World Health Organization

2018 Update of antibacterial agents in clinical development

Key messages

As of 1 July 2018, a total of **48 antibiotics** (including combinations) and **10 biologicals** that target the **WHO priority pathogens,** ***Mycobacterium tuberculosis*** *and* ***Clostridium difficile*** were in the pipeline. The biggest gap and need is for innovative antibacterials to treat the priority pathogens, in particular critical Gram-negative bacteria.

The antibacterial agents in the pipeline are the following:

- **38** new therapeutic entities (30 antibiotics and 8 biologicals) and 4 combinations targeting priority pathogens.
- **10 agents** targeting *Mycobacterium tuberculosis.*
- **6 agents** (4 antibiotics and 2 biologicals) targeting *Clostridium difficile.*
- Of the **30** antibiotics targeting priority pathogens:
  - **15** are oral formulations;
  - **11** are expected to have some activity against at least one critical Gram-negative priority pathogen; and
  - **5** fulfill at least one of the four criteria for innovation, 1 agent against Gram-negative bacteria.
- **3** antibiotics and combinations containing a new chemical entity have gained market authorization between 2 May 2017 and 1 July 2018.

The World Health Organization's 2018 update of antibacterial agents in clinical development is based on the outcome of the second advisory group meeting that was held on 12 July 2018. The update follows the methodology described in the WHO 2017 publication *Antibacterial agents in clinical development – an analysis of the antibacterial clinical development pipeline, including tuberculosis*. The update period is from 2 May 2017 to 1 July 2018 and includes a targeted search of products in development in China. Funding for this report was kindly provided by the Governments of Austria and Germany.

Agents with market authorization

Table 1. Antibiotics and combinations containing a new chemical entity that have gained market authorization since June 2017

Name (trade name)	Approved by (date)	Antibiotic class	Route of administration (market authorization holder)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela)	FDA (6/2017)	Fluoroquinolone	iv & oral (Melinta)	○	○	○	●	–	–	–	–
Vaborbactam + meropenem (Vabomere)	FDA (8/2017)	Boronate BLI + carbapenem	iv (Melinta)	○	○	●[1]	/	?	✓	–	–
Plazomicin (Zemdri)	FDA (6/2018)	Aminoglycoside	iv (Achaogen)	○	○	●	/	–	–	–	–

Pathogen activity: ● *active;* **?** *possibly active;* ○ *not or insufficiently active;* **/** *activity not assessed as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods.*
Innovation assessment: ✓ *criterion fulfilled;* **?** *inconclusive data or no agreement among the advisory group;* – *criterion not fulfilled.*
Abbreviations: *BLI, β-lactamase inhibitor; CC, new chemical class; CRAB, A. baumannii, carbapenem-resistant; CRE, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; CRPA, P. aeruginosa-, carbapenem-resistant; FDA, Food and Drug Administration; iv, intravenous; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; OPP, other priority pathogens on the WHO priority pathogens list (PPL) ("high" and "medium" priority); T, new target.*
Underlined agents: *New chemical class.*
[1] *Active against K. pneumoniae carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae.*

Agents in clinical development

Table 2. Antibiotics and combinations containing a new chemical entity that are being developed for PPL pathogens

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Eravacycline	NDA[1] MAA[1]	Tetracycline	iv (Tetraphase)	?	○	●	/	–	–	–	–
Omadacycline (Nuzyra)	NDA[2]	Tetracycline	iv & oral (Paratek)	○	○	○	●	–	–	–	–
Iclaprim	NDA[3]	DHFR inhibitor	iv (Motif Bio)	/	/	/	●	–	–	–	–
Lascufloxacin	NDA[4]	Fluoroquinolone	iv & oral (Kyorin)	○	○	○	?	–	–	–	–
Relebactam + imipenem/cilastatin	3	DBO-BLI + carbapenem/ degradation inhibitor	iv (MSD)	○	?	●[5]	/	–	–	–	–
Cefiderocol	3	Siderophore cephalosporin	iv (Shionogi)	●	●	●	/	?	–	–	–
Lefamulin	3	Pleuromutilin[6]	iv & oral (Nabriva)	/	/	/	●	?	✓[6]	–	✓
Sulopenem, sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○[7]	/	–	–	–	–
Murepavadin (POL 7080)	3	Novel membrane targeting antibiotic	iv & inhaled (Polyphor)	/	●	/	/	✓	✓	✓	✓
Solithromycin	3[8]	Macrolide	iv & oral (Cempra/Melinta)	/	/	/	●	–	–	–	–
Levonadifloxacin Alalevonadifloxacin	3[9]	Fluoroquinolone	iv (Wockhardt) oral (Wockhardt)	○	○	○	?	–	–	–	–
Cefilavancin (TD-1792)	3[10]	Glycopeptide cephalosporine conjugate	iv (Thervance/ R-Pharm)	/	/	/	●	–	–	–	–
AAI101 + Cefepime	3	β-lactam BLI + cephalosporin	iv (Allecra)	○	○	○[11]	/	–	–	–	–
Contezolid Contezolid acefosamil	2/3[12]	Oxazolidinone	oral (MicuRx) iv (MicuRx)	/	/	/	●	–	–	–	–
Gepotidacin	2	NBTI (Triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●	✓	✓	–	✓
Zoliflodacin	2	NBTI (Spiropyrimidenetrione)	oral (Entasis/GARDP)	/	/	/	●	✓	✓	–	✓
ETX2514 + sulbactam	2	DBO-BLI /PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	–	–	–	–
Nafithromycin (WCK 4873)	2	Macrolide	oral (Wockhardt)	/	/	/	●	–	–	–	–
Afabicin(Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
BOS-228 (LYS-228)	2	Monobactam	iv (Boston Pharmaceuticals)	○	○	●	/	–	–	–	–
Zidebactam + cefepime	1	DBO-BLI/ PBP2 binder + cephalosporin	iv (Wockhardt)	○	?	●	/	–	–	–	–
Nacubactam + meropenem	1	DBO-BLI/ PBP2 binder + meropenem	iv (Roche)	○	?	●[5]	/	–	–	–	–
VNRX-5133 + cefepime	1	Boronate-BLI + cephalosporin	iv (VenatoRX)	?	?	●	/	?	–	–	?
ETX0282 + cefpodoxime	1	DBO-BLI + cephalosporin	oral (Entasis)	○	○	●[5]	/	–	–	–	–
SPR 741 + β-lactam	1	Polymyxin + β-lactam	iv (Spero)	?	?	?	/	–	–	–	–
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	○	○	○	●	–	–	–	–
TP-271	1	Tetracycline	iv & oral (Tetraphase)	?	○	○	●	–	–	–	–
TP-6076	1	Tetracycline	iv (Tetraphase)	●	○	?	/	–	–	–	–
TNP-2092	1	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?	–	–	–	–
AIC 499 + unknown BLI	1	β-lactam + BLI	iv (AiCuris)	?	?	?	/	–	–	–	–

Pathogen activity: ● *active;* **?** *possibly active;* ○ *not or insufficiently active;* **/** *activity not assessed as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. The only agents assessed against OPP were those that are not active against critical priority pathogens. OPP includes Gram-positive cocci, in the case of gepotidacin, zoliflodacin, solithromycin and delafloxacin, also Neisseria gonorrhoeae.*

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

Abbreviations: *BLI, β-lactamase inhibitor; CC, new chemical class; CRAB, A. baumannii, carbapenem-resistant; CRE, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; CRPA, P. aeruginosa-, carbapenem-resistant; DBO, diazabicyclooctane; DHFR, dihydrofolate reductase; EMA, European Medicines Agency; FDA, Food and Drug Administration; iv, intravenous; MoA, new mode of action; NBTI, novel bacterial topoisomerase II inhibitor; NCR, no cross-resistance to other antibiotic classes; NDA, new drug application (FDA); MAA, Marketing Authorization Application (EMA). OPP, other priority pathogens on the WHO priority pathogens list (PPL) ("high" and "medium" priority); PBP, penicillin-binding protein; T, new target.*

Underlined agents: *New chemical class*

[1]MAA submitted on 17 August 2017 and NDA submitted on 2 January 2018 for the iv form only for cIAI; PDUFA date 28 August 2018. [2]NDA submitted on 5 February 2018; PDUFA date, approved Oct 2, 2018. [3]Completed NDA submission 14 June 2018. [4]NDA in Japan only. [5]Active against K. pneumoniae carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae. [6]First systemic formulation of this class, which was previously and currently used topically and in animals. [7]Active against extended-spectrum β-lactamase-producing cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae. [8]Withdrawn MAA; FDA complete response letter; currently no development activities outside of Japan. [9] Phase-3 trial ongoing only in India, Phase 1 oral studies in the USA in 2014 (alalevonadifloxacin). [10]Developed only for Russian Federation. [11]Active against extended-spectrum β-lactamase-producing cephalosporin-resistant and some KPC-producing carbapenem-resistant Enterobacteriaceae. [12]Contezolid acefosamil: Phase 2 in USA not yet recruiting. Contezolid: NDA in China expected end of 2018.

Table 3. Antibiotic combinations that do not contain a new chemical entity

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity agains priority pathogens			
				CRAB	CRPA	CRE	OPP
Aztreonam + avibactam	3	Monobactam + DBO-BLI	iv (Pfizer)	○	○	●	○
Cefepime + tazobactam	1	Cephalosporin + β-lactam BLI	iv (Wockhardt)	○	○	?	○
Ceftibuten + clavulanic acid (C-Scape)	1	Cephalosporin + β-lactam BLI	oral (Achaogen)	○	○	○[1]	○
Colistin + zidovudine	1	Polymyxin + nucleoside analogue reverse transcriptase inhibitor	iv (Helperby)	●	●	●	○

Pathogen activity: ● *active;* **?** *possibly active;* ○ *not or insufficiently active.*
Abbreviations: *BLI, β-lactamase inhibitor; CRAB, A. baumannii, carbapenem-resistant; CRE, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; CRPA, P. aeruginosa-, carbapenem-resistant; DBO, diazabicyclooctane; iv, intravenous; OPP, other priority pathogens on the WHO priority pathogens list (PPL) ("high" and "medium" priority). Innovativeness assessment is not shown for these non-new chemical entity agents, as none of the four criteria are met.*
[1]*Active against cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae.*

Table 4. Agents for the treatment of tuberculosis in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
Pretomanid (PA 824)	3	Nitroimidazole	oral (TB Alliance)	?	–	–	?
SQ-109[1]	2/3	Diamine	oral (Sequella/Infectex)	?	–	✓	✓
Delpazolid (LCB01-0371)[2]	2	Oxazolidinone	oral (LegoChem)	–	–	–	–
Sutezolid[3]	2	Oxazolidinone	oral (TB Alliance/Sequella)	–	–	–	–
Telacebec (Q 203)	2	Imidazopyridine amide	oral (Qurient/Infectex)	✓	✓	✓	✓
Macozinone (PBTZ 169)	1 (2)	DprE1 inhibitor (benzothiazinone)	oral (Innovative Medicines for Tuberculosis Foundation/ Nearmedic Plus[4])	✓	✓	✓	✓
GSK-070 (GSK-3036656)	1	Leu RS inhibitor (oxaborole)	oral (GlaxoSmithKline)	✓	✓	✓	✓
OPC-167832	1	DprE1 inhibitor	oral (Otsuka)	?	✓	✓	✓
TBA-7371	1	DprE1 inhibitor	oral (TB Alliance)	✓	✓	✓	✓
TB-166[5]	1	Riminophenazine (clofazimine-analogue)	oral (Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College)	–	–	–	–

Innovation assessment: ✓ *criterion fulfilled;* **?** *inconclusive data;* **–** *criterion not fulfilled.*
Abbreviations: *CC, new chemical class; DprE1, decaprenylphosphoryl-β-D-ribose 2-epimerase; MoA, new mode of action; NCR, no cross resistance to other antibiotic classes; T, new target.*
Underlined agents: *New chemical class. These agents are being developed for use against tuberculosis (TB); their activity against other priority pathogens was not assessed.*
[1]*Chemically close to ethambutol.*
[2]*Delpazolid also completed a Phase 1 trial as injectable for MRSA and vancomycin-resistant Enterococcus spp. infections.*
[3]*Developed by Sequella and independently by the Global Alliance for TB Drug Development; non-exclusive patent is held by Sequella and by the Medicines Patent Pool.*
[4]*In Russian Federation developed by Nearmedic Plus.*
[5]*Clofazimine is approved for leprosy and used for TB.*

Table 5. Agents 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	2	Bis-benzimidazole	oral, not absorbed (Summit)	✓	✓	✓	✓
OPS-2071	2	Quinolone	oral (Otsuka)	–	–	–	–
DNV-3837 (MCB-3837)	1	Oxazolidinone-quinolone hybrid	iv (Deinove)	–	–	–	–
MGB-BP-3	1	DNA minor groove binder (distamycin)	oral, not absorbed (MGB Biopharma)	✓	✓	✓	✓

Innovation assessment: ✓ *criterion fulfilled;* **?** *inconclusive data or no agreement by the advisory group;* **–** *criterion not fulfilled.*
Abbreviations: *CC, new chemical class; iv, intravenous; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; T, new target.*
Underlined agents: *New chemical class. These agents are being developed for C. difficile infections; their activity against priority pathogens list (PPL) pathogens was not assessed.*

Table 6. Biological antibacterial agents in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens		
				PA	SA	CD
SAL-200	2	Phage endolysin	iv (Intron)	/	●	/
CF-301	2	Phage endolysin	iv (Contrafect)	/	●	/
Suvratoxumab[1]	2	Anti-*S. aureus* IgG monoclonal antibody	iv (MedImmune)	/	●	/
MEDI-3902[1]	2	Anti-*P. aeruginosa* IgG monoclonal antibody	iv (MedImmune)	●	/	/
AR-105 (Aerucin)	2	Anti-*P. aeruginosa* IgG monoclonal antibody	iv (Aridis)	●	/	/
IMM-529	1/2	Anti-*C. difficile* polyclonal antibody	oral (Immuron)	/	/	●
AR-301 (tosatoxumab)	1/2	Anti-*S. aureus* IgM monoclonal antibody	iv (Aridis)	/	●	/
514G3	1/2	Anti-*S. aureus* IgG monoclonal antibody	iv (XBiotech)	/	●	/
DSTA 4637S	1	Anti-*S. aureus* IgG monoclonal antibody/rifamycin	iv (Genentech/Roche)	/	●	/
PolyCab	1	Anti-*C. difficile* polyclonal antibody	iv (MicroPharm)	/	/	●

Pathogen activity: ● *active;* / *not applicable.*
Abbreviations: *CD, C. difficile; IgG, immunoglobulin G; IgM, immunoglobulin M; iv, intravenous; PA, P. aeruginosa; SA, S. aureus.*
These biologics are not influenced by conventional resistance mechanisms, and the criterion of innovation was not applied.
[1]*These products are in trials for pre-emptive indications only.*

Table 7. Agents where the development was suspended or for which there is no recent information

Name (synonym)	Phase	Antibiotic class	Developer
CB-618	1	DBO-BLI	Merck
IDP-73152	1	Peptide deformylase (PDF) inhibitor	IIDong
TD-1607	1	Glycopeptide-cephalosporin hybrid	Theravance
Benapenem	1	Carbapenem	Xuanzhu/KBP BioSciences
KBP-5081	1	Oxazolidinone	Xuanzhu/KBP BioSciences
KBP-0078	1	Oxazolidinone	Xuanzhu/KBP BioSciences
DS-2969	1	GyrB inhibitor	Daiichi Sankyo
YF-49-92.MLS	1	Nitroimidazole	C & O Pharmaceutical
GSK-3342830	1	Siderophore-cephalosporin	GSK
Ramoplanin	2	Lipodepsipeptide	Nanotherapeutics
Panobacumab	2	Anti-*P. aeruginosa* IgG monoclonal antibody	Aridis
CG 400549	2	FabI inhibitor	CrystalGenomics
Finafloxacin	2	Fluoroquinolone	MerLion
Brilacidin	2	Novel Membrane-targeting antibiotic	Innovation Pharmaceuticals
Kelimycin	3	Macrolide	IMB/ CAMS /Shenyang Tonglian

WORLD HEALTH ORGANIZATION
Essential medicines and
health products
20 avenue Appia
CH-1211 Geneve 27
Tel.: (+41) 22 791 46 11
iauinfo@who.int
http://who.int/medicines

LINKS TO ADDITONAL INFORMATION

WHO report (http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/)
Global Health Observatory on Health R&D
(http://www.who.int/research-observatory/monitoring/processes/antibacterial_products/en/)
Lancet Article (http://dx.doi.org/10.1016/S1473-3099(18)30513-9)

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