2020 ANTIBACTERIAL AGENTS IN CLINICAL AND PRECLINICAL DEVELOPMENT

an overview and analysis

World Health Organization

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Abbreviations and acronyms

ABC	*A. baumannii*-calcoaceticus complex
ABSSSI	acute bacterial skin and skin structure infection
AP	acute pyelonephritis
AWaRe	Access, Watch, and Reserve (WHO classification)
bid	twice a day
BLI	β-lactamase inhibitor
BSI	bloodstream infections
CAP	community-acquired pneumonia
CDAD	*Clostridioides difficile*-associated diarrhoea
CDI	*Clostridioides difficile* infections
CF	cystic fibrosis
cIAI	complicated intra-abdominal infection
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem-resistant Enterobacterales
CRISPR	clustered regularly interspaced short palindromic repeats
CRPA	carbapenem-resistant *Pseudomonas aeruginosa*
CTA	clinical trial application
cUTI	complicated urinary tract infection
DBO	diazabicyclooctane
DOI	declaration of interest
DprE1	decaprenylphosphoryl-β-D-ribose 2-epimerase
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
FDA	Food and Drug Administration
FimH	type 1 fimbrin D-mannose specific adhesin
FtsZ	filamenting temperature-sensitive Z
GARDP	Global Antibiotic Research and Development Partnership
GIT	gastrointestinal tract
HABP	hospital-acquired bacterial pneumonia
HAP	hospital-acquired pneumonia
ICTRP	International Clinical Trials Registry Platform
IAI	intra-abdominal infection
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
MAA	marketing authorisation application
MBL	metallo-β-lactamase
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
m-MITT	microbiologic-modified intent-to-treat
m-MITTR	microbiologic-modified intent-to-treat resistant
m-MITTS	microbiologic-modified intent-to-treat susceptible
MoA	mode of action
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NAAT	nucleic acid amplification test
NDA	new drug application
NDM	New Delhi metallo-β-lactamase
OPP	other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority)
OUCRU	Oxford University Clinical Research Unit
OXA	oxacillinase
PBP	penicillin-binding protein
PK/PD	pharmacokinetics/pharmacodynamics
PO	per os
qid	four times a day
R&D	research and development
RCT	randomized control trial
Rhu-pGSN	rhu-plasma gelsolin
rRNA	ribosomal RNA
SBL	serine-β-lactamase
SME	*Serratia marcescens* enzyme
SpA	protein A
TB	tuberculosis
tet	tetracycline resistance encoding gene
tRNA	transfer RNA
T3SS	type III secretion system
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	extremely drug resistant

Executive summary

This report is the World Health Organization's (WHO) fourth annual analysis of the clinical antibacterial pipeline and the second review of the preclinical pipeline. The analysis covers traditional (direct-acting small molecules) and non-traditional antibacterial agents in clinical and preclinical development worldwide. It assesses to what extent the clinical pipeline addresses WHO priority pathogens, *Mycobacterium tuberculosis* and *Clostridioides difficile*. The report also provides an assessment of the traditional agents with respect to whether they meet criteria for innovation (absence of known cross-resistance, new target, mode of action and/or class).

Key facts about the clinical pipeline:

- The current clinical antibacterial pipeline contains 43 antibiotics and combinations with a new therapeutic entity and 27 non-traditional antibacterial agents.
- Of the 43 antibiotics, 26 are active against the WHO priority pathogens, 12 against *M. tuberculosis* and five against *C. difficile*.
- Of the 26 antibiotics active against the WHO priority pathogens:
  - seven fulfil at least one of the innovation criteria; only two of these are active against the critical multidrug-resistant (MDR) Gram-negative bacteria; and
  - over 40% (*n* = 10) are β-lactam and β-lactamase inhibitor (BLI) combinations with a major gap in activity against metallo-β-lactamase (MBL) producers.
- Of the 27 non-traditional antibacterials, nine are antibodies, four bacteriophages and phage-derived enzymes, eight microbiome-modulating agents, two immunomodulating agents and four miscellaneous agents.
- Eleven new antibiotics have been approved by either the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) or both since 1 July 2017. With some exceptions, the newly approved agents have limited clinical benefit over existing treatment, as over 80% (9/11) are from existing classes where resistance mechanisms are well established and rapid emergence of resistance is foreseen.
- Notably, cefiderocol was approved by the US FDA and the EMA. Cefiderocol is active against all three critical Gram-negative bacteria and has activity against a variety of β-lactamases, including ESBL and AmpC.
- Of the traditional antibacterials, three new products entered the clinical pipeline whereas seven were discontinued or for which there was no recent information.
- Overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.

Key facts about the preclinical pipeline:

- There are 162 commercial and non-commercial entities progressing 292 diverse antibacterial agents.
- Developers are widely distributed geographically, with the majority, 72 (44.4%), in the European Region, 64 (39.5%) in the Region of the Americas, 20 (12.3%) in the Western Pacific Region and 6 (3.7%) in the South-East Asia Region.
- The pipeline contains 115 (39.4%) direct-acting small molecules, 101 (34.6%) non-traditional products including bacteriophages, virulence inhibitors, immunomodulatory compounds and potentiator agents, 47 (16.1%) vaccines and 30 (10.2%) adjuvant antimicrobial peptides.
- Of the 292 antibacterial agents, 152 (52%) target a single pathogen, of which 60 target the WHO critical Gram-negative bacteria and 41 target *M. tuberculosis*.
- Of the agents under development 40 target cell wall synthesis, 62 act directly on the cell membrane, 56 act through immunomodulation, 28 target protein synthesis and 22 target virulence factors.
- The pre-clinical pipeline continues to be dominated by small and medium-size enterprises (n= 140, or 86.4% of developers who submitted data): 74 micro institutions (<10 employees), 40 small institutions (11-50 employees), and 26 medium sized institutions (51-500 employees).

Recent marketing approvals

Since 2017, 11 new antibacterial drugs have been approved (Table 1). Two, vaborbactam + meropenem and lefamulin, were classified as meeting at least one of the WHO innovation criteria (absence of known cross-resistance, new target, mode of action and/or class) and represent new chemical classes. Cefiderocol was classified as inconclusive on meeting the innovation criteria of absence of known cross-resistance. Vaborbactam is a BLI that contains a cyclic boronate pharmacophore and, in combination with meropenem, is active against *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant Enterobacterales (CRE). Lefamulin is a pleuromutilin which is a new class for systemic use that has been used mostly topically in humans, and is an established class for systemic use in veterinary medicine. The other newly approved antibiotics are derivatives of known classes, such as the two tetracycline derivatives eravacycline and omadacycline. Almost half of the newly approved agents (*n* = 5) target CRE. Only one, cefiderocol, a cephalosporin linked to a siderophore with the ability to penetrate the outer membrane of Gram-negative bacteria and accumulate in the periplasmic space, targets in addition to CRE carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPA), highlighting the unmet need for new agents to treat infections caused by these pathogens. Pretomanid, a nitroimidazo-oxazine, was approved for the treatment of extremely drug resistant tuberculosis (XDR-TB) and drug-intolerant or non-responsive MDR-TB.

Overall, the newly approved agents have limited clinical benefit over existing treatment, as over 80% (9/11) are from existing classes where resistance mechanisms are well established and rapid emergence of resistance is foreseen.

Traditional antibacterial pipeline in clinical development

As of 1 September 2020, there are 43 antibiotics with a new therapeutic entity (new substance, chemical entity, biological entity and/or new molecular entity (1)) in the clinical pipeline (Phases 1–3) targeting the WHO priority pathogens, *M. tuberculosis* and *C. difficile* (Fig. 1). Of the 43 antibiotics, 26 target the WHO priority pathogens, and half (*n* = 13) of those are active against at least one of the critical Gram-negative pathogens. Of these, nine are in Phase 1. Twelve antibiotics are in development for TB and five for the treatment of *C. difficile* infections.

Innovativeness

Of the 26 antibiotics under development that target the WHO priority pathogens, seven fulfill at least one of the four WHO innovation criteria (absence of known cross-resistance, new target, mode of action and/or class). Only two of these are active against the critical Gram-negative bacteria. The current antibiotic pipeline continues to be dominated by β-lactam/BLI combinations (*n* = 11, 42% of antibiotics targeting WHO priority pathogens). Of the 12 agents being developed against *M. tuberculosis*, six meet the innovation criteria "absence of known cross-resistance".

Potential for clinical utility of Phase 3 antibiotics

For the first time, this review also includes a description of the potential for clinical utility for each of the Phase 3 traditional antibiotics. The information draws from published information on planned, ongoing or completed Phase 3 programmes and expected microbiological characteristics, to highlight certain drug attributes that are relevant for their potential clinical use, and when relevant, clinical trial study design and results. Additional, more detailed information on each Phase 3 antibiotic is provided in Annex 2.

Non-traditional antibacterials in the clinical pipeline

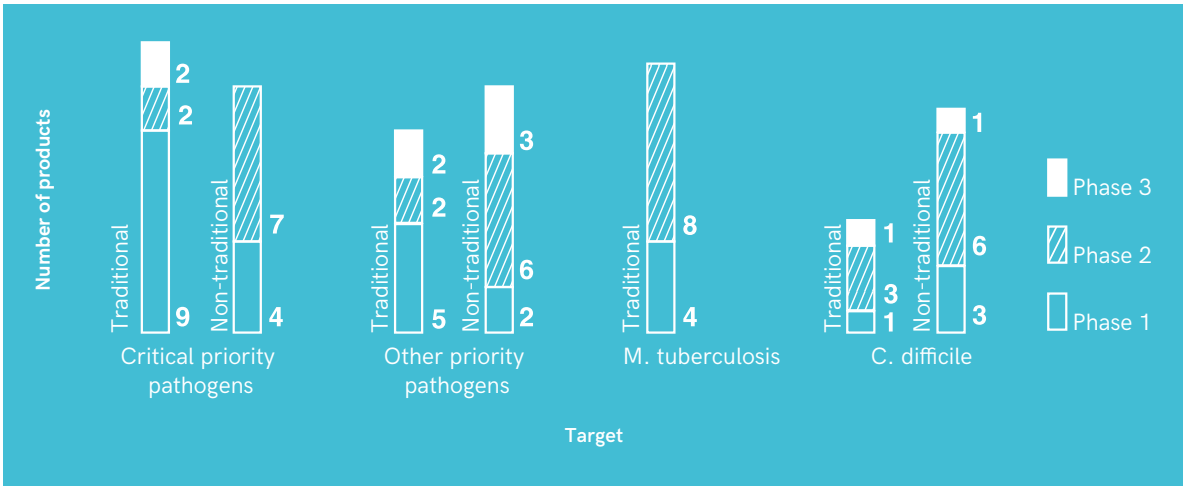
The analysis of the clinical antibacterial pipeline has been expanded from traditional antibiotics and biologics such as monoclonal antibodies and endolysins in 2019 to a more comprehensive overview of

non-traditional antibacterial agents. There are currently 27 non-traditional antibacterials in the clinical antibacterial pipeline (Fig. 1).

- Eighteen target Gram-positive bacteria (nine against *Staphylococcus aureus* and nine against *C. difficile*).
- Seven target Gram-negative bacteria (three against *P. aeruginosa* and *Escherichia coli*, respectively, and one against *Campylobacter jejuni/E. coli*).
- Two have broad-spectrum activity against Gram-positive and Gram-negative bacteria.

There is diversity in the non-traditional approaches, including nine antibodies, four bacteriophages and phage-derived enzymes, eight microbiome-modulating agents, two immunomodulating agents and four miscellaneous agents that include anti-virulence agents.

Fig. 1. Number of traditional and non-traditional antibacterials in clinical development (Phases 1–3) per target pathogen



Preclinical antibacterial pipeline

The preclinical pipeline database capture 292 antibacterial agents in preclinical development that were submitted via the WHO data call and/or for which information is 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, and vaccines that are being developed by commercial and non-commercial entities. The WHO preclinical pipeline database is dynamic and innovative, including a wide range of drug development projects that are using different approaches to target the WHO bacterial priority pathogens list.

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

Clinical pipeline: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products/en/

Preclinical pipeline: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products_preclinical/en

BOX 1. PRIORITIZATION OF PATHOGENS TO GUIDE RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS

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.

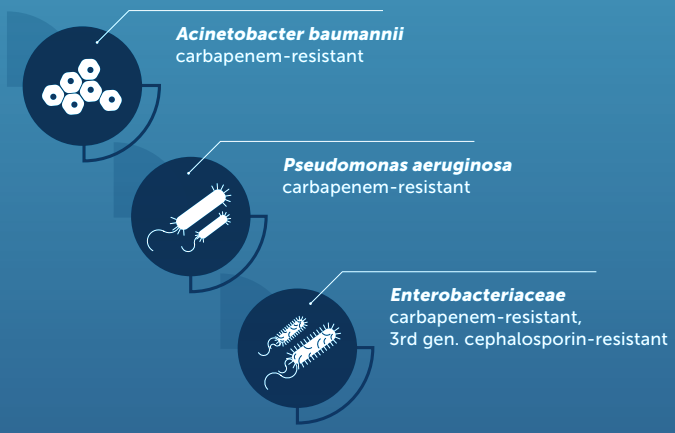
5

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

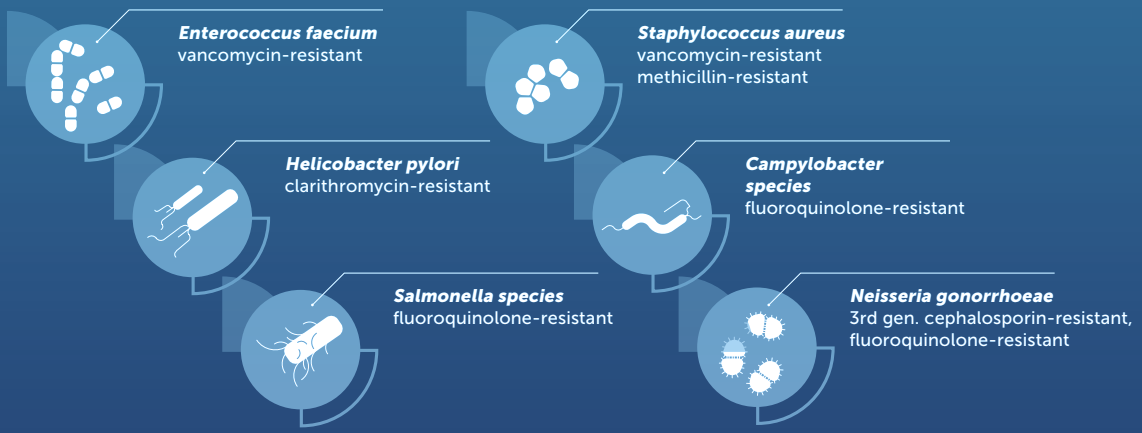


Acinetobacter baumannii
carbapenem-resistant

Pseudomonas aeruginosa
carbapenem-resistant

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

HIGH PRIORITY



Enterococcus faecium
vancomycin-resistant

Staphylococcus aureus
vancomycin-resistant
methicillin-resistant

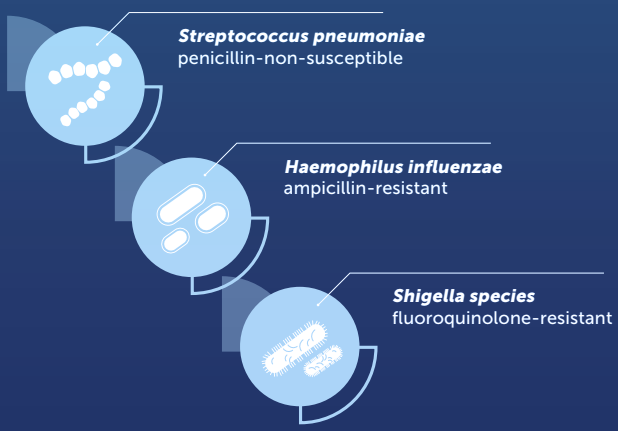
Helicobacter pylori
clarithromycin-resistant

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

1. Introduction

The emergence of antibacterial resistance is a normal evolutionary process for bacteria. However, this process is amplified through the selective pressure exerted by the widespread use and misuse of antibacterial agents in human and animal health. The recent *WHO Global Antimicrobial Resistance and Use Surveillance System* (GLASS) report confirms that antibacterial resistance is on the rise, specifically in low-and middle-income countries, causing significant mortality and morbidity *(2)*. 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 *(3)*.

Thus, new antibacterial treatments are urgently needed. This fourth WHO analysis of the clinical antibacterial development pipeline and second review of the preclinical pipeline allows policymakers, clinicians and researchers to assess which antibacterial agents will potentially reach the bedside over the next 8–10 years. While there are some innovative products in the pipeline, it is likely that only a fraction of these will ever come to market due to the high failure rates in the drug development process.

The report for the first time includes a comprehensive overview of non-traditional products, such as monoclonal antibodies, bacteriophages, antimicrobial peptides, anti-bacterial enhancers and other products in the clinical development pipeline. In conjunction with the WHO preclinical antibacterial agents database, this allows monitoring of the 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 recently launched AMR Action Fund will be crucial to ensure that the most innovative and promising products receive the required funding. Although the fund can help bridge the financing gap until pre-market 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. Nearly all of these 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 *(4)*. 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 will require new thinking about how to procure and reimburse these products.

Consequently, several countries have undertaken different reforms of their reimbursement and procurement systems, including moving to alternative models from volume-based reimbursement. These balancing efforts are improving the situation, notably for reserve antibiotics. While these interventions are welcome, they differ from one country to another, which will increase the translational costs for companies that have to assess and navigate these different national mechanisms *(5)*. 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 research and development (R&D) and innovation, to ensure that that the global community has a robust pipeline of innovative new products that demonstrate clinical benefit.

2. Agents that obtained market authorization since 1 July 2017

Since WHO's first analysis of the clinical antibacterial pipeline in 2017, 11 new antibiotics, including one for the treatment of TB, have been approved. Most of these are derivatives of known classes, such as the fluoroquinolone derivatives delafloxacin, lascufloxacin and levonadifloxacin/alalevonadifloxacin or the tetracycline derivatives eravacycline and omadacycline. The majority target CRE (*n* = 5) and other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority) (*n* = 5). Two of the approved agents, vaborbactam (approved in combination with meropenem) and lefamulin, represent new chemical classes. Vaborbactam is a BLI that contains a cyclic boronate pharmacophore and, in combination with meropenem, is active against KPC-producing CREs. Lefamulin is a pleuromutilin, which is an established class of antibiotics for systemic use in veterinary medicine, that had been newly introduced for systemic an topical use in humans, but has mostly been used topically in human. Pretomanid, a nitroimidazo-oxazine, was approved for use in XDR-TB and for the treatment of intolerant or non-responsive MDR-TB.

Three new antibacterials were approved between 2 September 2019 and 1 September 2020, which was the date range for this update. They include cefiderocol, a β-lactam with the ability to penetrate the outer membrane of Gram-negative bacteria and accumulate in the periplasmic space. Cefiderocol has activity against all three critical Gram-negative bacteria and is also active against a variety of β-lactamases, including ESBL and AmpC. Cefiderocol received US FDA approval for complicated urinary tract infections (cUTIs), and EMA approval for Gram-negative bacterial infections.

In addition, two fluoroquinolone derivatives have been approved, lascufloxacin and levonadifloxacin/alalevonadifloxacin, which were registered in Japan and India, respectively. Lascufloxacin is a fluoroquinolone optimized for Gram-positive and respiratory tract infection. Lascufloxacin was approved for community-acquired pneumonia (CAP) and otorhinolaryngological and respiratory tract infections. Levonadifloxacin/alalevonadifloxacin (iv and oral prodrug) with a similar spectrum to lascufloxacin were approved for skin and soft tissue infections.

In 2021 WHO will classify all new antibiotics that have been approved since 2019 as "access", "watch" or "reserve" antibiotics under WHO's AWaRe classification. In general, further evidence and studies are needed regarding the added clinical value and effectiveness of these of these newly approved antibacterial agents. There is still no post-approval usage data made available to evaluate the indications and adequacy of their use in different populations and countries.

Table 1. Antibiotics that gained market authorization between 1 July 2017 and 1 September 2020

Name (trade name)	Market authorization holder	Approved by (date)	Antibiotic class	Route of administration	Indication/s	WHO EML & AWaRe	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela)	Melinta	FDA (6/2017 ABSSSI, 10/2019 CAP) MAA	Fluoroquinolone	iv & oral	ABSSSI, CAP	AWaRe: Watch	O	O	O	●	-	-	-	-
Vaborbactam + meropenem (Vabomere)	Melinta	FDA (8/2017) EMA (11/2018)	Boronate BLI + carbapenem	iv	cUTI	WHO EML & AWaRe: Reserve	O	O	●[1]	/	?[2]	✓	-	-
Plazomicin (Zemdri)	Achaogen	FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML & AWaRe: Reserve	O	O	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	AWaRe: Reserve	?	O	●	/	-	-	-	-
Omadacycline (Nuzyra)	Paratek	FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSSI (iv, oral)	AWaRe: Reserve	O	O	O	●	-	-	-	-
Relebactam + imipenem/ cilastatin (Recarbrio)	MSD	FDA (7/2019 cUTI/ cIAI, 7/2020 HAP/ VAP)	DBO-BLI + carbapenem/ degradation inhibitor	iv	cUTI, cIAI, HAP/VAP		O	?	●[1]	/	-	-	-	-
Lefamulin (Xenleta)[5]	Nabriva	FDA (8/2019)	Pleuromutilin	iv & oral	CAP		/	/	/	●	?	✓[3]	-	-
Pretomanid (PA-824)	TB Alliance	FDA (8/2019) EMA (7/2020)	Nitroimidazole	oral	XDR-TB and treatment intolerant or non-responsive MDR-TB		/	/	/	●[4]	-	-	-	-
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PMDA (8/2019)	Fluoroquinolone	iv & oral	CAP, otorhinolaryngological		O	O	O	?	-	-	-	-
Cefiderocol (Fetroja)	Shionogi	FDA (11/2019) EMA (4/2020)	Siderophore cephalosporin	iv	cUTI		●	●	●	/	?	-	-	-
Levonadifloxacin (Emrok) Alalevonadifloxacin (Emrok O)	Wockhardt	DCGI (1/2020)	Fluoroquinolone	iv & oral	ABSSSI		O	O	O	●	-	-	-	-

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

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

Abbreviations: CC, new chemical class; EML, essential medicines list; MoA, new mode of action; NCR, no cross-resistance to other antibiotic in the same or other class; MAA, marketing authorisation application (EMA); OPP, other priority pathogens; PMDA, Japan's Pharmaceuticals and Medical Devices Agency; T, new target.

[1] Active against KPC-, but not MBL-producing Enterobacterales.
[2] New reports suggest that cross-resistance can be obtained when levels of the porin OmpK36 are 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] Cross resistance with linezolid and chloramphenicol have been reported.

3. Clinical antibacterial pipeline

The following sections describe the current clinical antibacterial development pipeline with activity against the WHO priority pathogens, *M. tuberculosis* and *C. difficile*. Sections 3.1–3.3 provide an overview and analysis of the traditional, direct-acting small molecule clinical antibacterial pipeline:

- 3.1 antibiotics targeting WHO priority pathogens;
- 3.2 antibiotics targeting *M. tuberculosis*; and
- 3.3 antibiotics targeting *C. difficile*.

For Phase 3 traditional antibacterials, additional information on the potential for clinical utility has been included based on planned, ongoing or completed Phase 3 programmes and anticipated microbiological features and clinical use, with a full summary of the products in Annex 2.

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.

3.1 Antibiotics being developed against WHO priority pathogens

There are currently 26 antibiotics in Phase 1–3 clinical development targeting WHO priority pathogens, of which half (*n* = 13) have confirmed activity against at least one of the critical Gram-negative bacteria (Table 2).

Most of the antibiotics in the clinical pipeline are derivatives of existing classes. Of the 26 antibiotics, only seven fulfil at least one of the four WHO innovation criteria. Three of these (taniborbactam, zoliflodacin and gepotidacin) are in Phase 3 clinical trials, one novel FabI (enoyl-acyl carrier protein reductase) inhibitor (afabicin) is in Phase 2, and three (VNRX-7145, TXA-709 and PLG0206) are in Phase 1. Only two of the seven innovative antibiotics (taniborbactam in combination with cefepime and VNRX-7145 in combination with ceftibuten) target at least one of the critical Gram-negative bacteria.

Two new antibiotics have entered Phase 1 since the last update: PLG0206, a cationic peptide, and a combination of QPX7728 + QPX2014, which is a boronate BLI partnered with an undisclosed β-lactam. This brings the total number of agents currently in Phase 1 to 14. Two further antibacterials (solithromycin and contezolid) moved from Phase 3 to the New Drug Application (NDA) filing stage.

Cefilavancin (Phase 2), BOS-288 (Phase 2) and BCM-0184 (Phase 1) were moved to Section 3.5, as no recent activity has been reported. Developers discontinued the development of SPR-741 and AIC-499, both in Phase 1, which were also moved to Section 3.5. SPR-741 was discontinued by Spero Therapeutics and are instead moving forward with SPR-206 *(6)*.

Table 2. Antibiotics being developed against WHO priority pathogens

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Solithromycin	NDA[1]	Macrolide	iv & oral (Melinta/Fujifilm Toyama Chemical)	/	/	/	●	-	-	-	-
Contezolid, Contezolid acefosamil	NDA[2]	Oxazolidinone	oral (MicuRx) iv & oral (MicuRx)	/	/	/	●	-	-	-	-
Sulopenem, Sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○[3]	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate-BLI + cephalosporin	iv (Venatorx/ GARDP)	○	?	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	β-lactam BLI + cephalosporin	iv (Allecra)	○	○	○[4]	/	-	-	-	-

Table 2. Contd.

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Zoliflodacin	3	Topoisomerase inhibitor (spiropyrimidenetrione)	oral (Entasis/GARDP)	/	/	/	●	✓	✓	-	✓
Gepotidacin	3	Topoisomerase inhibitor (triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●	?	✓	-	✓
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
Nafithromycin (WCK-4873)	2	Macrolide	oral (Wockhardt)	/	/	/	●	-	-	-	-
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?	-	-	-	-
Benapenem	2[5]	Carbapenem	iv (Sichuan Pharmaceutical)	O	O	O	/	-	-	-	-
Zidebactam + cefepime	1	DBO-BLI/PBP2 binder + cephalosporin	iv (Wockhardt)	●	●	●	/	-	-	-	-
Nacubactam + meropenem	1	DBO-BLI/PBP2 binder + meropenem	iv (NacuGen Therapeutics)	O	O[6]	●	/	-	-	-	-
ETX0282 + cefpodoxime	1	DBO-BLI/PBP2 binder + cephalosporin	oral (Entasis)	O	O	●	/	-	-	-	-
VNRX-7145 + ceftibuten	1	Boronate-BLI + cephalosporin	oral (Venatorx)	O	O	●	/	?	✓	-	-
SPR-206	1	Polymyxin	iv (Spero)	●	●	●	/	-	-	-	-
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	●	O	O	●	-	-	-	-
TP-271	1	Tetracycline	iv & oral (La Jolla Pharmaceutical)	?	O	O	●	-	-	-	-
TP-6076	1	Tetracycline	iv (La Jolla Pharmaceutical)	●	O	?	/	-	-	-	-
EBL-10031 (apramycin)	1[7]	Aminoglycoside	iv (Juvabis)	?	O	?	/	-	-	-	-
TNP-2198	1	Rifamycin-nitroimidazole conjugate	oral (TenNor)	/	/	/	●	-	-	-	-
TXA-709	1	FtsZ inhibitor	oral & iv (Taxis)	O	O	O	●	✓	✓	✓	✓
ARX-1796 (oral avibactam prodrug)	1	DBO-BLI + β-lactam	oral (Arixa Pharmaceuticals)	O	O	●[8]	/	-	-	-	-
PLG0206 (WLBU2)	1	Cationic peptide	iv (Peptilogics)	?	?	?	●	?	✓	?	?
QPX7728 + QPX2014	1	Boronate-BLI + unknown	iv (Qpex Biopharma)	●	?	●	/	?	-	-	-

Pathogen activity:

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

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

Abbreviations: GSK: GlaxoSmithKline.

[1] NDA submitted in Japan in April 2019.
[2] NDA submitted in China in December 2020.
[3] Active against ESBL-producing cephalosporin-resistant but not carbapenem-resistant Enterobacterales.
[4] Active against ESBL-producing cephalosporin-resistant and some KPC-producing CREs.
[5] Clinical development only for China.
[6] Activity against AmpC-producing and KPC-producing CRPA.
[7] Previously used as an antibacterial treatment in animals.
[8] Active against KPC- but not MBL-producing Enterobacterales.

3.1.1 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 subsequently disrupting peptidoglycan biosynthesis. This class includes penicillins, cephalosporins, carbapenems and monobactams *(7)*.

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 *(7)*.

There are four β-lactamase structural classes, known as A, B, C and D *(8)*. 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) *(9)*.

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

Over the past years, some new BLI combinations with carbapenems or cephalosporins have entered the market (e.g. ceftolozane + tazobactam and ceftazidime + avibactam) *(10)*. However, they are not active against all β-lactamase classes, such as Class B MBLs (e.g. NDM-1) and have only selected activity against some Class D (OXA) enzymes produced by *Acinetobacter*.

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

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

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

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

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. This table shows that the majority do not have activity against all clinically relevant β-lactamases. With the exception of taniborbactam + cefepime and QPX7728 + QPX2014, there is a notable development gap for agents that inhibit β-lactamase producers, specifically Class B (MBLs).

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.

It is important to point out that some BLIs in the pipeline – such as ETX-2514 and nacubactam – have intrinsic antibacterial activity, based on binding to PBP2, and may result in synergistic antibacterial activity in some Enterobacterales *(11)*.

Nevertheless, other mechanisms may still confer resistance to β-lactam/BLI combinations, despite their inhibition of β-lactamases *(12–14)*.

Legend: Expected activity against priority pathogens:

CRAB	CRPA	CRE	OPP
○	?	●	/

Pathogen activity: ● active; ? possibly active; ○ not or insufficiently active; / activity not assessed.
Potential for clinical differentiation of Phase 3 antibiotics: in darker grey.

Sulopenem, iv/oral **Phase 3**

○ ○ ○ /

- Synthetic penem; sulopenem etzadroxil oral prodrug.
- Activity against Enterobacterales, including ESBL producers; Gram-positive activity similar to carbapenems.
- Active against ESBL-producing cephalosporin-resistant but not carbapenem-resistant Enterobacterales.

- It is intended to provide the possibility of an oral switch early during treatment in stable patients, opening the option of early discharge from the hospital, or to avoid hospitalization. Sulopenem could provide an outpatient treatment option for infections caused by ESBL-producing bacteria, common in urinary tract infections (UTIs).
- Phase 3 trials (NCT03354598, NCT03357614, NCT03358576) completed: evaluating iv and oral formulations for the treatment of uncomplicated UTI (uUTI) (oral), cUTI and complicated intra-abdominal infection (IAI) (iv/oral prodrug) due to Enterobacterales.
- Cross-resistance with existing carbapenems reported *(15)*.

Durlobactam + sulbactam, iv **Phase 3**

● ○ ○ /

- Durlobactam (ETX-2514) is a modified diazabicyclooctane (DBO)-type BLI 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 (16)*.

- The combination is being studied for an empiric pathogen-specific treatment (narrow spectrum) for hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) infections due to drug-resistant *A. baumannii* infections (mainly MDR and carbapenem-resistant *A. baumannii* calcoaceticus complex [ABC] isolates).
- Phase 3 trial in cUTI completed (NCT03445195) and one in HAP/VAP currently recruiting (NCT03894046). Phase 3 trial is ongoing studying the efficacy and safety of the combination in treatment of hospitalized patients with ABC infections, including HAP/VAP, compared to colistin (superiority design), on background treatment of imipenem/cilastatin.
- 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 *(17)*.

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 [not universal] and VIM) and D (OXA-48) β-lactamases in CRE. It does not cover IMPs *(18)*.
- It is being studied as a broad-spectrum treatment for cUTI and acute pyelonephritis (AP) due to clinically important carbapenemase-producing carbapenem-resistant Gram-negative bacilli, including CRE and possibly CRPA *(19)*.
- Phase 3 trial for cUTI infection (NCT03840148) is recruiting: a non-inferiority study 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.
- No reported cross-resistance.

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.
- Inhibitory activity against ESBL 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.
- Phase 3 trial (EudraCT 2017-004868-35, NCT03687255) completed to evaluate the efficacy and safety of enmetazobactam + cefepime to piperacillin + tazobactam in the treatment of 1034 cUTI patients, including AP, in 115 sites in 19 countries.
- No reported cross-resistance.

Benapenem, iv **Phase 2**

○ ○ ○ /

- A carbapenem which has completed a Phase 2 trial (NCT03578588).
- Clinical development only for China.
- Complete cross-resistance to other carbapenems.

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 *(20–22)*.
- Synergistic activity in Enterobacterales with Class A β-lactamases, including ESBL and KPC, but elevated minimum inhibitory concentrations (MICs) in MBL producers *(23, 24)*.
- Phase 1 trials completed (NCT02532140, NCT02942810, NCT02707107).

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 *(25, 26)*.
- Combination partner is meropenem; synergistic activity with various partners in Enterobacterales, including some MBL producers (elevated MICs) *(27)*; BLI activity only in *P. aeruginosa* and not carbapenem-resistant *P. aeruginosa*; no added benefit in treating carbapenem-resistant *A. baumannii (28)*.
- Phase 1 pharmacokinetics trial with meropenem (NCT03174795) is completed.

ETX0282 + cefpodoxime, oral **Phase 1**

○ ○ ● /

- ETX0282 is an oral BLI of the DBO type 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 completed.

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.
- Phase 1 trial recruiting (NCT04243863).

ARX-1796, oral **Phase 1**

○ ○ ● /

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

QPX7728 + QPX2014, iv **Phase 1**

● ? ● /

- QPX7728 is a boronate-type BLI which inhibits serine- and metallo-β-lactamases of Classes A, B, C, and D in *A. baumannii*, *P. aeruginosa* and Enterobacterales *(29, 30)*.
- Phase 1 trial in combination with an undisclosed β-lactam QPX2014 registered (NCT04380207); not yet recruiting.

3.1.2 Tetracyclines

Tetracyclines are broad-spectrum bacteriostatic antibiotics that were discovered in 1948 with activity against Gram-positive and Gram-negative bacteria. Tetracyclines bind to the A site of the 30S ribosomal subunit and inhibit binding of aminoacyl-transfer RNA (tRNA), preventing synthesis of polypeptides *(31)*. 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 *(32)*. Since their introduction, more than 1000 tetracycline resistance genes have been reported that are often associated with mobile genetic elements, including efflux pumps, ribosomal protection proteins, tetracycline-inactivating enzymes (*tet*), mosaic genes and mutations in ribosomal proteins. The semi-synthetic parenteral glycycline, tigecycline, was approved in 2005 and overcomes certain class-specific resistance mechanisms. In 2018, the US FDA approved both iv and oral formulations of eravacycline, a fully synthetic fluorocycline, and omadacycline, a semi-synthetic aminomethylcycline analogue of minocycline. Currently, three tetracycline derivatives, two synthetic and one semi-synthetic, are in Phase 1 trials.

KBP-7072, oral **Phase 1**

● ○ ○ ●

- An aminomethylcycline, optimized for Gram-positive respiratory pathogens and in vitro activity against *A. baumannii (33)*.
- Limited information available *(34)*.
- Two Phase 1 trials are completed (NCT02454361, NCT02654626).

TP-271, iv/oral **Phase 1**

? ○ ○ ●

- Synthetic tetracycline vulnerable to *tet*(A) and *tet*(X).
- Similar activity to tigecycline against *Haemophilus influenzae* and Gram-positive pathogens, including vancomycin-resistant *Enterococcus faecium (35).*
- One Phase 1 trial completed (NCT02724085) and a second Phase 1 trial (NCT03024034) status unknown after acquisition of Tetraphase by La Jolla Pharmaceuticals.

TP-6076, iv **Phase 1**

● ○ ? /

- Synthetic tetracycline optimized for Gram-negative pathogens; little influence on tet (M, Q, K, A, B and D); elevated MICs in *A. baumannii* overexpressing adeAB *(36)*.
- MICs lower than those of tigecycline in Enterobacterales and *A. baumannii*; higher MICs in cases of carbapenem resistance, especially in tigecycline co-resistant strains *(37)*.
- Phase 1 trial ongoing (NCT03691584).

3.1.3 Aminoglycosides

Aminoglycosides are bactericidal and active against Gram-negative bacteria such as *Pseudomonas*, *Acinetobacter* and *Enterobacter* spp. They 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 the production of bacterial ribosome-modifying enzymes (16S rRNA methylases), which often occur in NDM-producing Enterobacterales *(38)*. The recently approved aminoglycoside

plazomicin has been optimized to address most aminoglycoside-modifying enzymes. There is currently one aminoglycoside in Phase 1.

EBL-10031, iv **Phase 1**

? - ? /

- EBL-10031 (apramycin) was licensed in 1980 for oral therapy in animals.
- First warning of resistance in 1986 *(39)*, resistance described by AAC(3)-IV, acetylation of the 1-amino group *(40)*.
- Phase 1 trial completed (NCT04105205).

3.1.4 Topoisomerase inhibitors

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 II topoisomerases: DNA gyrase and topoisomerase IV. They bind preferentially to the gyrase subunit GyrA and to the topoisomerase IV subunit ParC *(41)*. 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 *(42, 43)*. These new agents target Gram-positive pathogens, respiratory tract infection pathogens and *Neisseria 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 to fluoroquinolones (GyrA) *(44)*.
- Being studied for the treatment of uncomplicated *N. gonorrhoeae* with potential to be effective in treating infections caused by fluoroquinolone-resistant strains.
- Phase 3 trial for treatment of uncomplicated gonorrhoea currently recruiting (NCT03959527): a multicentre, open-label, randomized, non-inferiority trial comparing a single oral dose of zoliflodacin to 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).

Zoliflodacin (cont.)

- Early findings indicate no cross-resistance with fluoroquinolones (or other topoisomerase inhibitors) *(45, 46)*.

Gepotidacin, iv/oral **Phase 3**

/ / / ●

- Novel bacterial topoisomerase II inhibitor (triazaacenaphthylene scaffold) that selectively inhibits bacterial DNA replication by interacting on 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.
- High oral dose due to poor absorption (53% of the oral dose is eliminated through the faecal route due to poor gastrointestinal tract (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 currently recruiting for treatment of uUTI (NCT04020341) and uncomplicated gonorrhoea infections (NCT04010539).
- Some cross-resistance with fluoroquinolones reported *(47)*.

3.1.5 FabI inhibitor

FabI (a NADH-dependent enoyl acyl carrier protein reductase, encoded by *fabI*) is 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[1] for TB treatment and the nonspecific biocide and slow-binding FabI inhibitor triclosan. These agents have different binding characteristics *(48)*. It is not known whether they exert selection pressure on staphylococci, which could lead to cross-resistance *(49, 50)*.

Afabicin, iv/oral **Phase 2**

/ / / ●

- Afabicin (Debio-1450) is a new *Staphylococcus*-specific antibiotic class developed for *S. aureus* infections as iv and oral form (prodrug) *(51)*.
- Inhibits FabI, which is a key enzyme in bacterial fatty acid biosynthesis *(52)*.

1 In addition to inhibiting FabI, isoniazid also inhibits the InhA enzyme (an enoyl acyl carrier protein reductase).

Afabicin (cont.)

- 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 *(53)*. Risk for emergence of high-level resistance may be offset by high affinity for the target *(50, 54, 55)*.
- Phase 2 trial in staphylococcal acute bacterial skin and skin structure infections (ABSSSIs) (NCT02426918) completed and a second Phase 2 trial for bone or joint infections registered (NCT03723551).

3.1.6 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 *(56, 57)*.

TXA-709, iv/oral **Phase 1**

○ ○ ○ ●

- The orally bioavailable methylbenzamide antibiotic TXA-709 and its active metabolite TXA-707 target FtsZ and have been tested against *S. aureus (58).*
- Phase 1 trial not registered.

3.1.7 Oxazolidinones

Oxazolidinones inhibit protein synthesis through binding at the peptidyltransferase centre of the 50S ribosomal subunit and interfering with the incoming tRNA *(59)*. 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 TB infections.

Contezolid, iv/oral **NDA**
Contezolid acefosamil

/ / / ●

- Activity against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* and penicillin-resistant *S. pneumoniae*.

Contezolid (cont.)

- Little information published, and potential differences with linezolid are unclear *(60)*.
- 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.

3.1.8 Macrolides and ketolides

Macrolides inhibit protein synthesis through binding to the 50S ribosomal subunit peptidyltransferase centre (at the nascent peptide exit tunnel) *(61)*. 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 *(62)*. Ketolides are a subclass of the macrolides, which 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 *(63)*.

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 *(62, 64, 65)*.
- 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 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 2**

/ / / ●

- In vitro activity similar to telithromycin, the first ketolide approved in 2001 to have safety issues *(66)*.

Nafithromycin (cont.)

- Active against some macrolide- and ketolide-resistant pneumococci.
- Reported cross-resistance in *ermB*-induced pneumococci, staphylococci and group A streptococci. High MICs to *H. influenzae*.
- Safety and potential liver toxicity unknown.
- Phase 2 trial completed (NCT02903836); a Phase 3 trial for treatment of CAP is planned in India (CTRI/2019/11/021964).

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 (including one against *C. difficile*) 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 *(67, 68)*.
- Activity comparable to rifamycin; clinical development of oral form against gastrointestinal pathogens, including *Helicobacter pylori* iv form; against prosthetic joint infections, including *S. aureus (69).*
- Phase 2 trial for treatment of ABSSSI completed (NCT03964493).

TNP-2198, oral **Phase 1**

/ / / ●

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

3.1.10 Polymyxins

Polymyxins are cationic polypeptides that were resurrected as a last-resort antibiotic against XDR Gram-negative bacteria, despite their well-documented side effects (nephro- and neurotoxicity) compared to newer Gram-negative antibiotics *(70)*. Colistin and polymyxin B are increasingly used, but resistance has also emerged in response to the increased use. A new polymyxin derivative, SPR-206, is in early clinical development, but the antibiotic potentiator SPR-741 was discontinued.

SPR-206, iv **Phase 1**

● ● ● /

- Polymyxin nonapeptide analogue *(71)*.
- It is still unclear whether lower MIC values will translate into useful activity in colistin-resistant strains and what role nephrotoxicity will play in the clinical management of patients.
- Phase 1 trial completed (NCT03792308).

PLG0206 (WLBU2), iv **Phase 1**

? ? ? ●

- An engineered cationic peptide with broad-spectrum activity against biofilms, tested against MRSA and methicillin-susceptible *S. aureus* (MSSA).
- Received orphan drug status for prosthetic joint infection in the USA.
- Phase 1 trial recruiting (ACTRN12618001920280).

3.2 Agents in development for treating TB infections

Most human TB is caused by *M. tuberculosis*. Among the estimated 10 million new TB cases occurring worldwide in 2019, an estimated 206 030 cases were caused by MDR or rifampicin-resistant *M. tuberculosis*, a 10% increase from 186 883 in 2018 *(72).* Innovative new treatments, particularly for drug-resistant TB, are urgently needed. Currently, 12 agents are being developed against *M. tuberculosis*, of which six meet the innovation criteria of the absence of known cross-resistance. Several new targets are being pursued, including decaprenylphosphoryl-β-D-ribose 2-epimerase (DprE1) and leucyl-tRNA synthetase (LeuRS), that are essential enzymes for cell wall biosynthesis and mycobacterium protein synthesis, respectively. Among agents in development for treating TB, three target DprE1, one targets LeuRS, and one is a GyrB inhibitor. In addition, three oxazolidinones, a riminophenazine (clofazimine analogue), a diarylquinoline and an imidazopyridine amide are in clinical development (Table 4). A Phase 3 agent (SQ-109) was moved to section 3.5 as there has been no development activity reported since 2017.

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

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
GSK-3036656 (GSK070)	2	LeuRS inhibitor (oxaborole)	oral (GSK)	✓	✓	✓	✓
Delpazolid (LCB01-0371)	2b[1]	Oxazolidinone	oral (LegoChem Biosciences/HaiHe Biopharma)	-	-	-	-
Sutezolid	2[2]	Oxazolidinone	oral (TB Alliance/Sequella)	-	-	-	-
Telacebec (Q-203)	2	Imidazopyridine amide	oral (Qurient)	✓	✓	✓	✓
BTZ-043	2	DprE1 inhibitor (benzothiazinone)	oral (University of Munich; Hans Knöll Institute, Jena; German Center for Infection Research)	✓	✓	✓	✓
TBA-7371	2	DprE1 inhibitor (azaindole)	oral (TB Alliance, Bill & Melinda Gates Medical Research Institute, Foundation for Neglected Disease Research)	✓	✓	✓	✓
SPR-720[4]	2a	GyrB inhibitor (benzimidazole ethyl urea)	oral (Spero, Bill & Melinda Gates Foundation)	-	✓	-	-
OPC-167832	1/2	DprE1 inhibitor (3,4-dihydrocarbostyril)	oral (Otsuka)	✓	✓	✓	✓
Macozinone (PBTZ-169)	1	DprE1 inhibitor (benzothiazinone)	oral (Innovative Medicines for Tuberculosis Foundation) [3]	✓	✓	✓	✓
TBI-166[5]	1	Riminophenazine (clofazimine-analogue)	oral (Institute of Materia Medica, TB Alliance, Chinese Academy of Medical Sciences & Peking Union Medical College)	-	-	-	-
TBI-223	1	Oxazolidinone	oral (TB Alliance/Institute of Materia Medica)	-	-	-	-
TBAJ-876	1	Diarylquinoline	oral (TB Alliance)	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; - criterion not fulfilled.

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

[1] Delpazolid also completed a Phase 1 trial as an injectable for MRSA and VRE spp. infections.
[2] Developed by Sequella and independently by TB Alliance; non-exclusive patent licence held by Sequella and by the Medicines Patent Pool.
[3] In Russia developed by Nearmedic Plus.
[4] The GyrB/ParE inhibitor novobiocin is no longer in clinical use.
[5] Clofazimine is approved for leprosy and used also for MDR-TB (off-label).

GSK-3036656, oral **Phase 2**

- GSK-3036656 (GSK070) belongs to a novel class (oxoborole) with a new mechanism of action that inhibits LeuRS.
- Phase 2 early bactericidal activity trial currently recruiting patients with proven rifampin-susceptible *M. tuberculosis* infection (NCT03557281).

Delpazolid, oral **Phase 2b**

- Delpazolid (LCB01-0371) is an oxazolidinone.
- Phase 2 early bactericidal activity trial completed (NCT02836483). A Phase 2b for pulmonary TB is registered (NCT04550832); not yet recruiting.
- Phase 1 trial as an injectable for MRSA and vancomycin-resistant enterococci (VRE) is also completed.

Sutezolid, oral **Phase 2**

- Member of the oxazolidinone class.
- Phase 2 trial currently recruiting (NCT03959566).

Telacebec, oral **Phase 2**

- Telacebec (Q203) is an imidazopyridine amide that inhibits cytochrome bc1 in the respiratory chain.
- Phase 2 trial to evaluate early bactericidal activity completed (NCT03563599).

SPR-720, oral **Phase 2a**

- DNA gyrase GyrB inhibitor, developed for infections caused by non-tuberculous mycobacteria.
- Received orphan drug status and fast track status from the US FDA for non-tuberculous mycobacterium infections.
- Phase 1 trial completed (NCT03796910). Phase 2a trial registered (NCT04553406), but not yet recruiting.

TBI-166, oral **Phase 1**

- Clofazimine analogue, riminophenazine class.
- Clofazimine has been used in the treatment of leprosy since 1962.
- Phase 1 trial for TB indication registered in China (ChiCTR1800018780).

TBI-223, oral **Phase 1**

- An oxazolidinone.
- Phase 1 single ascending dose trial completed (NCT03758612).

TBAJ-876, oral **Phase 1**

- A diarylquinoline ATP (adenosine triphosphate) synthase inhibitor; bedaquiline analogue *(73)*.
- Phase 1 trial registered (NCT04493671); not recruiting.

BTZ-043, oral **Phase 2**

- DprE1 inhibitor, benzothiazinone.
- Phase 2 multiple ascending dose study registered to evaluate early bactericidal activity (NCT04044001); currently recruiting patients with drug-susceptible pulmonary TB.

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

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

TBA-7371, oral **Phase 2**

- DprE1 inhibitor, azaindole.
- Phase 1 trial completed (NCT03199339).
- Phase 2 trial to evaluate early bactericidal activity in pulmonary TB currently recruiting patients with rifampicin-susceptible TB (NCT04176250).

Macozinone, oral **Phase 1**

- Macozinone (PBTZ-169) is a DprE1 inhibitor, benzothiazinone.
- Phase 2a trial in the Russian Federation was terminated due to slow enrolment (NCT03334734).
- DprE1 inhibitor, benzothiazinone.
- Phase 1 trial completed (NCT03590600).

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

Infections with *C. difficile* can cause severe enterocolitis and are a serious public health threat in developed countries. *C. difficile* infections (CDIs) are primarily managed by prevention, control and antimicrobial stewardship activities, and have several treatment options currently available, which is why *C. difficile* was not included in the WHO priority pathogens list. However, for the pipeline analysis the advisory group felt it important to include, and Table 5 includes agents in development against *C. difficile (74).* Since the 2019 update, OPS-2071 (Phase 2) was discontinued, and ACX-362E has progressed from Phase 1 to Phase 2.

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

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

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

These agents are being developed for *C. difficile* infections; their activity against WHO priority pathogens was not assessed.

Ridinilazole, oral — Phase 3

- Non-absorbable *bis*-benzimidazole, with a new class, structure and mode of action; currently proposed to bind to the DNA minor groove, resulting in selective interference with cell division *(75–78)*.
- Early evidence indicates bactericidal activities and a decrease in toxins A and B concentrations of *C. difficile* strains exposed to ridinilazole *(79)*.
- 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) *(76)*.
- One Phase 2 study assessed the safety and efficacy of ridinilazole vs vancomycin for treatment of CDAD in 100 patients; 82% of those treated with ridinilazole had adverse effects (*n* = 41/50), mostly mild (40% GIT related), and one serious adverse effect (hypokalaemia).
- Two Phase 3 trials are currently recruiting (NCT03595553 and NCT03595566).

DNV-3837, iv — Phase 2

- DNV-3837 (MCB-3837) is a prodrug, oxazolidinone-quinolone hybrid for iv treatment *(80)*.
- No cross-resistance report in tested strains, but limited data available *(81)*.

DNV-3837 (cont.)

- Phase 2 trial is recruiting patients with non-severe or severe CDI, compared to standard of care (NCT03988855).

MGB-BP-3, oral — Phase 2

- Non-absorbable antibiotic with a novel chemical structure (distamycin derivative), a new target and antibacterial mode of action (DNA minor groove binder). It acts on multiple binding sites and interferes with transcription *(82, 83)*.
- Active against Gram-positive bacteria; resistance in Gram-negative bacteria through efflux pumps.
- Phase 2 trial comparing different MGB-BP-3 dosing regimens in patients with non-severe CDI completed (NCT03824795).

ACX-362E, oral — Phase 2

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

CRS3123, oral — Phase 1

- New chemical class with a new target and a new mode of action: a diaryldiamine derivative that inhibits methionyl-tRNA synthetase *(84)*.

CRS3123 (cont.)

- Active against Gram-positive bacteria, including *C. difficile*; inhibits toxin production in vitro.
- Little information is available regarding resistance.
- Systemic absorption only at higher doses.
- Phase 1 trial completed (NCT01551004 and NCT02106338); Phase 2 trial planned.

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 *(85)*. These alternatives are collectively known as "non-traditional" antibacterials. They aim to prevent or treat bacterial infections through direct or indirect inhibition of bacterial growth, virulence inhibition, antibacterial resistance amelioration, human immune system boosting, and positively altering and/or restoring a healthy microbiome *(86)*.

In this report, the 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.
- **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, 27 non-traditional antibacterials are under active clinical development: nine antibodies, four bacteriophages and phage-derived enzymes, eight microbiome-modulating agents, two immunomodulating agents and four agents in the miscellaneous category (Table 6). Four are in Phase 3, 14 in Phase 2, two in Phase 1/2, six in Phase 1 and one not assigned. Most of these non-traditional products are being tested and intended for use in combination with standard antibiotics.

Table 6. Non-traditional antibacterial agents in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens
AR-301 (tosatoxumab)	3	Anti-*S. aureus* immunoglobulin M (IgM) monoclonal antibody	iv (Aridis)	*S. aureus*
CF-301 (exebacase)	3	Phage endolysin	iv (ContraFect)	*S. aureus*
SER-109	3	Live biotherapeutic product	oral (Seres Therapeutics)	*C. difficile*
AB103 (reltecimod)	3	Antagonist of both superantigen exotoxins and the CD28 T-cell	iv (Atox Bio)	*S. aureus*
SYN-004 (ribaxamase)	2b	Antibiotic inactivator	oral (Synthetic Biologics)	*C. difficile*
OligoG (CF-5/20)	2b	Alginate oligosaccharide (G-block) fragment	Inhalation (AlgiPharma AS)	*P. aeruginosa*
SAL-200 (tonabacase)	2a	Phage endolysin	iv (iNtRON Biotechnology, Roivant Sciences)	*S. aureus*
AR-101 (panobacumab, Aerumab)	2a	Anti-*P. aeruginosa* serotype O11 IgG monoclonal antibody	iv (Aridis, Shenzen Arimab Biopharma)	*P. aeruginosa*
BT588 (trimodulin)	2	Human plasma-derived native polyvalent antibody preparation containing IgM, IgA and IgG	iv (Biotest)	*S. aureus*
MEDI-4893 (suvratoxumab)	2	Anti-*S. aureus* IgG monoclonal antibody	iv (AstraZeneca)	*S. aureus*

Table 6. Contd.

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens
514G3	2	Anti-*S. aureus* IgG monoclonal antibody	iv (Xbiotech)	*S. aureus*
IM-01	2	Anti-*C. difficile* polyclonal antibody derived from chicken egg	oral (ImmuniMed)	*C. difficile*
AR-105 (aerucin)	2	Anti-*P. aeruginosa* fully human IgG1 monoclonal antibody	iv (Serum Institute of India/ Aridis)	*P. aeruginosa*
LMN-101	2	Monoclonal antibody-like recombinant protein	oral (Lumen Bioscience)	*E. coli, C. jejuni*
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*
Ftortiazinon (fluorothyazinone) + cefepime	2	Thyazinone (type III secretion system inhibitor) + cefepime	oral (Gamaleya Research Institute of Epidemiology and Microbiology)	*P. aeruginosa*
PhageBank	1/2	Phage bank (process)	oral (Adaptive Phage Therapeutics and US Department of Defense)	*E. coli, K. pneumoniae*
Rhu-pGSN (rhu-plasma gelsolin)	1b/2a	Recombinant human plasma gelsolin protein	iv (BioAegis Therapeutics)	Non-specific Gram-positive and Gram-negative strains
DSTA4637S (RG7861)	1b	Anti-*S. aureus* IgG human monoclonal antibody/rifamycin	iv (Genentech/Roche)	*S. aureus*
LBP-EC01	1b	CRISPR-Cas3 enhanced phage	iv (Locus Bioscience)	*E. coli, K. pneumoniae*
CAL02	1	Broad spectrum anti-toxin liposomal agent and nanoparticle	iv (Combioxin SA)	*P. aeruginosa, A. baumannii*, Enterobacterales, *S. aureus, S. pneumoniae*
GSK3882347	1	FimH (type 1 fimbrin D-mannose specific adhesin) antagonist	oral (GSK)	*E. coli*
MET-2	1	Live biotherapeutic product	oral (NuBiyota/Takeda)	*C. difficile*
RBX7455	1	Live biotherapeutic product	oral (Ferring)	*C. difficile*
KB109	N/A	Synthetic glycan	oral (Kaleido Biosciences)	Enterobacterales, *C. difficile*

Colour coding: Green, antibodies; blue, bacteriophages and phage-derived enzymes; red, microbiome-modulating agents; purple, immunomodulating agents; orange, miscellaneous.

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, while polyclonal antibodies are a heterogeneous group produced by different clones of plasma B cells and can 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 including oncology,

inflammation, multiple sclerosis, lupus, respiratory syncytial virus and, most recently, COVID-19. In addition, they are receiving increasingly more attention for the treatment of bacterial infections. 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 *(87)*.

Currently nine antibodies are in clinical development, with eight targeting selected bacteria, albeit with different mechanisms and antibody compositions. Five of these are being developed against *S. aureus* (AR-301, DSTA46375, MEDI-4893, 514G3 and DSTA4637S), two against *P. aeruginosa* (AR-101 and AR-105), one against *C. difficile* (IM-01), and one against *C. jejuni* and *E. coli* (LMN-101).

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

- Anti-*S. aureus* immunoglobulin G1 (IgG1) monoclonal antibody targets virulence factor α-toxin *(88)*.
- Phase 3 trial ongoing as an adjunctive treatment of *S. aureus* VAP (NCT03816956).

AR-101 (panobacumab, KBPA101), iv **Phase 2**

- Anti-*P. aeruginosa* serotype 011 IgG1 monoclonal antibody binds to surface polysaccharide alginate to enhance immune response.
- Phase 2a trial as adjunctive was completed for HAP in 2009 (NCT00851435) *(89)*.
- Phase 3 trial is planned.

Trimodulin (BT588, BT086), iv **Phase 2**

- Native polyvalent antibody preparation derived from human plasma containing IgM, IgA and IgG *(90)*.
- Phase 1/2 trial finished in 2015 as an adjunctive therapy for the treatment of CAP (NCT01420744).
- Started a Phase 2 trial in 2020 as an adjunctive to standard of care for the treatment of COVID-19 (NCT04576728).

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

- Anti-*S. aureus* IgG monoclonal antibody targets the virulence factor α-toxin and surface-localized clumping factor A *(91)*.
- Phase 2 trial completed in 2018 as a non-adjunctive treatment of mechanically ventilated adults colonized and at high risk of *S. aureus* pneumonia (NCT02296320).
- Long half-life, estimated to be 80–112 days *(92)*.

514G3, iv **Phase 2**

- Anti-*S. aureus* IgG3 monoclonal antibody targets a cell wall virulence factor, protein A (SpA), which was originally cloned from the B cells of a healthy human donor with pre-existing antibodies against SpA *(93)*.
- Phase 1/2 trial completed for adjunctive treatment of bacteraemia caused by *S. aureus* in 2017 (NCT02357966).

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 *(94)*.
- Phase 2 trial started in 2019 as a potential non-adjunctive treatment for mild to moderate CDI (NCT04121169).

AR-105, iv **Phase 2**

- Fully human IgG1 monoclonal antibody targeted against *P. aeruginosa* alginate *(95)*.
- Phase 2 trial as an adjunctive treatment for *P. aeruginosa* pneumonia was completed in 2019 (NCT03027609).
- Licensed in 2019 to the Serum Institute of India and Shenzhen Hepalink Pharmaceutical Group.

LMN-101, iv **Phase 1**

- Variable heavy chain-derived protein designed to bind and inhibit *C. jejuni* FlaA, which is a flagellin filament protein. LMN-101 is delivered via whole spray-dried spirulina biomass.
- Phase 1 trial completed in 2020 (NCT04098263).
- Phase 2 human challenge trial comparing LMN-101 alone to placebo to start in February 2021 (NCT04182490).

DSTA-46375, iv **Phase 1b**

- Antibody drug conjugate with an anti-*S. aureus* IgG1 monoclonal antibody bound to a rifamycin derivative (average stoichiometry one monoclonal antibody to two rifamycin units).
- Antibody binds to *S. aureus* surface proteins and releases a rifamycin derivative to kill intracellular *S. aureus (96)*.
- Phase 1 trial evaluating pharmacokinetics and safety in patients with *S. aureus* bacteraemia receiving standard-of-care antibiotics completed in 2020 (NCT03162250).

3.4.2 Bacteriophages and phage-derived enzymes

Bacteriophages (also colloquially 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 *(97).* With the increase in antibacterial resistance, there has been an added emphasis on evaluating phages as a source of new antibacterials as well as for their use in the food industry.

Phages produce enzymes called lysins, which degrade bacterial cell walls and which can be identified directly from a phage or a prophage. Phage combinations derived from phage banks are being used to treat patients as personalized medicine specific to their infection as well as a vehicle to deliver lysins and bactericidal payloads. Work is also being undertaken using synthetic biology techniques to develop new "synphages" with more potent activity and broader activity spectra.

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

- Recombinantly produced phage endolysin protein, which was identified as an anti-staphylococcal lysin encoded within a prophage of the *Streptococcus suis* genome *(98, 99)*.
- Phase 3 trial started in 2020 evaluating CF-301 with standard-of-care antibiotics compared against standard of care alone for the treatment of *S. aureus* BSI, including right-sided infective endocarditis (NCT04160468).

SAL-200 (tonabacase), iv **Phase 2a**

- Recombinantly produced SAL-1 phage endolysin protein, originally isolated from the staphylococci infecting bacteriophage SAP-1.
- Fast killing of *S. aureus,* synergistic with antibacterial drugs but short half-life *(100)*.
- A Phase 2 trial was started in 2018 for treatment of persistent *S. aureus* bacteraemia with standard-of-care antibacterial drugs, but there has been no recent update (NCT03089697).
- Roivant Sciences licensed SAL-200 in November 2018, but no clinical trial has been registered and it is not listed in their company pipeline.

PhageBank (process), iv **Phase 1/2**

- Bacteriophage cocktails from the phage bank will be personalized for each patient with *E. coli* and *K. pneumoniae* infections selected from phage susceptibility testing.
- Phase 1/2 against UTI is scheduled to start in December 2020 (NCT04287478); however, the phage bank is already available for emergency use.

LBP-ECO1, iv **Phase 1**

- Phage cocktail engineered with clustered regularly interspaced short palindromic repeats (CRISPR) Cas3 construct targeting the *E. coli* genome, which combines phage lytic activity with the DNA-targeting activity of Cas3.
- Phase 1 trial started in 2019 evaluating safety, tolerability, and pharmacokinetics and -dynamics (PK/PD) in patients with lower-tract *E. coli* colonization (NCT04191148).

3.4.3 Microbiome-modulating agents

There has been considerable recent interest in investigating the composition and role that the human gut microbiome plays in human health *(101, 102)*. For example, the gut microbiome is involved in food digestion and production of some vitamins, and also helps to modulate immune responses and the gut-brain axis. Some antibacterial drugs alter the microbiome's balance, which can lead to illness or facilitate drastic change where some pathogens, such as *C. difficile*, become dominant and cause harmful effects. There are eight microbiome-modulating agents currently in clinical trials. Five of these are

live biotherapeutic products being evaluated to treat CDI: SER-109 (spores), and VE303, CP101, MET-2 and RBX7455 (live bacteria). KB109 is a synthetic glycan that is being trialled to enhance the growth of beneficial gut microbes to boost the immune response. There are also two antibiotic inactivators in clinical trials that help maintain gut microbes using two different mechanisms: SYN-004 is a BLI enzyme that degrades excess penicillin and cephalosporins in the gut, while DAV132 uses activated charcoal to absorb excess antibiotics and their degradative metabolites to better preserve the intestinal microbiota.

SER-109, oral **Phase 3**

- A live biotherapeutic product that contains a consortium of pathogen-free, purified bacterial spores of multiple *Firmicute* species, derived from healthy human donor stools *(103).*
- Results released in August 2020 from a Phase 3 trial (ECOSPOR III, NCT03183128) showed a statistically significant benefit for SER-109 vs placebo administered following cure of recurrent CDI, to prevent reoccurrence.
- An open-label Phase 3 trial (NCT03183141) for recurrent CDI is ongoing.

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

- Recombinant BLI enzyme orally administered with iv administered β-lactams (penicillins and cephalosporins).
- Degrades excess antibiotic in the proximal GIT, which will help preserve the gut microbiome *(104)*.
- Phase 2 trial successfully completed in 2016 that investigated the prevention of CDI in hospitalized patients receiving iv ceftriaxone with a diagnosis of a lower respiratory tract infection (NCT02563106) *(105)*.

VE303, oral **Phase 2**

- A live biotherapeutic product that consists of eight types of clonal human commensal bacteria.
- Phase 2 trial started in 2018 is ongoing for the prevention of recurrent CDI (NCT03788434).

CP101, oral **Phase 2**

- A live biotherapeutic product derived from the stools of normal healthy donors from a clinically structured donation programme.

CP101 (cont.)

- Phase 2 trial (NCT03110133) that finished in February 2020 met its primary efficacy end-point of reducing CDI recurrence.
- An open-label extension Phase 2 trial (NCT03497806) also investigating CDI recurrence is ongoing.

DAV132, oral **Phase 2**

- Activated charcoal which acts as an antibiotic inactivator by irreversibly absorbing antibiotic residues in the colon *(106)*.
- A Phase 2 trial completed in 2019 investigated hospitalized patients at high risk for CDI and who receive 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 *(107)*.
- Phase 1 trial evaluating the dose-dependent engraftment of MET-2 commensal bacteria for the treatment of mild to moderate recurrent CDI started in 2019 (NCT02865616).

RBX7455, oral **Phase 1**

- A live biotherapeutic product manufactured from a microbiota-based suspension prepared from human stool.
- Phase 1 trial on the treatment of recurrent CDI was completed in July 2020 (NCT02981316) *(108)*.

KB109, oral **Not defined**

- Synthetic glycan which modulates microbial metabolism to enhance the growth of beneficial bacteria in the human gut associated with immune response.
- A clinical study was initiated in 2019 to evaluate its effect on the gut microbiome in subjects whose GITs are colonized with MDR bacteria (NCT03944369).
- Also being evaluated in a clinical study on gut microbiome structure and function for COVID-19 patients (NCT04486482).

3.4.4 Immunomodulating agents

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

AB103 (reltecimod), iv **Phase 3**

- Synthetic octapeptide antagonist that inhibits Gram-positive (including *S. aureus* and *S. pyogenes*) superantigen activation of the T-lymphocyte receptor CD28 and impairs endotoxin-mediated activation of T cells *(109)*.
- Immunomodulatory activity is bacterial strain agnostic.
- Phase 3 study in patients with necrotizing soft tissue infections, as an adjunctive to standard of care, was completed in 2019 (NCT02469857) *(110)*.
- Phase 3 trial in peritonitis and acute kidney injury (as an adjunctive to standard of care) was terminated in 2020 due to slow enrolment (NCT03403751).

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

- Recombinantly produced human plasma protein gelsolin, an actin-binding protein that helps regulate inflammatory homeostasis *(111)*.
- Immunomodulatory activity is bacterial strain agnostic.
- Phase 1b/2a trial was completed in 2019 as an adjunctive to standard of care for CAP (NCT03466073).
- Also being evaluated in a COVID-19 Phase 2 trial (NCT04358406).

3.4.5 Miscellaneous

Four antibacterial non-traditionals in the pipeline fall under the miscellaneous category: OligoG, an alginate oligosaccharide fragment being trialled in the treatment of cystic fibrosis (CF) patients; CAL02, a liposome that binds bacterial toxins; and two anti-virulence agents which have different mechanisms of action. Ftortiazinon is a bacterial type III secretion system (T3SS) inhibitor being developed in combination with cefepime, while GSK3882347 is an adhesion protein inhibitor that has just started Phase 1 trials.

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 *(112)*.
- Phase 2 trials started in 2018 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 *(113)*.
- Phase 1 trial completed in 2018 for patients with severe pneumonia caused by *S. pneumoniae* (as an addition to the standard-of-care antibiotic treatment) (NCT02583373) *(114)*.

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

- Bacterial T3SS small molecule inhibitor which is highly conserved in many Gram-negative bacteria, including *P. aeruginosa (115).*
- Phase 2 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 inhibiter of an *E. coli* adhesive protein, FimH, which prevents binding of *E. coli* to the bladder wall and helps to prevent infection *(116)*.
- Phase 1 trial for the prevention and/or treatment of UTI caused by *E. coli* among healthy participants, started in 2020 (NCT04488770).

3.5 Agents that are 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 the product may be bought by another company or that they can continue development at a later stage. Such compounds are still listed in the (online) clinical development pipelines, but typically do not move through the clinical development pathway. If such products 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 2015 are also listed in Table 7.

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

Name (synonym)	Phase	Antibiotic class	Pathogen activity	Developer	Year activity last reported
Discontinued					
CB-618 (MK-6183)	1	DBO-BLI	Gram-negative bacteria	Merck	2015
TBA-354	1	Nitroimidazole	TB	TB Alliance	2016
GSK-3342830	1	Siderophore-cephalosporin	Gram-negative bacteria	GSK	2017
AIC-499 + unknown BLI	1	β-lactam + BLI	Gram-negative bacteria	AiCuris	2017
DS-2969	1	GyrB inhibitor	*C. difficile*	Daiichi Sankyo	2017
SPR-741+ β-lactam	1	Polymyxin (potentiator) + β-lactam	Gram-negative bacteria	Spero/Everest Medicines	2018
Cefilavancin (TD-1792, RD-1792)	3	Glycopeptide-cephalosporin conjugate	*S. aureus*	R Pharm/Theravance	2018
Ramoplanin	2	Lipodepsipeptide	*C. difficile*	Nanotherapeutics	2018
RC-01 (T 1228)	1	LpxC, a deacetylase inhibitor	Gram-negative bacteria	Recida/FUJIFILM Toyama	2019
GT-1	1	Siderophore-cephalosporin	Gram-negative bacteria	Geom	2019
MK-3866	1	BLI	Gram-negative bacteria	Merck	2019
MEDI-3902 (gremubamab)	2	Anti-*P. aeruginosa* IgG monoclonal antibody	*S. aureus*	AstraZeneca (MedImmune)	2020
OPS-2071	2	Quinolone	*C. difficile*	Otsuka	2020
No recent information					
SQ-109	2/3	Ethambutol derivative	TB	Sequella	2017
BOS-228 (LYS-228)	2	Monobactam	CRE	Boston Pharmaceuticals	2018
BCM-0184	1	Not disclosed	*S. aureus*	Biocidium	2019

Underlined: New chemical class.

4. Preclinical antibacterial pipeline

To complement the analysis of the clinical antibacterial pipeline, since 2019 WHO also undertakes a regular update of the WHO preclinical pipeline database of antibacterial agents in preclinical development targeting the WHO priority pathogens, *M. tuberculosis* and *C. difficile*. All of the data collected is made available in an interactive database and downloadable on the WHO Global R&D Health Observatory. The interactive database includes preclinical drug candidates from lead optimization to CTA/IND-enabling studies covering traditional antibiotics, as well as biological agents and non-traditional approaches such as bacteriophages, and vaccines that are being developed world wide.

4.1 Individual entities developing preclinical projects

The 2020 database captures 292 antibacterial agents targeting the WHO priority pathogens, *M. tuberculosis* and *Clostridioides difficile* that were submitted via the WHO data call and/or information is available in the public domain. There are 162 commercial and non-commercial entities progressing the diverse antibacterial agents which have a wide geographical distribution (Fig. 2.). Most of the data collected was from the European Region (n=72, 44.4%), followed by the Region of the Americas (n=20, 12.3%), and the South-East Asia Region (n=6, 3.7%).

Most of the institutions are commercial entities (n=142, 87.6%), followed by academic institutions (n=17, 10.5%) and foundations (n=3, 1.8%) (Fig. 3.). In addition the preclinical pipeline is dominated by small and medium-size enterprises (n= 140, or 86.4% of developers who submitted data): 74 micro institutions (<10 employees), 40 small institutions (11-50 employees), 26 medium sized institutions (51-500 employees).

Fig. 2. Geographical distribution of the 162 developers

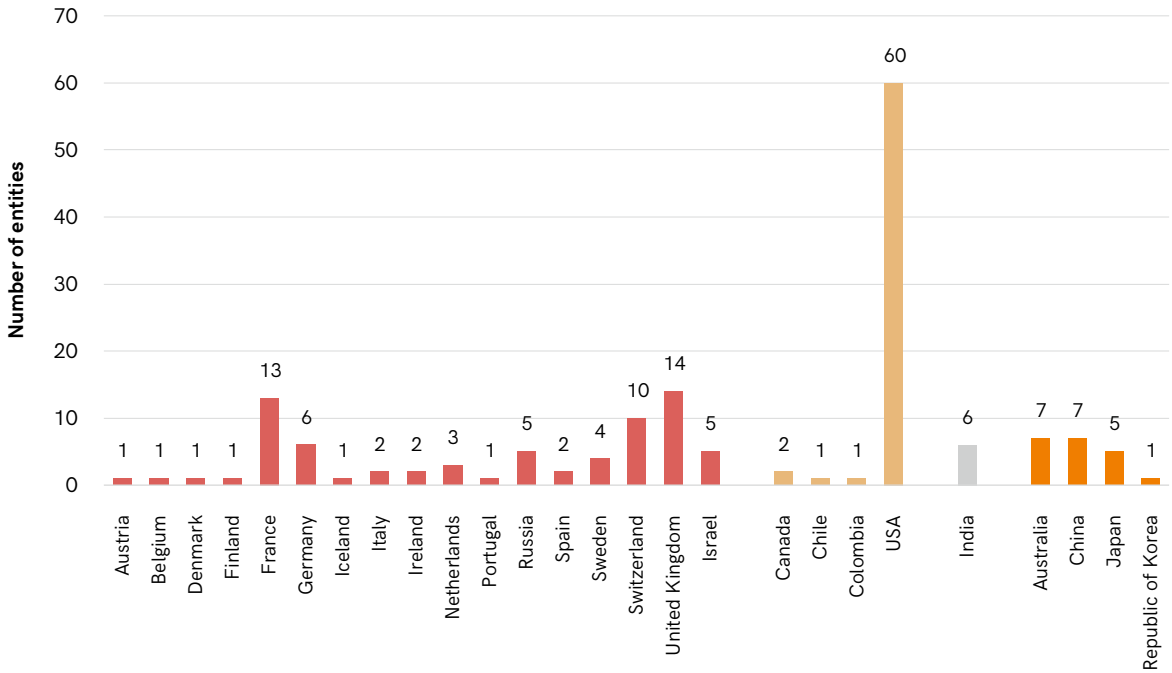


Fig.3. Categorization of entities that responded to the 2020 data call

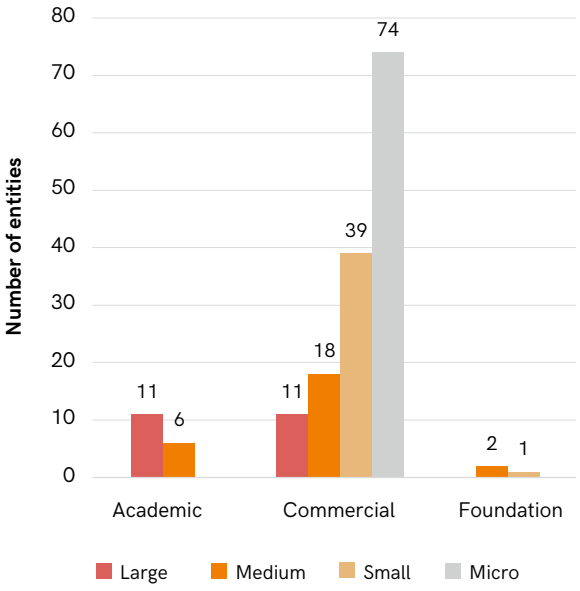
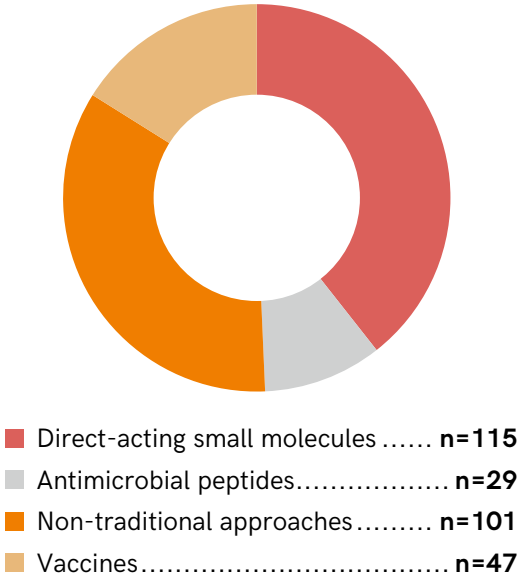


Fig. 4. Distribution of preclinical programmes by antibacterial agent and vaccine category



4.2 Categorization of preclinical agents

The pipeline contains a large range of different agents in preclinical development. There are 115 (39.4%) direct-acting small molecules, 101 (34.6%) non-traditional products including bacteriophages, virulence inhibitors, immunomodulatory compounds and potentiator agents, 47 (16.1%) vaccines and 29 (9.9%) adjuvant antimicrobial peptides (Fig. 4.).

Table 8 shows the 292 products categorized according to their antibacterial mode of action and preclinical development stage. Of the agents under development, 40 target cell wall synthesis, 62 act directly on the cell member, 56 act through immunomodulation, 28 target protein synthesis and 22 target virulence factors.

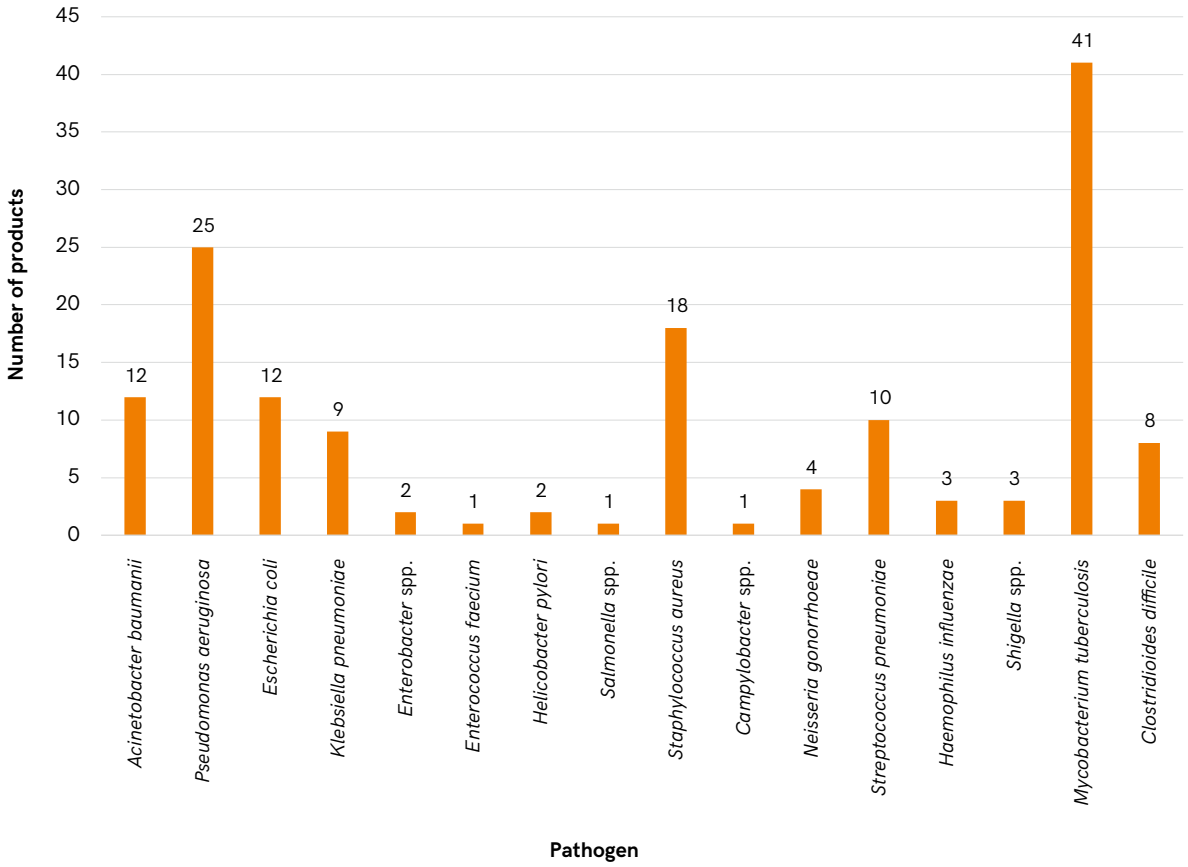
Table 8. Distribution of preclinical programmes by mode of action and development stages

Mode of action	Total (%)	Development stage		
		LO	PCC	CTA/IND
Cell wall synthesis	40 (13.7)	9	22	9
Cell membrane	62 (21.1)	17	40	5
DNA replication	16 (5.5)	10	6	0
Protein synthesis	28 (9.6)	14	9	5
RNA synthesis	5 (1.7)	3	1	1
Cell metabolism	6 (2.1)	1	4	1
Immunomodulation	56 (19.2)	18	34	4
Anti-virulence	22 (7.5)	13	5	4
Other	26 (8.9)	12	12	2
Not disclosed	31 (10.6)	18	10	3
Total	292 (100)	115	143	34

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

The 2017 WHO priority pathogen list identified pathogens that cause antibiotic-resistant infections for which there is an urgent global need for new antibacterial treatments. Review of the preclinical pipeline projects identified that a significant number of products (n=152, 52.1%) that are focused on a single pathogen species (Fig. 5.). A total of 60 products target the WHO critical Gram-negative priority pathogens, and a further 41 target *M. tuberculosis*.

Fig. 5. Pathogens targeted by a single pathogen target product



5. Discussion

5.1 New agents mainly derivatives of existing classes

Of the 11 new antibiotics that have been approved since 2017, including three new approvals since 2019, only two – vaborbactam + meropenem and lefamulin – represent a new class. One antibiotic, pretomanid, was approved as part of a three-drug combination, all-oral regimen for the treatment of adult patients with XDR-TB and treatment-intolerant or non-responsive MDR pulmonary TB. The other newly approved antibiotics are derivatives of known classes with limited added clinical benefit over existing treatments and where multiple resistance mechanisms already exist. Thus, the possibility of the emergence of resistance to these newly approved agents is likely.

One antibiotic, cefiderocol, has broad-spectrum activity against the three critical priority pathogens (CRE, CRAB and CRPA), is intrinsically more stable against β-lactamases and is expected to show activity against Class A, B and D β-lactamases. Cefiderocol is also the first antibacterial agent that uses the bacteria's iron uptake to help facilitate cell entry and received a "?" for the innovation criterion of absence of known cross-resistance.

In 2019 vaborbactam + meropenem and plazomicin were added to the *WHO Model List of Essential Medicines* as essential antibiotics. Delafloxacin was classified as a "watch" antibiotic in the WHO AWaRe classification, whereas vaborbactam + meropenem along with eravacycline, omadacycline and plazomicin were classified as "reserve" antibiotics (to be used as last-resort antibiotics and a key target in antimicrobial stewardship activities). The three new antibiotics that have come to market since 2019 will be classified by the WHO AWaRe classification in 2021.

Most of the new antibiotics have been approved for classic syndrome-based indications, for example treatment of cUTI, cIAI, CAP and/or ABSSSI. Further evidence is needed to evaluate the true effectiveness and added clinical value of these agents. Post-approval usage data will need to be made available to evaluate real-life pathogen-specific indications and the relevance of their usage 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 appear reluctant to use new antibiotic agents to treat infectious syndromes that were the initial target of regulatory approval (e.g. cUTI and cIAI).

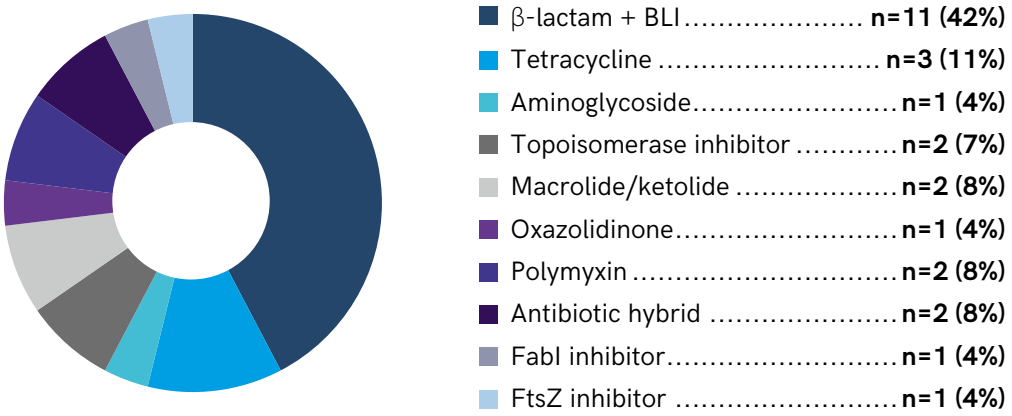
5.2 The clinical "traditional" pipeline is still insufficient against priority pathogens

Overall, there are currently 43 traditional antibacterials and combinations in the clinical pipeline (Phases 1–3) targeting the WHO priority pathogens, TB and *C. difficile:* 26 products targeting the WHO priority pathogens, 12 targeting TB and seven targeting *C. difficile* infections. Of the 26 antibiotics targeting the WHO priority pathogens, half target at least one of the critical Gram-negative bacteria. Two of these – zidebactam + lascufloxacin and SPR-206 (both are in Phase 1) – have activity against all three critical priority pathogens.

Most antibiotics that target the WHO priority pathogens are β-lactam/ BLI combinations (*n* = 11), followed by tetracyclines (*n* = 3) (Fig. 6).

However, antibacterial agents in clinical development unfortunately do not address the problem of extensively or pan-drug-resistant Gram-negative bacteria. Novel antibiotics targeting the 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 ESBLs and CRE that could allow treatment outside of a health-care facility or shorten the duration of treatment in the facility.

Fig. 6. Number of antibiotics in the clinical pipeline targeting WHO priority pathogens



5.3 Innovation remains a challenge for Gram-negatives

Only seven of the 26 antibiotics being developed for the treatment of priority pathogens meet at least one of the innovation criteria. These include two boronate BLIs (taniborbactam + cefepime and VNRX-7145 + ceftibuten), two topoisomerase inhibitors (zoliflodacin and gepotidacin), as well as a new FabI inhibitor (afabicin), an FtsZ inhibitor (TXA709) and a cationic peptide (PLG0206). The two novel bacterial topoisomerase II inhibitors are chemically distinct but are in the same functional class, and there is little information on potential cross-resistance, with only some cross-resistance reported for gepotidacin.

A major gap is in antibiotics that meet at least one of the WHO innovation criteria and target the critical Gram-negative bacteria. Only two – taniborbactam and VNRX-7145 – are active against CRE, for example. In general, however, 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.

The anti-TB clinical antibacterial pipeline is more innovative, with half of the antibacterials meeting at least one of the innovation criteria. Four of these agents have a new chemical structure and inhibit DprE1, which is important for cell wall synthesis. In addition, four innovative agents target *C. difficile* infections.

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 addressing new targets and using new modes of action *(117)*.

Finding novel chemical structures with new binding sites and new modes of action is, however, scientifically difficult, and success rates are lower than in drug discovery in other medical fields *(118)*. 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 the potential toxicity due to the high concentrations required to kill bacteria.

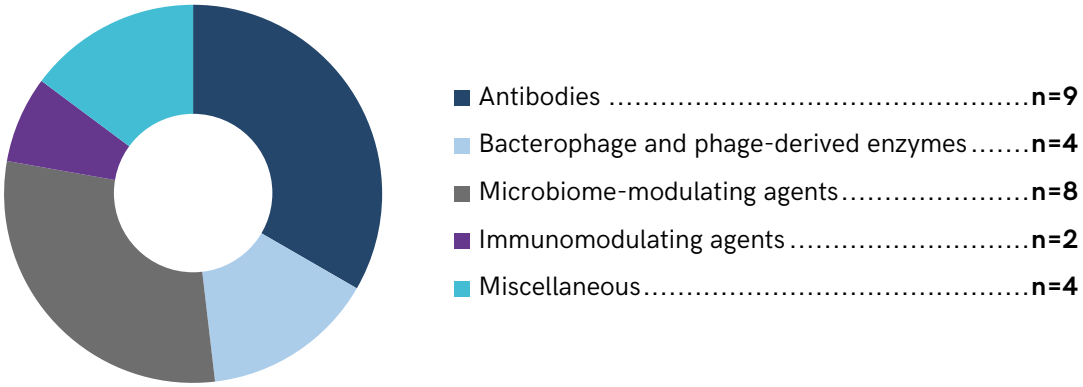
5.4 Diversity in non-traditional approaches

Non-traditional antibacterials may have the potential through their diverse and novel modes of action to reduce the selective pressure driving resistance to traditional antibacterial agents. There are 27 diverse non-traditional antibacterials included in this report, namely nine antibodies, four bacteriophages and phage-derived enzymes, eight microbiome-modulating agents, two immunomodulating agents as well as anti-virulence agents (Fig. 7.).

The majority of these non-traditional agents are in early clinical stages (eight in Phase 1 and 14 in Phase 2), and it is likely that many of these will face scientific and regulatory hurdles as/if they progress through the pipeline. In addition, over 90% (n = 25) of the non-traditionals are pathogen-specific strategies, a majority of which target *S. aureus* (n = 9) and *C. difficile* (n = 9). This

selectivity is a challenge that requires significant diagnostic certainty for optimal use, which is often not available outside of specialized health-care facilities and poses a challenge in low-resource settings *(86, 119)*

Fig. 7. Number of non-traditional antibacterials in the clinical pipeline.



There are four Phase 3 non-traditionals; an anti-*S. aureus* IgM monoclonal antibody, a phage endolysin, a peptide and a live biotherapeutic product. SER-109, the live biotherapeutic product which is a spore-based treatment to prevent the recurrence of CDI, has recently met its primary end-points in a Phase 3 trial and received breakthrough therapy and orphan drug designations from the US FDA *(120)*.

The potential public health impact and ability to counter antimicrobial resistance of these non-traditional approaches requires a more in-depth assessment. Many of them do not have stand-alone therapeutic utility and hence must be used as adjunctive treatment in combination with traditional antibiotics. The need for combination use both complicates development and obviates the potential for sparing use of traditional antibacterial agents *(121)*. An additional challenge is to demonstrate the added value of adjunctive treatments in clinical trials. In general, failure rates for these non-traditional products will be higher than for new derivatives of existing antibiotic classes.

5.5 A dynamic preclinical pipeline database

Overall there is a broad geographical distribution of preclinical pipeline projects as well as a large variety in the mode of action of the products. The main focus remains on the critical Gram-negative pathogens and is combined with a shift towards narrow-spectrum agents focusing on a single pathogen. Further development of these agents is likely to require the increased use of rapid diagnostics and evolution of clinical development strategies.

The WHO preclinical pipeline database is dynamic and innovative, including a wide range of drug development projects that are using different approaches to target the WHO bacterial priority pathogens list.

5.6 The pipeline outlook is slightly improved but remains unfavourable

Given the average progression rates and development duration, the current pipeline could lead to the approval of a further eight new antibiotics in the next 5 years *(122)*. The major gap in the treatment landscape will be the approval of new antibacterial drugs that treat carbapenem-resistant *A. baumannii* and/or *P. aeruginosa*.

Of the 10 antibiotics in Phase 1 that are possibly active or active against the critical Gram-negative bacteria, only one will likely make it to market in the next 10 years (using an attrition rate estimate of 14% for antibiotics for Phase 1 products). With the launch of the AMR Action Fund, which will primarily support antibacterials in Phase 2 and 3 trials, the number of products coming to market may increase. This is a slightly more favourable outlook than was reported in 2019.

6. Methods

The evaluation of the antibacterial clinical development pipeline was conducted through consensus agreement by an advisory group comprising clinicians, microbiologists and experts in antibiotic R&D, PK/PD and antimicrobial resistance (see Acknowledgements). The experts reviewed the quality criteria and assessed each agent against those criteria during a 2-day virtual advisory group meeting (23–24 November 2020). The group was assisted by members of the WHO Secretariat. 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 antibiotics and this report were 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 *(123)*:

- **Traditional antibacterials** are small molecules that directly inhibit the growth or kill bacteria 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.

The traditional and non-traditional agents are further classified by structure and development goal (Table 9).

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); or
- new formulations of existing treatments.

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

The analysis only includes agents that are in active development 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 2015 were

Table 9. Structure and development goals of traditional and non-traditional antibacterials

	Traditional	Non-traditional
Structure	Small molecules	Antibodies, bacteriophages, lysins, live biotherapeutics, oligonucleotides, etc.*
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

Source: Adapted from Rex JH, Lynch HF, Cohen IG, Darrow JJ, Outterson K. Designing development programs for non-traditional antibacterial agents. Nat Commun. 2019;10:3416. doi:10.1038/s41467-019-11303-9.
*Antimicrobial peptides are included among non-traditionals in this report.

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) (124). They are also encouraged to share their RCT methodologies and results.

6.1.2 Search strategy

This 2020 clinical pipeline update is based on the 2017 publication of *Antibacterial Agents in Clinical Development* and the subsequent update in 2018 and 2019 (125, 126). Information on agents in development was sought from a variety of sources. The cut-off point was 1 September 2020, 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 was collected through desktop research as well as from relevant stakeholders, including different associations of pharmaceutical companies active in the area, global and regional public and private funders, and foundations (see Acknowledgements).

Sources were consulted as follows:

- Journal articles (review articles published since 1 September 2019 through 1 September 2020; search terms: "antibacterial pipeline" OR "antibiotic pipeline") on the clinical antibacterial pipeline were retrieved from PubMed and conference abstracts and posters. For Phase 1 agents where limited data was available, information from company websites was used and evaluated by the advisory group for credibility for inclusion.
- The list of antibiotics in clinical development of the Pew Charitable Trusts and the Access to Medicines Foundation's Antimicrobial Resistance Benchmark were consulted.
- The ICTRP and ClinicalTrials.gov were searched.
- In collaboration with the EMA, the commercial database AdisInsight was searched.
- The 2019 pipeline data was sent to various stakeholders, including alliances for pharmaceutical companies and small and medium-sized enterprises, as well as global public and private R&D funding bodies for submission of updates with supporting documentation.
- A targeted desktop search of products was carried out with national experts from Japan and the Russian Federation.
- 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 and 2019 WHO reports *(126, 127)*.

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.

6.1.3.1 Expected activity against priority pathogens

Both in vitro and in vivo (when available) data was reviewed for activity against WHO priority pathogens. In assessing activity, the advisory group made judgements about whether the agent was potentially clinically active against the selected bacteria based on published MICs and their pharmacokinetics. When available, data on PK/PD, as well as information on non-clinical or clinical efficacy, was considered in the assessment. Drugs that have shown activity in vitro but are currently not being developed for relevant indications were not assessed against the respective pathogens.

The advisory group classified agents for which there was inconclusive data as "possibly active", represented by a question mark. For agents for which there was little or no data on their activity against specific pathogens, the advisory group classified the agents as "possibly active" if drugs of the same class are known to be active against the respective pathogen *(128)*.

6.1.3.2 Innovation

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

Surrogate predictors for the absence of cross-resistance which were also assessed include the following *(129)*:

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

All four innovation criteria were separately assessed for each agent.

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 better safety profile than the standard of care, a less invasive route, or better clinical outcomes or increased activity against priority pathogens could provide improvements but need to be proven in clinical trials. These developmental products are not reviewed in this report.

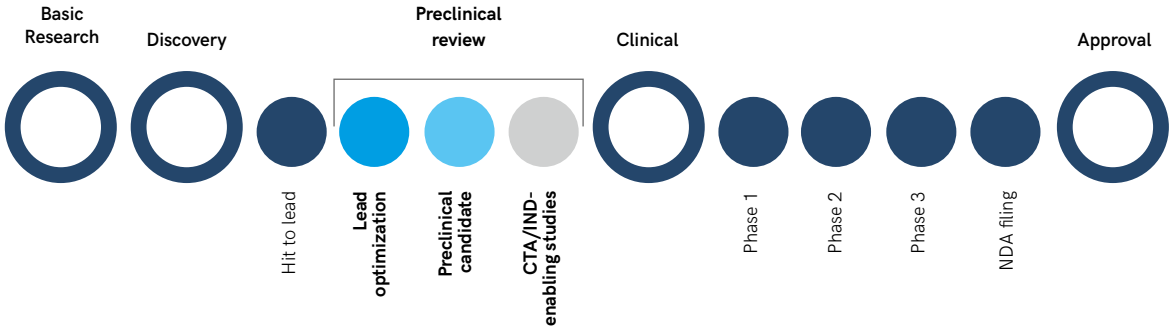
6.2 Preclinical pipeline review

6.2.1 Scope and inclusion/exclusion criteria

The review focuses on antibacterial agents that target the WHO priority pathogens (Box 1), *M. tuberculosis* and *C. difficile*. The scope of this preclinical pipeline review (Fig. 8.) is products that are in the lead optimization phase of discovery or the preclinical candidate phase, or that are ready for a formal CTA/IND. For regulatory authorities that do not use CTA/IND, this stage indicates the commencement of human testing.

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

Fig. 8. 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.

6.2.2 Data collection

A WHO online call held from 1 April to 1 August 2020 generated the primary data. In addition, a targeted search of products in preclinical development was undertaken in Japan and Russia through contractual partners who were experts in the field and conducted a desktop review in the respective languages. This data was supplemented with information from the Beam Alliance, CARB-X, REPAIR Impact Fund, GARDP, Global AMR R&D Hub, Wellcome Trust, Pew Charitable Trusts and the TB Alliance. In addition, programs that were included in the 2019 report were included if the program information was still presented on the organization's website. Data presented is self-declared from the institutions. Where possible, WHO corroborated the data through a scoping study of publications, conference abstracts or posters, institutional websites and other information in the public domain.

6.3 Methodological considerations

6.3.1 Variable data quality

The aim of this report is to provide a complete, accurate picture of 2020 clinical 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 and quality of the 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. We considered such products only when the information about them was publicly available.

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

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

Assessments of innovations were also subject to certain limitations. Lack of known cross-resistance is the most relevant criterion of innovation in the context of antibiotic resistance. A new chemical scaffold, a new target/binding site and a new mode of action are "surrogate markers" and good predictors of lack of cross-resistance. For these reasons, the four aspects were assessed separately. There is, however, no clear definition of "surrogate markers", and a "?" in some instances indicates that the experts could not agree whether a criterion had been fulfilled. For some compounds, lack of information (e.g. structure not published) made 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 categorization of a compound.

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 advisory group, which may raise the potential for selection bias. These limitations were addressed through 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 will be reviewed and adjusted on a regular basis.

The review of the preclinical pipeline relies largely on data submitted by the respective developers through the open WHO data call. A thorough data

cleaning was undertaken and where available other sources were used to identify 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 and database should be considered a snapshot and not an analysis.

All individuals and/or companies are encouraged to register clinical trials in line with the *WHO International Standards for Clinical Trial Registries* and through the ICTRP. The WHO Secretariat welcomes any additional information and/or feedback on the data presented in this document, which should be sent to antibacterialpipeline@who.int for incorporation in subsequent publications.

7. References

1. Branch SK, Agranat I. "New drug" designations for new therapeutic entities: new active substance, new chemical entity, new biological entity, new molecular entity. J Med Chem. 2014;57(21):8729–65.

2. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2020. Geneva: World Health Organization; 2020.

3. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K et al. Access to effective antimicrobials: a worldwide challenge. Lancet. 2016;387(10014):168–75.

4. The 2019 WHO AWaRe classification of antibiotics for evaluation and monitoring of use. Geneva: World Health Organization; 2019.

5. Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy. 2020.

6. Spero Therapeutics, Inc. Form 10-K. Washington (DC): United States Securities and Exchange Commission; 2019 (https://www.sec.gov/Archives/edgar/data/1701108/000156459020010998/spro-10k_20191231.htm, accessed 23 January 2021).

7. Bush K, Bradford PA. β-Lactams and β-lactamase inhibitors: an overview. Cold Spring Harb Perspect Med. 2016;6(8):a025247.

8. Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci. 1980;289(1036):321–31.

9. Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. Int J Antimicrob Agents. 2015;45(6):568–85.

10. Papp-Wallace KM, Bonomo RA. New β-lactamase inhibitors in the clinic. Infect Dis Clin North Am. 2016;30(2):441–64.

11. Bush K. Game changers: new β-lactamase inhibitor combinations targeting antibiotic resistance in Gram-negative bacteria. ACS Infect Dis. 2018;4(2):84–7.

12. Nowak P, Paluchowska P. *Acinetobacter baumannii*: biology and drug resistance – role of carbapenemases. Folia Histochem Cytobiol. 2016;54(2):61–74.

13. Pulzova L, Navratilova L, Comor L. Alterations in outer membrane permeability favor drug-resistant phenotype of Klebsiella pneumoniae. Microb Drug Resist. 2017;23(4):413–20.

14. Moradali MF, Ghods S, Rehm BH. Lifestyle: a paradigm for adaptation, survival, and persistence. Front Cell Infect Microbiol. 2017;7:39.

15. Hamilton-Miller JM. Chemical and microbiologic aspects of penems, a distinct class of beta-lactams: focus on faropenem. Pharmacotherapy. 2003;23(11):1497–507.

16. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD et al. Targeting multidrug-resistant acinetobacter spp.: sulbactam and the diazabicyclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio. 2019;10(2):e00159-19.

17. McLeod SM, Moussa SH, Hackel MA, Miller AA. In vitro activity of sulbactam-durlobactam against *Acinetobacter baumannii*-calcoaceticus complex isolates collected globally in 2016 and 2017. Antimicrob Agents Chemother. 2020;64(4):e02534-19.

18. Liu B, Trout REL, Chu GH, McGarry D, Jackson RW, Hamrick JC et al. Discovery of taniborbactam (VNRX-5133): a broad-spectrum serine- and metallo-β-lactamase inhibitor for carbapenem-resistant bacterial infections. J Med Chem. 2020;63(6):2789–801.

19. Hamrick JC, Docquier JD, Uehara T, Myers CL, Six DA, Chatwin CL et al. VNRX-5133 (taniborbactam), a broad-spectrum inhibitor of serine- and metallo-β-lactamases, restores activity of cefepime in Enterobacterales and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2020;64(3):e01963-19.

20. Moya B, Barcelo IM, Bhagwat S, Patel M, Bou G, Papp-Wallace KM et al. WCK 5107 (zidebactam) and WCK 5153 are novel inhibitors of PBP2 showing potent "β-lactam enhancer" activity against *Pseudomonas aeruginosa*, including multidrug-resistant metallo-β-lactamase-producing high-risk clones. Antimicrob Agents Chemother. 2017;61(6):e02529-16.

21. Karlowsky JA, Hackel MA, Bouchillon SK, Sahm DF. In vitro activity of WCK 5222 (cefepime-zidebactam) against worldwide collected Gram-negative bacilli not susceptible to carbapenems. Antimicrob Agents Chemother. 2020;64(12):e01432-20.

22. Bhagwat SS, Hariharan P, Joshi PR, Palwe SR, Shrivastava R, Patel MV et al. Activity of cefepime/zidebactam against MDR *Escherichia coli* isolates harbouring a novel mechanism of resistance based on four-amino-acid inserts in PBP3. J Antimicrob Chemother. 2020;75(12):3563–7.

23. Livermore DM, Mushtaq S, Warner M, Vickers A, Woodford N. In vitro activity of cefepime/zidebactam (WCK 5222) against Gram-negative bacteria. J Antimicrob Chemother. 2017;72(5):1373–85.

24. Sader HS, Rhomberg PR, Flamm RK, Jones RN, Castanheira M. WCK 5222 (cefepime/zidebactam) antimicrobial activity tested against Gram-negative organisms producing clinically relevant β-lactamases. J Antimicrob Chemother. 2017;72(6):1696–703.

25. Morinaka A, Tsutsumi Y, Yamada M, Suzuki K, Watanabe T, Abe T et al. OP0595, a new diazabicyclooctane: mode

of action as a serine β-lactamase inhibitor, antibiotic and β-lactam "enhancer". J Antimicrob Chemother. 2015;70(10):2779–86.

26. Doumith M, Mushtaq S, Livermore DM, Woodford N. New insights into the regulatory pathways associated with the activation of the stringent response in bacterial resistance to the PBP2-targeted antibiotics, mecillinam and OP0595/RG6080. J Antimicrob Chemother. 2016;71(10):2810–4.

27. Mushtaq S, Vickers A, Woodford N, Haldimann A, Livermore DM. Activity of nacubactam (RG6080/OP0595) combinations against MBL-producing Enterobacteriaceae. J Antimicrob Chemother. 2019;74(4):953–60.

28. Okujava R, Garcia-Alcalde F, Haldimann A, Zampaloni C, Morrissey I, Magnet S et al. 1359. Activity of meropenem/nacubactam combination against Gram-negative clinical isolates: ROSCO Global Surveillance 2017. Open Forum Infect Dis. 2018;5(Suppl 1):S416.

29. Hecker SJ, Reddy KR, Lomovskaya O, Griffith DC, Rubio-Aparicio D, Nelson K et al. Discovery of cyclic boronic acid QPX7728, an ultrabroad-spectrum inhibitor of serine and metallo-β-lactamases. J Med Chem. 2020;63(14):7491–507.

30. Nelson K, Rubio-Aparicio D, Sun D, Dudley M, Lomovskaya O. In vitro activity of the ultrabroad-spectrum-beta-lactamase inhibitor QPX7728 against carbapenem-resistant. Antimicrob Agents Chemother. 2020;64(8):e00757-20.

31. Grossman TH. Tetracycline antibiotics and resistance. Cold Spring Harb Perspect Med. 2016;6(4):a025387.

32. Lye SC. From molds to molecules: the development of tetracycline antibiotics and the transformation of the pharmaceutical industry, 1943–1963 [thesis]. Cambridge (MA): Harvard University; 1998.

33. Huband MD, Mendes RE, Pfaller MA, Lindley JM, Strand GJ, Benn VJ et al. In vitro activity of KBP-7072, a novel third-generation tetracycline, against 531 recent geographically diverse and molecularly characterized *Acinetobacter baumannii* species complex isolates. Antimicrob Agents Chemother. 2020;64(5):e02375-19.

34. Zhang B, Wang Y, Chen Y, Yang F. Single ascending dose safety, tolerability, and pharmacokinetics of KBP-7072, a novel third generation tetracycline. Open Forum Infect Dis. 2016;3(1):1996.

35. Grossman TH, Fyfe C, O'Brien W, Hackel M, Minyard MB, Waites KB et al. Fluorocycline TP-271 is potent against complicated community-acquired bacterial pneumonia pathogens. mSphere. 2017;2(1):e00004-17.

36. Seifert H, Stefanik D, Olesky M, Higgins PG. In vitro activity of the novel fluorocycline TP-6076 against carbapenem-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents. 2020;55(1):105829.

37. Falagas ME, Skalidis T, Vardakas KZ, Voulgaris GL, Papanikolaou G, Legakis N et al. Activity of TP-6076 against carbapenem-resistant *Acinetobacter baumannii* isolates collected from inpatients in Greek hospitals. Int J Antimicrob Agents. 2018;52(2):269-71.

38. Wangkheimayum J, Paul D, Dhar D, Nepram R, Chetri S, Bhowmik D et al. Occurrence of acquired 16S rRNA methyltransferase-mediated aminoglycoside resistance in clinical isolates of Enterobacteriaceae within a tertiary referral hospital of northeast India. Antimicrob Agents Chemother. 2017;61(6):e01037-16.

39. Wray C, Hedges RW, Shannon KP, Bradley DE. Apramycin and gentamicin resistance in *Escherichia coli* and salmonellas isolated from farm animals. J Hyg (Lond). 1986;97(3):445–56.

40. Juhas M, Widlake E, Teo J, Huseby DL, Tyrrell JM, Polikanov YS et al. In vitro activity of apramycin against multidrug-, carbapenem- and aminoglycoside-resistant Enterobacteriaceae and *Acinetobacter baumannii*. J Antimicrob Chemother. 2019;74(4):944–52.

41. Fàbrega A, Madurga S, Giralt E, Vila J. Mechanism of action of and resistance to quinolones. Microb Biotechnol. 2009;2(1):40–61.

42. Bax BD, Chan PF, Eggleston DS, Fosberry A, Gentry DR, Gorrec F et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. Nature. 2010;466(7309):935–40.

43. Lahiri SD, Kutschke A, McCormack K, Alm RA. Insights into the mechanism of inhibition of novel bacterial topoisomerase inhibitors from characterization of resistant mutants of *Staphylococcus aureus*. Antimicrob Agents Chemother. 2015;59(9):5278–87.

44. Bradford PA, Miller AA, O'Donnell J, Mueller JP. Zoliflodacin: an oral spiropyrimidinetrione antibiotic for the treatment of *Neisseria gonorrheae*, including multi-drug-resistant isolates. ACS Infect Dis. 2020;6(6):1332–45.

45. Unemo M, Ringlander J, Wiggins C, Fredlund H, Jacobsson S, Cole M. High in vitro susceptibility to the novel spiropyrimidinetrione ETX0914 (AZD0914) among 873 contemporary clinical *Neisseria gonorrhoeae* isolates from 21 European countries from 2012 to 2014. Antimicrob Agents Chemother. 2015;59(9):5220–5.

46. Alm RA, Lahiri SD, Kutschke A, Otterson LG, McLaughlin RE, Whiteaker JD et al. Characterization of the novel DNA gyrase inhibitor AZD0914: low resistance potential and lack of cross-resistance in *Neisseria gonorrhoeae*. Antimicrob Agents Chemother. 2015;59(3):1478–86.

47. Taylor SN, Morris DH, Avery AK, Workowski KA, Batteiger BE, Tiffany CA et al. Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a Phase 2, randomized, dose-ranging, single-oral dose evaluation. Clin Infect Dis. 2018;67(4):504–12.

48. Payne DJ, Miller WH, Berry V, Brosky J, Burgess WJ, Chen E et al. Discovery of a novel and potent class of FabI-directed antibacterial agents. Antimicrob Agents Chemother. 2002;46(10):3118–24.

49. Yao J, Maxwell JB, Rock CO. Resistance to AFN-1252 arises from missense mutations in *Staphylococcus aureus* enoyl-acyl carrier protein reductase (FabI). J Biol Chem. 2013;288(51):36261–71.

50. Yao J, Rock CO. Resistance mechanisms and the future of bacterial enoyl-acyl carrier protein reductase

(FabI) antibiotics. Cold Spring Harb Perspect Med. 2016;6(3):a027045.

51. Parsons JB, Frank MW, Subramanian C, Saenkham P, Rock CO. Metabolic basis for the differential susceptibility of Gram-positive pathogens to fatty acid synthesis inhibitors. Proc Natl Acad Sci U S A. 2011;108(37):15378–83.

52. Wittke F, Vincent C, Chen J, Heller B, Kabler H, Overcash JS et al. Afabicin, a first-in-class antistaphylococcal antibiotic, in the treatment of acute bacterial skin and skin structure infections: clinical noninferiority to vancomycin/linezolid. Antimicrob Agents Chemother. 2020;64(10):e00250-20.

53. Kaplan N, Albert M, Awrey D, Bardouniotis E, Berman J, Clarke T et al. Mode of action, in vitro activity, and in vivo efficacy of AFN-1252, a selective antistaphylococcal FabI inhibitor. Antimicrob Agents Chemother. 2012;56(11):5865–74.

54. Flamm RK, Rhomberg PR, Kaplan N, Jones RN, Farrell DJ. Activity of Debio1452, a FabI inhibitor with potent activity against *Staphylococcus aureus* and coagulase-negative *Staphylococcus* spp., including multidrug-resistant strains. Antimicrob Agents Chemother. 2015;59(5):2583–7.

55. Tsuji BT, Harigaya Y, Lesse AJ, Forrest A, Ngo D. Activity of AFN-1252, a novel FabI inhibitor, against *Staphylococcus aureus* in an in vitro pharmacodynamic model simulating human pharmacokinetics. J Chemother. 2013;25(1):32–5.

56. Araújo-Bazán L, Ruiz-Avila LB, Andreu D, Huecas S, Andreu JM. Cytological profile of antibacterial FtsZ Inhibitors and synthetic peptide MciZ. Front Microbiol. 2016;7:1558.

57. Kusuma KD, Payne M, Ung AT, Bottomley AL, Harry EJ. FtsZ as an antibacterial target: status and guidelines for progressing this avenue. ACS Infect Dis. 2019;5(8):1279–94.

58. Lepak AJ, Parhi A, Madison M, Marchillo K, VanHecker J, Andes DR. In vivo pharmacodynamic evaluation of an FtsZ inhibitor, TXA-709, and its active metabolite, TXA-707, in a murine neutropenic thigh infection model. Antimicrob Agents Chemother. 2015;59(10):6568–74.

59. Wilson DN, Schluenzen F, Harms JM, Starosta AL, Connell SR, Fucini P. The oxazolidinone antibiotics perturb the ribosomal peptidyl-transferase center and effect tRNA positioning. Proc Natl Acad Sci U S A. 2008;105(36):13339–44.

60. Wu J, Wu H, Wang Y, Chen Y, Guo B, Cao G et al. Tolerability and pharmacokinetics of contezolid at therapeutic and supratherapeutic doses in healthy Chinese subjects, and assessment of contezolid dosing regimens based on pharmacokinetic/pharmacodynamic analysis. Clin Ther. 2019;41(6):1164–74.e4.

61. Kannan K, Kanabar P, Schryer D, Florin T, Oh E, Bahroos N et al. The general mode of translation inhibition by macrolide antibiotics. Proc Natl Acad Sci U S A. 2014;111(45):15958–63.

62. Dinos GP. The macrolide antibiotic renaissance. Br J Pharmacol. 2017;174(18):2967–83.

63. Zhanel GG, Walters M, Noreddin A, Vercaigne LM, Wierzbowski A, Embil JM et al. The ketolides: a critical review. Drugs. 2002;62(12):1771–804.

64. Fernandes P, Martens E, Bertrand D, Pereira D. The solithromycin journey – it is all in the chemistry. Bioorg Med Chem. 2016;24(24):6420–8.

65. McGhee P, Clark C, Kosowska-Shick KM, Nagai K, Dewasse B, Beachel L et al. In vitro activity of CEM-101 against *Streptococcus pneumoniae* and *Streptococcus pyogenes* with defined macrolide resistance mechanisms. Antimicrob Agents Chemother. 2010;54(1):230–8.

66. Flamm RK, Rhomberg PR, Sader HS. In vitro activity of the novel lactone ketolide nafithromycin (WCK 4873) against contemporary clinical bacteria from a global surveillance program. Antimicrob Agents Chemother. 2017;61(12):e01230-17.

67. Ma Z, Lynch AS. Development of a dual-acting antibacterial agent (TNP-2092) for the treatment of persistent bacterial infections. J Med Chem. 2016;59(14):6645–57.

68. Robertson GT, Bonventre EJ, Doyle TB, Du Q, Duncan L, Morris TW et al. In vitro evaluation of CBR-2092, a novel rifamycin-quinolone hybrid antibiotic: studies of the mode of action in *Staphylococcus aureus*. Antimicrob Agents Chemother. 2008;52(7):2313–23.

69. TenNor Therapeutics. R&D pipeline [website] (http://www.tennorx.com/en/, accessed 28 January 2021).

70. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care. 2006;10(1):R27.

71. Brown P, Abbott E, Abdulle O, Boakes S, Coleman S, Divall N et al. Design of next generation polymyxins with lower toxicity: the discovery of SPR206. ACS Infect Dis. 2019;5(10):1645–56.

72. Global tuberculosis report 2020. Geneva: World Health Organization; 2020.

73. Sarathy JP, Ragunathan P, Cooper CB, Upton AM, Grüber G, Dick T. TBAJ-876 displays bedaquiline-like mycobactericidal potency without retaining the parental drug's uncoupler activity. Antimicrob Agents Chemother. 2020;64(2):e01540-19.

74. Tsutsumi LS, Owusu YB, Hurdle JG, Sun D. Progress in the discovery of treatments for *C. difficile* infection: a clinical and medicinal chemistry review. Curr Top Med Chem. 2014;14(1):152–75.

75. Mann J, Taylor PW, Dorgan CR, Johnson PD, Wilson FX, Vickers R et al. The discovery of a novel antibiotic for the treatment of *Clostridium difficile* infections: a story of an effective academic-industrial partnership. Medchemcomm. 2015;6(8):1420–6.

76. Cho JC, Crotty MP, Pardo J. Ridinilazole: a novel antimicrobial for *Clostridium difficile* infection. Ann Gastroenterol. 2019;32(2):134–40.

77. Vickers RJ, Tillotson GS, Nathan R, Hazan S, Pullman J, Lucasti C et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of *Clostridium difficile* infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Lancet Infect Dis. 2017;17(7):735–44.

78. Carlson TJ, Endres BT, Bassères E, Gonzales-Luna AJ, Garey KW. Ridinilazole for the treatment of *Clostridioides difficile* infection. Expert Opin Investig Drugs. 2019;28(4):303–10.

79. Bassères E, Endres BT, Khaleduzzaman M, Miraftabi F, Alam MJ, Vickers RJ et al. Impact on toxin production and cell morphology in *Clostridium difficile* by ridinilazole (SMT19969), a novel treatment for C. difficile infection. J Antimicrob Chemother. 2016;71(5):1245–51.

80. Dalhoff A, Rashid MU, Kapsner T, Panagiotidis G, Weintraub A, Nord CE. Analysis of effects of MCB3681, the antibacterially active substance of prodrug MCB3837, on human resident microflora as proof of principle. Clin Microbiol Infect. 2015;21(8):767.e1-4.

81. Freeman J, Pilling S, Vernon J, Wilcox MH. In vitro activities of MCB3681 and eight comparators against *Clostridium difficile* isolates with known ribotypes and diverse geographical spread. Antimicrob Agents Chemother. 2017;61(3):e02077-16.

82. Khalaf AI, Waigh RD, Drummond AJ, Pringle B, McGroarty I, Skellern GG et al. Distamycin analogues with enhanced lipophilicity: synthesis and antimicrobial activity. J Med Chem. 2004;47(8):2133–56.

83. Nieminen L, Lemonidis K, Browning D, Hunter I, Suckling C, Tucker N. Transcriptomic analysis indicates the mode of action of the novel antibiotic MGB-BP-3 against *Staphylococcus aureus*. Access Microbiol. 2019;1(1A).

84. Green LS, Bullard JM, Ribble W, Dean F, Ayers DF, Ochsner UA et al. Inhibition of methionyl-tRNA synthetase by REP8839 and effects of resistance mutations on enzyme activity. Antimicrob Agents Chemother. 2009;53(1):86–94.

85. Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA et al. Alternatives to antibiotics – a pipeline portfolio review. Lancet Infect Dis. 2016;16(2):239–51.

86. Theuretzbacher U, Piddock LJV. Non-traditional antibacterial therapeutic options and challenges. Cell Host Microbe. 2019;26(1):61–72.

87. Motley MP, Banerjee K, Fries BC. Monoclonal antibody-based therapies for bacterial infections. Curr Opin Infect Dis. 2019;32(3):210–6.

88. François B, Mercier E, Gonzalez C, Asehnoune K, Nseir S, Fiancette M et al. Safety and tolerability of a single administration of AR-301, a human monoclonal antibody, in ICU patients with severe pneumonia caused by *Staphylococcus aureus*: first-in-human trial. Intensive Care Med. 2018;44(11):1787–96.

89. Que YA, Lazar H, Wolff M, François B, Laterre PF, Mercier E et al. Assessment of panobacumab as adjunctive immunotherapy for the treatment of nosocomial *Pseudomonas aeruginosa* pneumonia. Eur J Clin Microbiol Infect Dis. 2014;33(10):1861–7.

90. Welte T, Dellinger RP, Ebelt H, Ferrer M, Opal SM, Singer M et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). Intensive Care Med. 2018;44(4):438–48.

91. Tkaczyk C, Semenova E, Shi YY, Rosenthal K, Oganesyan V, Warrener P et al. Alanine scanning mutagenesis of the MEDI4893 (suvratoxumab) epitope reduces alpha toxin lytic activity. Antimicrob Agents Chemother. 2018;62(11):e01033-18.

92. Yu XQ, Robbie GJ, Wu Y, Esser MT, Jensen K, Schwartz HI et al. Safety, tolerability, and pharmacokinetics of MEDI4893, an investigational, extended-half-life, anti-staphylococcus aureus alpha-toxin human monoclonal antibody, in healthy adults. Antimicrob Agents Chemother. 2017;61(1):e01020-16.

93. Varshney AK, Kuzmicheva GA, Lin J, Sunley KM, Bowling RA, Kwan TY et al. A natural human monoclonal antibody targeting *Staphylococcus* Protein A protects against Staphylococcus aureus bacteremia. PLoS One. 2018;13(1):e0190537.

94. Maiti PK. Polyclonal antibodies against *Clostridium difficile* and uses thereof. US Patent 9873732B2; 2018 (https://patents.google.com/patent/US9873732B2/en, accessed 23 January 2021).

95. Loos A, Weich N, Woo J, Lalonde G, Yee L, Dummer W et al. 674. Pre-clinical and Phase I safety data for Anti-*Pseudomonas aeruginosa* human monoclonal antibody AR-105. Open Forum Infect Dis. 2019;6:S307–S8.

96. Zhou C, Cai H, Baruch A, Lewin-Koh N, Yang M, Guo F et al. Sustained activity of novel THIOMAB antibody-antibiotic conjugate against *Staphylococcus aureus* in a mouse model: longitudinal pharmacodynamic assessment by bioluminescence imaging. PLoS One. 2019;14(10):e0224096.

97. Summers WC. The strange history of phage therapy. Bacteriophage. 2012;2(2):130–3.

98. Gilmer DB, Schmitz JE, Euler CW, Fischetti VA. Novel bacteriophage lysin with broad lytic activity protects against mixed infection by *Streptococcus pyogenes* and methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2013;57(6):2743–50.

99. Schuch R, Khan BK, Raz A, Rotolo JA, Wittekind M. Bacteriophage lysin CF-301, a potent antistaphylococcal biofilm agent. Antimicrob Agents Chemother. 2017;61(7):e02666-16.

100. Jun SY, Jung GM, Yoon SJ, Choi YJ, Koh WS, Moon KS et al. Preclinical safety evaluation of intravenously administered SAL200 containing the recombinant phage endolysin SAL-1 as a pharmaceutical ingredient. Antimicrob Agents Chemother. 2014;58(4):2084–8.

101. Cryan JF, Dinan TG. Talking about a microbiome revolution. Nat Microbiol. 2019;4(4):552–3.

102. Smith LK, Wissel EF. Microbes and the mind: how bacteria shape affect, neurological processes, cognition, social relationships, development, and pathology. Perspect Psychol Sci. 2019;14(3):397–418.

103. McGovern BH, Ford CB, Henn MR, Pardi DS, Khanna S, Hohmann EL et al. SER-109, an investigational microbiome drug to reduce recurrence after *Clostridioides difficile* infection: lessons learned from a Phase 2 trial. Clin Infect Dis. 2020 Apr 7:ciaa387.

104. Kaleko M, Bristol JA, Hubert S, Parsley T, Widmer G, Tzipori S et al. Development of SYN-004, an oral beta-lactamase treatment to protect the gut microbiome from antibiotic-mediated damage and prevent Clostridium difficile infection. Anaerobe. 2016;41:58–67.

105. Kokai-Kun JF, Roberts T, Coughlin O, Le C, Whalen H, Stevenson R et al. Use of ribaxamase (SYN-004), a β-lactamase, to prevent *Clostridium difficile* infection in β-lactam-treated patients: a double-blind, phase 2b, randomised placebo-controlled trial. Lancet Infect Dis. 2019;19(5):487–96.

106. Guk J, Guedj J, Burdet C, Andremont A, de Gunzburg J, Ducher A et al. Modeling the effect of DAV132, a novel colon-targeted adsorbent, on fecal concentrations of moxifloxacin and gut microbiota diversity in healthy volunteers. Clin Pharmacol Ther. 2020. doi:10.1002/cpt.1977.

107. Chinna Meyyappan A. The safety, efficacy, and tolerability of microbial ecosystem therapeutic-2 in people with major depression and/or generalized anxiety disorder: protocol for a Phase 1, open-label study. JMIR Res Protoc. 2020;9(6):e17223.

108. Khanna S, Pardi DS, Jones C, Shannon WD, Gonzalez C, Blount K. RBX7455, a room temperature-stable, orally-administered investigational live biotherapeutic, is safe, effective, and shifts patients' microbiomes in a phase 1 study for recurrent *Clostridioides difficile* infections. Clin Infect Dis. 2020 Sep 23:ciaa1430.

109. Edgar RC, Cohen A, Hillman D, Kaempfer R, Shirvan A. Prolonged benefit of reltecimod despite short plasma half-life. Int J Pept Res Ther. 2020;26:2399–410.

110. Bulger EM, May AK, Robinson BRH, Evans DC, Henry S, Green JM et al. A novel immune modulator for patients with necrotizing soft tissue infections (NSTI): results of a multicenter, Phase 3 randomized controlled trial of reltecimod (AB 103). Ann Surg. 2020 Jul 8. doi:10.1097/SLA.0000000000004102.

111. DiNubile MJ, Levinson SL, Stossel TP, Lawrenz MB, Warawa JM. Recombinant human plasma gelsolin improves survival and attenuates lung injury in a murine model of multidrug-resistant *Pseudomonas aeruginosa* pneumonia. Open Forum Infect Dis. 2020;7(8):ofaa236.

112. Ermund A, Recktenwald CV, Skjåk-Braek G, Meiss LN, Onsøyen E, Rye PD et al. OligoG CF-5/20 normalizes cystic fibrosis mucus by chelating calcium. Clin Exp Pharmacol Physiol. 2017;44(6):639–47.

113. Azeredo da Silveira S, Shorr AF. Critical parameters for the development of novel therapies for severe and resistant infections – a case study on CAL02, a non-traditional broad-spectrum anti-virulence drug. Antibiotics (Basel). 2020;9(2):94.

114. Laterre PF, Colin G, Dequin PF, Dugernier T, Boulain T, Azeredo da Silveira S et al. CAL02, a novel antitoxin liposomal agent, in severe pneumococcal pneumonia: a first-in-human, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis. 2019;19(6):620–30.

115. Sheremet AB, Zigangirova NA, Zayakin ES, Luyksaar SI, Kapotina LN, Nesterenko LN et al. Small molecule inhibitor of type three secretion system belonging to a class 2,4-disubstituted-4H-[1,3,4]-thiadiazine-5-ones improves survival and decreases bacterial loads in an airway. Biomed Res Int. 2018;2018:5810767.

116. CARB-X funds GSK to develop a new drug for urinary tract infections (UTI) caused by *Escherichia coli* bacteria: CARB-X [website] Boston: Boston University; 2021 (https://carb-x.org/carb-x-news/carb-x-announces-funding-for-gsk-to-develop-a-new-drug-for-urinary-tract-infections-uti-caused-by-escherichia-coli-bacteria/, accessed 23 January 2021).

117. Theuretzbacher U. Antibiotic innovation for future public health needs. Clin Microbiol Infect. 2017;23(10):713–7.

118. Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat Rev Drug Discov. 2007;6(1):29–40.

119. Rex JH, Fernandez Lynch H, Cohen IG, Darrow JJ, Outterson K. Designing development programs for non-traditional antibacterial agents. Nat Commun. 2019;10(1):3416.

120. Garber K. First microbiome-based drug clears phase III, in clinical trial turnaround. Nat Rev Drug Discov. 2020;19(10):655–6.

121. Hansford KA. Nontraditional antibiotics – challenges and triumphs. Antibiotics (Basel). 2020;9(4):169.

122. A financial model for an impact investment fund

for the development of antibacterial treatments and diagnostics: a user guide. Geneva: World Health Organization; 2020.

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

124. International standards for clinical trial registries – Version 3.0. Geneva: World Health Organization; 2018.

125. Antibacterial agents in clinical development. Geneva: World Health Organization; 2018.

126. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019.

127. Antibacterial agents in clinical development. Geneva: World Health Organization; 2017.

128. Pulcini C, Bush K, Craig WA, Frimodt-Møller N, Grayson ML, Mouton JW et al. Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. Clin Infect Dis. 2012;54(2):268–74.

129. Theuretzbacher U, Gottwalt S, Beyer P, Butler M, Czaplewski L, Lienhardt C et al. Analysis of the clinical antibacterial and antituberculosis pipeline. Lancet Infect Dis. 2019;19(2):e40–e50.

Annex 1. Declaration of interests of advisory group members

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

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

Experts were also asked to disclose academic or scientific activities that included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about an antibacterial product. In addition, at the start of the meeting, all members were asked to update their declaration if any new conflicts had arisen in the meantime. The experts who declared no potential conflicts of interest were Richard Alm, Mark Butler, Lloyd Czaplewski, Stephan Harbarth, Christian Lienhardt and Mical Paul. These experts were allowed full participation in the meeting. In addition, François Franceschi, Jennie Hood and Mike Sharland participated as observers.

The experts who disclosed potentially significant conflicts of interest were Cesar Arias, Prabha Fernandes, Roman Kozlov, Norio Ohmagari, John Rex, Lynn Silver, Melvin Spigelman and Guy Thwaites. These participants were excluded from discussions involving products from commercial entities or other organizations listed below.

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 and Dohme AG and Entasis.

Prabha Fernandes is the chair of the Scientific Advisory Committee of GARDP. She disclosed that she received remuneration or has current investments or interests in the past 4 years from GARDP.

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 and Dohme AG.

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 had received support for research in the past 4 years from Merck Sharp and Dohme AG, Kyorin and Shionogi Inc.

John H. Rex is chief medical officer and director of F2G Ltd, chief strategy officer of CARB-X, non-executive director and consultant of Adenium Biotech ApS, operating partner and consultant of Advent Life Sciences and expert-in-residence at the Wellcome Trust. He disclosed in his DOI having provided consulting services in the past 4 years for Allecra Therapeutics GmbH, AstraZeneca, Peptilogics, Polyphor, Novo REPAIR fund and Shionogi Inc.

Lynn Silver is president of LL Silver Consulting LLC. In her DOI, she reported having provided consulting services in the past 4 years for Debiopharm, CARB-X, REPAIR Impact Fund and Taxis.

Melvin Spigelman is president and chief executive officer of TB Alliance. In his DOI he declared receiving remuneration from TB Alliance in the past 4 years.

Guy Thwaites is the director of OUCRU in Viet Nam. In his DOI he disclosed that he has provided consulting services in the past 4 years to GSK.

All the reported interests were disclosed to the meeting participants by the technical unit in a slide show presentation; they are also disclosed in this meeting report and will be disclosed 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, mode of action and target:** β-Lactam (cell wall inhibition).
- **Bacterial spectrum/coverage:** Activity against ESBL-producing cephalosporin-resistant Enterobacterales (but not carbapenem-resistant).
- **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 500 mg PO twice daily for 5 days. Adverse effects reported (SURE 1). Diarrhoea was the most reported adverse effect, affecting 12.4% (*n* = 103/883) of patients receiving the drug, of whom 7.2% (*n* = 60/883) had clinically significant diarrhoea with a median duration of 3 days. Other side effects reported include nausea (3.7%), headache (2.2%) and vomiting (2.2%).
  - 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, through a series of Phase 3 RCTs labelled sulopenem for resistant *Enterobacteriaceae* (SURE) 1 through 3 (NCT03354598, NCT03357614, NCT03358576).
- **Sulopenem SURE 1 Phase 3 study** (NCT03354598).
  - **Time period:** 1 August 2018 to 16 January 2020 (final data collection date).
  - **Study design:** A prospective, randomized, multicentre, double-blind study that compared the efficacy and safety of oral sulopenem-etzadroxil/probenecid to 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 www.clinicaltrials.gov Trial identifier no. 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 test-of-cure (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 microbiologic-modified intent-to-treat (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 12.4% of the patients (*n* = 103/883 in the sulopenem arm) receiving the drug, of whom 7.2% (*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 (3.7%, *n* = 31/883), headache (2.2%, *n* = 18/883) vomiting (2.2%, *n* = 18/883) and dizziness (1.1%, *n* = 9/883).
- **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 of 147 patients) in the sulopenem arm compared with 36% (*n* = 50 of 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 of 370 patients) in the sulopenem arm compared with 78.6% (*n* = 326 of 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 to 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, randomized, multicentre, double-blind, double-dummy, 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, randomized, multicentre, double-blind, non-inferiority study that compared the efficacy and safety of sulopenem followed by sulopenem-etzadroxil/probenecid to 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 patient diagnosed with intraabdominal GI organ perforation, undergoing surgery within 12 hours to 24 hours. Those with any intra-abdominal non-infectious primary pathology. In addition, excluded were patient with simple or complicated biliary infections, without rupture, or simple appendicitis; or infected necrotizing pancreatitis or pancreatic abscess. Patient 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 via www.clinicaltrials.gov Trial identifier no. 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, 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, in 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%.

References

1. Hamilton-Miller JM. Chemical and microbiologic aspects of penems, a distinct class of beta-lactams: focus on faropenem. Pharmacotherapy. 2003 Nov;23(11):1497-507. doi:10.1592/phco.23.14.1497.31937.

2. Dunne M, Dunzo E, Puttagunta S. A phase 1 study to assess the pharmacokinetics of sulopenem etzadroxil (PF-03709270). Open Forum Infect Dis. 2017;4(suppl_1): S525–S526.

3. Karlowsky JA, Adam HJ, Baxter MR, Denisuik AJ, Lagacé-Wiens PR, Walkty AJ et al. In vitro activity of sulopenem, an oral penem, against urinary isolates of Escherichia coli. Antimicrobial Agents Chemotherapy. 2019;63(1):e01832-18.

4. Dunne MW, Das AF, Zelasky M, Akinapelli K, Boucher MD, Aronin SI. Efficacy and safety of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin in the treatment of uncomplicated urinary tract infections (uUTI) in adult women: results from the SURE-1 trial [website]. Dublin: Iterum Therapeutics; 2020 (https://www.iterumtx.com/our-science/publications/posters-presentations, accessed 26 January 2021)

5. Efficacy and safety of intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid versus intravenous ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate in the treatment of complicated urinary tract infections (cUTI): results from the SURE-2 Trial [website]. Dublin: Iterum Therapeutics; 2020 (https://www.iterumtx.com/our-science/publications/posters-presentations, accessed 26 January 2021)

6. Iterum Therapeutics Announces Top line Results from its Phase 3 Clinical Trial of Oral Sulopenem for the Treatment of Uncomplicated Urinary Tract Infections. Published June 29, 2020. [website]. Dublin: Iterum Therapeutics; 2020 (https://bit.ly/2BL6e3n, access 29 January 2021).

7. Fleming, Michaela. " Sulopenem Narrowly Misses Primary End Point in Phase 3 cIAI Study ". Published 11 December 2019 (website). MJH Life Sciences and Contagion Live Infectious Diseases Today. Philadelphia, MJH Life Sciences and Contagion Live (https://www.contagionlive.com/view/sulopenem-narrowly-misses-primary-end-point-in-phase-3-ciai-study, accessed 29 January 2021).

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 hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) due to commonly MDR ABC.

- **Route of administration and formulation:** 3 h iv infusion q6h (every 6 h) for 7 days up to 14 days.
- **Class, mode of action and target:** BL/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 with broad activity against Class A, C and D β-lactamases. It binds to PBP2 (intrinsic activity).
- **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 antimicrobial resistance.
- **Cross-resistance:** No reported cross-resistance. An in vitro study of the combination against a globally diverse set of *A. baumannii* isolates reported that antimicrobial resistance 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 the 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 to colistin (superiority design) (NCT03894046, EudraCT 2017-004868-35).
  - **Time period:** 3 April 2019 to 19 July 2020 (estimated, still recruiting).
  - **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 to colistin (superiority design).
  - **Study population:** 300 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 a 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 who are resistant to or have failed colistin treatment (with the patients in this subgroup also receiving the background therapy).
  - The trial took place in 16 countries (Belarus, Brazil, China, Greece, Hungary, India, Israel, Korea, Lithuania, Mexico, Peru, Russian Federation, Taiwan, Thailand, Turkey and USA).
  - **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 and who received any amount of the study drug.

References

1. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JDet al. Targeting multidrug-resistant acinetobacter spp.: sulbactam and the diazabicyclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio. 2019;10(2):e00159-19. doi:10.1128/mBio.00159-19.

2. Durand-Réville TF, Guler S, Comita-Prevoir J, Chen B, Bifulco N, Huynh H et al. ETX2514 is a broad-spectrum β-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including Acinetobacter baumannii. Nat Microbiol. 2017;2:17104. doi:10.1038/nmicrobiol.2017.104.

3. Shapiro AB, Gao N, Jahić H, Carter NM, Chen A, Miller AA. Reversibility of covalent, broad-spectrum serine β-lactamase inhibition by the diazabicyclooctenone ETX2514. ACS Infect Dis. 2017;3(11):833–44. doi:10.1021/acsinfecdis.7b00113.

4. Penwell WF, Shapiro AB, Giacobbe RA, Gu RF, Gao N, Thresher J et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii. Antimicrob Agents Chemother. 2015;59(3):1680–9.

5. Seifert H, Müller C, Stefanik D, Higgins PG, Miller A, Kresken M. In vitro activity of sulbactam/durlobactam against global isolates of carbapenem-resistant Acinetobacter baumannii. J Antimicrob Chemother. 2020;75(9):2616–21.

6. McLeod SM, Moussa SH, Hackel MA, Miller AA. In vitro activity of sulbactam-durlobactam against Acinetobacter baumannii-calcoaceticus complex isolates collected globally in 2016 and 2017. Antimicrob Agents Chemother. 2020;64(4):e02534-19.

7. Miller A, McLeod S, Mathur T, Morrissey I. 694. In vitro antibacterial activity of sulbactam–durlobactam (ETX2514SUL) against 121 recent acinetobacter baumannii isolated from patients in India. Open Forum Infect Dis. 2019;6(Suppl_2):S314. doi:10.1093/ofid/ofz360.762.

8. Foulds G, Stankewich JP, Marshall DC, O'Brien MM, Hayes SL, Weidler DJ et al. Pharmacokinetics of sulbactam in humans. Antimicrob Agents Chemother. 1983;23(5):692–9. doi:10.1128/aac.23.5.692.

9. Sagan O, Yakubsevitch R, Yanev K, Fomkin R, Stone E, Hines D et al. Pharmacokinetics and tolerability of intravenous sulbactam-durlobactam with imipenem-cilastatin in hospitalized adults with complicated urinary tract infections, including acute pyelonephritis. Antimicrob Agents Chemother. 2020;64(3):e01506-19. doi:10.1128/AAC.01506-19.

10. O'Donnell J, Preston RA, Mamikonyan G, Stone E, Isaacs R. Pharmacokinetics, safety, and tolerability of intravenous durlobactam and sulbactam in subjects with renal impairment and healthy matched control subjects. Antimicrob Agents Chemother. 2019;63(9):e00794-19. doi:10.1128/AAC.00794-19.

11. Papp-Wallace KM. The latest advances in β-lactam/β-lactamase inhibitor combinations for the treatment of Gram-negative bacterial infections. Expert Opin Pharmacother. 2019;20(17):2169–84.

12. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD et al. Targeting multidrug-resistant acinetobacter spp.: sulbactam and the diazabicyclooctenone β-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio. 2019;10(2):e00159-19. doi:10.1128/mBio.00159-19.

13. Durand-Réville TF, Guler S, Comita-Prevoir J, Chen B, Bifulco N, Huynh H et al. ETX2514 is a broad-spectrum β-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including Acinetobacter baumannii. Nat Microbiol. 2017; 2:17104. doi:10.1038/nmicrobiol.2017.104.

14. Shapiro AB, Gao N, Jahić H, Carter NM, Chen A, Miller AA. Reversibility of covalent, broad-spectrum serine β-lactamase inhibition by the diazabicyclooctenone ETX2514. ACS Infect Dis. 2017;3(11):833–44. doi:10.1021/acsinfecdis.7b00113.

15. Penwell WF, Shapiro AB, Giacobbe RA, Gu RF, Gao N, Thresher J et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii. Antimicrob Agents Chemother. 2015;59(3):1680–9.

16. Miller A, McLeod S, Mathur T, Morrissey I. 694. In vitro antibacterial activity of sulbactam–durlobactam (ETX2514SUL) against 121 recent acinetobacter baumannii Isolated from patients in India. Open Forum Infect Dis. 2019;6(Suppl_2):S314 doi:10.1093/ofid/ofz360.762.

17. Foulds G, Stankewich JP, Marshall DC, O'Brien MM, Hayes SL, Weidler DJ et al. Pharmacokinetics of sulbactam in humans. Antimicrob Agents Chemother. 1983;23(5):692–9. doi.1128/aac.23.5.692.

18. Sagan O, Yakubsevitch R, Yanev K, Fomkin R, Stone E, Hines D et al. Pharmacokinetics and tolerability of intravenous sulbactam-durlobactam with imipenem-cilastatin in hospitalized adults with complicated urinary tract infections, including acute pyelonephritis. Antimicrob Agents Chemother. 2020;64(3):e01506-19. doi:10.1128/AAC.01506-19.

19. O'Donnell J, Preston RA, Mamikonyan G, Stone E, Isaacs R. Pharmacokinetics, safety, and tolerability of intravenous durlobactam and sulbactam in subjects with renal impairment and healthy matched control subjects. Antimicrob Agents Chemother. 2019;63(9):e00794-19. doi:10.1128/AAC.00794-19.

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, mode of action 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 CREs: 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:** No reported cross-resistance.
- **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, randomized, double-blind, 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 (NCT03894046, EudraCT 2017-004868-35).
  - **Time period:** 7 August 2019 to 27 February 2021 (active).
  - **Study design:** Interventional, explanatory, double-blinded, 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 9 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 are 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 of Gram-negative target pathogens found at study entry ≥ 10^5 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.

References

1. Liu B, Trout RE, Chu GH, McGarry D, Jackson RW, Hamrick JC et al. Discovery of taniborbactam (VNRX-5133): a broad-spectrum serine- and metallo-β-lactamase inhibitor for carbapenem-resistant bacterial infections. J Med Chem. 2020;63(6):2789–801.

2. Daigle D, Hamrick J, Chatwin C, Kurepina N, Kreiswirth BN, Shields RK et al. 1370. Cefepime/VNRX-5133 broad-spectrum activity is maintained against emerging KPC- and PDC-variants in multidrug-resistant K. pneumoniae and P. aeruginosa. Open Forum Infect Dis. 2018;5(Suppl_1):S419–20).

3. Wang X, Zhao C, Wang Q, Wang Z, Liang X, Zhang F et al. In vitro activity of the novel β-lactamase inhibitor taniborbactam (VNRX-5133), in combination with cefepime or meropenem, against MDR Gram-negative bacterial isolates from China. J Antimicrob Chemother. 2020;75(7):1850–8. doi:10.1093/jac/dkaa053. Erratum in: J Antimicrob Chemother. 2020;75(7):2019.

4. Hamrick JC, Docquier JD, Uehara T, Myers CL, Six DA, Chatwin CL et al. VNRX-5133 (taniborbactam), a broad-spectrum inhibitor of serine- and metallo-β-lactamases, restores activity of cefepime in Enterobacterales and Pseudomonas aeruginosa. Antimicrob Agents and Chemother. 2020;64(3):e01963-19.

5. Piccirilli A, Segatore B, Brisdelli F, Amicosante G, Perilli M. Potent inhibitory activity of Taniborbactam towards NDM-1 and NDM-1Q119X mutants, and "in vitro" activity of cefepime/taniborbactam against MBLs producing Enterobacterales. Int J Antimicrob Agents. 2020;57(1):106228.

6. List of all posters and conference abstracts/presentations on cefepime-taniborbactam (formerly cefepime/VNRX-5133) can be viewed at: https://www.venatorx.com/posters/cefepime-taniborbactam-formerly-cefepimevnrx-5133/ (accessed 26 January 2021).

7. Abdelraouf K, Almarzoky Abuhussain S, Nicolau DP. In vivo pharmacodynamics of new-generation β-lactamase inhibitor taniborbactam (formerly VNRX-5133) in combination with cefepime against serine-β-lactamase-producing Gram-negative bacteria. Journal of Antimicrobial Chemotherapy. 2020 Dec;75(12):3601-10.

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, mode of action and target:** BLI-β-lactam 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 cephalosporin-resistant Enterobacterales and some CREs (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 to piperacillin/tazobactam in the treatment of 1034 cUTI patients, including AP (NCT03687255, EudraCT 2017-004868-35).
  - **Time period:** 24 September 2018 to 15 February 2021.
  - **Study design:** Interventional, explanatory, double-blinded, 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/mm^3 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 ≥ 10^5 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** is 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 (< 10^3 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.

References

1. Bernhard F, Odedra R, Sordello S, Cardin R, Franzoni S, Charrier C et al. Pharmacokinetics-pharmacodynamics of enmetazobactam combined with cefepime in a neutropenic murine thigh infection model. Antimicrob Agents Chemother. 2020;64(6):e00078-20.

2. Tselepis L, Langley GW, Aboklaish AF, Widlake E, Jackson DE, Schofield TW et al. In vitro efficacy of imipenem-relebactam and cefepime-AAI101 against a global collection of ESBL-positive and carbapenemase-producing Enterobacteriaceae. Int J Antimicrob Agents. 2020;56(1):105925.

3. Belley A, Huband MD, Fedler KA, Watters AA, Flamm RK, Shapiro S et al. Development of broth microdilution MIC and disk diffusion antimicrobial susceptibility test quality control ranges for the combination of cefepime and the novel β-lactamase inhibitor enmetazobactam. J Clin Microbiol. 2019;57(8):e00607-19.

4. Morrissey I, Magnet S, Hawser S, Shapiro S, Knechtle P. In vitro activity of cefepime-enmetazobactam against Gram-negative isolates collected from US and European hospitals during 2014–2015. Antimicrob Agents Chemother. 2019;63(7):e00514-19.

5. Papp-Wallace KM, Bethel CR, Caillon J, Barnes MD, Potel G, Bajaksouzian S et al. Beyond piperacillin-tazobactam: cefepime and AAI101 as a potent β-lactam–β-lactamase inhibitor combination. Antimicrob Agents Chemother. 2019;63(5):e00105-19.

6. Crandon JL, Nicolau DP. In vitro activity of cefepime/AAI101 and comparators against cefepime non-susceptible Enterobacteriaceae. Pathogens. 2015;4(3):620–5.

7. Crandon JL, Nicolau DP. In vivo activities of simulated human doses of cefepime and cefepime-AAI101 against multidrug-resistant Gram-negative Enterobacteriaceae. Antimicrob Agents Chemother. 2015;59(5):2688–94.

8. 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. 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, mode of action, 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:** Mean = 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 to 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 August 2021 (active).
  - **Study design:** An explanatory, open-label, randomized, non-inferiority clinical trial comparing a single (3 g) oral dose of zoliflodacin to a combination of ceftriaxone (500 mg, IM) and azithromycin (1 g, oral), using 2:1 randomization design. Like the Phase 2 study, the Phase 2 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 (other secondary 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.

References

1. Taylor SN, Marrazzo J, Batteiger BE, Hook III EW, Seña AC, Long J et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. New Engl J Med. 2018;379(19):1835–45.

2. Bradford PA, Miller AA, O'Donnell J, Mueller JP. Zoliflodacin: an oral spiropyrimidinetrione antibiotic for the treatment of Neisseria gonorrheae, including multi-drug-resistant isolates. ACS Infect Dis. 2020;6(6):1332–45.

3. Biedenbach DJ, Huband MD, Hackel M, de Jonge BLM, Sahm DF, Bradford PA. In vitro activity of AZD0914, a novel bacterial DNA gyrase/topoisomerase IV inhibitor, against clinically relevant Gram-positive and fastidious Gram-negative pathogens. Antimicrob Agents Chemother. 2015;59(10):6053–63.

4. Basarab GS, Kern GH, McNulty J, Mueller JP, Lawrence K, Vishwanathan K et al. Responding to the challenge of untreatable gonorrhea: ETX0914, a first-in-class agent with a distinct mechanism-of-action against bacterial Type II topoisomerases. Sci Rep. 2015;5(1):1–4.

5. Waites KB, Crabb DM, Duffy LB, Huband MD. In vitro antibacterial activity of AZD0914 against human mycoplasmas and ureaplasmas. Antimicrob Agents Chemother. 2015;59(6):3627–9.

6. Damiaõ Gouveia AC, Unemo M, Jensen JS. In vitro activity of zoliflodacin (ETX0914) against macrolide-resistant, fluoroquinolone-resistant and antimicrobial-susceptible Mycoplasma genitalium strains. J Antimicrob Chemother. 2018;73(5):1291–4.

7. Kohlhoff SA, Huband MD, Hammerschlag MR. In vitro activity of AZD0914, a novel DNA gyrase inhibitor, against Chlamydia trachomatis and Chlamydia pneumoniae. Antimicrob Agents Chemother. 2014;58(12):7595–6.

8. Su XH, Wang BX, Le WJ, Liu YR, Wan C, Li S et al. Multidrug-resistant Neisseria gonorrhoeae isolates from Nanjing, China, are sensitive to killing by a novel DNA gyrase inhibitor, ETX0914 (AZD0914). Antimicrob Agents Chemother. 2016;60(1):621–3.

9. Alm RA, Lahiri SD, Kutschke A, Otterson LG, McLaughlin RE, Whiteaker JD et al. Characterization of the novel DNA gyrase inhibitor AZD0914: low resistance potential and lack of cross-resistance in Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2015;59(3):1478–86.

10. Huband MD, Giacobbe RA, Lane DJ, Minyard M, Panchal RG, Mueller JP et al., eds. In vitro antibacterial activity of AZD0914: a new spiropyrimidinetrione bacterial DNA gyrase inhibitor against potential agents of bioterrorism. In: 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Poster F-462, 5–9 September 2014, Washington (DC).

11. Jacobsson S, Golparian D, Alm RA, Huband M, Mueller J, Jensen JS et al. High in vitro activity of the novel spiropyrimidinetrione AZD0914, a DNA gyrase inhibitor, against multidrug-resistant Neisseria gonorrhoeae isolates suggests a new effective option for oral treatment of gonorrhea. Antimicrob Agents Chemother. 2014;58(9):5585–8.

12. Unemo M, Ringlander J, Wiggins C, Fredlund H, Jacobsson S, Cole M. High in vitro susceptibility to the novel spiropyrimidinetrione ETX0914 (AZD0914) among 873 contemporary clinical Neisseria gonorrhoeae isolates from 21 European countries from 2012 to 2014. Antimicrob Agents Chemother. 2015;59(9):5220–5.

6. 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, mode of action and target:** Novel bacterial topoisomerase II inhibitor (triazaacenaphthylene). Selectively inhibits bacterial DNA replication by interacting on 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 (2 × 750 mg tablets) of gepotidacin twice daily (bid); every q12h for 5 days. Uncomplicated urogenital gonorrhoea: 3000 mg oral dose (4 750 mg tablets) at the study site, followed by 3000 mg oral dose (4 × 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 (iv dose is 59% urinary eliminated). 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 uUTIs and uncomplicated gonorrhoea infections 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 28 April 2021 (active).
  - **Study design:** Interventional, randomized, multicentre, open-label study in adolescent and adult participants comparing the efficacy and safety of gepotidacin to 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 for 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 endpoint:** Successful microbiological outcome at TOC visit. TOC is defined (for urogenital site) as culture-confirmed bacterial eradication of *N. gonorrhoea* observed 3–7 days post-treatment.

- **EAGLE-2** (NCT04020341 – efficacy and safety of gepotidacin compared to nitrofurantoin for treatment of uUTI).
  - **Time period:** 22 October 2019 to 28 April 2021 (active).
  - **Study design:** Interventional, randomized, multicentre, parallel-group, double-blind study in adolescent and adult females, comparing the efficacy and safety of oral gepotidacin to 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.

References

1. Bax BD, Chan PF, Eggleston DS, Fosberry A, Gentry DR, Gorrec F et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. Nature. 2010;466(7309):935–40. doi:10.1038/nature09197.

2. Overcash JS, Tiffany CA, Scangarella-Oman NE, Perry CR, Tao Y, Hossain M et al. Phase 2a pharmacokinetic, safety, and exploratory efficacy evaluation of oral gepotidacin (GSK2140944) in female participants with uncomplicated urinary tract infection (acute uncomplicated cystitis). Antimicrob Agents Chemother. 2020;64(7):e00199-20.

3. Jacobsson S, Golparian D, Scangarella-Oman N, Unemo M. In vitro activity of the novel triazaacenaphthylene gepotidacin (GSK2140944) against MDR Neisseria gonorrhoeae. J Antimicrob Chemother. 2018;73(8):2072–7.

4. Taylor SN, Morris DH, Avery AK, Workowski KA, Batteiger BE, Tiffany CA et al. Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a phase 2, randomized, dose-ranging, single-oral dose evaluation. Clin Infect Dis. 2018;67(4):504–12.

5. Scangarella-Oman NE, Hossain M, Dixon PB, Ingraham K, Min S, Tiffany CA et al. Microbiological analysis from a phase 2 randomized study in adults evaluating single oral doses of gepotidacin in the treatment of uncomplicated urogenital gonorrhea caused by Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2018;62(12):e01221-18.

6. Farrell DJ, Sader HS, Rhomberg PR, Scangarella-Oman NE, Flamm RK. In vitro activity of gepotidacin (GSK2140944) against Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2017;61(3):e02047.

7. Biedenbach DJ, Bouchillon SK, Hackel M, Miller LA, Scangarella-Oman NE, Jakielaszek C et al. In vitro activity of gepotidacin, a novel triazaacenaphthylene bacterial topoisomerase inhibitor, against a broad spectrum of bacterial pathogens. Antimicrob Agents Chemother. 2016;60(3):1918–23. doi:10.1128/AAC.02820-15.

8. Flamm RK, Farrell DJ, Rhomberg PR, Scangarella-Oman NE, Sader HS. Gepotidacin (GSK2140944) in vitro activity against Gram-positive and Gram-negative bacteria. Antimicrob Agents Chemother. 2017;61(7):e00468-17.

9. Negash K, Andonian C, Felgate C, Chen C, Goljer I, Squillaci B et al. The metabolism and disposition of GSK2140944 in healthy human subjects. Xenobiotica. 2016;46(8):683–702.

7. Ridinilazole

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

- **Route of administration and formulation:** Oral.
- **Class, mode of action and target:** Proposed mechanism of action 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 to 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, twice daily (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 *C. difficile* infection 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 to two conventional antibiotics, fidaxomicin and vancomycin.
- **The first of two Phase 2 studies compared ridinilazole with vancomycin for the treatment of CDAD** (NCT02092935).
  - **Time period:** 26 June 2014 to 31 August 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 *C. difficile*-associated diarrhoea (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 treatments 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 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 June 2021 (active).
  - Interventional, quadruple-blinded, parallel assignment randomized, non-inferiority, active-controlled 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%.

References

1. Goldstein EJ, Citron DM, Tyrrell KL, Merriam CV. Comparative in vitro activities of SMT19969, a new antimicrobial agent, against Clostridium difficile and 350 gram-positive and gram-negative aerobic and anaerobic intestinal flora isolates. Antimicrob Agents Chemother. 2013;57(10):4872-6. doi:10.1128/AAC.01136-13.

2. Vickers R, Robinson N, Best E, Echols R, Tillotson G, Wilcox M. A randomised phase 1 study to investigate safety, pharmacokinetics and impact on gut microbiota following single and multiple oral doses in healthy male subjects of SMT19969, a novel agent for Clostridium difficile infections. BMC Infect Dis. 2015;15:91. doi:10.1186/s12879-015-0759-5.

3. Vickers RJ, Tillotson GS, Nathan R, Hazan S, Pullman J, Lucasti C et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Lancet Infect Dis. 2017;17(7):735-44. doi:10.1016/S1473-3099(17)30235-9.

4. Bassères E, Endres BT, Khaleduzzaman M, Miraftabi F, Alam MJ, Vickers RJ et al. Impact on toxin production and cell morphology in Clostridium difficile by ridinilazole (SMT19969), a novel treatment for C. difficile infection. J Antimicrob Chemother. 2016;71(5):1245-51. doi:10.1093/jac/dkv498.

5. Cho JC, Crotty MP, Pardo J. Ridinilazole: a novel antimicrobial for Clostridium difficile infection. Ann Gastroenterol. 2019;32(2):134.

6. Carlson TJ, Gonzales-Luna AJ, Garey KW. Recent developments in antimicrobial therapy for gastrointestinal infections. Curr Opin Gastroenterol. 2021;37(1):30–6. doi:10.1097/MOG.0000000000000696.

7. Qian X, Yanagi K, Kane AV, Alden N, Lei M, Snydman DR et al. Ridinilazole, a narrow spectrum antibiotic for treatment of Clostridioides difficile infection, enhances preservation of microbiota-dependent bile acids. Am J Physiol Gastrointest Liver Physiol. 2020;319(2):G227–37.

8. Mitra M, Chilton C, Freeman J, Wood H, Quirke P, Taylor M et al. Preservation of gut microbiome following ridinilazole vs. fidaxomicin treatment of Clostridium difficile infection. Open Forum Infect Dis. 2017;4(Suppl_1):S526–7. doi:10.1093/ofid/ofx163.1372.

9. Cho JC, Crotty MP, Pardo J. Ridinilazole: a novel antimicrobial for Clostridium difficile infection. Ann Gastroenterol. 2019;32(2):134–40. doi:10.20524/aog.2018.0336.

10. Bassères E, Endres BT, Vickers R, Alam MJ, Begum K, Garey K. Transcriptome functional analysis of Clostridium difficile exposed to ridinilazole: insight into potential mechanism of action. In: Abstracts of the Twenty-seventh European Congress of Clinical Microbiology and Infectious Diseases. Vienna, Austria: Abstract EP0404. Hoboken (NJ): Blackwell; 2017.

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