Analysis of the clinical antibacterial and antituberculosis pipeline

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This analysis of the global clinical antibacterial pipeline was done in support of the Global Action Plan on Antimicrobial Resistance. The study analysed to what extent antibacterial and antimycobacterial drugs for systemic human use as well as oral non-systemic antibacterial drugs for *Clostridium difficile* infections were active against pathogens included in the WHO priority pathogen list and their innovativeness measured by their absence of cross-resistance (new class, target, mode of action). As of July 1, 2018, 30 new chemical entity (NCE) antibacterial drugs, ten biologics, ten NCEs against *Mycobacterium tuberculosis*, and four NCEs against *C difficile* were identified. Of the 30 NCEs, 11 are expected to have some activity against at least one critical priority pathogen expressing carbapenem resistance. The clinical pipeline is dominated by derivatives of established classes and most development candidates display limited innovation. New antibacterial drugs without pre-existing cross-resistance are under-represented and are urgently needed, especially for geographical regions with high resistance rates among Gram-negative bacteria and *M tuberculosis*.

Background

Although improved preventive measures have reduced resistance in some pathogens, antibacterial drug resistance has increased worldwide, posing an enormous clinical and public health burden.[1–3] This is not surprising given the strong selection pressure caused by extensive antibacterial drug use in humans, animals, agriculture, and the food chain, which has also led to considerable environmental pollution. In contrast to the first decades of the antibiotic era, the rise in resistance has not been sufficiently countered by the development of new antibiotics. Ever rising resistance rates have increased society's awareness of this issue, which has prompted political commitment and global initiatives. The 68th World Health Assembly, Geneva endorsed the Global Action Plan on Antimicrobial Resistance in 2015 and the United Nations General Assembly, New York reinforced these commitments in 2016 at a high-level meeting on antimicrobial resistance. This public health issue is on the agenda of the G7 and the G20, which both supported actions to encourage the development of new antibacterial treatments.

One of the strategic objectives of the Global Action Plan is to increase research and development for new antibacterial drugs to ensure the sustained availability of treatment options. The WHO Priority Pathogen List (PPL) for antibiotic research and development identifies the priorities on which research and development of new antimicrobials should be focused.[4] This effort was complemented with a comprehensive analysis of the global clinical pipeline of antibacterial and antimycobacterial drugs (hereinafter, collectively referred to as antibacterial). This review presents a catalogue of all antibacterial drugs in clinical development and assesses both their potential activity against PPL pathogens including *Mycobacterium tuberculosis* and *Clostridium difficile* as well as their degree of innovation. Unlike earlier clinical pipeline reviews of antibacterial drugs, this analysis focuses on the assessment of the pipeline against global public health needs, its

potential innovation, and clinical value globally. This analysis, in conjunction with the WHO PPL, supports the identification of research and development gaps from a public health perspective and allows for better focused public research and development investment. As drug development is subject to rapid changes, the analysis will be annually updated and the data made openly available at the WHO Global Observatory on Health Research and Development.[5]

Methods

We did a systematic review of the antibacterial drugs in the clinical pipeline with exhaustive efforts to identify all antibacterial drugs under study. We carefully evaluated evidence to identify limitations on specific antibacterial effects. All identified molecules and detailed assessment were transparently reported to inform decision making. Publicly available information concerning antibacterial drugs in clinical development was identified by scrutinising existing pipeline reviews,[6–8] including the Stop TB Partnership (https://www.newtbdrugs.org), international

Key messages

- The current clinical pipeline contains 30 new antibacterial drugs with activity against priority pathogens and is dominated by derivatives of established classes
- New antibacterial drugs to address the problem of extensively or even pan-drug resistant Gram-negative bacteria without pre-existing cross-resistance to existing drug classes are under-represented and are urgently needed
- Extensive efforts to develop new classes of antibacterial drugs, especially against Gram-negative bacteria, have not yet been translated into clinical development
- The clinical pipeline analysis highlights the continued need for innovative antibacterial drugs against the WHO critical priority pathogens and *Mycobacterium tuberculosis*

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	Approved by (date)	Antibiotic class	Route of administration (market authorisation holder)	Indication	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela)	FDA (6/2017)	Fluoroquinolone	IV + oral (Melinta)	ABSSSI (CAP, Ph3)	-	-	-	A	..	..	..	..
Vaborbactam + meropenem (Vabomere)	FDA (8/2017)	Boronate BLI + carbapenem	IV (Melinta)	cUTI (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*)	-	-	A*	na	ID	✓	..	..
Plazomicin (Zemdri)	FDA (6/2018)	Aminoglycoside	IV (Achaogen)	cUTI	-	-	A	na	..	..	..	..

See Table 2 for definitions. ABSSSI=acute bacterial skin and skin structure infection. cUTI=complicated urinary tract infection. *Active against *Klebsiella pneumoniae* carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae.

Table 1: Antibiotics and combinations containing a new chemical entity that are being developed against priority pathogens, approved by FDA 2017/2018

trial registry platforms (Clinical Trials; WHO trial registry platform), the commercial database Adis Insight (http://adis.springer.com), a patent database (the Lens; https://www.lens.org), conference abstracts, publications, and press releases. These sources were supplemented by searches through PubMed for peer-reviewed journal articles in all languages and Google for grey literature. The search cutoff date was July 1, 2018. Additional details about the search strategy and selection criteria are described in the WHO report.[9]

For some agents, some data sources reported different phases of development in different countries. In that situation, both or the most advanced development phase reported has been listed. The dataset retrieved through the previously mentioned searches was shared with relevant stakeholders, including industry associations, and verified feedback was included in the dataset. Companies that sponsor research were not contacted. Whenever possible, the pipeline evaluation was based on peer-reviewed literature, searching known names and synonyms of each drug to build a dedicated dossier. In the assessment of early clinical development stage agents, publicly available presentations and posters from scientific conferences, and information published by the developers were also evaluated and included if considered scientifically sound. The resulting data documentation was provided to an advisory group of international experts with expertise in drug discovery, drug development, microbiology, chemistry, pharmacokinetics or pharmacodynamics, infectious diseases, and global health. The advisory group was selected according to complementary expertise taking into account geographical representation and gender balance (appendix). The experts assessed each agent for activity against the WHO priority pathogens and the innovation criteria at a face-to-face advisory group meeting on June 12–13, 2017, in Geneva. A new cycle of evaluation evolved through several iterations, over a period of 12 months, including an additional virtual advisory group meeting on July 12, 2018. Consensus agreement of the

advisory board was reached during the advisory group meetings. Potential conflicts of interest were managed following the *World Health Organization Handbook for Guideline Development*.[9,10] Members of the advisory group who had conflicts of interest with respect to a particular drug were excluded from the discussion on that drug. Experts' feedback informed all evaluation steps and final decisions were incorporated into the pipeline evaluation.

Our analysis included new therapeutic entities that were in clinical development for systemic human use, had publicly available information, and did not yet have regulatory approval anywhere in the world for human use. The review was restricted to agents that could be used to treat bacterial infections and have a specific antibacterial effect. Oral, non-systemic antibacterial drugs for *C difficile* infections were also reviewed. Additionally, the analysis included fixed-dose combinations of potentiators (molecules that enhance the effectiveness of antibacterial drugs but are not necessarily antibacterial themselves) and antibacterial drugs, even if they did not contain a new therapeutic entity. Excluded were preventive medicines (eg, vaccines or topical decolonising agents), immunomodulating or microbiome-modulating agents, non-specific inorganic substances, biodefence agents, agents only for topical application, and new formulations of approved drugs. Only antibacterial drugs that were in active development were included. Drugs that were identified as under development but which had not progressed through the pipeline since Jan 1, 2015, were excluded from this analysis.

The advisory group classified each included drug on the basis of its expected activity against WHO priority pathogens (carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacteriaceae or others) and its innovative potential assessing whether cross-resistance to other used antibacterial drugs was documented or suspected. The expanded biological definition of innovation as no cross-resistance was applied on the basis of the overarching requirement that

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

Pathogen activity: A=active; ?=possibly active; -=not or insufficiently active; na=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. Innovation assessment: ✓=criterion fulfilled; ID=inconclusive data or no agreement among the advisory group; ..=criterion not fulfilled; NCR=no cross-resistance to other antibiotic classes; CC=new chemical class; T=new target; MoA=new mode of action; BLI=β-lactamase inhibitor; CRAB=*Acinetobacter baumannii*, carbapenem-resistant; CRPA=*Pseudomonas aeruginosa*, carbapenem-resistant; CRE=Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; OPP=other priority pathogens on the WHO PPL (high and medium priority); OPP includes usually Gram-positive cocci, in the case of gepotidacin, zoliflodacin, solithromycin and delafloxacin, also *Neisseria gonorrhoeae*; DBO=diazabicyclooctane; DHFR=dihydrofolate reductase; iv, intravenous; NBTI=novel bacterial topoisomerase II inhibitor; NDA=new drug application (FDA); PBP=penicillin-binding protein. See panel for details on antibiotics and combinations.

Table 2: Antibiotics and combinations containing a new chemical entity that are being developed against priority pathogens

a drug shall not be affected by known cross-resistance to existing drugs in the organisms and indications for which it is intended to be used. Additionally, the three traditional criteria for innovation—a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site), and a novel mode of action were applied. The basis for these criteria of innovation have been laid out in a recent publication.[11] The assessment of

activity and innovation was based on peer-reviewed publications when available and additional information from presentations and posters at scientific conferences. In-vitro activity of drugs that are not being developed for relevant indications was not considered in the evaluation. A specific focus was placed on the assessment of in-vitro and in-vivo or clinical characteristics (when available). Additionally, minimum inhibitory concentrations, in-vivo models, and if available, data on pharmacokinetics or pharmacodynamics were analysed. Based on these critical evaluations, the antibacterial activity of the drugs was classified according to the categories active, not or insufficiently active, or possibly active in case of inconclusive or insufficient data. For modified compounds of a known class with few or no data on their activity against specific pathogens, the advisory group made assumptions on the basis of the properties of the known antibiotic class to classify the agents as possibly active on the basis the activity of similar drugs with activity against the respective pathogen. Pathogen-focused drugs against *M tuberculosis* and *C difficile* developed specifically against these pathogens were therefore not assessed for their activity against PPL pathogens. The same applied to the species-specific biological products.

Results

Three antibiotics have been approved by the US Food and Drug Administration since the first WHO report in September, 2017:[9] delafloxacin, meropenem-vaborbactam, and plazomicin (table 1). By the cutoff date of July 1, 2018, 30 new chemical entity (NCE) antibacterial drugs against PPL pathogens (table 2; panel), ten biologics (table 3), ten NCEs against *M tuberculosis* (table 4), and four NCEs

	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens		
				P seudomonas aeruginosa	*Staphylococcus aureus*	*Clostridium difficile*
DSTA-4637S	1	Anti- *S aureus* IgG monoclonal antibody/rifamycin	IV (Genentech/Roche)	NA	A	NA
PolyCab	1	*C difficile* polyclonal antibody	IV (MicroPharm)	NA	NA	A
IMM-529	1/2	*C difficile* polyclonal antibody	Oral (Immuron)	NA	NA	A
AR-301 (tosatoxumab)	1/2	Anti-*S aureus* IgM monoclonal antibody	IV (Aridis)	NA	A	NA
514G3	1/2	Anti-*S aureus* IgG monoclonal antibody	IV (XBiotech)	NA	A	NA
SAL-200	2	Phage endolysin	IV (Intron)	NA	A	NA
CF-301 (exebacase)	2	Phage endolysin	IV (Contrafect)	NA	A	NA
Suvratoxumab*	2	Anti-*S aureus* IgG monoclonal antibody	IV (MedImmune)	NA	A	NA
MEDI-3902*	2	Anti-*P aeruginosa* IgG monoclonal antibody	IV (MedImmune)	A	NA	NA
AR-105 (Aerucin)	2	Anti-*P aeruginosa* IgG monoclonal antibody	IV (Aridis)	A	NA	NA

These biologics are not influenced by conventional resistance mechanisms and the criterion of innovation was not applied. *These products are in trials for pre-emptive indications only. Pathogen activity: A=active. NA=not applicable. These biologics are not influenced by conventional resistance mechanisms and the criterion of innovation was not applied. *These products are in trials for pre-emptive indications only.

Table 3: Biological antibacterial agents in clinical development

	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
Pretomanid (PA-824)	3	Nitroimidazole	Oral (TB Alliance)	ID	..	..	ID
SQ-109*	2/3	Diamine	Oral (Sequella/Infectex)	ID	..	✓	✓
Delpazolid (LCB01-0371)†	2	Oxazolidinone	Oral (LegoChem)	..	..	..	..
Sutezolid‡	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)§	✓	✓	✓	✓
GSK070 (GSK-3036656)	1	Leu RS inhibitor (oxaborole)	Oral (GlaxoSmithKline)	✓	✓	✓	✓
OPC-167832	1	DprE1 inhibitor	Oral (Otsuka)	ID	✓	✓	✓
TBA-7371	1	DprE1 inhibitor	Oral (TB Alliance)	✓	✓	✓	✓
TBI-166¶	1	Riminophenazine (clofazimine analogue)	Oral (Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College)	..	..	..	..

Innovation assessment: ✓criterion fulfilled; ID=inconclusive data; ..=criterion not fulfilled. NCR=no cross-resistance to other antibiotic classes; CC=new chemical class; T=new target; MoA=new mode of action; DprE1=decaprenylphosphoryl-β-D-ribose 2-epimerase. *Chemically close to ethambutol. †Delpazolid also completed a phase-1 trial as injectable for meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp infections. ‡Developed by Sequella and independently by the Global Alliance for TB Drug Development, non-exclusive patent held by Sequella and by The Medicines Patent Pool. These agents are being developed for use against tuberculosis; their activity against other priority pathogens was not assessed. §In Russia developed by Nearmedic Plus. ¶Clofazimine is approved for leprosy and used for tuberculosis.

Table 4: Antibiotics for the treatment of tuberculosis in clinical development

against *C difficile* (appendix) were identified. Additionally, four combinations of antibiotics and potentiators or enablers that do not contain new chemical entities were included.

Of the 30 NCEs, four have been submitted for review at FDA or the European Medicines Agency (EMA) or the Japanese Pharmaceuticals and Medical Devices Agency: eravacycline, iclaprim, omadacycline, and lascufloxacin. Eleven are expected to have some activity against at least one of the WHO critical priority pathogens that are resistant to carbapenems, and thus mostly extensively-drug resistant (XDR) according to the European Centre for Disease Prevention and Control.[12] From these 11 drugs, only the siderophore-conjugated cephalosporin cefiderocol provides coverage against all three critical priority pathogens: carbapenem-resistant *A baumannii*, carbapenem-resistant *P aeruginosa*, and carbapenem-resistant Enterobacteriaceae. Additionally, two other drugs have activity against carbapenem-resistant *A baumannii* (ETX2514/sulbactam, TP-6076) and only one against carbapenem-resistant *P aeruginosa* (murepavadin). Altogether, eight drugs have at least partial coverage of carbapenem-resistant Enterobacteriaceae.

Ten of the 11 new antibacterial drugs in the pipeline with activity against Gram-negative bacteria are derivatives of the existing classes of β-lactams (with or without β-lactamase inhibitors or tetracyclines; figures 1 and 2). All these derivatives are designed to address certain class-specific resistance mechanisms. Despite potential success with this approach, not all class-specific mechanisms can be overcome by using derivatives of the same class and class-independent co-resistance can occur. In particular, *P aeruginosa* and *A baumannii* have diverse resistance mechanisms beyond the production of
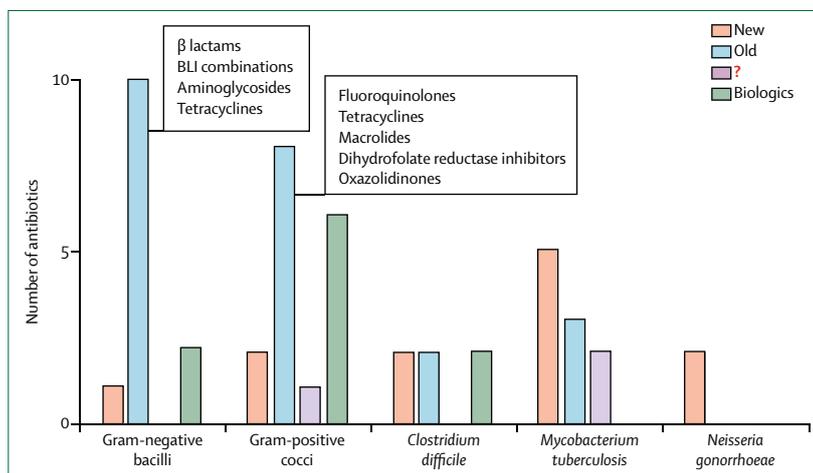

Figure 1: **Number of antibiotics in clinical development according to focus of activity**
Gram-negative bacilli were carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant Enterobacteriaceae; Gram-positive cocci were staphylococci and streptococci. Gepotidacin was counted in the category Gram-positive cocci and *Neisseria gonorrhoeae*. Drugs with inconclusive or unknown activity were not included. BLI=β-lactamase inhibitor. New=new chemical class small molecule. Old=modified class small molecule including combinations with BLIs; ?=Innovation status inconclusive or unknown.

β-lactamases with mechanisms such as a decreased permeability of the outer membrane, upregulated efflux pumps, and modified penicillin-binding proteins.[13–15] The inconsistent inhibitory oxacillinase (OXA) enzymes and the prominence of non-β-lactamase mediated resistance mechanisms explain why most new BLI combinations add no benefit in the case of *A baumannii* and only negligable benefits for *P aeruginosa*.

A new aspect of BLIs in the clinical pipeline is the evolution of the chemical class of diazabicyclooctanes which are non-β-lactam BLIs with avibactam as the first
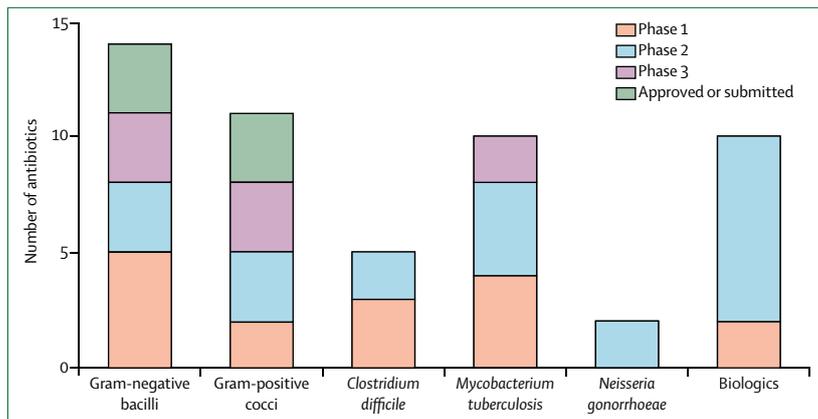
Figure 2: Number of antibiotics in clinical development phases and recent approvals according to focus of activity
Gram-negative bacilli: carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae; Gram-positive cocci: staphylococci, streptococci. Drugs with inconclusive or unknown activity were not counted. Drugs approved after June, 2017, were included.

representative.[16] Although BLIs have historically lacked intrinsic antimicrobial activity, the new subgroup of diazabicyclooctane-based molecules now includes development BLI candidates with intrinsic antibacterial activity. Antibacterial activity through binding to penicillin binding protein 2 becomes in some more recent compounds (nacubactam, ETX2514, and zidebactam) an important or even dominating factor in the combination and provides synergistic activity.[17–19]

Cefiderocol, a cephem, is intrinsically more stable to β-lactamases and hence not dependent on a BLI partner. In addition, cefiderocol's uptake is enhanced by siderophore-mediated use of the bacterial iron transport mechanism.[20] Based on data available, this compound has the broadest Gram-negative spectrum of any agent in the pipeline.[21]

Not surprisingly, pre-existing resistance is also seen in other derivatives of known classes. Tetracyclines are a good example, with more than 1000 resistance genes reported.[22] New tetracyclines in the clinical pipeline address some of the class-specific resistance mechanisms and improve coverage in a given species. In general, new tetracyclines have been optimised against either Gram-negative or Gram-positive bacteria.

Owing to their potential clinical benefit, we additionally analysed four combinations using pairs of already approved entities. Aztreonam plus avibactam combines an old monobactam with intrinsic stability against class B β-lactamases (metallo-β-lactamases) and the recently registered DBO BLI avibactam with inhibitory activity of class A and C β-lactamases.[23] Expansion of the spectrum is specifically expected for metallo-β-lactamase-producing Enterobacteriaceae due to the intrinsic stability of monobactams to these enzymes.[24] The combination of cefepime and tazobactam is expected to improve on piperacillin–tazobactam through better protection against extended spectrum beta-lactamases (ESBLs), as

cefepime is easier to potentiate than piperacillin with an optimised tazobactam dose.[25] Zidovudine is active against carbapenem and colistin resistant (mobilised colistin resistance [mcr] positive) Enterobacteriaceae and a fixed combination of zidovudine with colistin is in clinical development.[26] A new oral fixed combination of ceftibuten and clavulanic acid will target urinary tract infections caused by ESBL-producing Enterobacteriaceae.

All of the mentioned drugs are derivatives of extensively used antibacterial classes and pre-existing resistance is likely to appear quickly. Of the anti-Gram-negative antibacterial drugs included in the pipeline, only murepavidin is classified as being innovative as it belongs to a new chemical class.[27] It also has a new target and mode of action with no known cross-resistance mechanism to approved antibacterial drugs and is thus classified in this analysis as meeting the innovative criteria. It is active only against *P aeruginosa*.[28]

Most anti-Gram-negative NCEs in the pipeline will be available only as parenteral (intravenous) formulations with the exceptions of sulopenem, which is administered as a prodrug. This synthetic penem described in the 1980s has activity against both Gram-positive bacteria and ESBL-producing Enterobacteriaceae but no activity against carbapenem-resistant organisms. Data on its absorption and urinary recovery were not identified in the public domain. The oral carbapenem in clinical development, tebipenem, was not included in this analysis as it is an approved drug in Japan. A new addition to potential oral treatments is the BLI-cephalosporin combination, ETX0282/cefpodoxime, which has entered clinical development and is active against carbapenem-resistant Enterobacteriaceae except metallo-β-lactamase producers.[29]

Most drugs with focus on Gram-positive cocci are derivatives of known fluoroquinolones, tetracyclines, macrolides, dihydrofolate reductase inhibitors (trimethoprim), and oxazolidinone classes (table 2). The FabI inhibitor afabicin and potentially lefamulin (pleuromutilin) were classified as innovative for human use, although pleuromutilins have been used before in a topical formulation and in the animal sector.[30]

The functional class of bacterial topoisomerase inhibitors is not new but comprises new chemical structures and distinct but overlapping binding sites with fluoroquinolones without evident cross-resistance to date.[31] Both of the new bacterial topoisomerase inhibitors in development are orally available and their spectrum targets Gram-positive pathogens, respiratory tract infection pathogens and *Neisseria gonorrhoeae*.[32] No cross-resistance of zoliflodacin with fluoroquinolones has been described to date in *N gonorrhoeae*.[33] Although several antibacterial drugs in the pipeline have in-vitro activity against *N gonorrhoeae*, only the two new bacterial topoisomerase inhibitors are being developed for this indication at the time of writing.

Biologics comprise monoclonal and polyclonal antibodies, and phage-derived products (table 3). So far, only

one biologic, a monoclonal antibody against *C difficile* toxin B (bezlotoxumab), has been approved by the EMA and FDA. Three monoclonal antibodies against *P aeruginosa*, four monoclonal antibodies against *Staphylococcus aureus* (including one that is linked to an antibiotic) and two polyclonal antibodies against *C difficile* are in clinical development at the time of writing. One polyclonal antibody preparation against *C difficile* acts systemically against the *C difficile* toxin B, with the other active in the large intestine after oral application. Two engineered endolysins, which are enzymes used by bacteriophages to destroy the bacterial peptidoglycan cell wall, are being developed against *S aureus* infections. Insufficient information is available regarding the potential for resistance development either by immune response to the product or target alterations. The potential place of biologics in the prevention or treatment of infections will require completion and careful evaluation in clinical trials.

Ten drugs are being developed against *M tuberculosis*. Six of the ten new drugs in development qualified as innovative or probably innovative (table 4). Several new targets are pursued: DprE1 (cell wall synthesis), MmpL3 (membrane transporter), Leucyl-tRNA synthetase (protein synthesis), qcrB (subunit of the cytochrome bc1 complex), and enzymes of the respiratory electron transport chain. Three drugs in clinical development target DprE1.[33,34] As listed in table 4, most drugs in the pipeline are in early clinical phases and more information is needed to assess the individual drugs, especially the contribution they might have on the activity of specific combination regimens. Further time is needed to assess new antituberculosis medicines for potential or acquired resistance as resistance patterns might not clearly emerge even in advanced development phases.

Four new drugs against *C difficile* are in clinical development, with two of them representing new classes (appendix). Three of four small molecule drugs against *C difficile* are oral formulations with an active ingredient not sufficiently absorbed to be systemically relevant. This fact mitigates two commonly encountered hurdles in antibacterial drug research and development: pharmacokinetics and toxicity. Hence treatment of *C difficile* infection is a viable option to bring a new class of antibacterial drugs with such liabilities to the market. In addition to the small molecules in the clinical pipeline there are two polyclonal antibodies in development as previously described (table 3). In comparison with other acute bacterial infectious diseases, there is more innovation in the *C difficile* area despite demand for innovation related to resistance in *C difficile* being lower.

Discussion

Innovation is of key interest for this pipeline analysis. In the context of bacterial resistance and the corresponding need for new antibacterial drugs, each of the three traditional criteria for innovation on its own—a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site), and a novel mode of action—can be confounded by complex drug–bacteria interactions. Each of these criteria might be insufficient to characterise innovation if the goal is to develop new antibacterial drugs against the most resistant priority pathogens. Therefore, the overarching criteria of lack of known cross-resistance as the most relevant criterion when assessing innovation in the context of antibiotic resistance was used as a reasonable predictor of a drug's activity against XDR or pan-drug resistant bacteria.[11]

In contrast to the first WHO pipeline analysis in 2017, there are more antibacterial drugs active against Gram-negative bacilli than Gram-positive cocci in development, especially in phase 1. Gram-positive resistance, particularly in *S aureus*, emerged in the 1990s and early 2000s, raised public awareness, and led to research and development investment towards a stronger pipeline in that segment, including a few drugs that met the innovation criteria. Owing to this effort, there are now relatively few predicted gaps for adequate treatment of multiresistant *S aureus*. However, despite potential in-vitro activity of some current candidates, no antibiotic in development is specifically targeted at infections caused by *Enterococcus faecium*.

Efforts focusing on Gram-negatives began to emerge as multi-drug resistance (MDR) and XDR rose globally and concern increased substantially, but progress translating these discoveries has been slow, partly owing to the difficulty overcoming two lipid bilayer membranes and associated efflux pumps in Gram-negative bacteria.[35] The Gram-negative clinical pipeline displays little innovation and gaps remain with respect to critical PPL pathogens. Based on the long research and development timelines of 10 or more years for any discovery project, we have a pipeline in which anti-Gram-positive projects are sufficient in response to the medical need although innovation is also neglected in the Gram-positive space.

What are the implications of low innovation in the Gram-negative category? We predict substantial gaps in coverage, especially for carbapenem-resistant *A baumannii* and carbapenem-resistant *P aeruginosa*, but also carbapenem-resistant Enterobacteriaceae in some geographical areas. The anti-Gram-negative research and development has focused on the β-lactam class and BLIs, as these are very well validated starting points for improving efforts. So far, BLIs that inhibit classes A, C, and D of β-lactamases predominate. The epidemiology of β-lactamases establishes the usefulness of new BLI combinations in different geographical regions in pathogens with BLs as the main resistance mechanism in β-lactam antibiotics. Carbapenem-resistant Enterobacteriaceae are an important example as the production of various carbapenemases is the major resistance mechanism.[2] Most new BLIs inhibit *Klebsiella pneumoniae* carbapenemase (KPC) enzymes (prevailing in North America, Latin America, and in some European countries), whereas the metallo-β-lactamases (MBLs;

class B) are not inhibited (dominant in Asia, the south Pacific region and important in some European countries and Africa).[36] Similarly, OXA carbapenemases are mostly not covered (dominant in African countries and important in the Middle East and some European countries).[36,37] In countries with especially high rates of carbapenem resistance in Enterobacteriaceae and a high prevalence of β-lactams other than KPC, the gaps in coverage (MBLs and OXAs) of the new BLIs are most relevant.[36] Whether the new BLI VNRX-5133 with expanded coverage of the MBLs New-Delhi metallo (NDM), and Verona integron-encoded metallo-β-lactamase (VIM) holds its promise cannot be assessed owing to scarce information.[38] The next generation cephalosporin cefiderocol has improved β-lactamase stability and its structure incorporates a siderophore to facilitate penetration into the bacterial cell wall. These features might provide improved coverage of all three WHO critical priority pathogens.[39] The potential for cross-resistance to known resistance mechanisms and its relevance is not known so far.

Another concern is the lack of orally available innovative antibacterial drugs in the clinical pipeline. These are valuable in many settings but are especially needed for the treatment of common community-acquired infection, such as urinary tract infections caused by ESBL-producing and fluoroquinolone-resistant Enterobacteriaceae. In the community, non-judicious use of modified derivatives of existing antibiotic classes will increase selection pressure and the risk of even faster spread of resistance in Gram-negative bacteria in the community and health-care settings. This situation is especially risky in drugs with cross-resistance to carbapenems. Future oral penems or carbapenems (eg, sulopenem or tebipenem) might aggravate the selection pressure for carbapenem resistance if used widely. New antibacterial classes without co-selection pressure that are orally available, optimised for urinary tract infections, and restricted for targeted use are urgently needed.

It has been proposed that positive results in animal disease models have questionable value in the field of antibacterial biologics as they can be followed by clinical failure.[40] To date, only two monoclonal antibodies have been approved for infectious diseases outside the biothreat field: palivizumab, for the prevention of respiratory syncytial virus, and bezlotoxumab, which targets the *C difficile* toxin B to reduce recurrence risk. Technological advances in the field, moving to multi-specific, multi-functional strategies, and improved definition of patient groups at risk as well as commercial reasons have attracted multiple specialised companies to push their biologics into clinical trials.[41,42] Antibodies are usually studied as preventive or adjunctive therapy. A potential clinical effect of antibody use as adjunctive therapy has not yet been shown.

For *C difficile* infections, two new chemical classes are in phase 1 and 2 clinical development and it is not known

yet if they will show an additional benefit over vancomycin or metronidazole.[43] Although the burden of disease might be high, it is usually not associated with acquired resistance to antibiotics.[44]

The development of new antituberculosis drugs faces specific challenges, including the need to treat tuberculosis with a combination of at least three different antibacterial drugs. Unlike the large majority of tuberculosis patients worldwide who can expect a relapse-free cure with a 6-month course of first-line medication, patients with drug-resistant tuberculosis (usually including resistance to at least rifampicin, commonly combined with isoniazid resistance, or with further resistance to fluoroquinolones or aminoglycosides, or both) require treatment regimens which are longer, less effective, and less accessible than first-line regimens, but more costly, toxic, and complicated to deliver. Most second-line MDR-tuberculosis regimens are designed to last 9–24 months, presenting a formidable challenge to health service providers to ensure patient adherence and obtain sustainable cure.[45,46] New drugs and drug regimens are needed to shorten and simplify therapy for both drug-sensitive and drug-resistant *M tuberculosis*.[47] Intracellular environment, dormant forms, and complex pharmacokinetics add to the challenges of drug research and development in the tuberculosis arena. Although some new targets and new classes are listed in the pipeline, there were only ten drugs in clinical development at the time of writing. Given the high anticipated attrition rates that have been seen with other molecules, and the remaining challenge of identifying the optimal drug combination, the clinical pipeline for tuberculosis drugs is still insufficient.[48,49]

The limitations of our analysis are mainly grounded around information variability due to scarce publicly available data. Although great efforts were made to ensure that this analysis was as complete as possible and to base assessments on peer-reviewed publications, the availability and quality of data varied substantially between clinical candidates. Despite WHO's requirements on clinical trial transparency, some of the trials with products in this pipeline are not listed in any clinical trial registry. Lack of key information especially impeded the assessment of expected activity against PPL pathogens. Whereas for some agents, peer-reviewed activity assessments were available, for others we had to rely on scarce company information, or the comparison with other agents with a similar structure, if no data had been published. Furthermore, for some agents the assessment was made purely on the basis of in-vitro activities, whereas for others it was made on the basis of clinical activities and pharmacokinetics or pharmacodynamics.

The assessment of innovation was also subject to limitations. Lack of cross-resistance is the most relevant criterion when assessing innovation in the context of antibiotic resistance.[11] In early stages of development, sufficient information might not be available. Novel

chemical scaffolds, binding sites, and modes of action are reasonable predictors for a lack of cross-resistance. For these reasons, all four aspects were separately assessed. However, in some instances a question mark indicates where information was insufficient (eg, structure not published) or the experts could not reach a final agreement on novelty. This pipeline analysis should be regarded as a snapshot at the time of its creation. The field moves quickly as shown by the rapid changes captured by our analysis over a time period of 12 months; as more information becomes available, the innovation and spectrum of activity assessments might change.

Conclusion

The clinical pipeline of drugs against Gram-negative bacteria is dominated by derivatives of old classes, reflecting the lower research and development risk, the short-term horizon of investments, and the scientific challenges of pursuing innovative approaches. Owing to decades of selection pressure with existing antibacterial classes, new derivatives might offer only short-term activity against individual bacterial species, depending on the epidemiology and resistance mechanisms. The existing clinical pipeline does not sufficiently address the problem of XDR or even pan-drug resistant Gram-negative bacteria. Based on the WHO PPL, the critical priority pathogens—resistant *A baumannii*, *P aeruginosa*, and Entero-bacteriaceae—are insufficiently addressed in the clinical pipeline. New antibacterial drugs without pre-existing cross-resistance are urgently needed, especially in regions with high resistance rates among Gram-negative bacteria. Sustaining a focus on innovation in the development of new agents is essential to impede resistance development. Given the high attrition rate of medicines in early research and development phases, basic antibacterial research and applied antibacterial research addressing in particular antibiotic-specific challenges of drug discovery should be prioritised in public funding strategies. Expanding the pipeline requires improved understanding and use of basic science, cutting edge methodology, scientific creativity, improved data transparency, and a financial environment that allows for research and developemnt failures. In the meantime, it is essential to reinforce infection prevention and control activities as well as to foster appropriate use of existing and future antibacterial drugs through strong stewardship measures.

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