.

All data contained in this report can be downloaded from the WHO Global Observatory on Health R&D.

Clinical pipeline: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens

Preclinical pipeline: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/who-antibacterial-preclinical-pipeline-review

1

Introduction

1. Introduction

The emergence of antibacterial resistance is a normal evolutionary process for bacteria. However, this process is amplified through selective pressure exerted by the widespread use and misuse of antibacterial agents in human and animal health. The WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) *(2)* report confirms that antibacterial resistance is on the rise, specifically in low- and middle-income countries, causing significant mortality and morbidity *(5)*. Vulnerable populations such as children and neonates are disproportionately affected by antibiotic-resistant infections in these countries, with pneumonia and bloodstream infections (BSIs) 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 *(6)*.

New antibacterial treatments are thus urgently needed. This analysis of the preclinical and clinical antibacterial development pipeline allows policymakers, clinicians and researchers to assess which antibacterial agents will potentially reach the bedside over the next 8–10 years. While the pipeline features some innovative products, only a fraction of these are likely ever to come to market due to the high failure rate characteristic of the drug development process *(4)*.

As in the previous edition of 2020, the current report includes a comprehensive overview of non-traditional products such as monoclonal antibodies, bacteriophages, antimicrobial peptides, antibacterial enhancers and other products in the clinical development pipeline. In conjunction with the WHO preclinical antibacterial agents database, this clinical review allows monitoring of alternative innovative approaches being pursued. More work needs to be done to assess the potential public health impact of these new approaches.

The clinical pipeline is presented in Chapter 3 and the preclinical pipeline in Chapter 4. In addition, the databases can be downloaded from the WHO Global Observatory on Health R&D.

This report confirms that the preclinical and clinical pipeline continues to be driven by small- and medium-sized companies, which in general are struggling to find investors to finance late-stage clinical development up to regulatory approval. In this respect, the AMR Action Fund launched in 2020 will be crucial to ensuring that some of the most innovative and promising products receive the required funding. Although the fund can help to bridge the finance gap until registration, many companies will not be able to survive after registration unless they have adequate income to sustain their product supply chain, finance necessary post-registration studies and repay their investors. In addition, nearly all the new antibacterial treatments are likely to be categorized as "reserve" antibiotics in the WHO AWaRe (Access, Watch, Reserve) classification, which limits their sales volume and makes it challenging for companies to generate the necessary income *(7)*. While implementation of the AWaRe classification is important to ensure responsible use of antibacterials and to help preserve their effectiveness, more work needs to be done to make sure that new and needed reserve antibiotics remain on the market once registered, so they are truly held in reserve to be available when resistance levels rise. This urgently requires new strategies to procure and reimburse antibacterial agents as was highlighted throughout the United Kingdom's G7 (Group of Seven) presidency, including in the *G7 finance ministers' statement on actions to support antibiotic development*. The statement also provided an overview of examples of actions taken so far by G7 countries to improve the economic conditions for antibacterial drug development *(8)*.

More countries need to act, ideally in a coordinated manner, to develop a favourable market dynamic and create the financial incentives that are needed to drive antibiotic R&D and innovation. This will ensure that the global community has a robust pipeline of innovative new products that demonstrate clinical benefit. Notably, since 2020 WHO i is developing SECURE *(9)*. SECURE is an initiative being developed by WHO, GARDP, the United Nations Children's Fund (UNICEF) and the Clinton Health Access Initiative (CHAI) to build a global consortium of organizations and interested countries that together will improve regulated access to essential antibiotics. SECURE's goal is to give participating countries access to essential new antibiotics designed to address drug-resistant infections, alongside essential older antibiotics not widely available or subject to frequent supply chain disruptions.

BOX 1. WHO LIST OF PRIORITY PATHOGENS

TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEARCH AND DEVELOPMENT

FIVE REASONS WHY

1

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

2

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

3

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

4

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

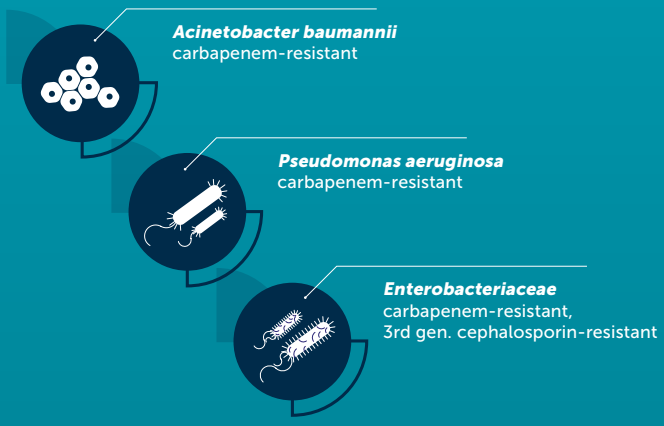
5

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

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

OTHER PRIORITY PATHOGENS

CRITICAL PRIORITY

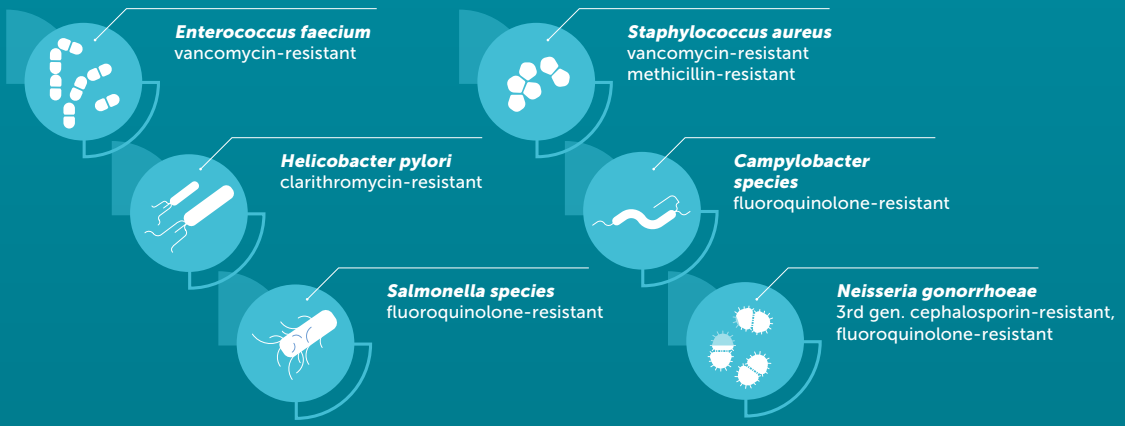


Acinetobacter baumannii
carbapenem-resistant

Pseudomonas aeruginosa
carbapenem-resistant

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

HIGH PRIORITY



Enterococcus faecium
vancomycin-resistant

Staphylococcus aureus
vancomycin-resistant
methicillin-resistant

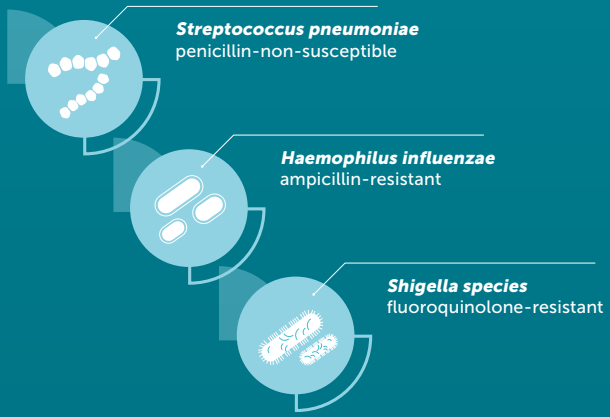
Helicobacter pylori
clarithromycin-resistant

Campylobacter species
fluoroquinolone-resistant

Salmonella species
fluoroquinolone-resistant

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

MEDIUM PRIORITY



Streptococcus pneumoniae
penicillin-non-susceptible

Haemophilus influenzae
ampicillin-resistant

Shigella species
fluoroquinolone-resistant

2

Agents that obtained market authorization since 1 July 2017

2. Agents that obtained market authorization since 1 July 2017

Since WHO's first analysis of the clinical antibacterial pipeline in 2017, 12 new antibiotics, including one for the treatment of XDR-TB, have been approved to market by either the US FDA, the EMA or both.

Innovation assessment

The innovation criteria are poorly addressed by authorized agents. Only two of the approved agents, vaborbactam (approved in combination with meropenem) and lefamulin, represent new chemical classes. Most recently approved agents are derivatives of known classes, including the cephalosporin cefiderocol; the fluoroquinolone derivatives delafloxacin, lascufloxacin and levonadifloxacin (developed as the prodrug alalevonadifloxacin); and the tetracycline derivatives eravacycline and omadacycline.

Evaluation against WHO priority pathogens list

In terms of activity, most of these agents have been approved for classic syndrome-based indications, for example treatment of complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), community-acquired pneumonia (CAP) and/or acute bacterial skin and skin structure infection (ABSSSI). Only one agent, cefiderocol, is active against both critical CRPA and CRAB, in addition to CRE. Five of the newly approved agents target CRE, and seven target other priority pathogens on the WHO priority pathogens list among high and medium priorities.

Product descriptions

Vaborbactam is a novel BLI that contains a cyclic boronate moiety and, in combination with meropenem, is active against *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE. Vaborbactam is optimized for inhibition of serine β-lactamases (particularly KPC). Vaborbactam does not inhibit class B MBLs and it does not enhance activity against *P. aeruginosa* or *Acinetobacter* spp. due to efflux/porin mutations. The combination with meropenem was developed and approved as an iv infusion.

Lefamulin is the first pleuromutilin for systemic use in humans. The drug was approved by the US FDA for treatment of CAP caused by susceptible organisms including *Streptococcus pneumoniae*, methicillin-susceptible *S. aureus, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae and Chlamydophila pneumoniae*. Pleuromutilins belong to an established class of antibacterials for systemic use in veterinary medicine and have been used as topical formulations in humans. Beyond US FDA approved use, in vitro activity of lefamulin has been demonstrated against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), multidrug-resistant *Neisseria gonorrhoeae* and *Mycoplasma genitalium*. Whether or not these in vitro activities will translate into clinical utility has yet to be demonstrated. Lefamulin can be administered as an iv injection or oral tablet.

Pretomanid, a nitroimidazo-oxazine, is approved for use in XDR-TB and for the treatment of intolerant or non-responsive MDR-TB in adult patients. It is administered per os (PO) in combination with bedaquiline and linezolid, as part of the bedaquiline, pretomanid and linezolid (BPaL) regimen. Pretomanid has been studied in 19 clinical trials in 14 countries in more than 1100 patients. Pretomanid is active against both replicating and non-replicating (hypoxic) *Mycobacterium tuberculosis*. The mechanism of action involves the inhibition of mycolic acid biosynthesis (similar to isoniazid) to disrupt cell wall formation, in addition to being combined with respiratory poisoning through nitric oxide release (similar to cyanide) *(11)* on non-replicating microorganisms. Pretomanid was approved by the US FDA in 2019, followed in 2020 by approval in India as conditional access under the National Tuberculosis Elimination Program and by the European Commission in the same year.

Cefiderocol is a broad-spectrum siderophore cephalosporin with the ability to be transported across the outer membrane of Gram-negative bacteria and accumulate in the periplasmic space. Cefiderocol received US FDA fast track approval for treatment of adults with cUTI and hospital-acquired and ventilator-associated pneumonia (HAP/VAP) and European Commission approval for treatment of aerobic Gram-negative organisms in adults with limited treatment options. Cefiderocol has activity against various molecular types of carbapenemase-producing pathogens. It has a broader activity than recently approved β-lactam/BL inhibitor combination drugs, which are only active against some molecular types (e.g. KPC, OXA-48), see Table 3. It is expected to be used in the treatment of MDR *Acinetobacter*, and *Enterobacterales* (New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM) and, IMP-carbapenemase – producing *Enterobacterales*) as well as infections caused by *Stenotrophomonas maltophila*. Cefiderocol has no activity against Gram-positive organisms. It is administered intravenously (iv infusion).

Another new product that has been authorized since the last review is contezolid, an oxazolidinone developed by MicuRx. It was approved in China by the National Medical Products Administration for complicated skin and soft tissue infections (cSSTIs) caused by Gram-positive bacteria, including MRSA and VRE infections.

In addition, two fluoroquinolone derivatives – lascufloxacin and levonadifloxacin/alalevonadifloxacin –were registered in Japan and India, respectively. Lascufloxacin is a fluoroquinolone with activity against Gram-positive pathogens and respiratory tract infections. Lascufloxacin was approved for CAP, otorhinolaryngological and other respiratory tract infections. Levonadifloxacin/alalevonadifloxacin (iv and oral prodrug), which has a similar spectrum to lascufloxacin, was approved for skin and soft tissue infections.

Table 1. Antibacterial agents that gained market authorization between 1 July 2017 and 1 November 2021

Name (trade name USA/ EU)	Market authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Indication/s	WHO EML & AWaRe classification	Expected activity against priority pathogens				Innovation			
								CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela / Quofenix)	Melinta Therapeutics (USA) (Menarini, EU)	US FDA (6/2017 ABSSSI, 10/2019 CAP) EMA (12/2019 ABSSSI, 02/2021 CAP)	Fluoroquinolone	iv & oral	ABSSSI, CAP	WHO EML: no AWaRe: Watch	○	○	○	●	-	-	-	-
Vaborbactam + meropenem (Vabomere / Vaborem)	Melinta Therapeutics (USA) (Menarini, EU)	US FDA (8/2017) EMA (11/2018)	Boronate BLI + β-lactam (carbapenem)	iv	cUTI, (cUTI, cIAI, HAP/VAP in EU)	WHO EML: yes AWaRe: Reserve	○	○	●[1]	/	?[2]	✓	-	-
Plazomicin (Zemdri)	Achaogen (Cipla USA/ QiLu Antibiotics, China)	US FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML: yes AWaRe: Reserve	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	US FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	WHO EML: no AWaRe: Reserve	?	○	●	/	-	-	-	-
Omadacycline (Nuzyra)	Paratek	US FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSSI (iv, oral)	WHO EML: no AWaRe: Reserve	○	○	○	●	-	-	-	-
Relebactam + imipenem / cilastatin (Recarbrio)	Merck Sharp & Dohme	US FDA (7/2019 cUTI/cIAI, 7/2020 HAP/VAP) EMA (2/2020 G-ve)	O-BLI + β-lactam (carbapenem) / degradation inhibitor	iv	cUTI, cIAI, HAP/VAP	WHO EML: no AWaRe: Reserve	○	?	●[1]	/	-	-	-	-
Lefamulin (Xenleta)	Nabriva (Sunovion Pharmaceuticals Canada)	US FDA (8/2019) EMA (7/2020)	Pleuromutilin	iv & oral	CAP	WHO EML: not yet evaluated AWaRe: Reserve	/	/	/	●	?	✓[3]	-	-

Pretomanid (Dovprela)	TB Alliance (Viatris)	US FDA (8/2019) EMA (8/2020) CDSCO (7/2020)	Nitroimidazole	oral	XDR-TB	WHO EML: not yet evaluated AWaRe: N/A to TB drugs	/	/	/	●[4]	-	-	-	-
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PDMA (8/2019)	Fluoroquinolone	iv & oral	CAP, otorhinolaryngological	WHO EML: not yet evaluated	○	○	○	●	-	-	-	-
Cefiderocol (Fetroja)	Shionogi	US FDA (11/2019 cUTI, 9/21 HAP/VAP) EMA (4/2020)	Siderophore β-lactam (cephalosporin)	iv	cUTI, HAP/VAP, aerobic G-ve[5]	WHO EML: yes AWaRe: Reserve	●	●	●	/	?	-	-	-
Levonadifloxacin (Emrok); alalevonadifloxacin (Emrok-O)	Wockhardt	CDSCO (1/2020)	Fluoroquinolone	iv & oral	ABSSSI	WHO EML: not yet evaluated AWaRe: Watch	○	○	○	●	-	-	-	-
Contezolid (Youxitai); contezolid acefosamil	MicuRx	NMPA (6/2021)	Oxazolidinone	iv & oral	cSSTI	WHO EML: not yet evaluated AWaRe: not yet evaluated	/	/	/	●	-	-	-	-

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. Agents not active against critical priority pathogens were assessed for activity against OPP, which includes the WHO high and medium priority pathogens.

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

ABSSSI: acute bacterial skin and skin structure infection; AWaRe: Access Watch Reserve; CAP: community-acquired pneumonia; CC: new chemical class; cIAI: complicated intra-abdominal infection; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant *Enterobacterales*; CRPA: carbapenem-resistant *P. aeruginosa*; cSSTI: complicated skin and soft tissue infection; cUTI: complicated urinary tract infection; CDSCO: Central Drugs Standard Control Organization of the Government of India; EMA: European Medicines Agency; EML: WHO Essential Medicines List; G-: Gram-negative; HAP: hospital-acquired pneumonia; iv: intravenous; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; MDR: multidrug-resistant; MoA: new mode of action; N/A: not applicable; NCR: no cross-resistance to other antibiotic classes; NMPA: China National Medical Products Administration; OPP: other priority pathogens; PDMA: Pharmaceuticals and Medical Devices Agency (Japan); T: new target; TB: tuberculosis; US FDA: US Food and Drug Administration; VAP: ventilator-associated pneumonia; XDR-TB: extensively drug-resistant TB.

[1] Active against KPC, but not MBL-producing Enterobacterales.

[2] New reports suggest that cross-resistance can be obtained when the porin OmpK36 level is varied.

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

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

[5] The EMA approved cefiderocol for the treatment of infections due to aerobic Gram-negative bacteria in adults with limited treatment options, which is broader than the US FDA approval.

3

Agents in clinical development

3. Agents in clinical development

The following sections describe the current clinical antibacterial development pipeline with activity against WHO priority pathogens, *M. tuberculosis* and *C. difficile*. It is organized as follows:

- Sections 3.1–3.3 provide an overview and analysis of the traditional, direct-acting small molecule clinical antibacterial pipeline:
  - 3.1 antibacterial agents targeting WHO priority pathogens;
  - 3.2 antibacterial agents targeting *M. tuberculosis*; and
  - 3.3 antibacterial agents targeting *C. difficile*.
- Section 3.4 provides an overview of non-traditional antibacterial agents in development.
- Section 3.5 includes agents that are not under active development or for which there is no recent information.
- Annex 2 contains full summaries of the potential clinical utility for Phase 3 traditional antibacterials based on planned, ongoing or completed programmes and their microbiological features.

3.1. Antibacterial agents being developed against WHO priority pathogens

Currently 27 antibacterial agents targeting WHO priority pathogens are in Phase 1–3 clinical development, of which half (*n* = 13) have confirmed activity against at least one of the critical Gram-negative bacteria (Table 2).

Since the last update: nafithromycin has entered Phase 3, sulopenem-etzadroxil/probenecid started a new Phase 3 trial for uncomplicated UTI (uUTI), and additional evidence for the activity of taniborbactam (VNRX-5133) + cefepime against CRPA was included. In addition, positive topline results were made public for durlobactam (ETX-2514) + sulbactam in a Phase 3 trial for CRAB infections. In addition, seven new products entered Phase 1. One of these, XNW4107, is being studied in combination with imipenem and cilastatin. The combination is developed as a BLI/β-lactam (carbapenem) paired with a degradation inhibitor and is expected to have activity against CRAB, CRPA and CRE. QPX7728 + QPX2015, a boronate BLI in combination likely with a β-lactam, entered Phase 1 and is being developed against CRE. Also entering Phase 1 are two new polymyxins, namely MRX-8 and QPX9003, which are being developed against Gram-negative infections. One undisclosed compound – RG6006 (Abx MCP, macrocyclic peptide) *(12)* – is also in Phase 1 against *A. baumannii*. A new topoisomerase inhibitor, BWC0977, also entered Phase 1 against both Gram-positive and Gram-negative bacteria. ARX-1796 is an oral avibactam prodrug developed against CRE. These new entries bring the total number of traditional agents currently in Phase 1 to 16.

Table 2. Antibacterial agents being developed against WHO priority pathogens

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
Solithromycin (T-4288)	NDA[2]	Macrolide	iv & oral	Fujfilm Toyama Chemical	/	/	/	●	-	-	-	-
Sulopenem; sulopenem etzadroxil / probenecid	3[3]	β-Lactam (penem)	iv & oral	Iterum Therapeutics	○	○	○[4]	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/ PBP1,3 binder	iv	Entasis Therapeutics	●	○	○	/	-	-	-	-

Table 2. Cont.

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	iv	VenatoRx Pharmaceuticals / GARDP	○	●	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	BLI + β-lactam (cephalosporin)	iv	Allecra Therapeutics	○	○	○[5]	/	-	-	-	-
Zoliflodacin	3	Spiropyrimidenetrione (topoisomerase inhibitor)	oral	Entasis Therapeutics / GARDP	/	/	/	●	✓	✓	-	✓
Gepotidacin	3[6]	Triazaacenaphthylene (topoisomerase inhibitor)	iv & oral	GSK	/	/	/	●	?[6]	✓	-	✓
Nafithromycin (WCK-4873)	3	Macrolide	oral	Wockhardt	/	/	/	●	-	-	-	-
Benapenem	2/3	β-Lactam (carbapenem)	iv	Xuanzhu Biopharm[7]	○	○	○	/	-	-	-	-
Afabicin (Debio-1450)	2	Pyrido-enamide (FabI inhibitor)	iv & oral	Debiopharm	/	/	/	●	✓	✓	✓	✓
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv & oral	TenNor Therapeutics	/	/	/	●	-	-	-	-
TNP-2198	1b/2a	Rifamycin-nitroimidazole conjugate	oral	TenNor Therapeutics	/	/	/	●	-	-	-	-
Zidebactam + cefepime	1[8]	DBO-BLI/ PBP2 binder[9] + cephalosporin	iv	Wockhardt	●	●	●	/	-	-	-	-
OP0595 (nacubactam) + meropenem	1	DBO-BLI/PBP2 binder[9] + β-lactam (carbapenem)	iv	Meiji Seika	○	○[10]	●	/	-	-	-	-
ETX0282 + cefpodoxime proxetil	1	DBO-BLI/PBP2 binder[9] + β-lactam (cephalosporin)	oral	Entasis Therapeutics	○	○	●	/	-	-	-	-
ARX-1796 (oral avibactam prodrug)	1	DBO-BLI + β-lactam (undisclosed)	oral	Arixa Pharmaceuticals / Pfizer[11]	○	○	●[12]	/	-	-	-	-
XNW4107 + imipenem + cilastatin	1	BLI + β-lactam (carbapenem) / degradation inhibitor	iv	Sinovent	?	?	?	?	?	?	?	?
VNRX-7145 + ceftibuten	1	Boronate-BLI + β-lactam (cephalosporin)	oral	VenatoRx Pharmaceuticals	○	○	●	/	?	✓	-	-
QPX7728 + QPX2014	1	Boronate-BLI + undisclosed	iv	Qpex Biopharma	●	●	●	/	?	-	-	-
QPX7728 + QPX2015	1	Boronate-BLI + undisclosed oral β-lactam	oral and iv	Qpex Biopharma	○	○	●	/	?	-	-	-

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
SPR-206	1	Polymyxin	iv	Spero Therapeutics	●	●	●	/	-	-	-	-
MRX-8	1	Polymyxin	iv	MicuRx	●	●	●	/	-	-	-	-
QPX9003	1	Polymyxin	iv	Qpex Biopharma	?	?	?	?	?	?	?	?
KBP-7072	1	Tetracycline	oral	KBP BioSciences	●	○	○	●	-	-	-	-
EBL-1003 (apramycin)	1[13]	Aminoglycoside	iv	Juvabis	●	?	●	/	-	-	-	-
TXA709	1	Difluorobenzamide (FtsZ inhibitor)	oral & iv	TAXIS Pharmaceuticals	○	○	○	●	✓	✓	✓	✓
RG6006 (Abx MCP)	1	Macrocyclic peptide	iv	Roche	?[14]	?	?	?	?	?	?	?
BWC0977	1	Topoisomerase	iv	Bugworks Research	?	?	?	?	?	?	?	?

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. Agents not active against critical priority pathogens were assessed for activity against OPP, which includes the WHO high and medium priority pathogens.

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

BLI: β-lactamase inhibitor; CC: chemical class; CRAB: carbapenem-resistant *A. baumannii*; CRE: carbapenem-resistant *Enterobacterales*; CRPA: carbapenem-resistant *P. aeruginosa*; ESBL: extended-spectrum β-lactamase; FabI: enoyl-acyl carrier protein reductase; DBO: diazabicyclooctane; FtsZ: filamenting temperature-sensitive Z; GARDP: Global Antibiotic Research and Development Partnership; iv: intravenous; KPC: *K. pneumoniae* carbapenemase; MOA: new mode of action; NCR: no cross-resistance; NDA: New Drug Application; OPP: other priority pathogens; PBP2: penicillin-binding protein 2; T: new target; uUTI: uncomplicated urinary tract infection.

[1] OPP target pathogens – solithromycin: *S. pneumoniae*; nafithromycin: *S. aureus* and *S. pneumoniae*; zoliflodacin: *N. gonorrhoeae*; gepotidacin: *N. gonorrhoeae* and *E. coli*; TNP-2198: *H. pylori*; afabicin, TNP-2092, KBP-7072 and TXA-109: *S. aureus*.

[2] Solithromycin NDA for otorhinolaryngological infections was submitted in Japan in April 2019.

[3] Iterum will undertake an additional Phase 3 uUTI study of sulopenem etzadroxil before any NDA resubmission.

[4] Active against ESBL-producing cephalosporin-resistant *Enterobacterales* but not carbapenem-resistant *Enterobacterales*.

[5] Active against ESBL-producing cephalosporin-resistant *Enterobacterales* and some KPC-producing CRE.

[6] See Annex 2.

[7] Xuanzhu Biopharm is a subsidiary of Sichuan Pharmaceutical Holdings but possesses fully independent intellectual property rights.

[8] A Phase 3 trial for zidebactam + cefepime was registered in July 2021 for cUTI or acute pyelonephritis (NCT04979806).

[9] The DBO-BLIs zidebactam, OP0595 (nacubactam) and ETX0282 also have some antibacterial activity and have been classified as β-lactam enhancers.

[10] Activity against AmpC-β-lactamase producing and KPC-producing CRPA.

[11] The original developer, Arixa Pharmaceuticals, was acquired by Pfizer in October 2020.

[12] Active against KPC but not MBL-producing *Enterobacterales*.

[13] Previously used as an antibacterial treatment in animals.

[14] RG6006 is being developed to treat *A. baumannii* infections.

3.1.1. Penicillin binding protein inhibitors - β-lactams

β-Lactams are a well-established group of antibiotics that inhibit bacterial cell wall formation through covalent linking to penicillin-binding proteins (PBPs) and subsequent disruption of peptidoglycan biosynthesis. This class includes penicillins, cephalosporins, carbapenems and monobactams *(13).*

The emergence of bacteria that produce enzymes (β-lactamases) that hydrolyse β-lactam antibiotics has rendered many of these agents ineffective. In addition, the spread of extended spectrum β-lactamases (ESBLs) that confer resistance to broad-spectrum cephalosporins, and of carbapenemases that confer resistance to carbapenems, is concerning *(13).*

There are four β-lactamase structural classes, known as A, B, C and D *(14)*. Class B enzymes are MBLs that contain a zinc ion in their active site. This zinc ion activates a water molecule which serves as the nucleophile that hydrolyses the β-lactam moiety. The remaining three classes (A, C and D) are serine-β-lactamases that use a serine nucleophile to hydrolyse β-lactams. ESBLs mostly belong to Class A. Enzymes with carbapenemase activity are found among Class A (KPC, IMI and SME), Class B MBLs (IMP, NDM, VIM) and Class D (OXA) *(15).*

The main strategy for circumventing hydrolysis of β-lactams is to combine a β-lactam antibiotic with a BLI to make the bacterium sensitive to the antibiotic again. Traditional BLIs (such as clavulanic acid, tazobactam and sulbactam) inhibit ESBLs but do not inhibit carbapenemases of the same Class A.

Over the past years, some new BLI combinations with carbapenems or cephalosporins have entered the market (e.g. ceftolozane + tazobactam and ceftazidime + avibactam, vaborbactam + meropenem) *(16)* in addition to a cephalosporin, cefiderocol which is effective against isolates carrying all β-lactamase classes.

Most of the BLIs in the clinical pipeline (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 approved since 2017 and currently in development against the most clinically relevant β-lactamases, including carbapenemases.

With the exception of four agents (cefiderocol, taniborbactam + cefepime, QPX7728 + QPX2014 and QPX7728 + QPX2015), a notable development gap exists generally for agents that inhibit β-lactamase producers, specifically Class B (MBLs).

QPX7728 + QPX2015 is being developed as a combination. Phase 1 studies reported that QPX7728 restored the potency of multiple β-lactam antibiotics against β-lactamase strains producing Gram-negative bacilli, including against carbapenem-resistant *A. baumannii*, KPC-producing *K. pneumoniae* and a "representative panel of *P. aeruginosa* isolates that reflects the current beta-lactam MIC [minimum inhibitory concentration] distributions". QPX2015 is an oral β-lactam which structure remains undisclosed.

The sulbactam-durlobactam (SUL-DUR) combination was evaluated in a successful Phase 3 trial for treatment of *A. baumannii* infections (ATTACK, see Annex 2 for more details) in hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) because of the choice of the specific pathogen selected, rather than the more typical approach of starting with a study in cUTI or cIAI against a broader range of bacterial species. The developer states than an NDA submission is planned for mid-2022. However, even if the SUL-DUR combination is approved, additional anti-CRAB agents are urgently needed to address the global public health threat posed by MDR infections by *A. baumannii*.

Finally, while some BLIs in the pipeline – such as ETX-2514, ETX-0282, nacubactam and zidebactam – have intrinsic antibacterial activity, based on binding to PBP2, and may result in synergistic antibacterial activity in some *Enterobacterales (17)*, other mechanisms may still confer resistance to β-lactam/BLI combinations, despite their inhibition of β-lactamases *(18–20)*. *P. aeruginosa* and, to a certain extent, *A. baumannii* have developed resistance mechanisms beyond the production of β-lactamases, including decreased permeability of the outer membrane and upregulation of efflux pumps and modified PBPs. This further confirms the need for more innovative compounds/strategies to address critical antibacterial resistant Gram-negative pathogens.

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

	CRE					
	A	A	D	B		
	ESBL (CTX-M)	KPC (KPC-2,-3)	OXA (OXA-48)	MBL (NDM)	CRAB	CRPA
Vaborbactam + meropenem	●	●	●	○	○	○
Relebactam + imipenem + cilastatin	●	●	●	○	○	?
Cefiderocol	●	●	●	●	●	●
Durlobactam (ETX-2514) + sulbactam	○	○	○	○	●	○
Enmetazobactam (AAI-101) + cefepime	●	?	○	○	○	○
Sulopenem	●	○	○	○	○	○
Taniborbactam (VNRX-5133) + cefepime	●	●	●	●	-	●
Benapenem	○	○	○	○	○	○
Zidebactam + cefepime	●	●	●	?	○	?
ARX-1796 (oral avibactam prodrug)	●	●	●	○	○	○
ETX-0282 + cefpodoxime proxetil	●	●	●	○	○	○
OP0595 (nacubactam) + meropenem	●	●	●	?	○	○
QPX7728 + QPX2014	●	●	●	●	●	●
QPX7728 + QPX2015	●	●	●	●	○	○
XNW4107 + imipenem + cilastatin	?	?	?	?	?	?
VNRX-7145 + ceftibuten	●	●	●	○	○	○

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

Grey shading: Agents with recent market approvals (since 1 July 2017).

CRAB: carbapenem-resistant *A. baumannii*; CRPA: carbapenem-resistant *P. aeruginosa*; CTX-M: CTX-M-type β-lactamase; ESBL: extended-spectrum β-lactamase; KPC: *K. pneumoniae* carbapenemase; MBL: metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; OXA: oxacillinase.

Legend: expected activity against priority pathogens:

CRAB	CRPA	CRE	OPP
○	?	●	/

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

Durlobactam + sulbactam, iv — Phase 3

● ○ ○ /

- Durlobactam (ETX-2514) is a modified diazabicyclooctane (DBO)-type BLI; it is an "unsaturated DBO" and can be considered as a DBO sub-series with broader activity against Class A, C and D β-lactamases. It has been proposed that durlobactam also binds to PBP2, providing intrinsic activity against some *Enterobacterales*.
- Restores the activity of sulbactam, a penicillanic acid sulfone β-lactam, in *A. baumannii (22)*.
- An in vitro study of the combination against a globally diverse set of *A. baumannii* isolates reported that drug resistance to the combination was low *(23)*.
- The combination is being studied for a pathogen-specific treatment (narrow spectrum) for HAP/VAP infections due to drug-resistant *A. baumannii* infections (mainly MDR and carbapenem-resistant *A. baumannii* calcoaceticus complex [ABC] isolates).
- Two Phase 3 trials in cUTI (NCT03445195) and one in HAP/VAP (NCT03894046) are completed. The most recent Phase 3 trial studied the efficacy and safety of the combination in treatment of hospitalized patients with ABC infections, including HAP/VAP, compared with colistin (superiority design), on background treatment of imipenem/cilastatin.
- A Phase 3 HAP/VAP (NCT03894046) study concluded that mortality analyses favoured SUL-DUR vs colistin in CRAB microbiologic-modified intent-to-treat (m-MITT) and all study populations.
- A statistically significant difference in clinical response favouring SUL-DUR over colistin at test of cure (TOC) was reported. The results also reported that the combination met the primary safety objective of the study *(24)*.
- The target date for NDA submission is mid-2022.

Enmetazobactam + cefepime, iv — Phase 3

○ ○ ○ /

- Enmetazobactam (AAI-101) is a tazobactam derivative (β-lactam scaffold) with enhanced bacterial cell penetration being studied in combination with cefepime.
- It shows inhibitory activity against ESBL-producing cephalosporin-resistant *Enterobacterales*.
- It is being studied as an empiric carbapenem-sparing treatment of cUTI and could be an empiric option for treatment of Gram-negative pathogens in endemic settings with a high incidence of ESBL-producing *Enterobacterales*.
- A Phase 3 trial (EudraCT 2017-004868-35, NCT03687255) to evaluate the efficacy and safety of enmetazobactam + cefepime versus piperacillin + tazobactam in the treatment of 1034 cUTI patients, including AP, in 115 sites in 19 countries is completed.
- No reported cross-resistance.
- More details are provided in Annex 2.

Sulopenem, iv/oral — Phase 3

○ ○ ○ /

- Synthetic penem; sulopenem etzadroxil oral prodrug. It is active against *Enterobacterales*, including ESBL-producers, but not CRE. The Gram-positive activity is similar to carbapenems.
- Intended to provide the possibility of an oral switch early during treatment in stable patients, opening the option of earlier discharge from the hospital or of avoiding hospitalization. Sulopenem could provide an outpatient treatment option for infections caused by ESBL-producing bacteria, common in UTIs.
- Phase 3 trials (NCT03354598, NCT03357614, NCT03358576) to evaluate iv and oral formulations for the treatment of uUTI (oral), cUTI and cIAI (iv/oral prodrug) due to *Enterobacterales* are completed.
- Cross-resistance with existing carbapenems has been reported *(21)*.

Taniborbactam + cefepime, iv **Phase 3**

○ ? ● /

- Taniborbactam (VNRX-5133) is a boronate-based BLI with inhibitory activity against Class A (ESBL CTX-M, KPC-2, -3), B (MBLs, especially NDM and VIM) and D (OXA-48) β-lactamases in CRE and Class C β-lactamases. It does not cover IMPs *(25)*.
- It is being studied as a broad-spectrum treatment for cUTI and acute pyelonephritis (AP) due to clinically important carbapenem-resistant Gram-negative bacilli, including CRE and CRPA *(26-29)*.
- A Phase 3 non-inferiority trial for cUTI infection (NCT03840148) is recruiting to evaluate the efficacy, safety and tolerability of cefepime + taniborbactam in 582 adults (43 sites in nine countries) with cUTI, including AP, compared with meropenem.
- More details are provided in Annex 2.

Benapenem, iv **Phase 2/3**

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- Carbapenem which has completed a Phase 2 trial (NCT03578588).
- Clinical development only in China.
- Complete cross-resistance to molecular mechanisms that provide resistance to other carbapenems.

ARX-1796, oral **Phase 1**

○ ○ ● /

- Oral prodrug of avibactam.
- Combination partner not known; active against KPC, Class C enzymes and OXA-48 but not MBL producers.
- A Phase 1 trial has been registered (NCT03931876) but is not yet recruiting.

ETX0282 + cefpodoxime proxetil, oral **Phase 1**

○ ○ ● /

- ETX0282 is an oral BLI of the DBO type; it is an "unsaturated DBO" and it can be considered as a DBO sub-series with some intrinsic antibacterial activity against *Enterobacterales* due to PBP2 inhibition.
- Active against ESBL, OXA-48 and KPC, but not MBL-producing *Enterobacterales*.
- A Phase 1 trial (NCT03491748) is complete.

OP0595 (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 *(35, 36)* and some of the Class D (OXA) enzymes *(37)*.
- Combination partner is meropenem; synergistic activity with various partners in *Enterobacterales*, including some MBL producers (elevated MICs) *(38)*; BLI activity only in *P. aeruginosa* and not carbapenem-resistant *P. aeruginosa*; no added benefit in treating carbapenem-resistant *A. baumannii (39).*
- A Phase 1 pharmacokinetics trial with meropenem (NCT03174795) is complete.

QPX7728 + QPX2014, oral/iv **Phase 1**

● ● ● /

- QPX7728 is a boronate-type BLI which inhibits serine- and MBLs of Classes A, B, C and D in *A. baumannii, P. aeruginosa* and *Enterobacterales (40-42).*
- A Phase 1 trial in combination with an undisclosed β-lactam (QPX2014) has been registered (NCT04380207) and is currently recruiting.

Note: estimates for trial timings might change due to the ongoing COVID-19 (coronavirus disease) pandemic.

QPX7728 + QPX2015, oral iv **Phase 1**

○ ○ ● /

- QPX7728 (see description above, first bullet) *(40–43)*.
- A Phase 1 trial in combination with an undisclosed β-lactam (QPX2015) has been registered (NCT04380207) and is currently recruiting.

XNW4107 + imipenem + cilastatin, iv **Phase 1**

/ / / ?

- XNW4107 is a BLI being developed in combination with imipenem and cilastatin. Cilastatin is a renal dehydropeptidase inhibitor with activity against that is used to prevent degradation of imipenem. The XNW4107 combination will be developed against both cUTI and HABP/VABP *(44)*.
- A Phase 1 trial started in March 2021 is ongoing (NCT04802863).

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 *Enterobacterales*.
- Not active against MBL producers.
- A Phase 1 trial is recruiting (NCT04243863).

Zidebactam + cefepime, iv **Phase 1**

● ● ● /

- Zidebactam is a DBO-type BLI with activity against *P. aeruginosa, A. baumannii* and some *Enterobacterales* due to PBP2 inhibition and inhibition of β-lactamases *(30–32)*.
- Synergistic activity of this combination against *Enterobacterales* (including ESBL-producers) and KPC, but elevated MICs in MBL producers *(33, 34)*.
- Phase 1 trials are completed (NCT02532140, NCT02942810, NCT02707107).

Note: estimates for trial timings might change due to the ongoing COVID-19 pandemic.

3.1.2. Protein synthesis inhibitors – tetracyclines

Tetracyclines are broad-spectrum bacteriostatic antibiotics that were discovered in 1948 to have activity against Gram-positive and Gram-negative bacteria. Tetracyclines bind to the A site of the 30S ribosomal subunit and inhibit the binding of aminoacyl-transfer RNA (tRNA), preventing synthesis of polypeptides *(45)*. 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 *(46)*. Since their introduction, more than 1000 tetracycline resistance genes have been reported. They are often associated with mobile genetic elements, including efflux pumps, ribosomal protection proteins, tetracycline resistance encoding genes *(tet)*, mosaic genes and mutations in ribosomal proteins.

The semi-synthetic parenteral glycycline, tigecycline, was approved in 2005. This agent overcomes certain class-specific resistance mechanisms. In 2018 the US FDA approved both iv and oral formulations of eravacycline (synthetic fluorocycline) and omadacycline (a semi-synthetic aminomethylcycline analogue of minocycline).

Currently, there is only one semi-synthetic tetracycline in Phase 1 trial.

KBP-7072, oral **Phase 1**

● ○ ○ ●

- An aminomethylcycline optimized for Gram-positive *(47)* respiratory pathogens and in vitro activity against *A. baumannii (48)*, *E. coli* and *K. pneumoniae*.
- In a recent study, KBP-7072 was found to be minimally affected by the presence of acquired tetracycline genes *(49).*
- KBP-7072 showed similar MIC values for tetracycline-susceptible and -resistant *S. aureus* strains compared with tigecycline and omadacycline.
- Three Phase 1 clinical trials have been reported, one completed in 2015 (NCT02454361), one in 2016 (NCT02654626) and one in October 2020 (NCT04532957).

3.1.3. Protein synthesis Inhibitors – aminoglycosides

Aminoglycosides are bactericidal and active against Gram-negative bacteria such as *Pseudomonas, Acinetobacter* and *Enterobacter* spp. They inhibit protein synthesis and are administered via iv or intramuscular (IM) 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 and, more recently, bacterial ribosome-modifying enzymes (16S rRNA methylases), which often occur in NDM-producing *Enterobacterales (50)*. The most recently approved aminoglycoside, plazomicin, was optimized to address most aminoglycoside-modifying enzymes.

EBL-1003, iv	**Phase 1**
? – ? /	

- EBL-1003 (apramycin) was licensed in 1980 for oral therapy in animals.
- Resistance first noted in 1986 *(51)*, resistance described by AAC(3)-IV, with resistance due to acetylation of the 1-amino group by AAC(3)-IV *(52)*.
- A Phase 1 trial is complete (NCT04105205).

3.1.4. Protein synthesis inhibitors – oxazolidinones

Oxazolidinones inhibit protein synthesis through binding at the peptidyltransferase centre of the 50S ribosomal subunit and interfering with incoming tRNA *(53)*. They have been in clinical use since 2000. Linezolid was the first drug of this class to be approved, followed by tedizolid in 2014. Modifications of the scaffold may address class-specific resistance mechanisms. Some oxazolidinones have also been developed for *C. difficile* and *M. tuberculosis* infections.

Contezolid , iv/oral **Contezolid acefosamil**	**New Drug Application (NDA)**
/ / / ●	

- Activity against MRSA, vancomycin-resistant *E. faecium* and penicillin-resistant *S. pneumoniae.*
- Little information published, and potential differences with linezolid are unclear *(54)*.
- An NDA submitted in China in December 2020 and a Phase 2 trial of contezolid acefosamil in patients with ABSSSI was completed (NCT02269319) in the USA in September 2015.

3.1.5. Protein synthesis inhibitors – macrolides and ketolides

Macrolides disrupt protein synthesis *(55)* through binding to the 50S ribosomal subunit peptidyltransferase centre (at the nascent peptide exit tunnel) *(56)*. 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 *(57)*. Ketolides, a subclass of the macrolides, are erythromycin derivatives that feature an additional cyclic carbamate and replacement of the cladinose sugar by a ketone. Ketolides have higher affinity than macrolides to domains II and V of the 23S rRNA and retain activity against the main resistance mechanisms of erythromycin (target-site modification by inducible methylation and efflux-pump-mediated resistance) *(58)*.

Solithromycin, iv/oral — **NDA**

- Activity in vitro is similar to that of telithromycin; however, solithromycin has three binding sites as opposed to two for telithromycin *(57, 59, 60)*.
- Fujifilm Toyama Chemical has acquired the rights to develop solithromycin in Japan and submitted an NDA in Japan in April 2019 for the treatment of ear, nose and throat infections.
- An NDA was filed but rejected by the US FDA because potential for liver toxicity had not been adequately characterized. The NDA was based on two Phase 3 trials for CAP (NCT01756339, NCT01968733) and one Phase 3 trial for the treatment of gonorrhoea (NCT02210325).
- Cross-resistance with telithromycin not commonly found; no cross-resistance with macrolides in pneumococci or group A streptococci, but cross-resistance reported in staphylococci.

Nafithromycin, oral — **Phase 3**

- Oral lactone-ketolide (macrolide derivative) that is being developed/optimized as a treatment for community-acquired bacterial pneumonia (CABP) in adults due to typical and atypical respiratory pathogens.
- In vitro activity similar to telithromycin, the first ketolide approved in 2001 *(61)*.
- Active against some macrolide- and ketolide-resistant pneumococci.
- Safety and potential liver toxicity unknown.
- A Phase 2 trial is complete (NCT02903836).
- Nafithromycin is currently being evaluated through a Phase 3 trial in India. The study has been registered with the clinical trial registry of India (registration no. CTRI/2019/11/021964).
- More details are provided in Annex 2.

3.1.6. Topoisomerase inhibitors – various classes

Topoisomerase inhibitors include quinolones, which are synthetic bactericidal antibiotics discovered in the 1960s. The drugs in use today are fluoroquinolones. They target two essential type IIA topoisomerases: DNA gyrase and topoisomerase IV. Fluoroquinolones bind preferentially to the gyrase subunit GyrA and to the topoisomerase IV subunit ParC *(62)*. 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 *(63, 64)*. These new agents target Gram-positive pathogens, pathogens causing respiratory tract infections and *N. gonorrhoeae*.

Zoliflodacin, oral — **Phase 3**

- Novel bacterial topoisomerase II inhibitor (spiropyrimidenetrione scaffold) with activity against *N. gonorrhoeae* and Gram-positive cocci; in clinical development for uncomplicated gonorrhoea in an oral, single-dose formulation.
- Utilizes a distinct DNA gyrase binding site in GyrB compared with fluoroquinolones (GyrA) *(65)*.
- Being studied for the treatment of uncomplicated *N. gonorrhoeae* with potential to be effective in treating infections caused by fluoroquinolone-resistant strains *(66)*.
- A Phase 3 trial for treatment of uncomplicated gonorrhoea is currently recruiting (NCT03959527): a multicentre, open-label, randomized non-inferiority trial comparing a single oral dose of zoliflodacin with a single dose combination of ceftriaxone + azithromycin in the treatment of 1092 adults with uncomplicated gonorrhoea in four countries (Netherlands, South Africa, Thailand and USA).
- Early findings indicate no cross-resistance with fluoroquinolones (or other topoisomerase inhibitors) *(67, 68)*.
- More details are provided in Annex 2.

Gepotidacin, iv/oral **Phase 3**

/ / / ●

- Novel bacterial topoisomerase II inhibitor (triazaacenaphthylene scaffold) that selectively inhibits bacterial DNA replication by interacting at a unique site on the GyrA subunit of bacterial DNA gyrase and the ParC subunit of bacterial topoisomerase IV.
- Being developed for the treatment of uncomplicated urogenital gonorrhoea and uUTI *(69)*.
- It is also being explored in ABSSSI *(70)*.
- High oral dose due to poor absorption (53% of the oral dose is eliminated through the faecal route due to poor GIT absorption. Adverse side effects, mainly diarrhoea, were reported in 95% (*n* = 21/22) of the participants of a Phase 2a trial.
- Phase 3 trials are currently recruiting for treatment of uUTI (NCT04020341) and uncomplicated gonorrhoea infections (NCT04010539).
- Some cross-resistance with fluoroquinolones has been reported *(71)*.
- More details are provided in Annex 2.

BWC0977, iv/oral **Phase 1**

? ? ? ?

- Topoisomerase inhibitor (undisclosed structure) that is being developed as an iv and oral step-down for the treatment for MDR infections, including Gram-negative bacteria.
- A Phase 1 trial recently started to evaluate iv administration (NCT05088421).

3.1.7. FabI inhibitor – pyrido-enamide

FabI (a NADH-dependent enoyl-acyl carrier protein reductase, encoded by *fabI*) is a critical enzyme 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 (in addition to inhibiting FabI, isoniazid also inhibits the InhA enzyme, an enoyl-acyl carrier protein reductase) for TB treatment and the non-specific biocide and slow-binding FabI inhibitor triclosan. These agents have different binding characteristics *(72)*. It is not known whether they exert selection pressure on staphylococci, which could lead to cross-resistance *(73, 74)*. One FabI inhibitor is currently in clinical development (Phase 2).

Afabicin, iv/oral **Phase 2**

/ / / ●

- Afabicin (Debio-1450) is a new *Staphylococcus*-specific antibiotic class developed for *S. aureus* infections in iv and oral form (prodrug) *(75)*.
- Inhibits FabI, which is a key enzyme in bacterial fatty acid biosynthesis *(76)*.
- 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 *(77)*. Risk for emergence of high-level resistance may be offset by high affinity for the target *(74, 78, 79)*.
- A Phase 2 trial in staphylococcal ABSSSIs (NCT02426918) is complete and a Phase 2 trial for bone or joint infections has been registered (NCT03723551).

3.1.8. FtsZ inhibitor

Filamenting temperature-sensitive Z (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 Z-ring to form the divisome. Inhibiting FtsZ blocks cell division, and thus it is an attractive antibacterial target *(80, 81)*. One FtsZ inhibitor is currently in clinical development (Phase 1).

TXA709, iv/oral **Phase 1**

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- The orally bioavailable methylbenzamide antibiotic TXA709 and its active metabolite TXA-707 target FtsZ and have been tested against *S. aureus (82)*.
- Phase 1 trial not registered.

3.1.9. Antibiotic hybrids

Antibiotic hybrids 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. Three conjugates are in clinical development, mostly against Gram-positive bacteria.

TNP-2092, iv/oral **Phase 2**

/ / / ?

- Rifamycin-quinolizinone hybrid, designed to reduce resistance to rifamycin and analogues *(83, 84)*.
- Activity comparable to rifamycin; clinical development of oral form against gastrointestinal pathogens, including *H. pylori* iv form, and against prosthetic joint infections, including *S. aureus (83).*
- Phase 2 trial for treatment of ABSSSI completed (NCT03964493).

TNP-2198, oral **Phase 1b/2a**

/ / / ●

- Rifamycin-nitroimidazole hybrid with activity against anaerobes, *C. difficile, H. pylori* and bacterial vaginosis.
- A Phase 1 trial has been registered in China (CTR20190734).

3.1.10. Cell membrane – polymyxins

Polymyxins are cationic polypeptides that act to disrupt the phospholipid structure of the cell membrane and increase cell permeability. They were resurrected as a last-resort antibiotic against XDR Gram-negative bacteria, despite their well-documented side effects (nephro- and neurotoxicity) compared with newer Gram-negative antibiotics *(85)*. Colistin and polymyxin B are increasingly used, but resistance has also emerged in response to increased use. A new polymyxin derivative, SPR-206, is in early clinical development, but the antibiotic potentiator SPR-741 has been discontinued.

SPR-206, iv **Phase 1**

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- Polymyxin analogue *(86)*.
- 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.
- A Phase 1 trial is complete (NCT03792308).

MRX-8, iv **Phase 1**

● ● ● /

- Polymyxin derivative (undisclosed structure) being developed for the treatment of Gram-negative infections, including *A. baumannii, P. aeruginosa* and *E. coli (87)*.
- The in vivo activity against *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* in neutropenic mouse thigh and lung infection models has been reported.
- A Phase 1 trial is ongoing (NCT04649541).

QPX9003, iv **Phase 1**

? ? ? ?

- Synthetic polymyxin derivative (undisclosed structure) licensed from Monash University, Australia, being developed in partnership with the Biomedical Advanced Research and Development Authority (BARDA).
- Being developed to treat drug-resistant infections caused by the WHO priority pathogens *P. aeruginosa* and *A. baumannii*.
- A Phase 1 trial started in June 2021 (NCT04808414).

3.1.11. Undisclosed compounds

RG6006, undisclosed **Phase 1**

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- RG6006 (Abx MCP or antibiotic macrocyclic peptide) is being developed as a treatment for *A. baumannii* infections and is currently in Phase 1 trials (Roche pipeline), but no further information has been disclosed.

3.1.12. Noteworthy compounds in development that do not meet inclusion criteria

This analysis mostly focuses on new antibacterial treatments. It does not include already authorized compounds that are being repurposed, pharmaceutically optimized (e.g. new formulation, route of administration) or studied for new indications.

However, improvement of existing agents, including combination of existing agents, as well as new paediatric or oral formulations can have significant clinical utility. Thus, this new section describes some of these development projects that do not meet the inclusion criteria but that the analysis identified as noteworthy:

- **Aztreonam+avibactam.** The aztreonam (monobactam-type β-lactam) and avibactam (DBO-type BLI inhibitor) combination (ATM-AVI) is being evaluated in two Phase 3 trials (NCT03580044, NCT03329092) to treat serious infection due to MBL-producing Gram-negative bacteria in BSI, cUTI, cIAI, HAP and VAP *(88–90)*. Aztreonam and avibactam were first approved by the US FDA in 1986 and 2015, respectively.
- **BV100.** BV100 is an iv formulation of rifabutin that is being developed to treat CRAB infections, and in three Phase 1 trials (NCT04636983, NCT05086107, NCT05087069) *(91, 92)*. Rifabutin is a semisynthetic rifamycin that was first approved in 1992 by the US FDA as an oral formulation for the prevention of disseminated *Mycobacterium avium* complex disease in patients with advanced HIV infection.
- **Tebipenem pivoxil hydrobromide (TBP-PI-HBr).** Tebipenem pivoxil (TBP-PI) has been approved in Japan since 2009 where it has been used for the treatment of ear, nose and throat infections, otitis media, and bacterial pneumonia. The active ingredient is tebipenem (TBP) and it has been modified (esterified) as an oral prodrug to provide oral bioavailability of 60%.

A Phase 3 trial (NCT03788967), which was completed in May 2020, showed TBP-PI was non-inferior to iv ertapenem in treatment of hospitalized adult patients with cUTI or AP. TBP-PI has activity against *Enterobacterales*, including ESBL-producing. and quinolone-resistant Gram-negative pathogens, as well as some Gram-positive activity similar to other carbapenems. It is active against ESBL-producing cephalosporin-resistant but not carbapenem-resistant *Enterobacterales*. It has no activity against *A. baumannii* and *P. aeruginosa*. Cross-resistance with existing carbapenems is expected.

TBP-PI-HBr's oral formulation provides the possibility of an early switch from iv treatment during treatment in stable patients, opening the option of early discharge from the hospital, or outpatient therapy.

3.2. Agents in development for treating TB

Most human TB is caused by *M. tuberculosis*. An estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB worldwide in 2019. Among them, an estimated 465 000 people fell ill with multidrug- or rifampicin-resistant TB (MDR/RR-TB). Of these, a total of 206 030 people with MDR/RR-TB were detected and notified in 2019, a 10% increase from 186 883 in 2018 *(93)*. Innovative new treatments, particularly for drug-resistant TB, are urgently needed.

Between 1 September 2020 and 1 November 2021, two new traditional agents for the treatment of *M. tuberculosis* entered Phase 1. TBAJ-587 is an oral diarylquinoline from the TB Alliance. TBAJ-587 is a compound from the same class as bedaquiline that is expected to be more potent and have reduced cardiovascular side effects. It is intended for use against TB, but no assessment was possible against the WHO innovation criteria due to the lack of data available. GSK2556286 (GSK286) is a compound whose antibacterial class has not been defined, although its mechanism of action involves cholesterol catabolism. It is in Phase 1 trial, sponsored by GSK, with assistance from the TB Drug Accelerator and the Bill & Melinda Gates Foundation.

Furthermore, TBI-166 (pyrifazimine) moved from Phase 1 to Phase 2 (NCT04670120) and BTZ-043 has started a new Phase 1/2 trial (NCT04044001).

Overall, 13 agents are being developed against *M. tuberculosis*. Of the 13 agents, six meet the innovation criterion of absence of known cross-resistance. Seven of the 13 traditional antibacterial agents belong to new classes, and nine have new antibacterial pharmacophores. Several new targets are being pursued, including decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1) and leucyl-tRNA synthetase (LeuRS), which are essential enzymes for cell wall biosynthesis and mycobacterium protein synthesis, respectively. Among agents in development for treating TB, three target DprE1 and one targets LeuRS. In addition, three oxazolidinones, a riminophenazine (clofazimine analogue), a diarylquinoline and an imidazopyridine amide are in clinical development (Table 4).

Table 4. Antibacterial agents for the treatment of TB and non-tuberculous mycobacteria in clinical development β-lactamases

Name (synonym)	Phase	Antibiotic class	Indication	Route of administration	Developer	Innovation			
						NCR	CC	T	MoA
BTZ-043	2	Benzothiazinone (DprE1 inhibitor)	TB	oral	University of Munich / Hans Knöll Institute, Jena / German Center for Infection Research	✓	✓	✓	✓
Delpazolid (LCB01-0371)	2b	Oxazolidinone	TB	oral	LegoChem Biosciences / Haihe Biopharma	-	-	-	-
GSK3036656 (GSK070)	2	Oxaborole (Leu-Rs inhibitor)	TB	oral	GSK	✓	✓	✓	✓
Sutezolid	2	Oxazolidinone	TB	oral	TB Alliance / Sequella	-	-	-	-
TBA-7371	2	Azaindole (DprE1 inhibitor)	TB	oral	TB Alliance / Bill & Melinda Gates Foundation / Foundation for Neglected Disease Research	✓	✓	✓	✓
Telacebec (Q203)	2	Imidazopyridine amide	TB	oral	Qurient / Infectex	✓	✓	✓	✓
OPC-167832	1/2	3,4-Dihydrocarbostyril (DprE1 inhibitor)	TB	oral	Otsuka	✓	✓	✓	✓
GSK2556286 (GSK286)	1	Class not defined	TB	oral	GSK / TB Drug Accelerator / Bill & Melinda Gates Foundation	?	✓	✓	?
Macozinone (PBTZ-169)	1	Benzothiazinone (DprE1 inhibitor)	TB	oral	Innovative Medicines for Tuberculosis / Nearmedic Plus	✓	✓	✓	✓
TBAJ-587	1	Diarylquinoline	TB	oral	TB Alliance	-	-	-	-
TBAJ-876	1	Diarylquinoline	TB	oral	TB Alliance	-	-	-	-
TBI-166 (pyrifazimine)[1]	2	Riminophenazine (clofazimine analogue)	TB	oral	Institute of Materia Medica / TB Alliance / Chinese Academy of Medical Sciences / Peking Union Medical College	-	-	-	-
TBI-223	1	Oxazolidinone	TB	oral	TB Alliance / Institute of Materia Medica	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data; - criterion not fulfilled.
CC: chemical class; DprE1: decaprenylphosphoryl-β-D-ribose 2'-epimerase; LeuRS: leucyl-tRNA synthetase; MOA: new mode of action; NCR: no cross-resistance; T: new target; TB: tuberculosis.

[1] The lead drug clofazimine is approved to treat leprosy and has been used off-label for TB.

BTZ-043, oral **Phase 2**

- DprE1 inhibitor, benzothiazinone.
- A Phase 1 trial is complete (NCT03590600).
- A Phase 2 multiple ascending dose study has been registered to evaluate early bactericidal activity (NCT04044001) and is currently recruiting patients with drug-susceptible pulmonary TB.

Delpazolid, oral **Phase 2b**

- Delpazolid (LCB01-0371) is an oxazolidinone.
- Phase 2 early bactericidal activity trial completed (NCT02836483). A Phase 2b trial for pulmonary TB is recruiting (NCT04550832).
- A Phase 1 trial as an injectable for MRSA and VRE is also complete.

GSK3036656, oral **Phase 2**

- GSK3036656 (GSK070) belongs to a novel class (oxoborole) with a new MoA that inhibits LeuRS.
- A Phase 2 early bactericidal activity trial is currently recruiting patients with proven rifampin-susceptible *M. tuberculosis* infection (NCT03557281).

Sutezolid, oral **Phase 2**

- Member of the oxazolidinone class.
- A Phase 2 trial is currently recruiting (NCT03959566) to evaluate different doses of sutezolid in combination with bedaquiline, delamanid and moxifloxacin.

TBA-7371, oral **Phase 2**

- DprE1 inhibitor, azaindole.
- A Phase 2 trial to evaluate early bactericidal activity in pulmonary TB is currently recruiting patients with rifampicin-susceptible TB (NCT04176250).
- Development is also being supported by the Foundation for Neglected Diseases Research and the Bill & Melinda Gates Medical Research Institute.

Telacebec, oral **Phase 2**

- Telacebec (Q203) is an imidazopyridine amide that inhibits cytochrome bc1 in the respiratory chain.
- A Phase 2 trial to evaluate early bactericidal activity (NCT03563599) was completed in September 2019.
- A Phase 2 trial is currently ongoing to evaluate effects on patients with mild COVID-19 (NCT04847583).

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

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

GSK2556286 (GSK286), oral **Phase 1**

- GSK2556286 belongs to a new antibacterial class with a new MoA, which is thought to involve cholesterol catabolism *(94)*.
- A Phase 1 safety and tolerability trial (NCT04472897) is recruiting.

Macozinone, oral **Phase 1**

- Macozinone (PBTZ-169) is a DprE1 inhibitor, benzothiazinone.
- A Phase 2a trial in the Russian Federation was terminated due to slow enrolment (NCT03334734).
- Phase 1 trials are complete (NCT03036163 and NCT0377500).

TBAJ-587, oral **Phase 1**

- TBAJ-587 is a diarylquinoline bedaquiline analogue.
- A Phase 1 safety and tolerability trial (NCT04890535) is recruiting.

TBAJ-876, oral **Phase 1**

- TBAJ-876 is a diarylquinoline bedaquiline analogue.
- A Phase 1 trial is active (NCT04493671).

TBI-166 (pyrifazimine), oral **Phase 1**

- Clofazimine analogue, riminophenazine class.
- Clofazimine has been used in the treatment of leprosy since 1962 and is sometimes used in the treatment of drug-resistant TB.
- An early bactericidal activity Phase 2 trial is ongoing in China (NCT04670120).

TBI-223, oral **Phase 1**

- Member of the oxazolidinone class.
- A Phase 1 single ascending dose trial is complete (NCT03758612), and a new Phase 1 trial is recruiting (NCT04865536).

3.3. Agents in development for treating CDIs

Infections with *C. difficile* can cause severe enterocolitis and are a serious public health threat. CDIs are primarily managed by prevention, control and antimicrobial stewardship activities. Several treatment options are currently available, which is why *C. difficile* was not included in the WHO priority pathogens list. However, data on agents in development are included in this report for completeness, as the larger use of antimicrobials relates to CDIs and the increase in resistance *(95)* is worrisome.

Five traditional antibacterials for the treatment of CDI are currently in clinical development, one in Phase 1 and four in Phase 2. Since the 2020 update, only one significant change is noted: CRS3123, an oral diaryldiamine from Crestone/NIAID (National Institute of Allergy and Infectious Diseases), advanced from Phase 1 to Phase 2. This product, as well as ridinilazole, positively addresses all four WHO innovation criteria, showing a new chemical class, a new MoA, no cross-resistance to existing agents and a new therapeutic target in the binding site.

Table 5. Traditional antibacterials in clinical development for the treatment of CDIs

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Innovation			
					NCR	CC	T	MoA
Ridinilazole	3	Bis-benzimidazole	oral, not absorbed	Summit Therapeutics	✓	✓	✓	✓
CRS3123	2	Diaryldiamine	oral	Crestone/NIAID	✓	✓	✓	✓
DNV3837 (MCB-3837)	2	Oxazolidinone-quinolone hybrid	iv	Deinove	?	-	-	-
Ibezapolstat (ACX-362E)	2	DNA polymerase IIIC inhibitor	oral, not absorbed	Acurx Pharmaceuticals	?	✓	✓	✓
MGB-BP-3	2	Distamycin (DNA minor groove binder)	oral, not absorbed	MGB Biopharma	?	✓	✓	✓

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

CC: chemical class; CDIs: *C. difficile* infections; iv: intravenous; MoA: new mode of action; NCR: no cross-resistance; NIAID: National Institute of Allergy and Infectious Diseases; T: new target.

Ridinilazole, oral **Phase 3**

- Nonabsorbable bis-benzimidazole, with a new class, structure and MoA; currently proposed to bind to the DNA minor groove, resulting in selective interference with cell division *(96–99)*.
- Early evidence indicates bactericidal activities and a decrease in toxin A and B concentrations of *C. difficile* strains exposed to ridinilazole *(100)*.
- Being developed as an option for treatment of patients with non-fulminant CDI.
- Seems to better preserve the gut microbiome than current standard of care (fidaxomicin, vancomycin) and hypothesized to lower the risk for CDI recurrence, supported by results from two completed Phase 2 trials (NCT02784002, NCT02092935) *(97)*.
- Two Phase 3 trials have been completed (NCT03595553, NCT03595566), and one Phase 3 trial is ongoing (NCT04802837).

Note: topline results for the completed Phase 3 which evaluated ridinilazole for treatment of and sustained clinical response (SCR) for CDI showed ridinilazole to have a higher SCR rate than vancomycin but did not meet the primary end-point for superiority. SCR was defined as achieving clinical response of the CDI episode and without recurrence of the infection 30 days after the end of treatment *(101)*.

CRS3123, oral **Phase 2**

- New chemical class with a new target and a new MoA: a diaryldiamine derivative that inhibits methionyl-tRNA synthetase *(106)*.
- Active against Gram-positive bacteria, including *C. difficile*; inhibits toxin production in vitro.
- Systemic absorption only at higher doses.
- A Phase 2 trial (NCT04781387) is currently recruiting.

DNV-3837, iv **Phase 2**

- DNV-3837 (MCB-3837) is a prodrug, oxazolidinone-quinolone hybrid for iv treatment *(102)*.
- No cross-resistance reported in tested strains, but limited data available *(103)*.
- A Phase 2 trial is recruiting patients with non-severe or severe CDI, compared with standard of care (NCT03988855).

Ibezapolstat (ACX-362E), oral **Phase 2**

- New chemical class with a new target and a new MoA: DNA polymerase IIIC inhibition.
- A Phase 2 trial is recruiting patients with non-severe CDI (NCT04247542).

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

- Nonabsorbable antibiotic with a novel chemical structure (distamycin derivative), a new target and antibacterial MoA (DNA minor groove binder). It acts on multiple binding sites and interferes with transcription *(104, 105)*.
- Active against Gram-positive bacteria; resistance in Gram-negative bacteria through efflux pumps.
- A Phase 2 trial comparing different MGB-BP-3 dosing regimens in patients with non-severe CDI is complete (NCT03824795).

3.4. Non-traditional antibacterials

There has been increased interest in the development of alternative strategies to direct-acting small molecule antibacterials and β-lactam/BLI combinations *(107)*. These alternatives are collectively known as non-traditional antibacterials. They aim to prevent or treat bacterial infections by directly or indirectly inhibiting bacterial growth, inhibiting virulence, ameliorating antibacterial resistance, boosting the human immune system and positively altering and/or restoring a healthy microbiome *(108)*.

In this report, non-traditional antibacterials are classified into five categories:

- **antibodies:** inactivation or neutralization of a pathogen, a virulence factor or a toxin or binders;

- **bacteriophages and phage-derived enzymes:** direct lysis of a target bacteria by phages or recombinant enzymes and/or phages that have been engineered as nano-delivery vehicles;
- **microbiome-modulating agents:** modification of the microbiome to eliminate or prevent carriage of resistant or pathogenic bacteria, manipulating the metabolism of microbiota;
- **immunomodulating agents:** augmenting/stimulating or suppressing host immune responses that modify the course of infection; and
- **miscellaneous agents:** inhibit the production or activity of virulence factors – toxin production and virulence factor secretion, impeding bacterial adhesion to host cells and biofilm formation, interrupting or inhibiting bacterial communication and downregulating virulence.

Overall, 32 non-traditional antibacterials are under active clinical development: six antibodies, nine bacteriophages and phage-derived enzymes, 10 microbiome-modulating agents, one immunomodulating agent and six agents in the miscellaneous category (Table 6). Two are under NDA/MAA (marketing authorization application) consideration, thus not counted as under active development; five are in Phase 3; 10 are in Phase 2; five are in Phase 1/2; 12 are in Phase 1; and one is not assigned.

The Phase 3 non-traditional agents include: an anti-*S. aureus* immunoglobulin M (IgM) monoclonal antibody, a phage endolysin, a peptide and two live biotherapeutic products both to prevent the recurrence of CDI. **SER-109,** the live biotherapeutic product, is a spore-based treatment. SER-109 has met its primary end-points in a Phase 3 trial (ECOSPOR III) and received breakthrough therapy and orphan drug designations from the US FDA *(109)*. Seres Therapeutics has completed enrolment in the SERES-013 ECOSPOR IV open-label study expected to define the SER-109 safety profile and support an NDA with the US FDA. RBX2660 met primary end-points in a Phase 3 (PUNCHCD3) clinical trial in reducing recurrence of CDI. RBX2660 has been granted fast track, orphan and breakthrough therapy designations from the US FDA.

Most non-traditional products are being tested and are intended for use in combination with standard antibiotics.

Table 6. Non-traditional antibacterial agents in clinical development

Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens
BB128	MAA[1]	Live biotherapeutic product	colonoscopy	BiomeBank	*C. difficile*
Reltecimod (AB103)	NDA[2]	Synthetic peptide antagonist of both superantigen exotoxins and the CD28 T-cell receptor	iv	Atox Bio	*S. aureus*
Tosatoxumab (AR-301)	3	Anti-*S. aureus* IgG1 antibody	iv	Aridis Pharmaceuticals	*S. aureus*
Exebacase (CF-301)	3	Phage endolysin	iv	ContraFect	*S. aureus*
Bacteriophage	3[3]	Phage	inhalation	Tashkent Pediatric Medical Institute	Gram-positive and Gram-negative
SER-109	3	Live biotherapeutic product	oral	Seres Therapeutics	*C. difficile*
RBX2660	3	Live biotherapeutic product	enema	Ferring Pharmaceuticals	*C. difficile*
LMN-101	2	mAb-like recombinant protein	oral	Lumen Bioscience	*E. coli, C. jejuni*
AR-302 (MEDI-4893, suvratoxumab)	2	Anti-*S. aureus* IgG mAb	iv	Aridis Pharmaceuticals, licensed from AstraZeneca	*S. aureus*
IM-01	2	Chicken egg-derived anti-*C. difficile* polyclonal antibody	oral	ImmuniMed	*C. difficile*
LSVT-1701 (N-Rephasin SAL200, tonabacase)	2a/1	Phage endolysin	iv	Roivant Sciences, licensed from iNtRON	*S. aureus*
Phage	1/2	Phage	iv	Adaptive Phage Therapeutics	*E. coli*
AP-PA02	1/2	Phage	inhalation	Armata Pharmaceuticals	*P. aeruginosa*

Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens
YPT-01	1/2	Phage	inhalation	Felix Biotechnology/Yale University	*P. aeruginosa*
BX004-A	1/2	Phage	inhalation	BiomX	*P. aeruginosa*
SYN-004 (ribaxamase)	2b	Antibiotic inactivator	oral	Synthetic Biologics	*C. difficile*
VE303	2	Live biotherapeutic product	oral	Vedanta Biosciences	*C. difficile*
CP101	2	Live biotherapeutic product	oral	Finch Therapeutics	*C. difficile*
DAV132	2	Antibiotic inactivator and protective colon-targeted adsorbent	oral	Da Volterra	*C. difficile*
Rhu-pGSN (rhu-plasma gelsolin)	1b/2a	Recombinant human plasma gelsolin protein	iv	BioAegis Therapeutics	Non-specific Gram-positive and Gram-negative
OligoG (CF-5/20)	2b	Alginate oligosaccharide (G-block) fragment	inhalation	AlgiPharma	*P. aeruginosa*
Ftortiazinon (fluorothyazinone) + cefepime	2	Thyazinone (type III secretion system inhibitor) + cephalosporin	oral	Gamaleya Research Institute of Epidemiology and Microbiology	*P. aeruginosa*
TRL1068	1	mAb	iv	Trellis Bioscience	Gram-positive and Gram-negative biofilms
9MW1411	1	mAb (α-toxin)	iv	Mabwell Bioscience	*S. aureus*
LBP-EC01	1b	CRISPR-Cas3 enhanced phage	iv	Locus Biosciences	*E. coli*
LMN-201	1b	Phage endolysin and three toxin-binding proteins (5D, E3 and 7F)	oral	Lumen Bioscience	*C. difficile*
MET-2	1	Live biotherapeutic product	oral	NuBiyota / Takeda	*C. difficile*
RBX7455	1	Live biotherapeutic product	oral	Ferring Pharmaceuticals (Rebiotix)	*C. difficile*
ART24	1	Live biotherapeutic product	oral	Artugen Therapeutics USA	*C. difficile*
SVT-1C469	1	Live biotherapeutic product	oral	Servatus	*H. pylori*
CAL02	1	Broad-spectrum anti-toxin liposomal agent and nanoparticle	iv	Eagle Pharmaceuticals, licensed from Combioxin	*S. pneumoniae*[4]
BVL-GSK098	1	Amido piperidine (inactivation of TetR-like repressor EthR2)	oral	BioVersys / GSK	*TB*
GSK3882347	1	Undisclosed (FimH antagonist)	oral	GSK	*E. coli*
ALS-4	1	Anti-virulence (staphyloxanthin biosynthesis inhibition)	oral	Aptorum Group	*S. aureus*

Legend

: antibodies; : bacteriophages and phage-derived enzymes; : microbiome-modulating agents; : immunomodulating agents; : miscellaneous (e.g. virulence, adhesion, biofilm and quorum sensing).

CDIs: *C. difficile infections*; FimH: type-1 fimbrin D-mannose-specific adhesin; IgG1: immunoglobulin G1; MAA: marketing authorization application; mAb: monoclonal antibody; NDA: New Drug Application; TB: tuberculosis.

[1] Submitted to the Australian Therapeutic Goods Association as a potential treatment for recurrent CDIs in June 2021.

[2] Submitted to the US FDA as a potential treatment for necrotizing soft tissue infections in December 2020.

[3] Tashkent Pediatric Medical Institute is evaluating a bacteriophage cocktail as a potential nebulized treatment for children with tonsillitis in an open-label, 128-patient clinical trial (NCT04682964).

[4] While the Phase 1 trial evaluated CAL02 on patients with severe pneumonia caused by *S. pneumoniae*, CAL02 has broad-spectrum effects against other bacteria, such as *P. aeruginosa, A. baumannii, Enterobacterales* and *S. aureus*.

3.4.1. Antibodies

When potentially harmful or foreign substances (antigens) such as pathogens or toxic chemicals are detected by the immune system, antibodies are produced that bind to the antigen (at the epitope) and facilitate their removal. Monoclonal antibodies are excreted as homogeneous groups of antibodies by a single clone of plasma B cells and interact with one specific epitope on the antigen. In contrast, polyclonal antibodies are a heterogeneous group produced by different clones of plasma B cells that interact with multiple epitopes of the antigen.

Due to multiple factors, including their homogeneity, selectivity and lower potential for cross-reactivity, in recent years monoclonal antibodies have emerged as an important treatment modality for several therapeutic areas. These areas include oncology, inflammation, multiple sclerosis, lupus, respiratory syncytial virus and, most recently, COVID-19. In addition, monoclonal antibodies are receiving increasing attention for the treatment of bacterial infections.

Historically antibodies have been used as antitoxins (toxin-neutralizing antibodies), as they are able to bind directly to a toxin, either causing its removal or blocking its active site. The diphtheria antitoxins discovered in 1891 provide an example. Only recently have antibodies been studied against bacteria themselves. Antibody therapies can target numerous bacterial epitopes and virulence factors, including surface proteins, bacterial toxins and polysaccharides. However, development challenges remain, including identifying optimal bacterial targets and clinical trial design *(110)*.

Currently six antibodies are in clinical development, with five targeting selected bacteria, albeit with different mechanism and antibody compositions. Three of these are being developed against *S. aureus* [AR-301, AR-302 (MEDI-4893), 9MW1411], one against *C. difficile* (IM-01), one against *C. jejuni* and *E. coli* (LMN-101), and one (TRL1068) against the biofilms caused by various Gram-positive and Gram-negative bacteria.

AR-301 (tosatoxumab), iv **Phase 3**

- Anti-*S. aureus* immunoglobulin G1 (IgG1) monoclonal antibody targets virulence factor α-toxin *(111).*
- Phase 3 trial as an adjunctive treatment of *S. aureus* VAP ongoing (NCT03816956).

AR-302 (MEDI-4893, suvratoxumab), iv **Phase 2**

- Anti-*S. aureus* IgG monoclonal antibody targets the virulence factor α-toxin and surface-localized clumping factor A *(112)*.
- A Phase 2 trial was completed in 2018 as a non-adjunctive treatment for mechanically ventilated adults colonized and at high risk of S. *aureus* pneumonia (NCT02296320).
- Long half-life estimated to be 80–112 days *(113)*.

IM-01, iv **Phase 2**

- Egg-derived anti-*C. difficile* polyclonal antibody from hens exposed to *C. difficile* bacteria, spores, and toxins A and B *(114)*.
- A Phase 2 trial was started in 2019 as a potential non-adjunctive treatment for mild to moderate CDI (NCT04121169).

LMN-101, iv **Phase 2**

- Variable heavy chain-derived protein designed to bind and inhibit *C. jejuni* FlaA, a flagellin filament protein. LMN-101 is delivered via whole spray-dried spirulina biomass.
- A Phase 1 trial was completed in 2020 (NCT04098263).
- A Phase 2 human challenge trial comparing LMN-101 alone with placebo is ongoing (NCT04182490).

TRL1068 **Phase 1**

- TRL1068 binds to DNABII homologues produced by Gram-positive and Gram-negative bacterial pathogens, disrupting biofilm formation.
- It is intended in combination with standard-of-care against a broad spectrum of Gram-positive and Gram-negative bacteria in periprosthetic joint infection.
- TRL1068 is expected to disrupt the pathogen biofilm in the prosthetic joint and surrounding tissue.
- Potential utility as a broad-spectrum agent for adjunctive therapy in difficult-to-treat bacterial infections.
- A Phase I study is currently recruiting (NCT04763759).

9MW1411 **Phase 1**

- 9MW1411 is a monoclonal antibody that binds to the pore-forming α-toxin (α-hemolysin) protein monomer, which inhibits its binding to the ADAM10 receptor on the cell membrane *(115)*. This reduces the toxicity of α-toxin and its detrimental effect in *S. aureus* infections *(116)*.
- A Phase 1 trial (NCT04784312) evaluating the safety, tolerability and pharmacokinetics of 9W1411 started in April 2021.

3.4.2. Bacteriophages and phage-derived enzymes

Bacteriophages (also known as phages) are viruses that infect and replicate in bacteria. Since their discovery in 1915, phages have been used to treat infections in the former Soviet Union, France and central Europe *(117)*. In recent years, evaluating phages as new antibacterial agents has attracted renewed interest, including in the food animal industry.

One option is to use the enzymes produced by phages called lysins, which degrade bacterial cell walls. Another option is to use combinations of different phages derived from phage banks that are prepared to treat individual patients with drug-resistant bacterial infection. A third option is to employ phage cocktails to overcome the specificity of single phages and to broaden the host range to allow empirical use. Some developers are also exploring synthetic biology techniques to engineer phages with more potent and broader activity spectra as vehicles to deliver lysins and bactericidal payloads.

In this review, only bacteriophage and phage-based therapeutics in clinical trial have been considered. Phage cocktails used under an Emergency Investigational New Drug (EIND) application, expanded access/compassionate use, national magistral frameworks or equivalent are not included in the present analysis.

Exebacase (CF-301), iv **Phase 3**

- Recombinantly produced phage endolysin protein, identified as an anti-staphylococcal lysin encoded within a prophage of the *Streptococcus suis* genome *(118, 119)*.
- A Phase 3 trial started in 2020 comparing CF-301 with standard-of-care antibiotics against standard of care alone for treatment of *S. aureus* BSI, including right-sided infective endocarditis (NCT04160468).

Bacteriophage, inhalation **Phase 3**

- A liquid bacteriophage complex against acute tonsillitis in children and adolescents is in a Phase 3 trial (NCT04682964) in Uzbekistan.

LSVT-1701 (N-Rephasin SAL200, tonabacase), iv **Phase 2a/1**

- Recombinantly produced phage-encoded anti-staphylococcal lysin whose mechanism of action is via cell wall enzymatic hydrolysis *(120)*.
- A Phase 2 trial, terminated by the sponsor for strategic reasons, was supposed to test single iv dose of LSVT-1701 in addition to the standard treatment for persistent *S. aureus* bacteraemia (NCT03089697).

Phage, iv **Phase 1/2**

- Phages (personalized to each patient) are being studied in a Phase 1/2 trial for UTI (NCT04287478).
- This study was called "PhageBank (process)" in the previous 2020 pipeline report.

AP-PA02, inhalation **Phase 1/2**

- A phage therapy trial in cystic fibrosis (CF) patients with chronic pulmonary *P. aeruginosa* infection (NCT04596319).

YPT-01, inhalation **Phase 1/2**

- Phage therapy to reduce sputum bacterial load in CF subjects with *P. aeruginosa* infections (NCT04684641).

BX004-A, inhalation **Phase 1/2**

- Phage therapy evaluated in patients with *P. aeruginosa* pulmonary infection (NCT05010577).

LBP-EC01, iv **Phase 1**

- Phage cocktail engineered with clustered regularly interspaced short palindromic repeats (CRISPR) technology targeting the *E. coli* genome. The cocktail combines phage lytic activity with the DNA-targeting activity of Cas3.
- A Phase 1 trial to evaluate the safety, tolerability and pharmacokinetics and pharmacodynamics (PK/PD) of LBP-EC01 in patients with lower-tract *E. coli* colonization was completed in November 2020 (NCT04191148).

LMN-201, oral **Phase 1**

- LMN-201 is a combination of a *C. difficile* targeting phage-derived endolysin and three toxin-binding proteins (5D, E3 and 7F) *(121)*. These three proteins all bind to the *C. difficile* virulence mediator TcdB2 but have different mechanisms.
- A Phase 1 trial (NCT04893239) was started in August 2021.

3.4.3. Microbiome-modulating agents

Recently, there has been considerable interest in investigating the composition and role that the human gut microbiome plays in human health and the impact of antibacterial treatments on this microbiome *(122, 123)*. For example, the gut microbiome is involved in food digestion and production of some vitamins and helps to modulate immune responses and the gut-brain axis. Some antibacterial agents alter the microbiome's balance, which can lead to illness or allow some pathogens, such as *C. difficile*, to become dominant and cause harmful effects. Ten microbiome-modulating agents are currently in clinical trials, and one agent is at the NDA stage. Eight of these agents are live biotherapeutic products under investigation to treat CDI – BB128, SER-109 (spores), RBX2660, CP101, MET-2, RBX7455 (live bacteria) and ART24 – and one product, SVT-1C469, targets *H. pylori*. In addition, two antibiotic inactivators in clinical trials aim at helping maintain gut microbes using two different mechanisms: SYN-004 is an oral ribaxamase enzyme that degrades iv penicillin and cephalosporins absorbed in the gut, while DAV132 uses activated charcoal to adsorb excess antibiotics and their degradative metabolites to better preserve the intestinal microbiota.

BB128, colonoscopy **MAA**

- BB128 is a lyophilized faecal microbiota biotherapeutic product.
- An MAA was submitted to the Australian Therapeutic Goods Administration in July 2021 for the treatment of C. *difficile* and mild to moderate ulcerative colitis.

SER-109, oral **Phase 3**

- A live biotherapeutic product that contains a consortium of pathogen-free, purified bacterial spores of multiple firmicutes, derived from healthy human donor stools *(124).*
- Results released in August 2020 from a Phase 3 trial (ECOSPOR III, NCT03183128) showed a statistically significant benefit of SER-109 vs placebo administered following cure of recurrent CDI to prevent reoccurrence.
- An open-label Phase 3 trial (NCT03183141) in recurrent CDI is ongoing.

RBX2660, enema **Phase 3**

- RBX260 is a microbiota-based live biotherapeutic product in Phase 3 PUNCHCD3 (NCT03244644) for recurrent CDI *(125)*.
- According to preliminary Phase 3 data, 90% of participants met the primary end-point of no CDI recurrence through 8 weeks after treatment, and participants' microbiome composition became more similar to RBX7455 after treatment *(126)*.

SYN-004 (ribaxamase), oral **Phase 2b**

- Recombinant BLI enzyme orally administered with iv-administered β-lactams (penicillins and cephalosporins) that degrades the excess of iv antibacterial agents in the proximal GIT, helping to preserve the gut microbiome *(127)*.
- A Phase 2 trial was successfully completed in 2016. It investigated the prevention of CDI in hospitalized patients with a diagnosis of a lower respiratory tract infection who were receiving iv ceftriaxone (NCT02563106) *(128)*.
- Phase 1/2 trial is testing on adult allogeneic haematopoietic cell transplantation recipients who develop fever after conditioning therapy following treatment with iv-administered β-lactam antibiotics (NCT04692181).

VE303, oral **Phase 2**

- A live biotherapeutic product that consists of eight types of clonal human commensal bacteria.
- A Phase 2 trial for the prevention of recurrent CDI (NCT03788434) was completed in June 2021.
- High-dose VE303 in Phase 2 achieved the primary end-point of preventing CDI recurrence at 8 weeks *(129)*.

CP101, oral **Phase 2**

- A live biotherapeutic product derived from the stool of normal healthy donors from a clinically structured donation programme.
- CP101 met its primary efficacy end-point of reducing CDI recurrence in a Phase 2 trial (NCT03110133) completed in February 2020.
- An open-label extension Phase 2 trial (NCT03497806) also investigating CDI recurrence is ongoing.

DAV132, oral **Phase 2**

- Activated charcoal that irreversibly adsorbs antibiotic residues in the colon *(130)*.
- A Phase 2 trial completed in August 2019 investigated hospitalized patients at high risk for CDI and who received fluoroquinolones or for prophylaxis of febrile neutropenia (NCT03710694).

MET-2, oral **Phase 1**

- A live biotherapeutic product that contains 40 strains of purified and lyophilized bacteria derived from the stool of a healthy 25-year-old donor *(131)*.
- A Phase 1 trial evaluating the dose-dependent engraftment of MET-2 commensal bacteria for treatment of mild-to-moderate recurrent CDI was completed in March 2020 (NCT02865616).
- A Phase 2 trial is evaluating its use for depression (NCT04602715).

RBX7455, oral **Phase 1**

- A live biotherapeutic product manufactured from a microbiota-based suspension prepared from human stool.
- A Phase 1 trial on the treatment of recurrent CDI was completed in July 2020 (NCT02981316) *(132).*
- The product is also under study in other therapeutic areas.

ART24, oral **Phase 1**

- Live biotherapeutic product that is being studied in patients with recent CDI who have completed a standard-of-care course of CDI antibiotics (NCT04891965).

SVT-1C469, oral **Phase 1**

- Live biotherapeutic product trialled as potential treatment for *H. pylori* infection (ACTRN12620000923965) *(133).*

3.4.4. Immunomodulating agents

The human immune system efficiently identifies and eliminates pathogens from the body. Sometimes, however, it is overwhelmed or blocked, which can lead to serious and even life-threatening infections caused by bacteria, fungi, virus or parasites. Currently, two immunomodulating non-traditional agents are being studied in clinical trials: reltecimod (AB103) inhibits bacterial activation of T-cells, and Rhu-pGSN is a recombinantly produced endogenous protein, gelsolin, which helps regulate inflammatory homeostasis.

Reltecimod (AB103), iv **NDA**

- Synthetic octapeptide antagonist that inhibits Gram-positive (including *S. aureus* and *Streptococcus pyogenes*) superantigen activation of the T-lymphocyte receptor CD28 and impairs endotoxin-mediated activation of T-cells *(134)*.
- Immunomodulatory activity is bacterial strain agnostic.
- A Phase 3 trial as an adjunct to standard of care in patients with necrotizing soft tissue infections was completed in 2019 (NCT02469857) (134), and an NDA was filed with the US FDA in December 2020. However, there has been no further update.
- A Phase 3 trial in peritonitis and acute kidney injury (as an adjunct to standard of care) was terminated in 2020 due to slow enrolment (NCT03403751).

Rhu-pGSN (gelsolin), iv **Phase 1b/2a**

- Recombinantly produced human plasma protein gelsolin is an actin-binding protein that helps regulate inflammatory homeostasis *(135)*.
- Immunomodulatory activity is bacterial strain agnostic.
- A Phase 1b/2a trial was completed in April 2019 as an adjunct to standard of care for CAP (NCT03466073).
- The potential role of Rhu-pGSN in sepsis treatment is currently being studied with BARDA *(136)*.
- A Phase 2 trial is ongoing for severe COVID-19 pneumonia (NCT04358406).

3.4.5. Miscellaneous

Six antibacterial non-traditional agents in the pipeline fall under the miscellaneous category: OligoG, an alginate oligosaccharide fragment trialled in the treatment of CF patients; CAL02, a liposome that binds bacterial toxins; BVL-GSK098, a small molecule that helps reduce enzyme-mediated resistance; and three small molecules, including two anti-virulence agents – Ftortiazinon, a bacterial type III secretion system (T3SS) inhibitor; GSK3882347, an adhesion protein inhibitor; and ALS-4 (target undisclosed).

OligoG (CF-5/20), iv **Phase 2b**

- Alginate oligosaccharide (G-block) fragment extracted and purified from the marine algae *Laminaria hyperborea*, which has anti-biofilm activity. Inhibition of bacterial growth normalizes CF mucus by chelating calcium *(137)*.
- Phase 2 trials started in May 2019 to evaluate the product as a potential treatment for CF through an increase in breath volume and a decrease in pulmonary exacerbations (NCT03822455).

CAL02, iv **Phase 1**

- Antitoxin agent which is a mixture of liposomes that create artificially large and stable liquid-ordered lipid microdomains. These microdomains function as docking sites for a large range of bacterial toxins *(138)*.
- A Phase 1 trial for patients with severe pneumonia caused by *S. pneumoniae* (as an addition to the standard-of-care antibiotic treatment) was completed in February 2018 (NCT02583373) *(139)*.
- CAL02 was recently licensed by Eagle Pharmaceuticals, who plan to undertake future Phase 2/3 development.

Ftortiazinon (fluorothyazinon) + cefepime, iv **Phase 2**

- Bacterial T3SS small molecule inhibitor (T3SS is highly conserved in many Gram-negative bacteria, including *P. aeruginosa*).
- A Phase 2 trial in combination with cefepime for the treatment of patients with cUTI caused by *P. aeruginosa* started in 2018 (NCT03638830).

GSK3882347, oral **Phase 1**

- Small molecule with undisclosed structure that is an inhibitor of an *E. coli* adhesive protein, FimH, which prevents *E. coli* from binding and infecting the bladder wall.
- A Phase 1 trial to prevent and/or treat UTI caused by *E. coli* among healthy participants was completed in May 2021 (NCT04488770).

BVL-GSK098, oral **Phase 1**

- Inactivates the TetR-like repressor *(140),* EthR2, which will help to overcome *M. tuberculosis* resistance to ethionamide *(141)*.
- Intended to be used clinically in combination with the TB drugs ethionamide or prothionamide.
- A Phase 1 trial started in December 2020 (NCT04654143).

ALS-4, oral **Phase 1**

- Small molecule anti-virulence agent that inhibits a key enzyme in the biosynthesis of the carotenoid pigment staphyloxanthin that is being evaluated as a treatment for *S. aureus* infections *(142)*.

3.5. Agents not under active development or for which there is no recent information

In the antibacterial field it is not uncommon for companies to suspend product development for several years, in the hope that they may find the necessary financing to continue development at a later stage or that the product may be bought by another company. In addition, some developmental programmes have been substantially halted by the COVID-19 outbreak.

Some of these compounds are still listed in the (online) clinical development pipelines of the sponsoring developers, but typically do not move through the clinical development pathway. If such products do not show any activity for at least 3 years, they are listed in Table 7 as agents that are not under active development or for which there is no recent information. Agents that were discontinued/terminated on or after 2017 are also listed in Table 7.

Six antibacterial agents have been added to this table since the last review: 514G3 (omodenbamab) completed a Phase 1/2 clinical trial (NCT02357966) in February 2017, while AR-105 was licensed to Serum Institute of India but there has been no recent information; AR-105 may re-enter clinical development. DSTA4637S is no longer in the Genentech development pipeline, while Kaleido Biosciences is focusing on developing KB109 against COVID-19. Tetraphase Pharmaceuticals was acquired in July 2020 by La Jolla Pharmaceutical Company, which is looking to license TP-271 and TP-6076.

Table 7. Agents not under active development

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
GSK-3342830	1	Siderophore-cephalosporin	Gram-negative	GSK	2017
AIC-499 + unknown BLI	1	β-Lactam + BLI	Gram-negative	AiCuris	2017
DS-2969	1	New class (GyrB inhibitor)	*C. difficile*	Daiichi Sankyo	2017
514G3 (omodenbamab)[1]	1/2	Anti-*S. aureus* IgG mAb	*S. aureus*	Xbiotech	2017
SQ-109	2/3	Ethambutol derivative (different MoA)	TB	Sequella	2017
SPR-741+ β-lactam	1	Polymyxin (potentiator) + β-lactam	Gram-negative	Spero Therapeutics / Everest Medicines	2018
Cefilavancin (TD-1792, RD-1792)	3	Glycopeptide-cephalosporin hybrid	*S. aureus*	R-Pharm / Theravance Biopharma	2018
Ramoplanin	2	Lipodepsipeptide	*C. difficile*	Nanotherapeutics	2018
Ancremonam (BOS-228, LYS-228)	2	Monobactam	CRE	Boston Pharmaceuticals	2018
Cadazolid	3	Oxazolidinone-quinolone hybrid	*C. difficile*	Actelion Pharmaceuticals	2019
RC-01 (T 1228)	1	New class (LpxC inhibitor)	Gram-negative	Recida Therapeutics / Fujifilm Toyama Chemical	2019
GT-1	1	Siderophore-cephalosporin	Gram-negative	Geom Therapeutics	2019
MK-3866	1	BLI	Gram-negative	Merck Sharp & Dohme	2019
Murepavadin (POL7080)[2]	3	Peptide	*P. aeruginosa*	Polyphor	2019
AR-105 (Aerucin)[1]	2	Anti-*P. aeruginosa* fully human IgG1 mAb	*P. aeruginosa*	Aridis Pharmaceuticals (Serum Institute of India)	2019
BCM-0184	1	Undisclosed (likely peptide)	*S. aureus*	Biocidium Pharmaceuticals	2019
Iclaprim	3	Trimethoprim	*S. aureus*	Motif Bio	2020
MEDI-3902 (gremubamab)	2	Anti-*P. aeruginosa* IgG mAb	*S. aureus*	AstraZeneca (MedImmune)	2020
OPS-2071	2	Quinolone	*C. difficile*	Otsuka	2020
DSTA4637S	1	Anti-*S. aureus* IgG mAb/ rifamycin conjugate	*S. aureus*	Genentech (Roche)	2021
KB109[1]	N/A	Synthetic glycan	Gram-positive and Gram-negative	Kaleido Biosciences	2021
TP-271[1]	1	Tetracycline	*S. aureus and S. pneumoniae*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021
TP-6076[1]	1	Tetracycline	*A. baumannii*	La Jolla Pharmaceutical Company (Tetraphase Pharmaceuticals)	2021

Underlined: New chemical class.

BLI: β-lactamase inhibitor; CRE: carbapenem-resistant *A. baumannii*; GyrB: DNA gyrase subunit B; IgG: immunoglobulin G; mAb: monoclonal antibody; MoA: mode of action.

[1] These antibacterials were previously listed as "in development" in the 2020 WHO pipeline report.

[2] The development of iv-administered murepavadin was discontinued in 2019. But after merging with Polyphor in September 2021, EnBiotix plans to develop murepavadin as an inhalation treatment for *P. aeruginosa* infections in patients with CF.

4

Agents in preclinical development

4. Agents in preclinical development

In addition to the analysis of the clinical antibacterial pipeline, since 2019 WHO has also undertaken an annual review of the preclinical pipeline. The aim is to assess the size of this pipeline, to identify developers active in the antibacterial research and development space and to provide an overview of the different approaches pursued worldwide. Ultimately, greater transparency in the preclinical pipeline coupled with the clinical pipeline should lead to stronger collaboration around potentially innovative but challenging projects, support a community of scientists and drug developers, and generate more interest and funding in drug development for novel antibacterial agents.

4.1. Geographical distribution

The review captures 217 preclinical projects that are affiliated with 121 institutions geographically distributed across four out of the six WHO regions (Fig. 3). Most data in the 2021 survey were collected from programmes within the European Region (*n* = 61, 50.4%) and the Region of the Americas (*n* = 45, 37.2%). The majority of data came from the USA (*n* = 44), followed by the United Kingdom (*n* = 12), France (*n* = 11) and Germany (*n* = 8).

The global distribution across the 2019, 2020 and 2021 analyses has been very similar (Fig. 3); the 2020 numbers notably included vaccine developers.

Fig. 3. The geographical distribution of the 121 institutions with preclinical pipeline projects across the 2019–2021 analysis

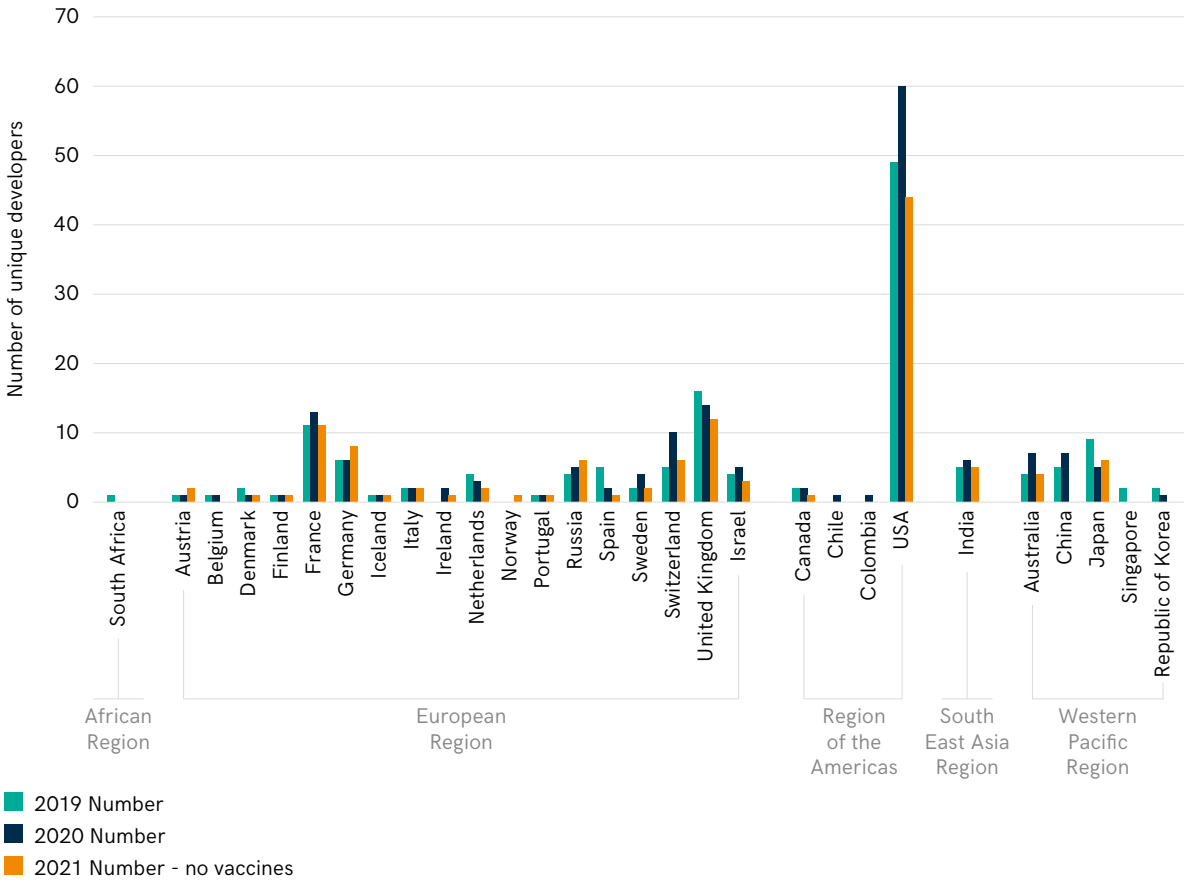
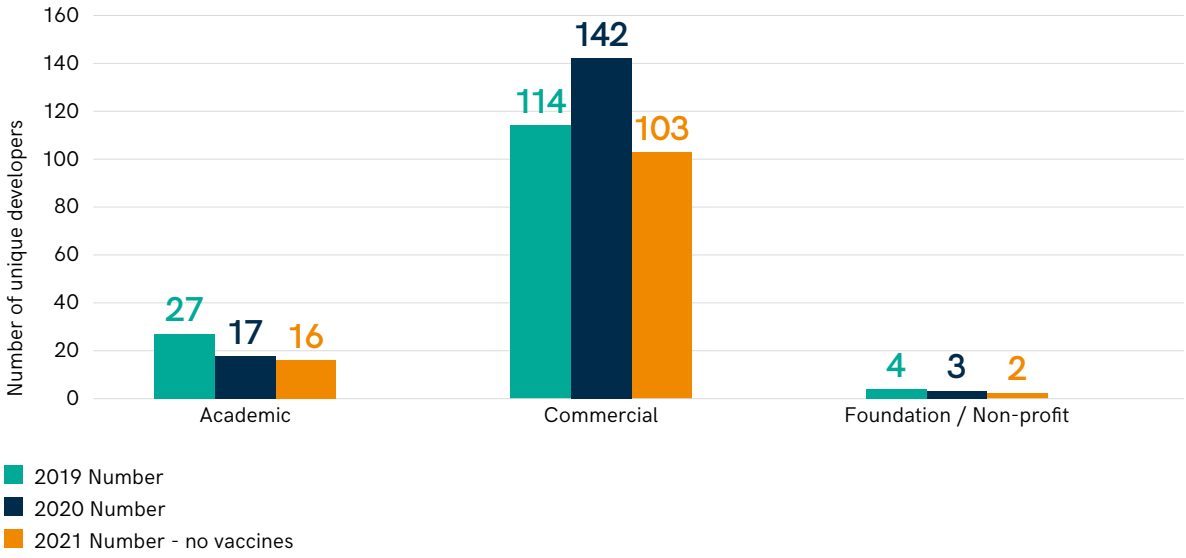


Fig. 4. Categorization of groups with preclinical pipeline projects by type

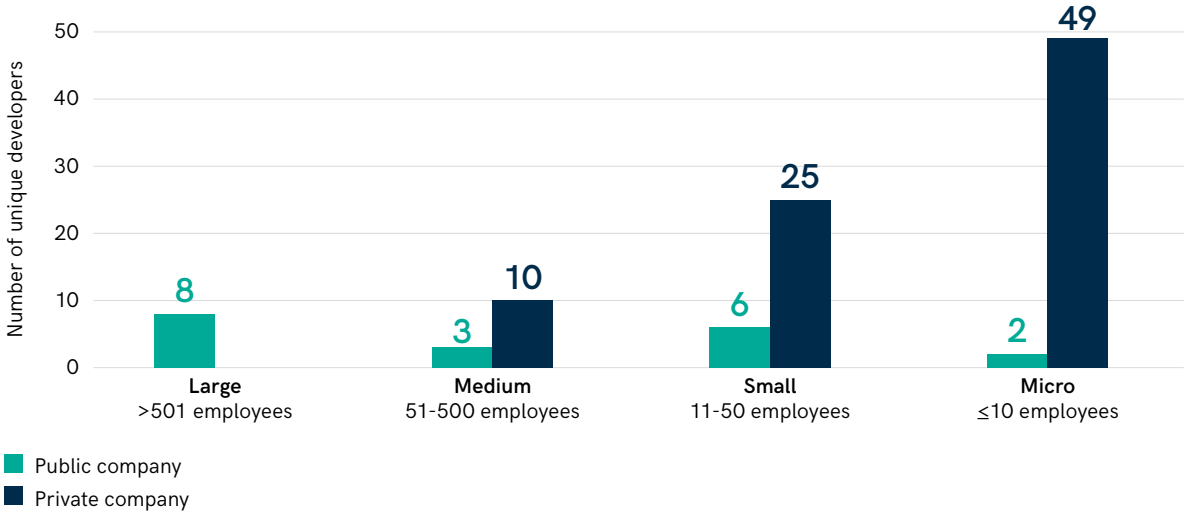


The 121 developers developing preclinical agents were classified as either academic universities, companies or foundations. Most institutions covered in the 2021 analysis were companies (*n* = 103, 85.1%), followed by academic institutions (*n* = 16; 13.2%) and foundations (*n* = 2, 1.7%). The dominance of companies performing antimicrobial product development has remained stable over the three consecutive years of analysis (Fig. 4).

The 103 companies were also further stratified by size as well as whether they were publicly traded or privately owned companies. Most of these companies were privately owned (*n* = 84, 81.6%), and a significant proportion had < 50 employees. Almost half of the 103 companies were small companies with < 10 employees (Fig. 5). The fact that most of the preclinical pipeline developers are small companies may indicate that large pharmaceuticals continue to exit the antibacterial discovery area. A certain bias can also be expected, since most large pharmaceutical companies remaining active in the area did not disclose their preclinical pipeline.

Forty-six of the developers who responded in the 2020 survey (from a total of 136 developers) did not submit information to the 2021 analysis. Therefore, the progress and status of the associated programme(s) from 2020 could not be verified for the 2021 analysis including through a review of publicly available information. It is, therefore, assumed that these products are likely discontinued. This high level of turnover in antimicrobial developers working in the highlights the fragility of the overall landscape.

Fig. 5. Categorization of companies with preclinical pipeline projects by ownership and size



4.2. Categorization of preclinical agents

The review reveals a large scope of different agents in preclinical development. Most of the programmes involved direct-acting small molecules (*n* = 90, 41.5%) (Table 8). There were also many direct-acting peptide programmes (*n* = 33, 15.2%) (Table 1). There were 92 non-traditional agents, representing 42.4% of the preclinical pipeline. Of these, the largest contributing groups were bacteriophage programmes (*n* = 28, 12.9%) and indirect-acting small molecules (*n* = 23, 10.6%) (Table 8, non-traditional modalities marked with *).

A total of 152 (70%) programmes were being developed as single agents, and 39 (18%) were being developed in combination with another agent. Twenty-six programmes disclosed no information on their development strategy.

Table 8. Distribution of preclinical programmes by antibacterial agent category

Product type	2021 Number - no vaccines	2021 %
Small molecule - direct acting	90	41.5
*Small molecule - indirect acting	23	10.6
Peptide - direct acting	33	15.2
*Peptide - indirect acting	2	0.9
*Large molecule - direct acting	15	6.9
*Large molecule - indirect acting	4	1.8
*Bacteriophage/Bacteriophage products	28	12.9
*Biologic (Antibody or other biotherapeutic)	8	3.7
*Nucleic acid based product	4	1.8
*Immunomodulators	7	3.2
*Microbiome modifying agents	1	0.5
Decolonization agents	2	0.9
Total	**217**	**100**

Several analyses were performed to understand the progression of the preclinical pipeline in 2021. Programmes were grouped by self-declared preclinical development stage and compared with data collected in 2019 and 2020 (Fig. 6). The relative proportion of programmes in each stage of development has remained relatively constant over the 3-year period, suggesting that as projects either fail or progress into clinical development, they are replaced by new programmes.

The 2020 analysis listed 34 programmes in the IND-enabling phase of preclinical development, eight of which have progressed into clinical studies. Eleven programmes from the 2020 analysis were not included in 2021, as their status could not be verified, including two programmes that had been acquired. The 2021 analysis also listed 34 products in the IND-enabling phase: 11 that carried over the classification from 2020; 19 that had progressed from an earlier development phase in 2020; and four new programmes that had not been captured during the 2020 analysis.

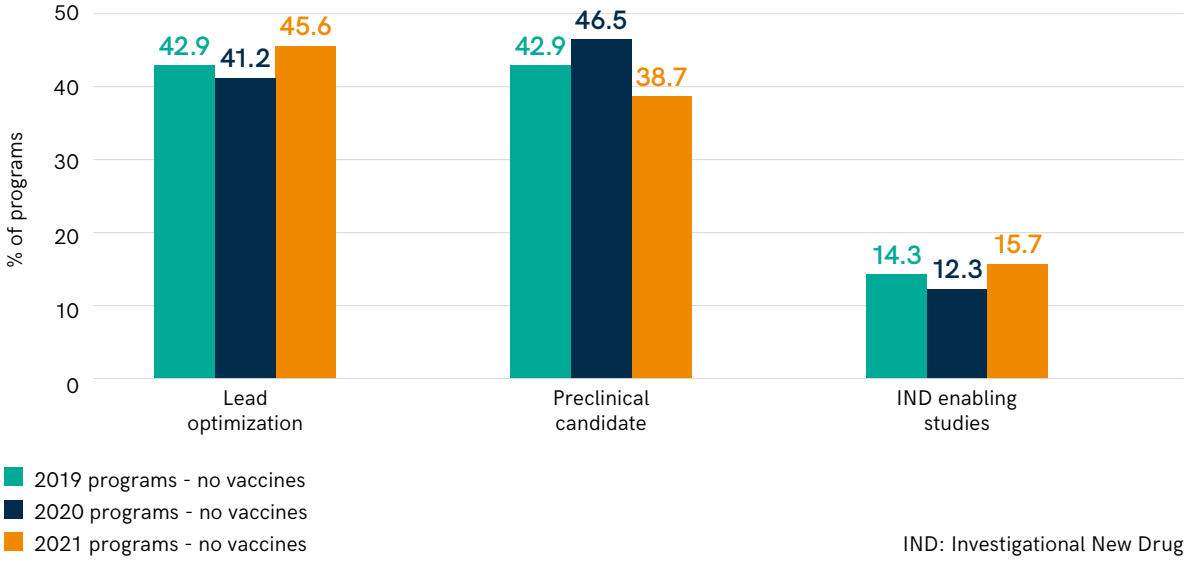
Table 9 shows the 217 products categorized by their antibacterial MoA against their self-declared preclinical development stage. Overall, the large number of direct-acting peptide and bacteriophage programmes resulted in a significant number (*n* = 56, 25.8%) of products that had a direct membrane effect. For 21 (9.6%) products, no information on MoA was available (either unknown or undisclosed) (Table 9).

Table 9. Distribution of programmes by MoA and preclinical development stage

MOA – Categorical	2021 Number	2021 %	Development stage		
			LO	PCC	IND
Anti-virulence	24	11.1	19	3	2
Cell wall synthesis - BL and/or BLI	8	3.7	0	2	6
Cell wall synthesis - Other	29	13.4	14	14	1
Central metabolism	7	3.2	2	4	1
Direct membrane effect	56	25.8	17	25	14
DNA replication/synthesis	12	5.5	6	5	1
Protein synthesis	18	8.3	7	7	4
RNA synthesis	3	1.4	2	1	0
Immunomodulation	10	4.6	3	7	0
Other cellular function	16	7.4	9	5	2
Potentiator or Enabling agent	10	4.6	5	4	1
Not disclosed	9	4.1	5	4	0
Unknown	12	5.5	10	2	0
De-colonisation	3	1.4	0	1	2
Total	**217**	**100**	**99**	**84**	**34**

BL: β-lactam; BLI: β-lactamase inhibitor; LO: lead optimization; PCC preclinical candidate; IND: Investigational New Drug/Clinical Trial Application-enabling studies; MoA: mode of action.

Fig. 6. Categorization of programmes by stage of preclinical development across three consecutive years



IND: Investigational New Drug

4.3. Antibacterial spectrum of agents in preclinical pipeline

The WHO priority pathogens list for 2017 identified pathogens that cause antibiotic-resistant infections for which there is an urgent global need for new antibiotics. Analysis of the disclosed microbiological spectrum of the preclinical pipeline against the WHO critical pathogens shows that 69 of the 217 products (31.8%) have activity against *P. aeruginosa* and 50 products (28%) have activity against *A. baumannii* (Table 10). The number of products with activity against key *Enterobacterales* was 23.5% (*Enterobacter* spp.); 26.7% of products had activity against *K. pneumoniae* and 28.6% against *E. coli* (Table 10).

Further examination of the preclinical pipeline projects indicated that a significant number of products (*n* = 95, 43.8%) were focused on a single pathogen, which may represent a shift towards more targeted therapies rather than broader spectrum agents. A total of 44 species-specific products targeted species in the WHO critical pathogen category, including 21 programmes directed against *P. aeruginosa*, eight directed against *A. baumannii* and 15 against key *Enterobacterales*. Twenty species-specific products were directed against *S. aureus* (WHO high priority) and 19 against *M. tuberculosis*, respectively (Table 10).

Table 10. Distribution of declared microbiological activity of species-specific programmes by WHO priority pathogen

Organism	Total products*	Species-specific products	WHO PPL
P. aeruginosa	69	21	Critical
A. baumannii	50	8	
E. coli	62	10	
K. pneumoniae	58	4	
Enterobacter spp.	51	1	
Enterobacterales spp.	22	0	
Salmonella spp.	20	0	High
N. gonorrhoeae	22	4	
H. pylori	6	1	
Campylobacter spp.	6	0	
S. aureus	74	19	
E. faecium	38	1	
Shigella spp.	18	0	Medium
H. influenzae	14	0	
S. pneumoniae	37	1	
M. tuberculosis	28	20	
C. difficile	20	5	
Not disclosed	9		
Broad G+/G-**	13		
Gram-negative**	3		
Total		**95**	

*Note that products with activity against multiple species will be counted against each species.
**Activity against individual bacterial species was not provided.
G+/G-: Gram-positive and Gram-negative bacteria; PPL: priority pathogens list; spp.: species; WHO: World Health Organization.

Examination of the 95 species-specific programmes by product type (Table 11) indicates that the species-specific products against *P. aeruginosa* and *S. aureus* were distributed across most of the different product types.

Table 11. Distribution of species-specific programmes by product type and WHO priority pathogen

		Bacterial Pathogen																
		Critical					High						Medium					
Product type	**Total (%)**	*P. aeruginosa*	*A. baumannii*	*E. coli*	*K. pneumoniae*	*Enterobacter* spp.	*Salmonella* spp.	*N. gonorrhoeae*	*H. pylori*	*Campylobacter* spp.	*S. aureus*	*E. faecium*	*Shigella* spp.	*H. influenzae*	*S. pneumoniae*	*M. tuberculosis*	*C. difficile*
Small molecule - direct acting	34 (35.8)	2	4	1				3			6				1	15	2
Small molecule - indirect acting	11 (11.6)	5						1			4						1
Peptide - direct acting	7 (7.4)	1	1								1					4	
Large molecule - direct acting	9 (9.5)	1		1	2	1			1			1				1	1
Large molecule - indirect acting	2 (2.1)										1						1
Bacteriophage/Bacteriophage products	22 (23.2)	8	1	6	2						5						
Biologic (Antibody or other biotherapeutic)	4 (4.2)	1	1	2													
Nucleic acid based product	3 (3.2)	1	1								1						
Immunomodulators	3 (3.2)	2									1						
Total	**95 (100)**	**21**	**8**	**10**	**4**	**1**		**4**	**1**		**19**	**1**			**1**	**20**	**5**

WHO: World Health Organization.

4.4. Discussion of preclinical data

This study represents WHO's third consecutive global analysis of publicly available preclinical antibacterial pipeline projects, and it suggests several trends: overall preclinical pipeline projects are broadly distributed geographically, and there is a large variety of product types. The focus has remained on Gram-negative pathogens combined with a continual shift towards narrow-spectrum agents focusing on a single pathogen. The preclinical pipeline is innovative and includes a large number of non-traditional approaches.

With respect to institutions, the preclinical antibacterial pipeline continues to rely on micro (< 10 employees) and small (< 50 employees) companies and academic institutions to progress the basic science and development of innovative products for treating drug-resistant infections. Analysis of groups with programmes in the preclinical antibacterial pipeline clearly indicates significant volatility and turnover in the R&D ecosystem. Over the 2019–2021 period, 258 unique groups were included in the data analysis, yet only approximately 30% of these were listed in all 3 years (excluding vaccine developers, which were not assessed over the full time period). Turnover thus amounts to approximately 25–30% year over year.

A year-over-year analysis of the later stages of preclinical development indicated that while programmes progressed to some degree, a significant number failed to progress successfully or their status could not be verified. Consequently, these programmes were not included in the 2021 analysis. Lack of progress could be due to failure of an individual programme, or of a company. Moreover, it should be noted that the COVID-19 pandemic may have had an impact on either, or both, of these scenarios.

WHO will continue to monitor the preclinical pipeline on a regular basis and make these data available on the WHO Global Observatory on Health R&D.

5

Discussion

5. Discussion

5.1. New agents mainly derivatives of existing classes with a limited focus on CRAB and CRPA

Of the 12 newly approved antibacterial agents only two represent a new class, while over 80% (10/12) are derivatives of known classes where multiple resistance mechanisms already exist increasing the risk of fast development of resistance.

Only one broad-spectrum agent – cefidorocol - targets CRAB and CRPA in addition to CRE; five antibacterial agents target one or more types of CRE and seven other priory pathogens from the WHO bacterial priority pathogens list.

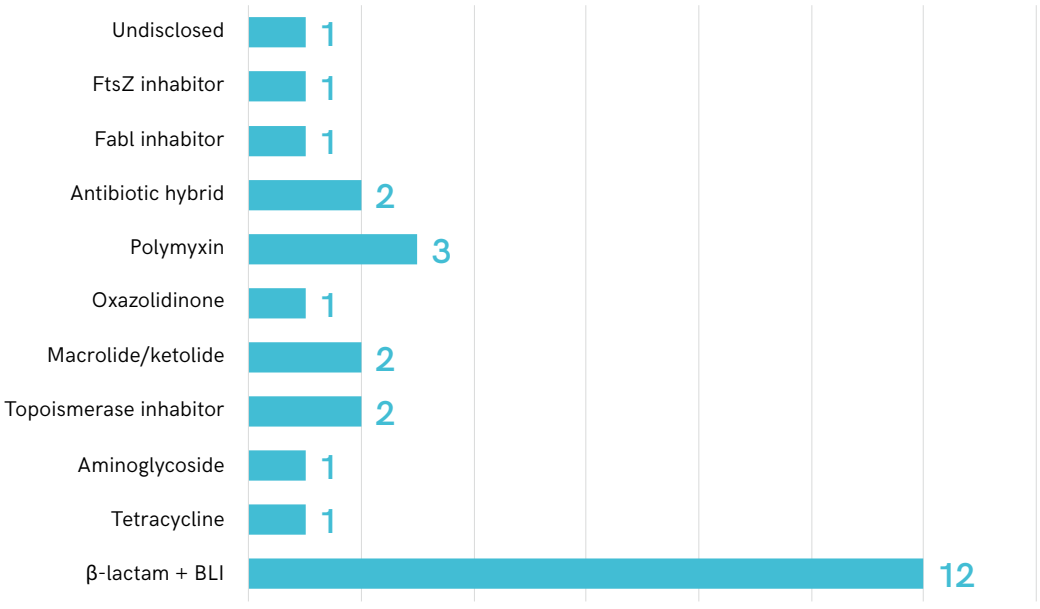
The majority (seven out of 12) of the newly approved antibiotics are classified as "reserve" according to the WHO 2021 AWaRe classification *(143)*, while three are in the "watch" group. Contezolid has not been evaluated yet but, as other oxazolidinones, is likely to follow within the reserve group in the next revision of the AWaRe classification. This confirms that most new agents presently in development, when approved, will likely be in the reserve group. Thus, they will be considered last-resort antibiotics to be used only where previous treatment lines have failed.

Further evidence is needed to evaluate the true effectiveness and added clinical value of these newly approved agents. Post-approval usage data will need to be made available to evaluate real-life pathogen-specific indications and the relevance of their use in different countries and populations. In addition, the lack of distinct benefit over existing treatment, not being included in clinical guidelines and their higher prices in comparison to existing generic standard therapies make it difficult to predict their clinical utility. Based on anecdotal evidence and current sales figures, clinicians do not use these new antibiotics to treat infectious syndromes that were the initial target of authorized therapies (e.g. cUTI and cIAI).

5.2. The clinical "traditional" pipeline is still insufficient against priority pathogens

Most antibiotics that target WHO priority pathogens are β-lactam/BLI combinations (*n* = 12, 12.4%), followed by polymyxins (*n* = 3, 3.11%) (Fig. 7).

Fig. 7. Summary of antibiotics in the clinical pipeline targeting WHO priority pathogens



BLI: β-lactamase inhibitor; FabI: enoyl-acyl carrier protein reductase; FtsZ: filamenting temperature-sensitive Z; WHO: World Health Organization.

Antibacterial agents in clinical development do not sufficiently address the problem of extensively or pan-drug-resistant Gram-negative bacteria. Novel antibiotics targeting critical WHO priority pathogens are still lacking; in particular, carbapenem-resistant *A. baumannii* and *P. aeruginosa* continue to be insufficiently addressed.

The pipeline also has a gap in terms of oral antibiotic treatment options for ESBL-producing bacteria and CRE that could allow treatment outside of a health-care facility or shorten the duration of treatment in the facility. Only one carbapenem (benapenem) and one penem (sulopenem) are currently being evaluated in late-stage clinical development against ESBL-producing infections. In addition, three β-lactam/BLI combinations (durlobactam + sulbactam, taniborbactam + cefepime and enmetazobactam + cefepime) are in Phase 3 development to treat ESBL-producing *Enterobacterales* infections that could spare the use of carbapenems. Increasing numbers of patients with complicated UTIs due to ESBL-bacteria have been reported from clinical practice even in patients that acquired it outside hospitals, as well as pregnant women with bacteriuria and simple UTIs. Bacteraemia caused by ESBL-producing *Enterobacterales* in the hospital is usually resistant to current oral medicines but can be cured with iv antibacterial treatment. Having new oral and iv/oral switch options would allow patients to be discharged without the need for home iv therapy. Gepotidacin, one of a new class of topoisomerase II inhibitors that can be administered both intravenously and orally, has activity against ESBL *Enterobacterales* infections. Some orally administered β-lactam/BLI combinations in Phase 1 may also have activity against ESBL-producing bacteria, namely ETX0282 + cefpodoxime proxetil, ARX-1796 + undisclosed, VNRX-7145 + ceftibuten and QPX7728 + QPX2015. Finally, new antibacterial drugs to treat ESBL-producing *Enterobacterales* infections should not increase carbapenem resistance.

5.3. Innovation remains a challenge for Gram-negative bacterial species

Most of the antimicrobial agents in the clinical pipeline are derivatives of existing classes.

Of the 27 antibiotics, only six fulfil at least one of the four WHO innovation criteria. Of these six, two topoisomerase inhibitors (zoliflodacin and gepotidacin) are in Phase 3; one novel pyrido-enamide (afabicin, a FabI inhibitor) is in Phase 2; two β-lactam/boronate BLI (taniborbactam and VNRX-7145 + ceftibuten) are in Phase 3 and 1, respectively; and one FtsZ inhibitor (TXA709) is in Phase 1. Only two of the six innovative antibiotics (taniborbactam and VNRX-7145 in combination with ceftibuten) target at least one of the critical Gram-negative bacteria. These two compounds are both a combination of a boronate BLI with a β-lactam, and the functional class of BLIs is predicted to show some cross-resistance to other BLI classes when used clinically, despite belonging to a new chemical class. Of the six innovative compounds, four target OPP. Among these, two novel bacterial topoisomerase II inhibitors (zoliflodacin and gepotidacin) are chemically distinct but target the same enzyme. There is little information on potential cross-resistance with other topoisomerase II inhibitors, although some cross-resistance has been reported for gepotidacin (see Chapter 3 above).

In conclusion, there is a major gap is in the development of antibacterial agents that meet at least one of the WHO innovation criteria and at the same time target critical Gram-negative bacteria.

The anti-TB clinical antibacterial pipeline is more innovative, with seven (53%) antibacterials meeting at least one innovation criterion for belonging to a new chemical class. Four of the seven agents inhibit DprE1, which is important for cell wall synthesis. Regarding CDIs, there are five products in the pipeline and four innovative agents, two of which address all four innovation criteria.

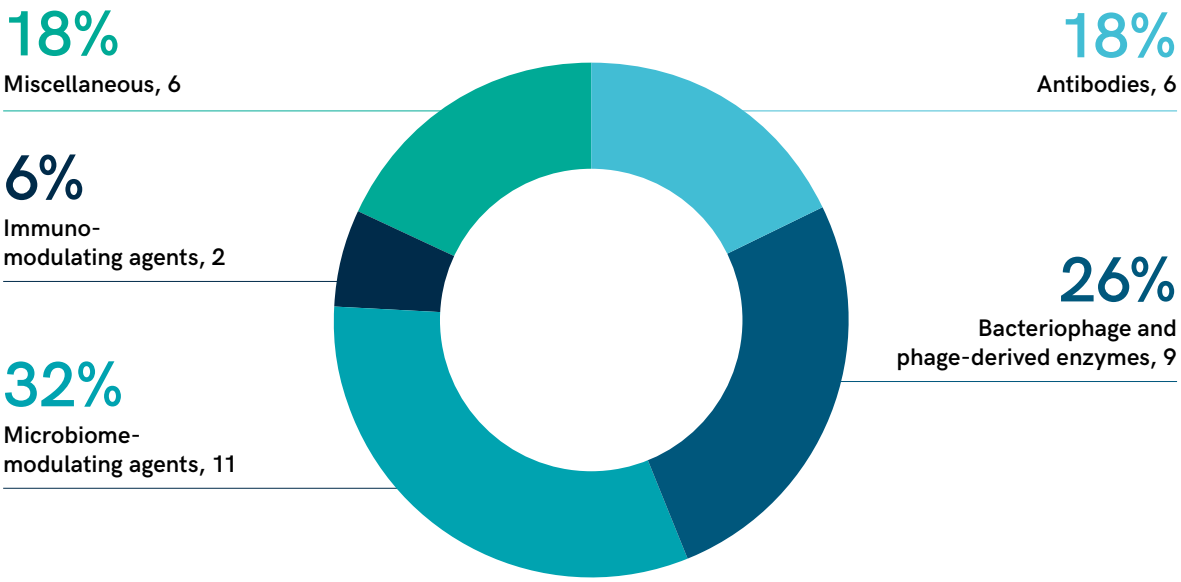
Overall, the clinical direct-acting small molecule ("traditional") pipeline remains dominated by improvements of existing classes. To overcome existing cross-resistance, more new classes of antibacterials are needed, including antibacterials that address new targets and employ new MoAs *(144)* or that otherwise ensurelow propensity for resistance development, at least by mutation, along with characteristics that promote cell permeation and/or efflux avoidance.

Finding novel chemical structures with new binding sites and new MoAs is, however, scientifically difficult. The challenges include finding compounds that have more than one binding site 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 potential toxicity due to the high concentrations required to kill bacteria or inhibit their growth.

5.4. Diversity in non-traditional approaches

Non-traditional antibacterials may have the potential through their diverse and novel MoAs to reduce the selective pressure that drives resistance to traditional antibacterial agents (Fig. 8).

Fig. 8. Summary of non-traditional antibacterials in the clinical pipeline



Two of the 34 non-traditional agents are in NDA/MAA stage. However, the majority are in early clinical stages, and it is likely that many of these will face development hurdles as/if they progress through the pipeline. In addition, over 90% (*n* = 30) of the non-traditional agents are pathogen-specific strategies, a majority of which target *S. aureus* (*n* = 7) and *C. difficile* (*n* = 12). This selectivity confirms a trend also observed in the preclinical space and requires significant diagnostic availability for optimal use, which is often not available outside of specialized health-care facilities and poses a challenge in low-resource settings *(107, 145)*.

Innovative approaches that could be used as an alternative to, or complementary and synergistic with, traditional antibacterial agents that are being pursued hold potential to curb AMR. In the present scenario, where traditional products have a limited lifespan before resistance emerges and their value is preserved by stewardship measures, unconventional approaches seem to offer opportunities to tackle AMR from different angles.

5.5. A dynamic but volatile preclinical pipeline

Overall, preclinical pipeline projects are well distributed geographically and feature products whose MoAs are very varied. The focus remains on critical Gram-negative pathogens and is combined with a shift towards narrow-spectrum agents targeting a single pathogen. Further development of these agents will require increased use of rapid diagnostics and evolution of clinical development strategies.

The preclinical pipeline is dynamic and innovative, including a wide range of drug development projects that use different approaches to target the WHO bacterial priority pathogens list. However, high turnover of programmes makes their progression unpredictable.

5.6. Outlook

Given the average progression rates and the development duration associated with traditional R&D models, the current pipeline will generate few new innovative antibiotics in the coming years *(4)*.

5.7. Gaps and constraints in the current clinical R&D landscape

Traditional antibacterial agents under development are still insufficient to adequately address the enormous threat posed by AMR, and there is a major gap in development of products addressing pathogens that possess a broad spectrum of resistance to current antibacterial agents.

Only one among the authorized products and few among the antibacterial agents under development address critical pathogens (CRAB, CRAP, CRE). Moreover, most of these agents are combinations of β-lactams with BLIs. Very few agents target MBLs, which continue to grow in prevalence. Thus, in terms of therapeutic targets, the pipeline remains largely inadequate for MDR *A. baumannii* and *P. aeruginosa* lacking innovative candidates to address these two critical pathogens.

Appropriate oral formulations for outpatient treatment along with optimized paediatric formulations are generally lacking across the entire clinical pipeline.

6

Methods

6. Methods

Evaluation of the antibacterial clinical development pipeline was conducted through the WHO Secretariat with the support of the WHO Advisory Group on the Research and Development of Antibacterial Treatments comprising clinicians, microbiologists and experts in antibiotic R&D, PK/PD and AMR (see Acknowledgements). The experts reviewed the criteria for inclusion/exclusion and innovation and assessed each agent against those criteria during a 2-day virtual advisory group meeting (29–30 November 2021). Members of the advisory group who had a conflict of interest (Annex 1) with a specific agent were excluded from this discussion. The draft evaluation of all antibacterial agents provided jointly with this report was circulated to all members of the advisory group for feedback before publication.

6.1. Clinical pipeline analysis

6.1.1. Scope and inclusion/exclusion criteria

This review covers traditional and non-traditional antibacterials in Phases 1–3 that do not have market authorization for human use anywhere in the world as well as antibacterial agents that were approved after 1 July 2017. It is restricted to agents that could potentially be used to treat bacterial infections caused by the WHO priority pathogens (Box 1), *M. tuberculosis* or *C. difficile* and that have a specific antibacterial effect. The following definitions are used for this report *(1)*:

- **Traditional antibacterials** are small molecules that directly inhibit the growth of (bacteriostatic) or kill bacteria (bactericidal) by targeting components necessary for bacterial growth.
- **Non-traditional antibacterials** are anything other than direct-acting small molecules and encompass a range of approaches for the treatment and prevention of bacterial infections, preventing the development or spread of drug resistance.

Repurposed antibacterial agents are included in this review if the primary indication is in a therapeutic area different from infectious disease.

Traditional and non-traditional agents are further classified by structure and development goal (Table 12).

Table 12. Structure and development goals of traditional and non-traditional antibacterials

	Traditional	Non-traditional
Structure	Small molecules	Anything that is different from a small molecule. This includes antibodies, bacteriophages, lysins, live biotherapeutics, oligonucleotides, etc.* (see 3.4. Non-traditional antibacterials)
Development goal	Treatment or prevention through directly acting to inhibit growth (bacteriostatic) or kill (bactericidal) bacteria	Treatment or prevention of bacterial infections through other approaches that can inhibit growth or kill bacteria: prevention of the development or spread of resistance, improving/restoring microbiome status and slowing the spread of resistance

*Antimicrobial peptides are included among non-traditional agents in the clinical review of this report.
Source: adapted from Rex et al. *(145)*.

The analysis does not include:

- vaccines;
- topical decolonizing agents;
- non-specific inorganic substances;
- biodefence agents;
- agents not developed for systemic use (injectable or oral formulations) or inhalation but only for topical application (e.g. creams or eye drops);
- new formulations of existing treatments; or
- antibacterials that have had their development terminated, are no longer listed in a company's pipeline and/or have not updated development for 3 years (1 November 2018).

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

Extension of indication of already approved antibacterial agents are not included in this revision.

The analysis includes only agents that are in active development or have been approved since 1 July 2017. Agents for which no progress or activity in clinical development has been recorded for 3 years or more are listed in a separate table. Agents that no longer appear in a company's development pipeline or were terminated before 2017 are excluded. One of the main sources of data is clinical trial registries; but not all trials are registered, and results of completed trials not always published. Thus, all companies and institutions are encouraged to register clinical trials in line with the WHO *International standards for clinical trial registries* and through the International Clinical Trials Registry Platform (ICTRP) *(146)*. They are also encouraged to share their randomized controlled trial (RCT) methodologies and results and to keep their product pipeline on the company website updated with references to published literature.

6.1.2. Search strategy

This 2021 clinical pipeline update is based on the 2017 publication of *Antibacterial agents in clinical development* and the subsequent updates in 2018, 2019 and 2020 *(147–149)*. These publications have evolved over time; from 2019 they also include antibacterial agents in preclinical development and from 2020 non-traditional agents in clinical and preclinical development and an innovation assessment for traditional agents.

Information on agents in development was sought from a variety of sources. The cut-off point was 1 November 2021, 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 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 were 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 September 2020 through 1 November 2021; 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 were available, information from company websites was used and evaluated by the advisory group for credibility of inclusion.
- The Access to Medicine Foundation's *Antimicrobial resistance benchmark* was consulted.
- The ICTRP and ClinicalTrials.gov were searched.
- In collaboration with the WHO Observatory, the commercial database AdisInsight was searched.
- A targeted desktop search of products was carried out with national experts from Japan and the Russian Federation. In addition, individual companies, the BEAM Alliance, CARB-X and the Novo Holdings REPAIR Impact Fund participating in the WHO preclinical data call were outreached (see Acknowledgements).

- Agents developed for use against TB were identified from published reviews of the TB pipeline, notably from the Stop TB Partnership Working Group on New TB Drugs and from TB Alliance.

The search strategy is described in more detail in the 2017, 2019 and 2020 WHO reports *(147, 149, 150)*.

6.1.3. 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 is publicly available and scientifically sound, as reviewed by the advisory group.

The evidence supporting the expected activity increases with the development stage. The first level of evidence is usually gained by in vitro experiments. Subsequently, preclinical results are produced using animal disease models in the sought indication or in a broader one. Moving to the clinical phases, safety and tolerability data in healthy volunteers are usually generated followed by dose–response and efficacy data. Advanced in silico simulations are also used to support clinical and preclinical development.

6.1.3.1. Expected activity against priority pathogens

Both in vitro and in vivo (when available) data were 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 MICs and the pharmacokinetics. When available, data on PK/PD, as well as information on nonclinical or clinical efficacy, were considered in the assessment. Drugs that have shown activity in vitro but are not currently being developed for relevant indications were not assessed against the respective pathogens.

The advisory group classified agents for which data were inconclusive as "possibly active", represented by a question mark. Agents for which little or no data were available on activity against specific pathogens were classified as "possibly active" if drugs of the same class are known to be active against the respective pathogen *(151)*.

6.1.3.2. Innovation

An agent was considered innovative if it had no 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 with 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 *(152)*:

- new class (new scaffold);
- new target (new binding site); and
- new MoA.

Each agent in clinical development or recently approved was evaluated against the four innovation criteria.

If products do not meet the innovation criteria, it does not necessarily mean that they do not have clinical utility for specific patients. For example, a safety profile that improves on the standard of care, a less invasive route of administration (e.g. oral versus iv), better clinical outcomes or increased activity against priority pathogens could provide improvements but need to be proven in clinical trials. However, the pharmaceutical optimization of existing products is not reviewed in this report.

6.2. Preclinical pipeline review

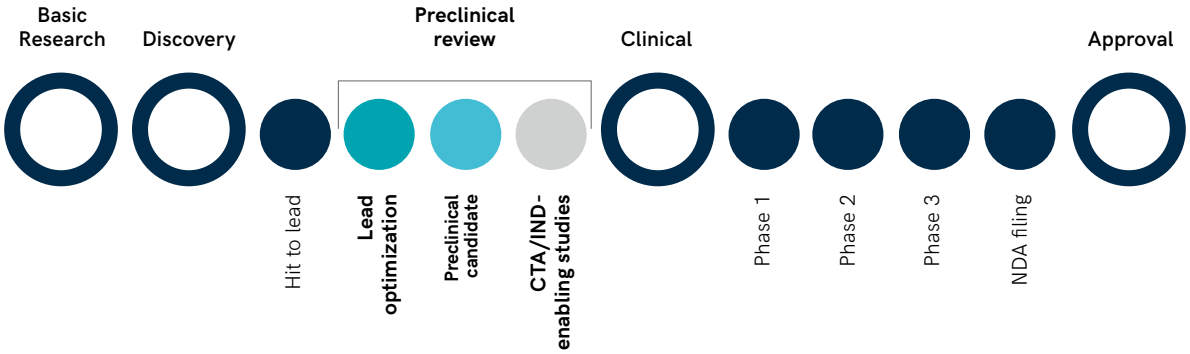
6.2.1 Scope and inclusion/exclusion criteria

The review focuses on antibacterial agents that target WHO priority pathogens (Box 1), *M. tuberculosis* and *C. difficile* that are in lead-optimization (post-hit expansion) preclinical candidates or at the formal IND or CTA stage (for regulatory authorities that do not use IND/CTA, this is indicative of the commencement of human testing) (Fig. 9.).

The review includes both traditional and non-traditional approaches including direct- and indirect-acting antibacterials, small and large molecules, anti-virulence agents and biofilm disruptors, potentiators, microbiome-modifying agents, immunomodulators, repurposed non-antibiotics and antibiotics from animal to human use, decolonization agents and combination therapies.

The review does not include vaccines, diagnostics, antifungals, antivirals or anti-parasitics. Wound-care agents, non-specific supportive treatments, medical devices, industrial or animal use agents were also not included. Vaccines against antibiotic-resistant pathogens of high concern at the clinical and preclinical stage are presented in a dedicated WHO report *(153)*.

Fig. 9. Traditional drug development phases showing the preclinical phases included in this report in red



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

6.2.2. Data collection

A WHO online call was held from 30 September to 30 October 2021 *(154)* and generated the primary data. A targeted search of products in preclinical development was undertaken in Japan and Russia. These data were supplemented with information from the Beam Alliance, CARB-X and the Novo Holdings REPAIR Impact Fund among others. In addition, programmes from the 2020 analysis were checked through a desk review and, where required, updates were solicited by email. Data presented are self-declared from the institutions. Where possible, WHO confirmed the data through publications, conference abstracts or posters, institutional websites and other information in the public domain.

6.3. Methodological considerations

6.3.1. Variable data quality

The aim of this report is to provide a complete, accurate picture of 2021 clinical and preclinical development activities based on 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, quality and amount of data continue to vary, especially for products in the early stages of development.

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. Such products were considered 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 development stages and from RCTs complicated the assessment of some agents in advanced development phases. It is essential that any public – and private – investment in antibacterial drug development include an obligation to adhere to clinical trial transparency standards by publishing 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 publicly available company information was used or comparisons with other agents with a similar structure if no data were 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 MoA are "surrogate markers" and good predictors of lack of cross-resistance. For these reasons, the four aspects were assessed separately for each compound. For some compounds, lack of information (e.g. structure not published) made any detailed 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 accurate categorization of compounds.

6.3.2. Limitations

The analysis of the clinical antibacterial pipeline was undertaken with certain limitations, including reliance on data available in the public domain and input from the WHO Technical Advisory Group on R&D, which may raise the potential for selection bias. These limitations were addressed through the final WHO impartial judgement, an additional effort to capture drug candidates being developed in Japan and the Russian Federation and surrounding countries to ensure a more comprehensive global analysis. Further targeted efforts will continue to be taken into consideration for future updates, including the expansion of the geographical representation of the advisory group and gender balance. The membership of the advisory group, in line with WHO rules of procedures, is reviewed and adjusted on a regular basis.

The analysis and assessment of the preclinical pipeline rely largely on data submitted by the respective developers through the open WHO data call. A thorough data cleaning was undertaken. Where available other sources were used for additional information, or the developer was contacted to clarify or fill gaps in the submission. In the absence of clinical data as well as detailed data on the different molecules in development, no independent assessment was undertaken with respect to the bacterial targets or innovativeness of the individual projects. This review should be considered a snapshot and not a complete analysis.

All individuals and/or companies are encouraged to register clinical trials in line with the *WHO International standards for clinical trial registries*, using ICTRP. The WHO Secretariat would welcome 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.

7

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Annexes

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 and preclinical pipeline. The declarations of interest (DOIs) were collected and thoroughly reviewed by the WHO Antimicrobial Resistance Division following WHO standard operating procedures.

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

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

The experts who declared no potential conflicts of interest were Stephan Harbarth and Christian Lienhardt. These experts were allowed full participation in the meeting.

The experts who disclosed potentially significant conflicts of interest were Cesar Arias, Lloyd Czaplewski, Prabha Fernandes, Roman Kozlov, Norio Ohmagari, Mical Paul, John Rex, Lynn Silver and Guy Thwaites.

Cesar Arias is a professor at the University of Texas Health Science Center, Houston, USA, and founder and scientific advisor at the Molecular Genetics and Antimicrobial Resistance Unit, International Center for Microbial Genomics, Universidad El Bosque, Colombia. In his DOI he disclosed that he had been awarded financial support in the past 4 years from Merck Sharp & Dohme and Entasis Therapeutics.

Lloyd Czaplewski is director at Chemical Biology Ventures in UK. In his DOI he disclosed that he had been awarded financial support in the past 4 years from Chemical Biology Ventures, Curza and Novo Holdings.

Roman Kozlov is rector of Smolensk State Medical University and 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 & Dohme, Pfizer and Astellas Pharma.

Norio Ohmagari is director of the Disease Control and Prevention Center at the National Center for Global Health and Medicine Hospital in Japan. In his DOI he disclosed that he or his unit had received support for research in the past 4 years from Sanofi and Shionogi.

Mical Paul is director of the Infectious Diseases Institute at Rambam Health Care Campus in Israel. In her DOI she disclosed that she had been awarded financial support in the past 4 years from Pfizer.

John H. Rex is chief medical officer and director of F2G, chief strategy officer of CARB-X, non-executive director and consultant of Adenium Biotech, operating partner and consultant of Advent Life Sciences and expert-in-residence at the Wellcome Trust. He disclosed in his DOI having been employed, provided consulting services, received research grants/support, held shares or commercial interest in the past 4 years from Bugworks Research Inc., Basilea Pharmaceutica, Forge Therapeutics, Novo Holdings, Roche, Sumitovant, Innocoll, Progenity, Nosopharm, Roivant Sciences, Shionogi, GSK, Pfizer, F2G and AstraZeneca.

Lynn Silver is president of LL Silver Consulting LLC. In her DOI, she reported having been awarded financial support or owning stocks in the past 4 years from Aileron Therapeutics, Appili Therapeutics, Curza, Debiopharm, DesignMedix, Forge Therapeutics, Taxis Pharmaceuticals, CDD-SPARK, AMED – Japan, the Novo Holdings REPAIR Impact Fund, Techulon and Prokaryotics.

Guy Thwaites is the director of the Oxford University Clinical Research Unit in Viet Nam. In his DOI he disclosed that he has provided consulting services in the past 4 years to the Wellcome Trust.

Having assessed the DOIs, the WHO technical unit granted full participation to Guy Thwaites, while Cesar Arias, Lloyd Czaplewski, Roman Kozlov, Norio Ohmagari, Mical Paul, John Rex and Lynn Silver were excluded from discussions involving products from commercial entities or other organizations listed above.

François Franceschi, Lesley Ogilvie, Melvin Spigelman and Mike Sharland participated in the meeting as observers.

Richard Alm and Mark Butler were hired by WHO as consultants in relation to this activity.

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

Annex 2. Background information on Phase 3 antibacterial products

1. Sulopenem

Sulopenem is a synthetic penem that is being evaluated in iv and oral formulations for the treatment of uUTI (oral), cUTI and cIAI (iv/oral prodrug) due to *Enterobacterales*, including ESBL-producers. The drug is intended to reduce or shorten the hospitalizations of patients treated for some MDR Gram-negative bacteria by providing a step-down oral therapy option.

- **Route of administration and formulation:** Intravenous/oral prodrug.
- **Class, MoA and target:** β-Lactam (cell wall inhibition).
- **Bacterial spectrum/coverage:** Activity against ESBL-producing cephalosporin-resistant *Enterobacterales* (but not CRE).
- **Cross-resistance:** Cross-resistance with existing carbapenems reported.
- **Half-life:** 0.76 and 1.10 h.
- **Dose and adverse effects:** Proposed dose in Phase 3 RCTs for treatment of:
  - **uUTI in females:** Sulopenem-etzadroxil/probenecid 500mg PO twice daily for 5 days. Adverse effects reported (SURE 1). The adverse effects from most to least common were diarrhea, nausea, headache, vomiting and dizziness (2-12% patients).
  - **cUTI and cIAI:** Sulopenem 1000 mg iv once daily for at least 5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO twice daily for 7–10 days. Adverse effects reported (SURE 2): Headache was the most reported adverse effect, affecting 3% of patients (*n* = 21/695) receiving the drug, followed by diarrhoea (2.7%) and nausea (1.3%).
- **Phase 3 study:** Sulopenem has been evaluated as a treatment for uUTI, cUTI and cIAI, in a series of Phase 3 RCTs labelled sulopenem for resistant *Enterobacterales* (SURE) 1 through 3 (NCT03354598, NCT03357614, NCT03358576).
- **Sulopenem SURE 1 Phase 3 study** (NCT03354598).
  - **Time period:** 1 August 2018 to 20 January 2020 (final data collection date).
  - **Study design:** A prospective, multicentre, double-blind, randomized study that compared the efficacy and safety of oral sulopenem-etzadroxil/probenecid with oral ciprofloxacin for treatment of uUTI in adult females.
  - **Study population:** 1671 adult female patients were randomized and parallelly assigned to receive either sulopenem-etzadroxil 500 mg/probenecid 500 mg bid (twice a day) for 5 days in addition to placebo (ciprofloxacin) for 3 days (*n* = 835), or ciprofloxacin 250 mg bid for 3 days and placebo (sulopenem) for 5 days (*n* = 836).
  - The study took place in the USA.
  - **Included in the study** were all adult women (≥ 18 years of age) presenting with 24 h to ≤ 96 h of at least two of the following uUTI symptoms/signs: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain, plus a midstream urine specimen positive for (a machine-read dipstick) and/or evidence of pyuria. Participants had to be able to provide informed consent.
  - **Excluded** were all participants with signs and symptoms suggestive of AP, and those who had received an antibacterial drug therapy potentially effective as treatment for uUTI within the prior 7 days, or those concurrently using non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI. (Note: more details on the inclusion and exclusion criteria can be found via ClinicalTrials.gov identifier NCT03358576).
  - **The primary outcome:** Overall success (combined clinical and microbiological success) in each arm of the microbiologic-modified intent-to-treat susceptible (m-MITTS) population and in each arm of the microbiologic-modified intent-to-treat resistant (m-MITTR) population at the TOC visit on day 12.

- **The primary efficacy end-point** used was the composite successful outcome of clinical success (symptom resolution and no new symptoms) and microbiological success (defined eradication of the baseline pathogen) at the TOC visit.
- **The primary efficacy evaluation** was performed in the m-MITT population. Superiority was tested in the quinolone-non-susceptible m-MITT population. Non-inferiority was tested in the quinolone-susceptible m-MITT population.
- **Adverse effects reported from the Phase 3 study to treat uUTI in females** (sulopenem-etzadroxil/probenecid 500 mg PO twice daily for 5 days): Diarrhoea was the most reported adverse effect, affecting to almost 12% of patients (*n* = 103/883 in the sulopenem arm) receiving the drug, of whom 6.8% (*n* = 60/883) had clinically significant diarrhoea. The overall number of diarrhoeal episodes reported was 781, with a median duration of 3 days. Other side effects reported included nausea, headache, vomitingand dizziness.
- **SURE 1 trial conclusions:** Sulopenem demonstrated superiority to ciprofloxacin in female patients with quinolone-resistant pathogens at baseline with an overall response rate (ORR) at TOC visit of 62.6% (*n* = 92/147 patients) in the sulopenem arm compared with 36% (*n* = 50/139 patients) in the ciprofloxacin arm, for a percentage difference of 26.6% (95% CI: 15.1–37.4; $P < 0.001$).
- However, sulopenem was found not to be non-inferior to ciprofloxacin in patients with organisms susceptible to quinolones, with an ORR at TOC visit of 66.8% (*n* = 247/370 patients) in the sulopenem arm compared with 78.6% (*n* = 326/415 patients) in the ciprofloxacin arm, for a percentage difference of 11.8% (95% CI: -18.0 to -5.6; $P < 0.001$).
- The developer attributed this difference in outcome to the lower rates of asymptomatic bacteriuria in patients receiving ciprofloxacin (3.9%) compared with those receiving sulopenem (12.7%) and called for further research on the influence of asymptomatic bacteriuria on the assessment of outcome of treatment of uUTI.

- **Sulopenem SURE 2 Phase 3 study** (NCT03357614).
  - **Time period:** 18 September 2018 to 14 December 2019 (final data collection date).
  - **Study design:** A prospective, multicentre, double-blind, double-dummy, randomized, non-inferiority study that compared the efficacy and safety of sulopenem followed by sulopenem-etzadroxil/probenecid vs ertapenem followed by ciprofloxacin for the treatment of cUTI in adults.
  - **Study population:** 1395 adult cUTI patients were randomized and parallelly assigned to receive either sulopenem iv once daily for 5 days followed by a bilayer tablet of sulopenem-etzadroxil and probenecid bid or ertapenem iv once daily for 5 days followed by either oral ciprofloxacin or amoxicillin-clavulanate bid, depending on the susceptibility of the baseline uropathogen.
  - The study took place in Estonia, Georgia, Hungary, Latvia and the USA.
  - **Included in the study** were all adults (≥ 18 years of age) presenting with pyuria, bacteriuria and over 24 h of clinical signs and symptoms of cUTI. Participants had to be able to provide informed consent.
  - **Excluded** were all participants who received an antibacterial drug therapy potentially effective as treatment for cUTI > 24 h during the previous 72 h and those with an organism isolated from the urine within the last year known to be resistant to ertapenem.
  - **The primary outcome:** Overall success (combined clinical and microbiological success) in each arm in the m-MITT population at the TOC visit on day 21.
  - **The primary efficacy end-point** used was the composite successful outcome of clinical success and microbiological success at the TOC visit on day 21.
  - **The primary efficacy evaluation** was performed in the m-MITT population. Non-inferiority was tested in the quinolone-susceptible m-MITT population.
  - **Adverse effects reported from the Phase 3 study to treat cUTI in adults** (sulopenem 1000 mg iv once daily for at least 5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO twice daily for 7–10 days): Headache was the most reported adverse effect, affecting 3% of patients (*n* = 21/695) receiving the drug, followed by diarrhoea (2.7%, *n* = 19/695) and nausea (1.3%, *n* = 9/695).
  - **Sure 2 trial conclusions:** Sulopenem followed by oral sulopenem-etzadroxil/probenecid was not non-inferior to ertapenem followed by oral step-down therapy for treatment of cUTI, with a difference in outcome of -6.1% (95% CI: -12.0 to -0.1) using a non-inferiority margin of 10%. Sulopenem, both iv and oral, was well tolerated; its oral formulation allowed patients with baseline pathogens resistant to both quinolones and β-lactams an opportunity to successfully step down from iv therapy.

- **Sulopenem SURE 3 Phase 3 study** (NCT03358576).
  - **Time period:** 18 September 2018 to 2 October 2019.
  - **Study design:** A prospective, multicentre, double-blind, randomized, non-inferiority study that compared the efficacy and safety of sulopenem followed by sulopenem-etzadroxil/probenecid vs ertapenem followed by ciprofloxacin-metronidazole for the treatment of cIAI in adults.
  - **Study population:** 674 cIAI adult patients were randomized and parallelly assigned to receive either sulopenem 1000 mg iv once daily for 5 days followed by a bilayer 500 mg tablet of sulopenem-etzadroxil/probenecid bid to complete 7–10 days of treatment, or ertapenem 1000 mg iv once daily for 5 days followed by oral ciprofloxacin 500 mg bid (or amoxicillin-clavulanate 875 mg bid, depending on the susceptibility of the baseline uro-pathogen), along with metronidazole 500 mg four times a day (qid).
  - The study took place in Bulgaria, Estonia, Georgia, Hungary, Latvia, Poland and the USA.
  - **Included in the study** were all adults (≥ 18 years of age) with cIAI. Participants had to be able to provide informed consent.
  - **Excluded** from the study were patients diagnosed with intra-abdominal gastrointestinal organ perforation, undergoing surgery within 12–24 h. Also excluded were patients with simple or complicated biliary infections without rupture, or simple appendicitis, or infected necrotizing pancreatitis or pancreatic abscess. Also excluded were patients known to have a cIAI caused by pathogens resistant to the study antimicrobial agents. (Note: more details on other inclusion and exclusion criteria can be found at ClinicalTrials.gov identifier NCT03358576).
  - **The primary outcome:** Overall success (combined clinical and microbiological success) at TOC visit on day 28. Clinical outcome at day 28 was defined as cure for patients who were alive and showed resolution of signs and symptoms of the index infection, and for whom no new antibiotics or interventions for treatment failure were required.
  - **The primary efficacy end-point:** Clinical response at day 28 in patients with a positive intra-abdominal culture at baseline.
  - **Adverse effects reported from the Phase 3 study to treat cIAI in adults** (sulopenem 1000 mg iv once daily for at least 5 days, followed by sulopenem-etzadroxil/probenecid 500 mg PO twice daily for 7–10 days): Treatment-related adverse events were reported in 6.0% and 5.1% of the 668 patients on sulopenem and ertapenem, respectively. Diarrhoea was the most reported adverse effect, affecting 2.4% of patients receiving the drug. Serious adverse events unrelated to study treatment were seen in 7.5% of patients on sulopenem and 3.6% of patients on ertapenem.
  - **Sure 3 trial conclusions:** Sulopenem was not non-inferior to the comparator (ertapenem), with a difference in outcome of 4.7% (95% CI: -10.3 to 1.0) using a non-inferiority margin of 10%.

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2. Durlobactam (ETX-2514) + sulbactam

The combination is studied as a pathogen-specific treatment (narrow spectrum) for infections due to drug-resistant *A. baumannii* in hospitalized adults (mainly MDR and carbapenem-resistant ABC isolates). It aims to provide an empiric treatment option (first 48 h) for patients with HABP or VABP due to commonly MDR ABC, including carbapenem-resistant infections.

- **Route of administration and formulation:** 3 h iv infusion q6h (every 6 h) for 7 days up to 14 days.
- **Class, MoA and target:** β-Lactam/DBO BLI combination. Sulbactam is a penicillanic acid sulfone β-lactam that is widely used as a BLI in combination. It has intrinsic activity against *A. baumannii*, including Class A β-lactamase producers (binds to PBP1 and PBP3).

  Durlobactam is a modified DBO BLI (diazabicyclooctane class of BLIs) with broad activity against Class A, C and D β-lactamases. It also binds to PBP2 (intrinsic antibacterial activity due to inhibition of PBP2. However, this is not how its action is mediated).

  Note: durlobactam enters *A. baumannii* cells through outer membrane porins (Omp A). The virulence of *A. baumannii* is corelated to the presence of Omp A; deletion of Omp A is an unlikely mechanism of developing resistance to durlobactam.
- **Bacterial spectrum/coverage:** Inhibitory activity against CRAB ABC. The combination is meant to restore the activity of sulbactam, which has been limited as a monotherapy against *A. baumannii* due to AMR.
- **Cross-resistance:** An in vitro study of the combination against a globally diverse set of *A. baumannii* isolates reported that AMR to the combination was relatively low.
- **Half-life:** Sulbactam, 1 h; durlobactam, 2.2 h.
- **Dose:** Studied for treatment of HAP, VAP due to ABC (Phase 3 proposed dose): 1 g q6h with a 3 h iv infusion (1:1 ratio, 1 g + 1 g) for 7 days and up to 14 days. Adverse effects reported (from Phase 2 study) in 37.7% (*n* = 20/53) of patients receiving the drug. All adverse effects reported were mild to moderate, with headache being the most common (9.4%) followed by phlebitis (5.7%). Other side effects reported include vascular pain, diarrhoea and vomiting (3.8%, *n* = 2 for each).
- **Phase 3 study:** The combination has been evaluated through an interventional, open-label, randomized, controlled clinical trial. The aim is to study the efficacy and safety of the combination (iv) of durlobactam (ETX-2514) + sulbactam in the treatment of hospitalized patients with ABC infections, including HABP and VABP, compared with colistin (superiority design). The study is referred to by the developer as ATTACK, which stands for Acinetobacter Treatment Trial Against Colistin (NCT03894046, EudraCT 2017-004868-35).
  - **Time period:** 3 April 2019 to 22 July 2021.
  - **Study design:** Interventional, open-label, randomized, controlled clinical trial to evaluate the efficacy and safety of the iv combination in treatment of patients with ABC infections compared with colistin (superiority design).
  - **Study population:** 207 adult (≥ 18 years of age) patients with ABC HAP, VAP or bacteraemia were randomized (**part A**, the randomized, controlled portion of the study) and parallelly assigned to receive either a durlobactam (1 mg) + sulbactam (1 g) combination (q6h iv infusion) or colistin (2.5 mg/kg) (q12h iv infusion), for 7 days, with patients in both arms receiving background therapy with imipenem + cilastatin (500 mg, q6h iv infusion). **Part B** of the study looked at the efficacy of the combination as a single intervention for treatment of the subgroup of the study population with ABC infections that are resistant to or have failed colistin treatment (with the patients in this subgroup also receiving the background therapy).
  - The trial took place in 95 clinical sites in 16 countries.
  - **Included in the study** were adult men and non-pregnant women ≥ 18 years) with confirmed diagnosis of serious infections due to ABC requiring iv antibiotic treatment for HABP, VABP (or one of the following indications: bacteraemia, cUTI or AP, or surgical or post-traumatic wound infections), and who have not received > 48 h of empiric therapy prior to enrolment; OR who have a recent history of treatment failure. Part B of the study included all patients with ABC infections resistant to colistin (according to predefined satisfactory evidence of colistin treatment failure or intolerance).

- **The primary outcome** is defined as the proportion of patients in the m-MITT population who achieve overall treatment success after receiving 7–14 days of treatment, as determined at the TOC visit, 28 days post-randomization.
- **The primary efficacy end-point:** 28-day all-cause mortality in the m-MITT population (in part A).
- **The primary efficacy evaluation:** Performed in m-MITT patients infected with ABC who received any amount of the study drug.

Phase 3 study results and conclusions:

Phase 3 registrational trial evaluating the safety and efficacy of SUL-DUR vs colistin in patients with infections caused by *A. baumannii*.

Part A results:

- In Part A of the study, SUL-DUR met the primary end-point of 28-day all-cause mortality in patients with carbapenem-resistant *Acinetobacter* infections (CRABC m-MITT* population = 125), demonstrating statistical non-inferiority vs colistin.
- Mortality analyses reported: Favoured SUL-DUR vs colistin in CRABC m-MITT and all study populations included in the topline results. Mortality was 19% (12/63) in the SUL-DUR arm compared with 32% (20/62) in the colistin arm (treatment difference of -13.2%; 95% CI: -30.0 to 3.5). Similar SUL-DUR favouring trends were reported for the 28-day and 14-day all-cause mortality across all study populations evaluated.
- Clinical response reported: At TOC the reported clinical response was 62% SUL-DUR compared with 40% in the colistin arm (95% CI: 2.9–40.3). The difference was statistically significant.

Part B results:

- In Part B, the reported 28-day all-cause mortality was 17.9% (5/28), consistent with that reported in Part A.

Safety results reported:

- Safety analyses were conducted in a total of 205 patients with at least one dose in Part A and Part B.
- Adverse events in the safety population were comparable between treatment groups, with 87.9% (80/91) in the SUL-DUR arm vs 94.2% (81/86) in the colistin arm in Part A, and 89.3% (25/28) in Part B.
- Drug-related adverse events were 12.1% (11/91) with SUL-DUR compared with 30.2% (26/86) with colistin in Part A, and 10.7% (3/28) in Part B.
- SUL-DUR met the primary safety objective of the study, and a statistically significant reduction in nephrotoxicity (as measured by the RIFLE** classification) was reported with SUL-DUR. Nephrotoxicity was 13.2% (12/91) versus 37.6% (32/85) of the colistin arm (P = 0. 0002).

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3. Taniborbactam (VNRX-5133) + cefepime

β-Lactam/BLI combination studied as a broad-spectrum treatment for cUTI and AP due to some clinically important β-lactamase-producing carbapenem-resistant Gram-negative bacilli, including CRE and possibly CRPA.

- **Route of administration and formulation:** q8h iv (2 h infusion). Three rounds of infusion over 19–23 days (prolonged iv treatment).
- **Class, MoA and target:** Taniborbactam (VNRX-5133) is a boronate-based BLI with activity against Class A, C and D β-lactamases. Also exerts action on MBL through competitive inhibition. Action on serine-β-lactamase (SBL): reversible covalent inhibition (and slow dissociation). Cefepime is a fourth-generation cephalosporin.
- **Bacterial spectrum/coverage:** Inhibitory activity against some CRE: Class A (ESBL CTX-M, KPC-2, -3), Class B (MBLs, especially NDM [not universal] and VIM) and Class D (OXA-48). Possible activity against CRPA. Does not cover IMP.
- **Cross-resistance:** Expected.
- **Indication, infection site:** Phase 3 clinical trial studied the combination's efficacy in cUTI patients, including those with AP.
- **Half-life:** 30–105 min.
- **Dose:** Studied for treatment of cUTI and AP: q8h iv (2 h infusion) for 19–23 days.
- **Phase 3 study (active):** The combination has been evaluated through an interventional, double-blind, randomized, active-controlled, non-inferiority study evaluating the efficacy, safety and tolerability of cefepime-taniborbactam in 582 adults with cUTI, including AP, compared with that of meropenem (NCT03840148).
  - **Time period:** 7 August 2019 to 14 December 2021.
  - **Study design:** Interventional, explanatory, double-blind, randomized, active-controlled, non-inferiority clinical trial. The study compares the efficacy and safety of cefepime-taniborbactam iv combination to iv meropenem in the treatment of adult cUTI, including AP.
  - **Study population:** 582 (estimated) randomized patients will be parallelly assigned to receive either treatment every 8 h as a 2 h continuous iv infusion.
  - The study is being conducted at 43 sites in nine countries
  - **Included in the study** were all adult men and non-pregnant women (≥ 18 years of age) with documented diagnosis of cUTI or AP as determined by principal investigators through clinical and laboratory assessment, due to a Gram-negative pathogen determined to be non-resistant to the intervention drugs.
  - **Excluded** were all participants who are receiving effective antibacterial drug therapy for cUTI (> 24 h over the 72 h before randomization), or those who require the use of non-study systemic antibacterial therapy, as well as participants with pathogens resistant to meropenem or with UTI due to non-Gram-negative or non-bacterial pathogens and those in whom more than two microorganisms were identified. Also excluded were participants with urinary tract symptoms due to sexually transmitted infections, prostatitis or with perinephric/renal abscess or renal transplantation or receiving haemodialysis or peritoneal dialysis.
  - **The primary outcome:** Defined as the proportion of patients in the m-MITT population who achieve overall treatment success after receiving three rounds of iv therapy, as determined at TOC visit (days 19–23).
  - **The primary efficacy end-point:** The composite successful outcome of clinical cure (symptom resolution or return to premorbid baseline of all UTI core symptoms and patient is alive, and patient has not received additional antibacterial therapy for cUTI) and microbiological eradication (defined as any Gram-negative target pathogens found at study entry ≥ 105 CFU/mL eradicated to < 103 CFU/mL) at TOC.
  - **The primary efficacy evaluation** was performed in the m-MITT population for patients infected with a Gram-negative pathogen determined to be non-resistant to study drugs.

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4. Enmetazobactam (AAI-101) + cefepime

The combination is being studied as an empiric (carbapenem-sparing) option for treatment of cUTI due to Gram-negative pathogens in some settings with a high incidence of ESBL-producing *Enterobacterales* (endemic settings).

- **Route of administration and formulation:** Intravenous (q8h 2 h infusion for 7–14 days).
- **Class, MoA and target:** β-lactam/BLI combination. Enmetazobactam is a penicillanic acid sulfone ESBL inhibitor with enhanced bacterial cell penetration. Cefepime is a fourth-generation cephalosporin.
- **Bacterial spectrum/coverage:** Inhibitory activity against ESBL-producing cephalosporin-resistant *Enterobacterales* and some CRE (Class A).
- **Cross-resistance:** No reported cross-resistance.
- **Half-life:** 2–3 h.
- **Dose (Phase 3 study):** Enmetazobactam 500 mg cefepime 2 g, q8h iv (2 h infusion) for 7–14 days.
- **Infection site, variation:** A Phase 3 clinical trial tested the combination's efficacy in 1034 cUTI patients, including upper UTI (AP). No variation was reported by the developer.
- **Phase 3 study:** Randomized, double-blind study to evaluate the efficacy and safety of cefepime-aai101 compared with piperacillin + tazobactam in the treatment of 1034 cUTI patients, including AP (NCT03687255, EudraCT 2017-004868-35).
  - **Time period:** 24 September 2018 to 15 February 2020.
  - **Study design:** Interventional, explanatory, double-blind, randomized, non-inferiority clinical trial compared the efficacy and safety of enmetazobactam (0.5 g) + cefepime (2 g) with tazobactam (0.5 g) + piperacillin (4 g) (the active control).
  - **Study population:** 1034 randomized patients who were parallelly assigned to receive either treatment every 8 h as 2 h continuous iv infusion. The participants were otherwise healthy adult patients (≥ 18 years of age) with cUTI or AP due to a Gram-negative pathogen determined to be non-resistant to intervention drugs.
  - The study took place in 19 countries.
  - **Included in the study** were all men and non-pregnant women ≥ 18 years of age presenting with clinical signs and symptoms; expectation that lab results consistent with cUTI or AP would require hospitalization and initial treatment with at least 7 days of iv antibiotics. Pyuria is defined as (i) white blood cell count > 10 cells/mm3 in unspun urine or ≥ 10 cells/high power field in spun urine sediment; or (ii) urinalysis/dipstick analysis positive for leukocyte esterase. Participants had to have a baseline urine culture specimen obtained within 48 h prior to randomization.
  - **Excluded** were participants with urine culture showing Gram-positive primary pathogen at ≥ 105 CFU/mL (not contaminant) or suspected Gram-positive pathogen by Gram staining (Gram staining was optional); history of significant hypersensitivity or allergic reaction to cefepime, piperacillin + tazobactam, any of the excipients used in the respective formulations, any β-lactam antibiotics or any BLIs; pregnant or breastfeeding women; known co-infections requiring the addition of antibiotic treatment; known chronic renal, hepatic, haematologic impairment or other condition interfering with the absorption, distribution or elimination of the drug, based on medical history and physical examination and other known conditions.
  - **The primary outcome** was the proportion of patients in the m-MITT population who achieve overall treatment success at TOC: 7 days after end of treatment (EOT) (± 2 days) (7 days of treatment); 19 days post-randomization (± 2 days) (> 7 days of treatment).
  - **The primary efficacy end-point** was the composite successful outcome of clinical cure (symptom resolution) and microbiological eradication (< 103 CFU/mL in urine culture) at TOC.
  - **The primary efficacy evaluation** was performed in the m-MITT population for patients infected with a Gram-negative pathogen determined to be non-resistant to enmetazobactam + cefepime (MIC ≤ 8 mg/L) and piperacillin + tazobactam (MIC ≤ 64 mg/L). A 10% non-inferiority margin was prespecified with superiority to be tested in the event of confirmed non-inferiority.

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List of all posters and conference abstracts/presentations on cefepime-enmetazobactam (formerly known as AAI101) can be viewed at: http://www.allecra.com/scientific-information (accessed 27 January 2021).

5. Nafithromycin (previously WCK 4873)

Nafithromycin is an oral lactone-ketolide (macrolide derivative) that is being developed/optimized as a treatment for community-acquired bacterial pneumonia (CABP) in adults due to typical and atypical respiratory pathogens, including penicillin- and macrolide-resistant pneumococcal strains.

Since the drug is a lactone-ketolide (macrolide derivative), it has the potential to provide all the clinical advantages of an oral macrolide in treatment of CABP while overcoming the macrolide resistance problem.

- **Route of administration and formulation:** Oral (tablets).
  - **Class, MoA and target:** Lactone ketolide class. Ketolides are a new class of macrolides. Nafithromycin is derived from the macrolide erythromycin A and is modified to overcome the problem of macrolide resistance. Like erythromycin A, nafithromycin and other ketolides, inhibit protein synthesis by acting on the bacterial 50S ribosomal subunit's peptidyl transferase site. Because they utilize multiple binding sites, ketolides bind to ribosomes with higher affinity than macrolides do.

Note: from available clinical data: pharmacodynamically, ketolides display an element of concentration-dependent killing as opposed to macrolides, which are time-dependent killers.

  - **Bacterial spectrum/coverage:** In vitro activity against Gram-positive aerobes and some Gram-negative aerobes. Nafithromycin has activity against drug-resistant *S. pneumoniae*, including efflux and some ribosomal protein mutation-mediated resistance.
  - **AMR:** No cross-resistance reported.

Note: macrolide resistance is mediated through two main mechanisms: drug-efflux pumps and modification of the drug target site in the ribosome brought about by the action of Erm methyltransferases. Nafithromycin interacts at multiple positions on the ribosome and thus might allow for activity against some macrolide-resistant strains.

- Half-life: 9.16 and 14.4 h
  - **Dose:** In the Phase 3 RCT trial in India, the proposed dose for treatment of CABP in adults is 800 mg (two 400 mg tablets) orally q24h for 3 days.
  - **Adverse effects** (from Phase 1 trials): In the multiple ascending dose study, single ascending oral doses of nafithromycin (100– 1200 mg) were administered in 30 adult healthy subjects in the treatment arm. In these subjects, all treatment-emergent adverse effects (TEAEs) were reported to be mild and self-limiting without sequelae at follow-up (11–18 days post-dose). The most common TEAEs reported were dysgeusia (27%), headache (19%), nausea (15%), flatulence (12%) and dizziness (12%). One moderate vomiting event was reported. (Phase 1 trials available at ClinicalTrials.gov under identifiers NCT03926962 and NCT03979859).
  - **Drug–drug interaction:** The potential inhibitory activity of nafithromycin against cytochrome P450 (CYP) was assessed in vitro. According to the results, nafithromycin did not inhibit key CYP enzymes and was found to be a weak inhibitor of CYP3A4/5.
- Phase 3 trial: Nafithromycin is currently being evaluated in a Phase 3 trial in India. The study has been registered with the clinical trial registry of India (registration no. CTRI/2019/11/021964).
  - **Time period:** Start of first enrolment (India) 31 December 2019. The estimated duration of the trial is 3 years.
  - **Study design:** Phase 3, randomized, multicentre, double-blind, comparative study to determine the efficacy and safety of oral nafithromycin vs oral moxifloxacin in the treatment of CABP in adults.
  - **Location:** India.
  - **Study population:** 488 adult patients were randomized and parallelly assigned to receive either nafithromycin 800 mg (two 400 mg tablets) administered orally every 24 h for 3 days, or moxifloxacin 400 mg orally every 24 h for 7 days.
  - **Inclusion criteria:** Male and female subjects ≥ 18–90 years of age with a diagnosis of CABP as defined by the study protocol (more details available via this link using trial registration no. CTRI/2019/11/021964 as keyword).

- Participants must be able to provide informed consent, and all female participants must have a negative urine or serum pregnancy test (beta human chorionic gonadotropin) at screening and must agree to the use one from a list of acceptable methods of contraception through TOC. All male participants must agree to use an acceptable barrier method of birth control.
- **Exclusion criteria:** Excluded from the study are patients with any of the following confirmed or suspected types of pneumonia:
  - aspiration pneumonia;
  - HABP (defined as pneumonia with onset of clinical signs and symptoms after at least 48 h hospitalization in an acute inpatient health-care facility);
  - health-care-associated bacterial pneumonia (defined as pneumonia acquired in a long-term care or subacute health-care facility, such as a nursing home; or pneumonia with onset after recent hospital discharge (within 90 days of current admission and previously hospitalized for ≥ 48 h);
  - VABP, defined as pneumonia with onset of clinical signs and symptoms after at least 48 h of endotracheal intubation;
  - pneumonia that may be caused by pathogen(s) resistant to any study drug (nafithromycin, moxifloxacin), including viral, mycobacterial or fungal pneumonia;
  - post-obstructive pneumonia;
  - pneumonia associated with CF, bronchiectasis or any other chronic pulmonary disease;
  - suspected or confirmed pleural empyema (a parapneumonic pleural effusion is not an exclusion criterion) or lung abscess; and
  - suspected or confirmed non-infectious causes of pulmonary infiltrates (e.g. pulmonary embolism, hypersensitivity pneumonia, congestive heart failure).

Also excluded are:

- any patient who receives one or more dose(s) of a potentially effective systemic antibacterial intervention for treatment of the current CABP within 72 h before randomization, except for prior therapy with a single dose of a short-acting antibacterial agent;
- patients requiring concomitant adjunctive or additional potentially effective systemic antibacterial treatment for management of CABP; and
- subjects with evidence of significant immunologic disease.

(Note: source and more details on the inclusion and exclusion criteria can be found via this link using trial registration no. CTRI/2019/11/021964 as keyword.)

- **Primary outcome:** To demonstrate that oral nafithromycin is non-inferior to oral moxifloxacin in the clinical response at TOC (= day 4) in the MITT analysis set and to assess the overall safety of oral nafithromycin in the safety analysis set.
- **The primary efficacy end-point** is defined as the successful outcome of clinical success (symptom resolution and no new symptoms) at the TOC visit.

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6. Zoliflodacin

Being developed for the treatment of uncomplicated gonorrhoea.

- **Route of administration and formulation:** Oral. Powder formulated for oral suspension (no information on the requirements, procedures or quality and infection control requirements expected to prepare the suspension safely and accurately). Single dose.
- **Class, MoA, target:** First in class (spiropyrimidinetrione). Topoisomerase type II enzyme (target) inhibition but with different binding sites in bacterial gyrase, distinct from those utilized by fluoroquinolones.
- **Bacterial spectrum/coverage:** Zoliflodacin is being studied for the treatment of *N. gonorrhoeae*. The new target (binding site) could be effective in treating infections caused by fluoroquinolone-resistant strains. Preclinical in vitro studies reported superior action against clinical isolates of *N. gonorrhoeae* (including high-level ciprofloxacin-resistant and MDR strains).
- **Cross-resistance:** Early findings indicate no cross-resistance with fluoroquinolones (or other topoisomerase inhibitors).
- **Half-life:** 5–6 h.
- **Dose proposed for Phase 3:** Single dose, 3 g PO.
- **Adverse effects:** Phase 2 RCT study in approximately 180 adult male and female subjects, ages 18–55, reported a total of 84 adverse events in 59 participants, 21 of which were attributed to zoliflodacin and were generally mild, self-limiting GIT-related events.
- **Infection site, variation:** The majority of uncomplicated urogenital and rectal gonococcal infections were successfully treated with oral zoliflodacin, but this agent was less efficacious in the treatment of pharyngeal infections.
- **Phase 3 study (active):** A multicentre, explanatory, open-label, randomized, non-inferiority clinical trial comparing a single 3 g oral dose of zoliflodacin with a combination of ceftriaxone (500 mg, IM) and azithromycin (1 g, oral) in the treatment of 1092 adult patients with uncomplicated gonorrhoea (NCT03959527, EudraCT 2019-000990-22).
  - **Time period:** 27 September 2019 to 31 July 2023.
  - **Study design:** An explanatory, open-label, randomized, non-inferiority clinical trial comparing a single (3 g) oral dose of zoliflodacin with a combination of ceftriaxone (500 mg, IM) and azithromycin (1 g, oral), using a 2:1 randomization design. Like the Phase 2 study, the Phase 3 trial specifies urogenital infections caused by *N. gonorrhoeae* as the main criterion for enrolment. The presence of uncomplicated extra-urogenital infections will also be studied as a secondary outcome in this Phase 3 study to explore the utility of zoliflodacin in these infections.
  - **Study population:** Estimated at 1092 participants with uncomplicated gonorrhoea.
  - The study is being conducted in four countries (the Netherlands, South Africa, Thailand, USA).
  - **Included in the study** are all men and non-pregnant women ≥ 12 years of age and with ≥ 35 kg body weight who present with signs and symptoms consistent with urogenital gonorrhoea, or untreated uncomplicated urogenital gonorrhoea, as determined by diagnostic testing – either a positive culture or nucleic acid amplification test (NAAT) or Gram stain or methylene blue test/gentian violet stain – in the past 14 days prior to the screening OR unprotected sexual contact with a person who had gonorrhoea in the 14 days before screening using the aforementioned diagnostic tests.
  - **Excluded** are patients with complicated or disseminated gonorrhoea (as indicated by pelvic inflammatory disease, epididymitis or other conditions), pregnant or breastfeeding women, or known co-infection requiring the addition of antibiotic treatment (e.g. chlamydia infection at the time of enrolment).
  - **The primary outcome** is defined as the proportion of patients in the m-MITT population who achieve overall treatment success at the primary end-point, the TOC, on day 6 post-treatment.
  - **The primary efficacy end-point** is the TOC, defined as microbiological cure as determined by culture at urethral or cervical sites at the TOC visit.

- **The primary efficacy evaluation** will be performed in the m-MITT patients with uncomplicated urogenital infection due to *N. gonorrhoeae* strain that is non-resistant to the intervention.
- Early results from a small Phase 2 RCT (141 patients in the m-MITT population) indicated potential for comparable action in various infection sites with some variations. Specifically, the study reported a cure rate of 96% in participants with urogenital infections (*n* = 113) and 100% cure for rectal infections (12 participants), while pharyngeal infections were cured in four of eight participants (50%) receiving 2 g of zoliflodacin and in nine of 11 participants (82%), who received 3 g of zoliflodacin.

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7. Gepotidacin

A novel topoisomerase inhibitor being developed for the treatment of uncomplicated urogenital gonorrhoea and uUTI (Gram-positive and Gram-negative cocci).

- **Route of administration and formulation:** Intravenous/oral.
- **Class, MoA and target:** Novel bacterial topoisomerase II inhibitor (triazaacenaphthylene). Selectively inhibits bacterial DNA replication by interacting at a unique site on the GyrA subunit of bacterial DNA gyrase and the ParC subunit of bacterial topoisomerase IV.
- **Bacterial spectrum/coverage:** Inhibitory activity against *N. gonorrhoeae*.
- **Cross-resistance:** Some cross-resistance with fluoroquinolones reported (potentially overlapping/close binding sites).
- **Infection site, variation:** Phase 3 clinical trial studied the combination's efficacy in uUTI (adult females) and uncomplicated urogenital gonorrhoea (adults).
- **Half-life:** 12.1–12.6 h. Oral bioavailability: approx. 50%.
- **Dose:** uUTI (tested in adult females only): oral, 1500 mg (two 750 mg tablets) of gepotidacin bid; every q12h for 5 days. Uncomplicated urogenital gonorrhoea: 3000 mg oral dose (four 750 mg tablets) at the study site, followed by 3000 mg oral dose (four 750 mg tablets) as an outpatient.
  - Oral dose is high due to the poor absorption. Fifty-three percent of the oral dose is eliminated through the faecal route due to poor GIT absorption (59% of the iv dose is eliminated through urine). Adverse effects (from Phase 2a study of 22 females with uUTI): 95% (n = 21/22) of the participants experienced adverse effects. Most reported were GIT-related adverse effects (> 10% of participants), including diarrhoea, nausea and vomiting. Another Phase 2 study for treatment of uncomplicated gonorrhoea in 105 patients reported the most frequent adverse effects to be diarrhoea (27%), flatulence (23%), abdominal pain (15%) and nausea (13%). The most reported adverse effect with the oral dose was diarrhoea (4/6, 67%).
- **Phase 3 study:** Being evaluated as a treatment for uUTI and uncomplicated gonorrhoea infection in adults, through two Phase 3 open-label RCTs (EAGLE-1 and EAGLE-2).
- **EAGLE-1** (NCT04010539 – efficacy and safety of gepotidacin compared with ceftriaxone + azithromycin in the treatment of uncomplicated urogenital gonorrhoea).
  - **Time period:** 22 October 2019 to 4 August 2023.
  - **Study design:** Interventional, randomized, multicentre, open-label study in adolescent and adult participants comparing the efficacy and safety of gepotidacin with ceftriaxone + azithromycin in the treatment of uncomplicated urogenital gonorrhoea caused by *N. gonorrhoeae*.
  - **Study population:** 600 participants presenting with uncomplicated urogenital gonorrhoeal infections are randomized/parallelly assigned to receive either gepotidacin PO (single dose at baseline, i.e. day 1 site visit, followed by a self-administered second PO dose as an outpatient 6–12 h after the first dose) OR a single IM dose of ceftriaxone plus a single PO dose of azithromycin at the baseline, day 1 visit.
  - The study is being conducted at 47 locations in five countries (Australia, Germany, Spain, United Kingdom, USA).
  - **Included in the study** are adolescents and adults (≥ 12 years of age), with > 45 kg weight, presenting with clinical suspicion of a urogenital gonococcal infection with or without pharyngeal and/or rectal gonococcal infection and one of the following: prior *N. gonorrhoeae*-positive culture or presumptive for Gram-negative intracellular diplococci from up to 5 days before screening (without treatment) or a positive Gram stain (urogenital specimens only), or a positive NAAT assay for *N. gonorrhoeae* from up to 7 days before screening (without treatment).
  - **Excluded** are patients with complicated or disseminated gonorrhoea (as indicated by pelvic inflammatory disease, epididymitis or other conditions), pregnant or breastfeeding women, known co-infection requiring the addition of antibiotic treatment (e.g. chlamydia infection at the time of enrolment), known allergies, drug use or chronic conditions that may not allow participation in the study per the protocol outlined.
  - **Primary outcome** is defined as the proportion of patients with culture-confirmed bacterial eradication of *N. gonorrhoeae* from the urogenital site at TOC, up to day 8 post-treatment.

- **Primary efficacy end-point:** Successful microbiological outcome at TOC visit. TOC is defined (for urogenital site) as culture-confirmed bacterial eradication of *N. gonorrhoeae* observed 3–7 days post-treatment.

- **EAGLE-2** (NCT04020341 – efficacy and safety of gepotidacin compared with nitrofurantoin for treatment of uUTI).
  - **Time period:** 22 October 2019 to 22 December 2022.
  - **Study design:** Interventional, randomized, multicentre, parallel-group, double-blind study in adolescent and adult females, comparing the efficacy and safety of oral gepotidacin with nitrofurantoin (the active comparator) in the treatment of uUTI (acute cystitis).
  - **Study population:** 2055 (estimated) female participants presenting with uUTI are randomized/parallelly assigned to receive either 1500 mg of gepotidacin PO treatment plus nitrofurantoin matching placebo or 100 mg of nitrofurantoin PO plus gepotidacin matching placebo (q12h, 5 days).
  - The study is being conducted in nine countries (Bulgaria, Germany, Greece, Hungary, India, Mexico, Spain, United Kingdom, USA).
  - **Included in the study** are all adolescent and adult non-pregnant women (≥ 12 years of age), with > 45 kg body weight who present with uUTI as determined by principal investigators through clinical assessment, utilizing predefined clinical criteria and/or laboratory diagnostic criteria.
  - **Excluded** are patients residing in nursing homes or dependent-care-type facilities, having < 45 kg body weight or complicated infections, a history of sensitivity/allergies to the study treatments, patients who are immunocompromised or who have a history of chronic or acute renal or liver diseases and/or compromised function, pregnant or breastfeeding women, patients with known co-infection requiring the addition of antibiotic treatment, known allergies, drug/medication use or chronic conditions that may not allow participation in the study.
  - **Primary outcome:** Proportion of patients achieving overall treatment response at TOC, up to day 13.
  - **The primary efficacy end-point** is the composite successful outcome of clinical and microbiological "success" at the TOC visit. All other combinations (other than clinical success + microbiological success) will be deemed failures for treatment response.

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8. Ridinilazole

A novel bis-benzimidazole antibacterial currently under development for the treatment of CDI.

- **Route of administration and formulation:** Oral.
- **Class, MoA and target:** Proposed MoA is selective interference with cell division (or cellular growth) potentially through binding to the DNA minor groove (new structure and class).
- **Bacterial spectrum/coverage:** Activity against *C. difficile*. Evidence from Phase 1 and 2 studies indicates bactericidal activities with minimal impact on gut microbiome compared with conventional therapy and an anti-inflammatory effect indicated by the reduction of bioactivity, IL-8 (interleukin-8) concentrations and toxin concentrations (A and B) in *C. difficile* strains exposed to ridinilazole. Collectively may potentially reduce the risk for CDI recurrence.
- **Cross-resistance:** No cross-resistance reported (new class and structure).
- **Dose:** Oral 200 mg, bid, every q12h for 10 days.
- **Adverse effects:** According to a Phase 2 study that assessed the safety and efficacy of ridinilazole vs vancomycin for treatment of CDI in 100 patients, 82% of those treated with ridinilazole had adverse effects (*n* = 41/50), mostly mild (40% GIT related). One serious adverse effect (hypokalaemia) was reported.
- **Phase 2 studies** have been conducted to evaluate the safety and efficacy of ridinilazole compared with two conventional antibiotics, fidaxomicin and vancomycin.
- **The first of two Phase 2 studies compared ridinilazole with vancomycin for the treatment of *C. difficile*-associated diarrhoea (CDAD)** (NCT02092935).
  - **Time period:** 26 June 2014 to October 2015.
  - **Study design:** Randomized, double-blind, active-controlled, non-inferiority clinical study to investigate the efficacy and safety of ridinilazole 200 mg PO bid for 10 days (with alternating 200 mg placebo bid), compared with vancomycin 25 mg capsule qid for 10 days for the treatment of CDAD.
  - **Study population:** 100 participants with clinical diagnosis of CDI plus laboratory diagnostic test.
  - The study is being conducted in 33 centres in the USA and Canada.
  - **Included in the study** were adults (≥ 18 years of age) with clinical diagnosis of CDI confirmed by laboratory diagnostic testing who have not received > 24 h antimicrobial treatment for their current CDAD.
  - **Excluded** were patients with life-threatening or fulminant colitis and those on antibiotics or any other treatment for CDAD at the time of the study.
  - **The primary end-point** was sustained clinical response, defined as clinical cure at the end of treatment and no recurrence within 30 days, which was used to establish non-inferiority (15% margin).
  - **Study results and conclusions:** The study reported that of 69 CDI patients included in the primary efficacy (ridinilazole group, *n* = 36; vancomycin group, *n* = 33) trial, ridinilazole demonstrated superiority over vancomycin with an ORR at TOC visit of 66.7% (*n* = 24/36) in the ridinilazole arm compared with 42.4% (14/33) of those in the vancomycin arm, for a percentage difference of 21.1% (90% CI: 3.1–39.1, *P* = 0.0004). Ridinilazole was also found to be well tolerated, with an adverse event profile like that of vancomycin.
- **The second of two Phase 2 studies compared ridinilazole with fidaxomicin for the treatment of CDI** (NCT02784002).
  - **Time period:** December 2014 to August 2016.
  - **Study design:** Randomized, open-label, active-controlled clinical study to investigate the safety and efficacy of ridinilazole (200 mg bid) for 10 days compared with fidaxomicin (200 mg bid) for 10 days for the treatment of CDI.
  - **Study population:** 27 participants with clinical diagnosis of CDI plus laboratory diagnostic test.

- The study was conducted in three countries (Czech Republic, United Kingdom, USA).
- **Included in the study** were adults (≥ 18 years of age) with clinical diagnosis of CDI confirmed by laboratory diagnostic test who had not received > 30 h antimicrobial treatment for their current CDI.
- **Excluded** were patients with life-threatening or fulminant CDI and those ≥ 2 episodes of CDI in the previous year and pregnant or breastfeeding women.
- **Study results and conclusions:** The study reported comparable sustained clinical response rates on day 30 post-EOT: 50% for ridinilazole compared with 46.2% for fidaxomicin; treatment difference, 2.9% (95% CI: -30.8 to 36.7). The study also reported that ridinilazole preserved gut microbiome diversity to a greater extent than fidaxomicin during CDI treatment. The study concluded that this finding is consistent with low CDI recurrence rates.

- **Phase 3 studies:** Two Phase 3 studies, Ri-CoDIFy 1 and Ri-CoDIFy 2, are currently active. The studies will compare the sustained clinical response rate of ridinilazole (200 mg bid/10 days) with that of vancomycin (125 mg qid/10 days).
- **Phase 3 studies:** Two identical studies (NCT03595553 and NCT03595566).
  - **Time period:** January 2019 to November 2021 .
  - Interventional, quadruple-blind, parallel assignment, randomized, active-controlled non-inferiority study to compare the efficacy and safety of ridinilazole with vancomycin for treatment of CDI.
  - **Study population:** 680 (estimated in each study) adult patients to be randomly parallelly assigned to receive either oral ridinilazole (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days.
  - The studies will take place in over 180 sites in 28 countries (Argentina, Australia, Belarus, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, Estonia, France, Georgia, Germany, Greece, Hungary, Israel, Korea, Latvia, Lithuania, Mexico, New Zealand, Peru, Poland, Portugal, Romania, Russia, Spain, USA).
  - **Included in the study** are adults (≥ 18 years of age) presenting signs and symptoms of CDI, including diarrhoea, such that in the investigator's opinion CDI antimicrobial therapy is required, and with presence of either toxin A and/or B of *C. difficile* in a stool sample determined by a positive free toxin test produced within 72 h prior to randomization.
  - **Excluded** are all participants receiving effective antibacterial drug therapy (> 24 h prior to randomization), or participants with moderate or severe liver disease, severe neutropenia, a baseline QTc (corrected QT interval) of > 500 ms, known history of congenital long QT syndrome, uncompensated heart failure, uncorrected abnormal K+ or Mg++ blood levels or severe left ventricular hypertrophy.
  - **The primary outcome** is clinical response determined by the investigator at the TOC visit.
  - **The primary efficacy end-point** is achievement of a sustained clinical response, defined as clinical cure at the TOC visit and no recurrence within 30 days post-EOT.
  - **The primary efficacy evaluation** is done on the m-MITT population (all individuals with CDI confirmed by the presence of free toxin in stool who were randomly assigned to receive one or more doses of the study drug).
  - **Non-inferiority margin:** 15%.

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