Addressing urgent priorities in antibiotic development: insights from WHO 2023 antibacterial clinical pipeline analyses

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Antimicrobial resistance continues to evolve and remains a leading cause of death worldwide, with children younger than 5 years being among those at the highest risk. Addressing antimicrobial resistance requires a comprehensive response, including infection prevention efforts, surveillance, stewardship, therapy appropriateness and access, and research and development. However, antimicrobial research and development is limited and lags behind the output of other fields, such as that of cancer or HIV research. The 2023 WHO analysis of the global antibacterial clinical pipeline serves as a tool to monitor and guide research and development efforts. The analysis emphasises the remaining gaps in developing a robust and effective antibacterial drug pipeline, drawing insights from trend analyses and assessment of the innovation potential of candidate antimicrobials. In the present analysis, we evaluated the activity of antibiotics against the new WHO bacterial priority pathogens list 2024, which reflects changing trends in resistance patterns, distribution of bacterial infections, and the emergence of new resistance mechanisms.

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Introduction

Antibiotics are essential tools and a cornerstone of modern health care. However, the continuous emergence of resistance mechanisms and their spread among bacteria has resulted in an insufficient number of available therapeutic options worldwide.[1] In an attempt to guide research and development to target urgent public health needs, WHO issued the 2017 list of bacterial priority pathogens (BPPs), a catalogue of bacteria divided into three categories—critical, high, and medium priority—according to the urgency of need for new antibiotics.[2] Between 2017 and 2023, 13 new antibiotics targeting WHO priority pathogens received market approval globally from stringent or WHO-listed regulatory authorities (table 1).[3] Of these agents, only two, cefiderocol and sulbactam-durlobactam, showed activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB), one of the most difficult-to-treat pathogens, whereas five, including cefiderocol, showed activity against carbapenem-resistant Enterobacterales (CRE), an order of Gram-negative bacteria also included in the WHO group of critical pathogens. To further focus efforts and resources on the development of effective antibiotics against drug-resistant bacteria that represent current therapeutic challenges, WHO has undertaken a two-step approach: a revision of the 2017 BPP list and an in-depth evaluation of the 2023 worldwide pipeline of antibacterial drugs against pathogens included in the new BPP list (appendix p 14).[4]

The present pipeline review focuses on traditional antimicrobials, small direct-acting molecules that kill pathogens or inhibit their proliferation (also termed antibiotics). In addition, for antimicrobials in development against *Mycobacterium tuberculosis*, the pipeline review also includes non-direct-acting agents, potentiating the efficacy of traditional antitubercular drugs. The analysis of the pipeline highlights the extent to which current research and development activities address the risks associated with BPPs, the adequacy of fulfilling unmet medical needs, and the remaining gaps, trends, and opportunities to counteract therapeutic emergencies. In this Review, we also provide an assessment of antibiotics to ascertain whether they meet a set of WHO-defined innovation criteria, namely the absence of cross-resistance and the involvement of a new target, a new mechanism of action, and a new chemical class.

Recently approved products against critical Gram-negative bacterial pathogens

The BPP list highlights the ongoing importance of drug-resistant Gram-negative bacteria. CRAB, CRE, and third-generation cephalosporin-resistant Enterobacterales (3GCRE) have been critical research and development priorities since 2017. However, effective treatment options for CRAB-related, CRE-related, and 3GCRE-related infections continue to represent an unmet medical need.

CRAB causes outbreaks of infections characterised by high mortality rates.[5] CRAB therapy remains challenging due to the acquisition of serine and metallo-β-lactamases by these bacteria[5,6] (appendix p 14) and their high resistance against aminoglycosides and fluoroquinolones, which further restricts treatment options.[1,2] The recent authorisation of two new antibiotics, cefiderocol in 2019 and the combination sulbactam-durlobactam in 2023, represents a step forward in the battle against CRAB but does not fully resolve the therapeutic needs. Cefiderocol has shown in-vitro stability in the presence of all types of β-lactamases, including metallo-β-lactamases, and clinical and microbiological efficacy similar to that of the best available therapy;[7] however, resistance development[8] and a higher number of deaths[7] were observed in patient subsets infected with *Acinetobacter* spp. Sulbactam-durlobactam was non-inferior to colistin in patients with CRAB infections.[9] The likelihood of clinical cure was higher with sulbactam-durlobactam than with colistin and was associated with reduced nephrotoxicity.[9] However, sulbactam-durlobactam is not active against CRAB strains producing metallo-β-lactamases.[10]

Widespread carbapenem use in past years has substantially contributed to increased resistance among CRE.[11,12] Moreover, the spread of CTX-M-type extended-spectrum β-lactamases (ESBLs) in communities worldwide, as well as

See Online for appendix

the emergence of 3GCRE among neonates with severe illnesses admitted to intensive care units, is of concern.[13] Of the 13 new antibiotics approved since 2017, five showed in-vitro activity against CRE and 3GCRE (table 1); however, their clinical utility is limited by the risk of resistance development and unfavourable pharmacokinetic or safety profiles. Among these, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol should be reserved to treat infections caused by multidrug-resistant (MDR) Gram-negative bacteria according to the WHO AWaRe classification.[14,15] The Infectious Diseases Society of America (IDSA) suggests reserving cefiderocol for infections with metallo-β-lactamase-producing bacteria because of its higher efficacy and reduced toxicity compared with that of polymyxin-based regimens.[16] The aminoglycoside plazomicin has shown efficacy in complicated urinary tract infections and pyelonephritis;[17] however, plazomicin is nephrotoxic and has limited availability worldwide. The aminomethylcycline eravacycline is indicated in the treatment of complicated intra-abdominal infections; however, few clinical data from randomised controlled trials are available regarding such infections caused by ESBL-producing bacteria.[18,19] To guide the attention of research and development towards 3GCRE-associated infections, 3GCRE have been disaggregated from CRE within the critical group of the 2024 WHO BPP list.

The updated WHO BPP list places rifampicin-resistant tuberculosis in the critical category, reflecting its considerable burden, contribution to antimicrobial resistance, and treatment complexities. Pretomanid, the latest addition to treat MDR tuberculosis, was approved by the US Food and Drug Administration (FDA) in 2019.

Methods

Search strategy and selection criteria

The 2023 WHO clinical pipeline review of antibiotics builds on the 2017 WHO publication *Antibacterial agents in clinical development* and its subsequent updates.[20,21] We set Dec 31, 2023 as the cutoff point for the pipeline update. We included new chemical entities that are in clinical development (from phase 1 to submission of application for marketing authorisation, including new drug applications [NDAs]), which do not have market authorisation for human use issued by any stringent or WHO-listed authority,[2] and might be used to treat severe, systemic bacterial infections caused by WHO priority pathogens (appendix p 14). We considered fixed-dose combinations only when they contained a new chemical entity. Based on our search strategy (appendix p 1), we retrieved trial data between January, 2017, and December, 2023, in English from different sources, including public databases and clinical trial registries (appendix p 2). To complement the review, we searched for conference abstracts and posters available online or provided by developers, as well as anti-tuberculosis drug reviews by the WHO Tuberculosis Programme,[22] the Treatment Action Group (TAG),[23] and the Stop TB Partnership. We also conducted a targeted desktop search of products with national experts from Japan and Russia. We reviewed a total of 261 publications concerning 51 antibiotic agents in clinical trials.

For information on the **Stop TB Partnership**, please see https://www.stoptb.org/

Assessment of innovation and activity against priority pathogens

The antibiotics in clinical development were evaluated through a rigorous WHO-led process in collaboration with the WHO Advisory Group on the Research and Development of Antibacterial Treatments (see Acknowledgments). We gathered evidence on activity against WHO priority pathogens and innovation primarily from peer-reviewed publications. For agents in the early development stages, information from scientific conferences and data published by developers or sponsors were also considered. In this Review, non-clinical evidence supporting the activity of a candidate antibacterial drug against an individual pathogen is considered sufficient (represented as a dot in figure 1) when both robust in-vitro and in-vivo data are publicly available (appendix pp 2–3). Notably, the evidence supporting an expected activity strengthens with the development stage. Therefore, WHO evaluation of antibacterial activity against priority pathogens is an ongoing assessment, and new information is integrated as it becomes available during drug development. The innovation potential is evaluated against the four WHO innovation criteria (ie, new chemical class, new mechanism of action, new target, and absence of cross-resistance; see appendix p 2) and is intended to serve as a tool to predict the potential contribution of each antibiotic to combating antimicrobial resistance. Ultimately, the key test of innovation is the (eventual) added clinical benefit shown by an individual agent.

Antibiotics in the 2023 clinical pipeline

As of Dec 31, 2023, the clinical pipeline contained 51 antibiotics or combinations that included at least one new therapeutic entity (figure 1). Of the 51 identified agents, 32 (63%) were active against WHO BPPs, and 19 (37%) were active against *M tuberculosis*. Drugs against *M tuberculosis* will be discussed separately from the agents targeting any of the other BPPs. Of the 32 agents intended for BPPs, 19 (59%) had both in-vitro and in-vivo evidence of activity against at least one of the Gram-negative pathogens listed as "critical" in the BPP list: nine targeted CRAB (five of which also targeted CRE or 3GCRE), and 15 targeted CRE or 3GCRE (figure 1).

Of the 32 antibiotics in development for BPPs, 13 showed activity against other priority pathogens that have high or medium priority on the WHO BPP list, including six targeting carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Although the classification of CRPA was changed from critical to high priority due to an observed regional decline in resistance rates,[4] research and development investments and efforts by developers and funders should remain undeterred. To maintain the research and development focus on this species, CRPA is separated from other priority pathogens in figure 1.

	Marketing authorisation holders	Approving authority (date)	Antibacterial class	Route of administration	Approved indications	WHO EML and AWaRe classification*	Expected activity against priority pathogens			
							CRAB	CRPA	CRE	OPP
Sulbactam plus durlobactam (Xacduro)	Innoviva (formerly Entasis Therapeutics)	US FDA (May, 2023)	BLI or PBP1,3 binder plus DBO-PBP2 binder	IV	HABP, VABP	WHO EML: not yet evaluated; AWaRe: not yet classified	Active	Not active	Not active	Not tested
Delafloxacin (Baxdela, Quofenix)	Melinta Therapeutics (USA), Menarini (EU)	US FDA (June, 2017 for ABSSSI, October, 2019 for CABP), EMA (December, 2019 for ABSSSI, February, 2021 for CAP)	Fluoroquinolone	IV	ABSSSI, CABP	WHO EML: no; AWaRe: watch	Not active	Not active	Not active	Active
Meropenem plus vaborbactam	Melinta Therapeutics (USA), Menarini (EU)	US FDA (August, 2017), EMA (November, 2018)	β-lactam (carbapenem) plus boronate BLI	IV	cUTI, (cUTI, cIAI, HABP, VABP in EU)	WHO EML: yes; AWaRe: reserve	Not active	Not active	Active†	Not tested
Plazomicin (Zemdri)	Achaogen (Cipla, USA; QiLu Antibiotics, China)	US FDA (August, 2018)	Aminoglycoside	IV	cUTI	WHO EML: yes; AWaRe: reserve	Not active	Not active	Active	Not tested
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	US FDA (August, 2018), EMA (September, 2018)	Tetracycline	IV	cIAI	WHO EML: no; AWaRe: reserve	Possibly active	Not active	Active	Not tested
Omadacycline (Nuzyra)	Gurnet Point Capital and Novo Holdings	US FDA (October, 2018)	Tetracycline	IV, PO	CABP (IV), ABSSSI (IV, PO)	WHO EML: no; AWaRe: reserve	Not active	Not active	Not active	Active
Imipenem plus cilastatin plus relebactam (Recarbrio)	Merck Sharp & Dohme	US FDA (July, 2019 for cUTI and cIAI, July, 2020 for HABP and VABP), EMA (February, 2020 for Gram-negative)	β-lactam (carbapenem) or degradation inhibitor plus DBO-BLI	IV	cUTI, cIAI, HABP, VABP	WHO EML: no, AWaRe: reserve	Not active	Possibly active	Active†	Not tested
Lefamulin (Xenleta)	Nabriva (Sunovion Pharmaceuticals Canada)	US FDA (August, 2019), EMA (July, 2020)	Pleuromutilin	IV, PO††	CABP	WHO EML: not yet evaluated; AWaRe: reserve	Not tested	Not tested	Not tested	Active
Pretomanid (Dovprela)	TB Alliance (Viatris)	US FDA (August, 2019), EMA (August, 2020), CDSCO (July, 2020)	Nitroimidazole	PO	XDR tuberculosis	WHO EML: yes; AWaRe: not yet classified	Not tested	Not tested	Not tested	Active‡
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PDMA (August, 2019)	Fluoroquinolone	IV, PO	CABP, otorhinolaryngological infections	WHO EML: not yet evaluated; AWaRe: watch	Not active	Not active	Not active	Active
Cefiderocol (Fetroja)	Shionogi	US FDA (November, 2019 for cUTI, September, 2021 for HAP and VAP), EMA (April, 2020)	Siderophore β-lactam (cephalosporin)	IV	cUTI, HABP, VABP, aerobic Gram-negative§	WHO EML: yes; AWaRe: reserve	Active	Active	Active	Not tested
Levonadifloxacin (Emrok), alalevonadifloxacin (Emrok O)	Wockhardt	CDSCO (January, 2020)	Fluoroquinolone	IV, PO	ABSSSI	WHO EML: not yet evaluated; AWaRe: watch and not yet classified¶	Not active	Not active	Not active	Active
Contezolid (Youxitai), contezolid acefosamil	MicuRx	NMPA (June, 2021)	Oxazolidinone	IV, PO	cSSTI	WHO EML: not yet evaluated; AWaRe: not yet classified	Not tested	Not tested	Not tested	Active

The activity against WHO bacterial priority pathogens was assessed according to the method detailed in the appendix (p 14). ABSSSI=acute bacterial skin and skin-structure infection. AWaRe=Access Watch Reserve. BLI=β-lactamase inhibitor. CABP=community-acquired bacterial pneumonia. cIAI=complicated intra-abdominal infection. CRAB=carbapenem-resistant *Acinetobacter baumannii*. CRE=carbapenem-resistant Enterobacterales. CRPA=carbapenem-resistant *Pseudomonas aeruginosa*. cSSTI=complicated skin and soft tissue infection. cUTI=complicated urinary tract infection. CDSCO=Central Drugs Standard Control Organization of the Government of India. DBO=diazabicyclooctane. EMA=European Medicines Agency. EML=WHO Essential Medicines List. HABP=hospital-acquired bacterial pneumonia. HAP=hospital-acquired pneumonia. IV=intravenous. NMPA=China National Medical Products Administration. OPP=other priority pathogens. PBP=penicillin-binding protein. PDMA=Pharmaceuticals and Medical Devices Agency (Japan). PO=per os. US FDA=United States Food and Drug Administration. VABP=ventilator-associated bacterial pneumonia. VAP=ventilator-associated pneumonia. XDR=extensively drug-resistant. *Regarding the inclusion in WHO EML: no=evaluated and not recommended and yes=evaluated and included in the list. †Active against *Klebsiella pneumoniae* carbapenemase but not metallo-β-lactamase-producing Enterobacterales. ††First systemic formulation of this class, which was previously used in animals and topically in humans. ‡Approved in combination with bedaquiline and linezolid for the treatment of XDR or treatment-intolerant or non-responsive multidrug-resistant tuberculosis. §The EMA approved cefiderocol for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options, which is a broader indication than that of the US FDA approval. ¶Only levonadifloxacin has been classified under AWaRe (watch). Alalevonadifloxacin has yet to be classified under AWaRe.

Table 1: **Antibiotics that target WHO priority pathogens and that have received market approval between 2017 and 2023**

Key

Peer-reviewed in-vitro data · Peer-reviewed in-vivo data · Non-peer-reviewed in-vitro data · Non-peer-reviewed in-vivo data

INN (company code)	Antibacterial class	Route of administration	Developer	Non-clinical data supporting the activity assessment	CRAB	CRE	3GCRE	CRPA	OPP *	NCR	CC	T	MoA
NDA/MAA													
Solithromycin (T-4288) - NDA	Macrolide or ketolide	IV or PO	Fujifilm Toyama Chemical		/	/	/	/	•	-	-	-	-
Cefepime plus Taniborbactam (VNRX-5133) - NDA	β-Lactam (cephalosporin) plus Boronate–BLI	IV	Venatorx Pharmaceuticals/GARDP/ Everest Medicines		X	•	•	•	/	?	✓	-	-
Cefepime (EXBLIFEP) plus Enmetazobactam (AAI-101) - NDA and MAA	β-Lactam (cephalosporin) plus BLI	IV	Allecra Therapeutics		X	X	•	X	/	-	-	-	-
Phase 3													
Sulopenem; Sulopenem Etzadroxil–Probenecid	β-Lactam (thiopenem)	IV or PO	Iterum Therapeutics		X	X	•	X	/	-	-	-	-
Zoliflodacin	Spiropyrimidenetrione (NBTI)	PO	Innoviva (formerly Entasis Therapeutics)/GARDP		/	/	/	/	•	✓†	✓	-	✓
Gepotidacin	Triazaacenaphthylene (NBTI)	IV or PO	GSK		/	/	?‡	/	?	?	✓	-	✓
Nafithromycin (WCK-4873)	Macrolide or ketolide	PO	Wockhardt/Jemincare		/	/	/	/	•	-	-	-	-
Cefepime plus Zidebactam (WCK 5222) ‖	β-Lactam (cephalosporin) plus DBO-BLI/PBP2 binder	IV	Wockhardt		?**	•	•	?**	/	††	-	-	-
Cefepime plus Nacubactam (OP0595) ‖	β-Lactam (cephalosporin) plus DBO-BLI/PBP2 binder	IV	Meiji Seika		/	•	•	?	/	-	-	-	-
Aztreonam plus Nacubactam (OP0595) ‖	β-Lactam (monobactam) plus DBO-BLI/PBP2 binder	IV	Meiji Seika		/	•	•	X	/	-	-	-	-
Funobactam (XNW4107) plus Imipenem plus Cilastatin	DBO-BLI plus β-Lactam (carbapenem) plus degradation inhibitor	IV	Evopoint Bioscience		?‡‡	?§§	?¶¶	X	/	-	-	-	-
Phase 2													
Benapenem	β-Lactam (carbapenem)	IV	Xuanzhu Biopharm §		X	X	?	X	/	-	-	-	-
Afabicin (Debio-1450)	Pyrido-enamide (FabI inhibitor)	IV or PO	Debiopharm		/	/	/	/	•	✓	✓	✓	✓
TNP-2092	Rifamycin–quinolizinone hybrid	IV or PO ¶	TenNor Therapeutics		/	/	/	/	•	-	-	-	-
Phase 1/2													
Recce-327 (R327)	Synthetic (acrolein) polymer	IV or Topical	Recce Pharmaceuticals.		?	?	?	?	?	?	?	?	?
Murepavadin (POL7080, iMPV)	Macrocyclic peptidomimetic compound	Inhaled ‖‖	Spexis AG		X	X	X	•	/	?	✓	✓	✓
Phase 1													
Meropenem plus Nacubactam (OP0595) ‖	β-Lactam (carbapenem) plus DBO-BLI/PBP2 binder	IV	Meiji Seika		X	•	•	?	/	-	-	-	-
Cefpodoxime proxetil plus ETX0282 ‖	β-Lactam (cephalosporin) plus DBO-BLI/PBP2 binder	PO	Entasis Therapeutics Inc.		X	•	•	X	/	-	-	-	-
Ceftibuten plus ledaborbactam (VNRX-7145)	β-Lactam (cephalosporin) plus Boronate–BLI	PO	Venatorx Pharmaceuticals		X	•	•	X	/	?	✓	-	-
Xeruborbactam (QPX7728) plus β-lactam (S-649228)	Boronate–BLI plus undisclosed IV β-Lactam	IV	Qpex Biopharma/Shionogi		•	•	•	•	/	?	✓	-	-
Upleganan (SPR-206)	Polymyxin	IV	Spero Therapeutics		•	•	•	•	/	-	-	-	-
MRX-8	Polymyxin	IV	MicuRx		•	•	•	•	/	-	-	-	-
QPX9003 (BRII-693)	Polymyxin	IV	Brii Biosciences		•	?	?	•	/	?***	-	-	-
Zifanocycline (KBP-7072)	Tetracycline (aminomethylcycline)	IV or PO	KBP BioSciences		•	?	?	X	•	✓	-	-	-
Apramycin (EBL-1003) †††	Aminoglycoside	IV	Juvabis		•	•	?	?	/	-	-	-	-
TXA709	Difluorobenzamide (FtsZ inhibitor)	IV or PO	TAXIS Pharmaceuticals		X	X	X	X	•	✓	✓	✓	✓
Zosurabalpin (RG6006)	Macrocyclic peptide	IV	Roche		•‡‡‡	X	X	X	X	?‡‡‡	✓	✓	✓
BWC0977	Pyrazino-oxazinones (NBTI)	IV or PO	Bugworks Research		?§§§	?§§§	?§§§	?§§§	?§§§	?§§§	?	?	✓
OMN6	Insect host defence peptide	IV	Omnix Medical		•	?	/	?	?	?	✓	✓	✓
Ertapenem plus Zidebactam ‖	β-Lactam (carbapenem) plus DBO-BLI/PBP2 binder	IV	Wockhardt/NIAID		X	•	•	?	/	-	-	-	-
Meropenem plus ANT3310	β-Lactam (carbapenem) plus DBO-BLI/PBP2 binder	IV	Antabio SAS		•	•	•	?	/	-	-	-	-
Meropenem plus KSP-1007 (MEROPEN)	β-Lactam (carbapenem) plus Boronate–BLI	IV	Sumitomo Dainippon Pharma		?	?	?	?	/	?	✓	-	-

Figure 1: **2023 Clinical pipeline of candidate antibiotics targeting WHO bacterial priority pathogens**

The activity of the antibiotics under clinical development was assessed according to the methodology detailed in the appendix (p 1). The activity is indicated as •=active,?=possibly active, X=not active, and /=not tested, as the antibiotic is developed for only either Gram-positive cocci or Gram-negative rods. Agents not active against critical-priority pathogens were assessed for activity against OPPs, which include WHO high-priority and medium-priority pathogens. The complete list of references consulted for evaluating the expected activity against priority pathogens and innovation is provided in the appendix (pp 2–13). The innovation assessment was performed by evaluating the absence of (known) cross-resistances to existing antibiotics. The assessment of potential innovation was performed by evaluating the absence of (known) cross-resistances to existing antibiotics. Surrogate predictors for the absence of cross-resistance, which were also assessed, included the following: new class (new scaffold), new target (new molecular binding site), and new MoA. BLI=β-lactamase inhibitor. CC=chemical class. CRAB=carbapenem-resistant *Acinetobacter baumannii*. CRE=carbapenem-resistant Enterobacterales. 3GCRE=third-generation cephalosporin-resistant Enterobacterales. CRPA=carbapenem-resistant *Pseudomonas aeruginosa*. CR-EC=carbapenem-resistant *Escherichia coli*. DBO=diazabicyclooctane. FabI=enoyl-acyl carrier protein reductase. FQ=fluoroquinolone. FtsZ=filamenting temperature-sensitive Z. GARDP=Global Antibiotic Research and Development Partnership. IV=intravenous. MAA=marketing authorisation application. MoA=mechanism of action. MRSA=meticillin-resistant *Staphylococcus aureus*. NBTI=novel bacterial topoisomerase inhibitor. NCR=no cross-resistance. NDA=new drug application. OPP=other priority pathogens. PBP2=penicillin-binding protein 2. PO=per os. T=new target. *OPP target pathogens – solithromycin: *Streptococcus pneumoniae*; nafithromycin: *S aureus* and *S pneumoniae*; zoliflodacin and gepotidacin: *Neisseria gonorrhoeae* and MRSA; afabicin, TNP-2092, and TXA709: MRSA; Zifanocycline (KBP-7072): MRSA and VR-*Enterococcus faecium*; BWC0977: VR-*E faecium*; MRSA, FQ-resistant *N gonorrhoeae*, VR-*E faecium*, macrolide-resistant *Pneumococcus*, macrolide-resistant group A *Streptococci*, FQ-resistant NT-*Salmonella*. †The GyrB D429N substitution reduces susceptibility to zoliflodacin. The GyrB D429N substitution can be acquired by *N gonorrhoeae* in the presence of ciprofloxacin, resulting in an increased minimum inhibitory concentration of ciprofloxacin, at least in some backgrounds.[24] ‡Non-clinical data and data from a small phase 2 clinical trial are available only against *E coli*.[25] §Xuanzhu Biopharm is a subsidiary of Sichuan Pharmaceutical Holdings but possesses fully independent intellectual property rights. ¶No clinical data are available for the PO formulation. ‖The DBO-BLIs zidebactam, OP0595 (nacubactam), and ETX0282 also have some antibacterial activity and have been classified as β-lactam enhancers. **A few data in animals obtained with regimens simulating human treatment suggest possible activity.[26] ††Activity against aztreonam-avibactam-resistant NDM-like producing *E coli* shown in one study.[27] ‡‡Activity towards OXA-23, OXA-27, and OXA-51 producing CRAB but the susceptibility rate is 57·5%. No activity against metallo-β-lactamases.[28] §§Activity towards *Klebsiella pneumoniae* carbapenemase-producing. No activity against CR-EC.[29] ¶¶Activity against third-generation cephalosporin-resistant *K pneumoniae* but insufficient data against third-generation cephalosporin-resistant *E coli*.[28,29] ‖‖Previously tested as IV in hospital-acquired and ventilator-associated pneumonia in two phase 3 trials terminated in 2019 due to safety concerns. ***Activity at higher doses against colistin-resistant strains.[30] †††Previously used as an antibacterial treatment in animals.[31] ‡‡‡Activity against colistin-resistant CRAB.[32,33] §§§No peer-reviewed data available.[34–38] No cross-resistance against FQ-resistant bacteria.[39]

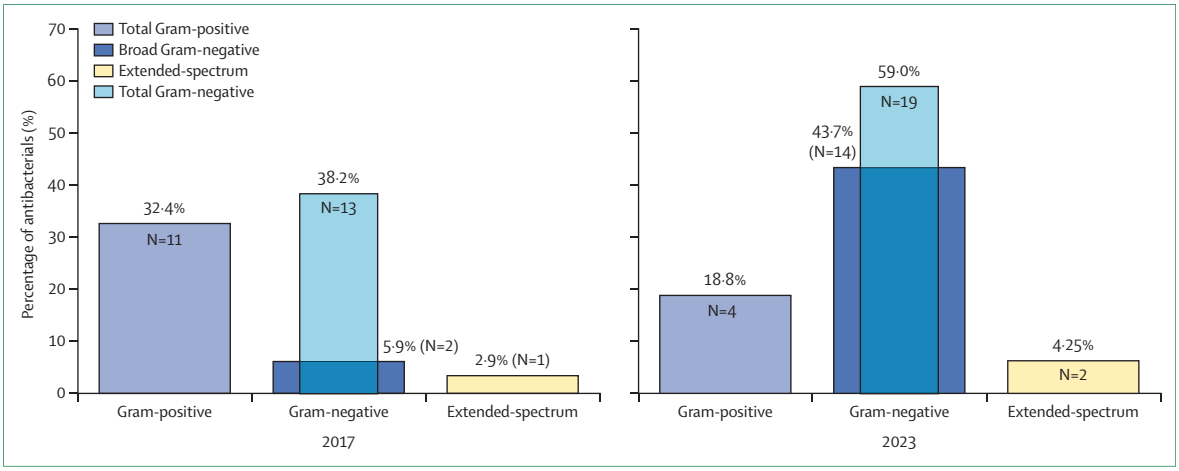

Figure 2: **Activities spectra of candidate antibiotics in the 2017 and 2023 clinical pipelines**
Differences in activity spectra of candidate antibiotics against WHO priority pathogens included in the 2017 and 2023 pipelines. Agents targeting *Mycobacterium tuberculosis* are not included in this analysis. Broad spectrum=agents with activity against more than one pathogen from the WHO bacterial priority pathogens list. Extended-spectrum=agents with activity against both Gram-negative and Gram-positive agents.

Progression, discontinuation, and changes in activity of the clinical antibiotic pipeline 2017–23

The first 2017 WHO pipeline analysis[20] helped to identify 41 antibiotics in clinical development against BPPs, including *M tuberculosis*. Since then, 13 agents have been approved, nine were discontinued, and 32 new entries were included. Thus, the 2023 list now contains 51 candidates, including 19 anti-tuberculosis drugs (appendix p 24). Excluding the anti-tuberculosis drugs from the analysis, the main change in the activity spectrum was a substantial shift in agents active against Gram-negative bacteria that increased from 38% (13 of 34) in 2017 to 56% (18 of 32) in 2023. Likewise, the number of broad-spectrum antibiotics (targeting two or more Gram-negative pathogens or orders of CRE and 3GCRE) increased from two (6%) in 2017 to 14 (44%) in 2023 (figure 2). The initial release of the WHO BPP list in 2017, with its emphasis on critical-priority Gram-negative pathogens, likely influenced developers and contributed to the observed upward trend as of 2023. The opposite trend was observed for agents active against Gram-positive bacteria, which might cause concern as both *Staphylococcus aureus* and *Streptococcus pneumoniae* are among the top three pathogens in the global mortality burden;[40] however, the analysis, performed in the updated WHO BPL report,[4] helped to identify both meticillin-resistant *S aureus* (MRSA) and macrolide-resistant *Pneumococcus* as highly treatable with the available antibiotic armamentarium, suggesting that country-specific limited access to effective therapies and anti-pneumococcal vaccination together with insufficient implementation of effective prevention and control measures[40] are probably the main drivers of mortality associated with these pathogens. Notably, the number of extended-spectrum agents targeting both Gram-positive and Gram-negative pathogens increased from 3% (one of 34) in 2017 to 6% (two of 32) in 2023. Enhancing access and implementing stewardship strategies for these agents could increase the rate of successful treatments.

Clinical formulations and availability of clinical study-informed paediatric posology 2017–23

The 2023 pipeline largely consisted of intravenous formulations, as did the 2017 pipeline. The proportion of oral antibiotics decreased from 47% (16 of 34) in 2017 to 37% (12 of 32) in 2023. Similarly, the number of agents with both intravenous and oral formulations decreased from 37% (12 of 34) to 25% (eight of 32) in 2023 (figure 3).

Parenteral formulations are essential for eliciting a rapid response, especially in difficult-to-treat infections, and facilitate stewardship programmes, which are typically administered directly by health-care providers. Oral formulations are required to transition individuals to outpatient treatment, especially in overburdened or under-resourced health-care systems. However, the availability of oral agents might increase the risk of misuse, thereby driving resistance evolution. Thus, a careful balance between access and stewardship should be maintained.

Although bacterial infections continue to be a leading cause of mortality among children younger than 5 years worldwide,[41] many marketed antibiotics have no authorised paediatric indications and optimal formulations for administration to children.[42] In the USA and EU, regulatory authorities require paediatric investigation studies (PIPs) for the paediatric development of new agents. However, a search in the European Medicines Agency PIP repository revealed that, of 14 antibiotics in the pipeline in phase 2 or beyond, only six have an approved or amended PIP, and none of the three products in phase 2 have presented a PIP yet. Moreover, for the few approved PIPs, a deferral is often granted, which delays the completion of the paediatric study. Consequently, a considerable time gap is anticipated between the approvals of the adult

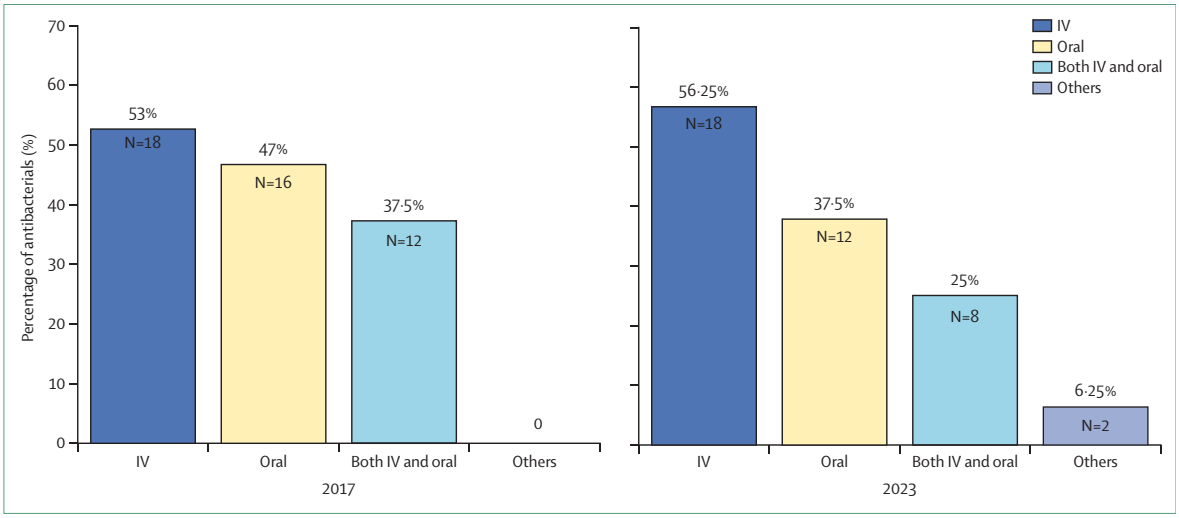

Figure 3: **Proportions of candidate antibiotics in the 2017 and 2023 clinical pipelines by formulation**
Proportions of candidate antibiotics in the 2017 and 2023 pipelines by formulation. Agents targeting *Mycobacterium tuberculosis* are not included in this analysis. IV=intravenous.

and paediatric indications. This delay could result in the administration of antibiotics to children without sufficient data to inform the correct dose regimen, which might cause either toxicity or insufficient treatment intensity, thereby facilitating the development of antimicrobial resistance.

Targets and foreseen indications of candidate antibiotics 2017–23

Typically, the 2023 clinical pipeline shows a substantial increase in the proportion of antibiotics targeting WHO critical pathogens (appendix p 25). Both the 2017 and 2023 pipeline analyses highlight that the most frequent indications among phase 2 and 3 antibacterial drugs are complicated or uncomplicated urinary tract infections and pulmonary infections (appendix p 26). This phenomenon is attributed to the feasibility of conducting initial studies in people with urinary tract infections, with subsequent extension of indications. Additionally, high mortality rates associated with respiratory infections, particularly among clinically vulnerable populations, contribute to this focus. Most of the agents target community-acquired infections. Only one phase 3 antibiotic (funobactam-imipenem-cilastatin) is under development for the treatment of hospital-associated and ventilator-associated bacterial pneumonia. Only three agents, apramycin, OMN6, and RECCE 327, have efficacy data in blood-stream infections (BSIs) listed among their study objectives, although the 2022 GLASS analysis[1] indicated high resistance in pathogens causing hospital-associated BSIs. Although the challenges of studies conducted to assess hospital-associated and ventilator-associated bacterial pneumonia and BSI likely contribute to the low number of agents being trialled, additional efforts in research and development are essential to develop new efficacious drugs for these conditions.

2023 candidate antibacterial drugs by antibiotic class

Most pipeline agents (n=26, 72%) belong to well known antibiotic classes, including three new topoisomerase inhibitors with an action mechanism partly different from that of older agents from the same class. Six antibiotic candidates (19%) are first-in-class compounds with distinct mechanisms of action and might have a lower likelihood of eliciting resistance in the near future. One product (3%) is a hybrid antibiotic from two existing classes, rifamycins and quinolones (figure 1).

2023 candidate antibacterial drugs belonging to existing antibiotic classes

Most antibiotics targeting WHO priority pathogens are β-lactams or β-lactam with β-lactamase inhibitor combinations (n=15, 47%). Most of them target class A (ESBL and *Klebsiella pneumoniae* carbapenemase), and some of them target class D enzymes, with only two products having in-vitro and in-vivo evidence of activity against class B enzymes (xeruborbactam-β-lactam S-649228 and aztreonam-nacubactam), and four additional agents deemed potentially active against metallo-β-lactamases (cefepime-taniborbactam, cefepime-zidebactam, cefepime-nacubactam, and meropenem-KSP-1007). While further efficacy data are being produced on the four agents, the addition of the recently approved cefiderocol results in three antibiotics that are active against metallo-β-lactamases, counting both pipeline and recently authorised agents. Although less common than genes encoding class A β-lactamases, those encoding metallo-β-lactamases have started to be more widely disseminated worldwide, with blaNDM-1 being the most prevalent.[43] Particularly, the prevalence of metallo-β-lactamases in livestock and food-producing and companion animals is concerning.[44] The notable developmental gap observed in the pipeline for agents that inhibit metallo-β-lactamases is thus of concern.

Since 2021, β-lactamase inhibitors with intrinsic antibacterial activity, based on their PBP2-binding ability, entered the pipeline. These include ETX0282, nacubactam, and zidebactam, all of which might confer synergistic antibacterial activity against some Enterobacterales[45] and are considered additional tools to tackle antimicrobial resistance. However, emerging mechanisms of resistance, including modified PBPs, decreased outer membrane permeability, and enhanced efflux pump activity, continue to pose major challenges in managing Gram-negative bacteria, including several strains of *P aeruginosa, A baumannii,* and the isolates of PBP3 insert + NDM *Escherichia coli* with an increasing prevalence.[46,47]

Polymyxins and novel bacterial type 2 topoisomerase inhibitors, represented by three agents each, are the second most represented antibiotic classes in the clinical pipeline. Polymyxins are cationic polypeptides that disrupt the phospholipid structure of the cell membrane, thereby increasing cell permeability. Despite their poorer safety profile that includes nephrotoxicity and neurotoxicity compared with that of newer Gram-negative antibiotics, polymyxin B and colistin are increasingly used against carbapenem-resistant Gram-negative bacteria, particularly CRAB, for which the available options are limited.[46,48,49] Three new polymyxin derivatives, MRX-8, QPX9003, and upleganan, with reportedly improved safety profiles, are in early clinical development. Upleganan and MRX-8 have shown in-vitro and in-vivo activity against all critical pathogens,[30,50,51] whereas QPX9003 has in-vitro and in-vivo evidence of activity only for CRAB (figure 1). Except for QPX9003, which, at higher doses, has shown activity against some colistin-resistant strains, the new polymyxin derivatives do not appear to overcome this problem.

Three novel bacterial type 2 topoisomerase inhibitors are under development. Zoliflodacin and gepotidacin, currently in phase 3, have new chemical structures with distinct (but potentially overlapping) binding sites with fluoroquinolones.[52,53] BWC0977, which is currently in phase 1 and had only non-peer-reviewed published data (appendix p 9), is claimed to have distinct binding sites and similar activity against DNA gyrase and topoisomerase IV, with no cross-resistance detected in vitro (appendix p 9). Gepotidacin targets *Neisseria gonorrhoeae* and 3GCREs and has shown in-vitro activity against MRSA. Gepotidacin has both non-inferiority (EAGLE-2 and EAGLE-3 phase 3 studies) and statistical superiority (EAGLE-3 study) to nitrofurantoin in treating uncomplicated urinary tract infections.[54] No data on treatment efficacy in MDR isolates from participants enrolled in EAGLE-2 and EAGLE-3 studies are currently available. Zoliflodacin has been developed for *N gonorrhoeae* infections but is also active against MRSA, whereas BWC0977 reportedly targets all critical Gram-negative pathogens and CRPA.

Recently, top-line results of a phase 3 study in uncomplicated gonorrhoea suggested non-inferiority of zoliflodacin regarding microbiological cure compared with intramuscular ceftriaxone and oral azithromycin.[55] *N gonorrhoeae*, 3GCR, and fluoroquinolone-resistant bacteria are spreading widely in some countries.[56] Whether zoliflodacin retains efficacy against these MDR strains remains unknown. Evolved resistance to zoliflodacin through experimental evolution was observed when *N gonorrhoeae* was cultured in the presence of ciprofloxacin.[57]

The antibiotic pipeline also includes four protein synthesis inhibitors belonging to the ketolide, tetracycline, and aminoglycoside classes. Ketolides are a macrolide subclass binding to ribosomes with higher affinity than that of the parent compounds. The two ketolides, nafithromycin and solithromycin, which are in phase 3 development, are claimed to retain activity against the main resistance mechanisms of erythromycin (target-site modification, ribosomal protection, and efflux-mediated resistance) prevalent in *Streptococcus* spp,[58] although cross-resistance with macrolides has been reported in *Staphylococcus* spp.[59,60]

Nafithromycin is being developed as an oral compliance-friendly three-day regimen for community-acquired bacterial pneumonia, including that associated with macrolide-resistant pneumococcal strains. In 2019, an NDA for solithromycin was submitted in Japan for the treatment of upper respiratory tract infections, following a phase 3 trial registered in Japan in which this drug showed non-inferiority to cephem antibiotics in individuals with sinusitis. No further information on this NDA is available. Previously, an NDA for the treatment of community-acquired bacterial pneumonia with solithromycin was filed but rejected by the FDA and withdrawn from submission to the European Medicines Agency because the potential of this drug for liver toxicity was not adequately characterised.[61] A phase 3 randomised controlled trial versus oral azithromycin in community-acquired bacterial pneumonia is ongoing in Japan.

The semisynthetic aminomethylcycline zifanocycline, currently in phase 1 clinical development, overcomes some tetracycline class-specific resistance mechanisms.[62] This drug has shown activity against CRAB both in vitro and in animal models of infection, but sufficient data are not available to assess its activity against CRE and 3GCRE.[63,64] Zifanocycline is being optimised to treat Gram-positive pathogens and is under investigation for acute bacterial skin and skin-structure infections, community-acquired bacterial pneumonia, and complicated intra-abdominal infections.

The aminoglycoside apramycin was first licensed in 1980 for oral therapy in animals.[65] Apramycin is currently in phase 1 development for treating BSI[66] and has shown activity in vitro and in vivo against 3GCRE, CRE, CRAB, CRPA,[67] and MDR *N gonorrhoeae*.[68] Notably, apramycin showed potent in-vitro activity against hypervirulent carbapenem-resistant *K pneumoniae* isolates, including those resistant to amikacin or gentamicin.[69] Aminoglycoside-modifying enzymes and rRNA methyltransferases did not render cross-resistance to apramycin in vitro.[70]

For information on the **Japan Registry of Clinical Trials**, please see https://jrct.niph.go.jp/

First-in-class candidate antibiotics: host defence peptides, tethered macrocyclic peptide, enoyl-acyl carrier protein reductase (FabI) and filamenting temperature-sensitive Z (FtsZ) inhibitors, ATP production disrupters, and antibiotic hybrids

Host defence peptides, also termed antimicrobial peptides, are naturally occurring peptides with direct microbicidal properties or potentiator effects on the immune responses of the host. Peptides from sequences of host defence peptides have recently been synthesised to optimise antimicrobial activity in vivo and improve the safety profile.[71] Two agents from this group, both targeting *P aeruginosa*, are under clinical development. OMN6 is bactericidal against Gram-negative bacteria and exerts no cytotoxicity towards eukaryotic cells. OMN6 binds to and penetrates bacterial membranes, thereby disrupting ionic gradients and causing bacterial death.[71] Murepavadin selectively targets the outer membrane lipopolysaccharide protein transporter LptD of *P aeruginosa*.[72] Although the evaluation of intravenous murepavadin for treating hospital-associated bacterial pneumonia was halted due to reports of kidney injury, an inhaled formulation of the antibiotic for treating *Pseudomonas* infections in patients with cystic fibrosis is under investigation.[72]

The macrocyclic peptide, zosurabalpin, is in phase 1 development for the treatment of hospital-associated and ventilator-associated bacterial pneumonia and CRAB-induced bacteraemia. The newly elucidated action mechanism of zosurabalpin involves blocking the transport of bacterial lipopolysaccharide from the inner membrane to its destination on the outer membrane by inhibiting the $LptB_2FGC$ complex.[33]

FabI inhibitors target an NADH-dependent enoyl-acyl carrier protein reductase that participates in the final step of bacterial fatty acid biosynthesis. One FabI inhibitor, afabicin, is under development.[73] Its in-vitro activity is similar to that of rifampicin and is likely independent of resistance patterns.[74] Afabicin was non-inferior to vancomycin-linezolid in a phase 2 trial in participants with acute bacterial skin and skin-structure infections.[73] A phase 2 open-label trial in individuals with bone and joint infection is ongoing (NCT03723551).

FtsZ inhibitors target a vital cell division protein that is conserved in most bacteria and, thus, are potentially endowed with broad-spectrum activity.[75] One FtsZ inhibitor, TXA709, is in phase 1 development against MRSA.

The ATP production disrupter group includes agents targeting bacterial ATP production as their main mechanism of action. One agent of this class, RECCE 327, is in phase 1 development as a broad-spectrum intervention in infected burn wound care, diabetic foot infection, and complicated urinary tract infection or urosepsis caused by ESBL-producing Enterobacterales. Currently, only non-peer-reviewed data are available. In-vitro and in-vivo data (appendix p 10) suggest broad-spectrum antibacterial activity against MDR strains of Gram-positive and Gram-negative bacteria (appendix p 10).

Antibiotic hybrids are conjugates of dual-acting agents aimed at reducing toxicity and increasing the activity of the constituent pharmacophores by improving on-site targeting, halting bacterial efflux, or conferring protection from enzymatic degradation. TNP-2092 is a rifamycin-quinolizinone hybrid that overcomes fluoroquinolone efflux pumps by steric interference from the rifamycin pharmacophore.[76] TNP-2092 is in phase 2 development for acute bacterial skin and skin-structure infections and received orphan designation for prosthetic joint infection. Online top-line data showed that the early clinical response rates of TNP-2092 were non-inferior to that of vancomycin.[77] In a subpopulation analysis, TNP-2092 appeared to be equally efficacious against infections caused by MRSA (about 50% of all isolated pathogens) and other pathogens.[62] More recently, TNP-2092 was proven to be effective in treating MRSA-associated prosthetic joint infection of the knee in an experimental rat model.[78]

Innovation assessment of candidate antibacterial drugs

Of the 32 antibiotics under development against BPPs, 13 (41%) meet at least one of the four WHO innovation criteria. Gepotidacin meets two innovation criteria for a new chemical class and a new mechanism of action at the molecular level. Four products, zoliflodacin, murepavadin, OMN6, and zosurabalpin, meet three innovation criteria. Only two, afabicin and TXA709, meet all four innovation criteria.

Four agents have data that support the absence of cross-resistance. Of these, afabicin and TXA709 meet all four innovation criteria; zoliflodacin belongs to a new chemical class and has a new mechanism of action, whereas zifanocycline, although having the same mechanism of action and target as other tetracyclines has a distinctive interaction pattern with the 30S ribosomal subunit and is minimally affected by the presence of acquired tetracycline genes.[79] The data for the assessment of cross-resistance are inconclusive for 12 agents. As development progresses, additional evidence will facilitate a more comprehensive assessment and might lead to the inclusion of at least some of these 12 antibacterial drugs among potentially innovative drugs. Ultimately, a thorough assessment of innovation will rely on the clinical performance characteristics of each product, which is unknown for drugs in development.

Of the 13 potentially innovative agents, only five (38%) are active against at least one of the WHO critical Gram-negative bacteria; these are zosurabalpin, OMN6, cefepime-taniborbactam, ceftibuten-ledaborbactam, and xeruborbactam-β-lactam S-649228. Of these, cefepime-taniborbactam, ceftibuten-ledaborbactam, and xeruborbactam-β-lactam S-649228 are combinations of β-lactams with boronate β-lactamase inhibitors but only two of them (cefepime-taniborbactam and xeruborbactam-β-lactam S-649228) have shown activity against metallo-β-lactamase-producing bacteria. However, heteroresistance to cefepime-taniborbactam in metallo-β-lactamase-encoding Enterobacterales has already been described.[80] Four of the

	Antibiotic class	Route of administration	Developer	Innovation			
				NCR	CC	T	MoA
Phase 3							
Sudapyridine (WX-081)	Mycobacterial ATP synthase inhibition	PO	Shanghai Jiatan Biotech	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
Phase 2							
BTZ-043	Benzothiazinone (DprE1 inhibitor)	PO	University of Munich; Hans Knöll Institute, Jena; German Center for Infection Research	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
Delpazolid (RMW2001, LCB01-0371)	Oxazolidinone	PO	LegoChem Biosciences, Haihe Biopharma	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
Ganfeborole, GSK3036656 (GSK070)	Oxaborole (LeuRs inhibitor)	PO	GSK	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
Sutezolid (PF-2341272, PNU-100480)	Oxazolidinone	PO	TB Alliance, Sequella, Gates MRI, Aurum Institute	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
TBA-7371	Azaindole (DprE1 inhibitor)	PO	TB Alliance, Gates MRI, Foundation for Neglected Disease Research	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
Telacebec (Q203)	Imidazopyridine amide	PO	Qurient, Infectex, TB Alliance	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
Quabodepistat (OPC-167832)	3,4-Dihydrocarbostyril (DprE1 inhibitor)	PO	Otsuka, Gates MRI	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
TBAJ-876	Diarylquinoline (bedaquiline analogue)	PO	TB Alliance	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
Pyrifazimine (TBI-166)*	Riminophenazine (clofazimine analogue)	PO	Institute of Materia Medica, TB Alliance, Chinese Academy of Medical Sciences, Peking Union Medical College	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
Alpibectir (BVL-GSK098) plus ethionamide	Amido piperidine (inactivation of TetR-like repressor EthR2) Spiroisoxazoline	PO	BioVersys, GSK	Criterion not fulfilled	Criterion fulfilled	Criterion not fulfilled	Criterion not fulfilled
Dovramilast (CC-11050, AMR-634)	Phosphodiesterase 4 (PDE4) inhibitor (host immune response)	PO	Medicines Development for Global Health	Criterion not fulfilled	Criterion fulfilled	Criterion not fulfilled	Criterion not fulfilled
SQ109	Ethylenediamine	PO	Sequella	Inconclusive data	Criterion not fulfilled	Criterion fulfilled	Criterion fulfilled
Sanfetrinem cilexetil	Tricyclic β-lactam	PO	GlaxoSmithKline, Gates MRI	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
Phase 1							
TBI-223	Oxazolidinone	PO	TB Alliance, Institute of Materia Medica	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
GSK2556286 (GSK286)	Adenylyl cyclase Rv1625c agonist	PO	GSK, TB Drug Accelerator, Gates MRI	Inconclusive data	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
Macozinone (PBTZ-169)	Benzothiazinone (DprE1 inhibitor)	PO	Innovative Medicines for Tuberculosis, Nearmedic Plus	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled	Criterion fulfilled
TBAJ-587	Diarylquinoline (bedaquiline analogue)	PO	TB Alliance	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled
TBD09 (MK7762)	Oxazolidinone	PO	Gates MRI	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled	Criterion not fulfilled

The activity of the antibiotics under clinical development against *Mycobacterium tuberculosis* was assessed according to the methodology detailed in the appendix (p 1). Antibiotics against *M tuberculosis* were evaluated for their innovation potential. The assessment of the potential innovation was performed by evaluating the absence of (known) cross-resistance to existing antibiotics. Surrogate predictors for the absence of cross-resistance, which were also assessed, included the following: new class (new scaffold), new target (new molecular binding site), and new MoA. CC=chemical class. DprE1=decaprenylphosphoryl-β-D-ribose 2′-epimerase. LeuRS=leucyl-tRNA synthetase. MoA=mechanism of action. NCR=no cross-resistance. PO=per os. T=new target. TB=tuberculosis. *The lead drug clofazimine is approved to treat leprosy and has been used off-label for tuberculosis.

Table 2: **Clinical pipeline of candidate antibiotics against *Mycobacterium tuberculosis* in 2023**

five potentially innovative agents with activity against WHO critical Gram-negative bacteria are in phase 1 clinical development, and thus, information regarding their clinical performance remains limited. The results of the phase 3 study on the efficacy of cefepime-taniborbactam in complicated urinary tract infection showed superior statistical efficacy versus meropenem (12·6 percentage points difference in the primary endpoint, 95% CI 3·1–22·2, p=0·009) and similar frequencies of serious adverse events.[81] However, clinical data on efficacy against infections caused by CRE, CRPA, or CRAB are not publicly available. Cefepime-taniborbactam is under regulatory evaluation by the FDA, which has issued a complete response letter identifying quality and manufacturing issues.

For further information, please see https://venatorx.com/pipeline/cefepime-taniborbactam/

Agents in development for treating drug-resistant tuberculosis

The 2023 tuberculosis pipeline includes 19 candidates under development, which is more than twice the number in the 2017 tuberculosis pipeline (appendix p 24). Several agents of these are promising candidates for new treatment strategies against drug-resistant *M tuberculosis* (table 2). Since the 2022 WHO antibacterial pipeline review[21] and WHO Global Tuberculosis Report 2022,[22] one new oxazolidinone agent, TBD09, entered phase 1, and three new tuberculosis drugs progressed to phase 2 development as follows:

(1) Alpibectir, a first-in-class bacterial transcriptional regulator, combined with low-dose ethionamide, increases the efficacy of ethionamide by stimulating its bioactivation. This combination might reduce dose-related adverse effects and prevent the emergence of resistance.[82]
(2) Dovramilast is a selective inhibitor of the enzyme PDE4, which downregulates the immunopathological response observed in tuberculosis.[83] The compound completed phase 2a clinical trials for tuberculosis in 2020 (NCT02968927).
(3) Sanfetrinem cilexetil, an orally available first-in-class tricyclic carbapenem, which was originally evaluated in phase 2 trials for upper respiratory infections in the 1990s, has now been repurposed for the treatment of drug-sensitive and drug-resistant tuberculosis.[84,85]

Both alpibectir and dovramilast act indirectly by potentiating antibiotic-mediated bacterial killing. As tuberculosis therapy is always administered as a polytherapy, these two agents have been included in this Review for a comprehensive approach.

Additionally, two tuberculosis drugs are currently in phase 2–3 and phase 3:

(1) SQ109 is a 1,2 ethylenediamine targeting the mycolic acid transporter MmpL3 in *M tuberculosis*.[86] A phase 2b study in Russia showed significantly higher cure rates at 6 months when SQ109 was combined with standard treatment regimens for MDR tuberculosis.[87]
(2) Sudapyridine is a novel diarylpyridine which showed better pharmacokinetic and safety profiles than those of bedaquiline both in vitro and in animal models of tuberculosis.[88] A phase 3 trial is ongoing in China (NCT05824871).

Innovation assessment of candidate drugs against *M tuberculosis*

Among the 19 agents against drug-resistant *M tuberculosis*, more than half (11 of 19) meet at least one innovation criterion; six show no cross-resistance, nine represent a new chemical class, and eight have new targets and mechanisms of action (table 2). Several candidates that could help to optimise treatment and increase tolerability are under development. However, a high unmet medical need for effective treatment regimens against extensively drug-resistant tuberculosis remains.[22,23]

Conclusions

Current candidate antibiotics are still insufficient to adequately address the threat of bacterial multidrug resistance. A major gap remains in the development of agents with activity against pathogens broadly resistant to existing antibacterial drugs. The number of anti-tuberculosis drugs has doubled since the 2017 pipeline revision; however, agents for extensively drug-resistant tuberculosis continue to represent an unmet therapeutic need. Since the release of the 2017 WHO BPP list, only two authorised products and several antibiotics under clinical development have sufficient available data to support activity against WHO critical pathogens. Only a few agents target metallo-β-lactamases, which are increasingly prevalent. Continuous efforts are essential for the identification of innovative molecular targets to curb antimicrobial resistance and for the optimisation of available formulations to improve patient compliance, facilitate outpatient treatment, and enable the treatment of newborns and children younger than 5 years.

Contributors

DM prepared the first draft of the manuscript. VG provided suggestions on the first draft. TR prepared the figures, tables, and references. VG, RAA, TR, and AMC reviewed the article and provided comments. All authors discussed the results and contributed to the editing of the manuscript. All authors have read and approved the final manuscript.

Declaration of interests

DM, RAA, and TR are WHO consultants to the WHO AMR division. DM, VG, TR, and AMC declare no competing interests. RAA works for CARB-X.

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