ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

An analysis of the antibacterial clinical development pipeline, including tuberculosis

World Health Organization

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Abbreviations and acronyms

BLI	β-lactamase inhibitor
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRE	carbapenem- and third-generation cephalosporin-resistant Enterobacteriaceae
CRPA	carbapenem-resistant *Pseudomonas aeruginosa*
DBO	diazabicyclooctane
DHFR	dihydrofolate reductase
ESBL	extended-spectrum β-lactamase
GARDP	Global Antibiotic Research and Development Partnership
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LeuRS	leucyl-tRNA synthetase
MBL	metallo-β-lactamase
MIC	minimum inhibitory concentration
MmpL3	mycobacterial membrane protein large 3
MoA	mode of action
MRSA	methicillin-resistant *Staphylococcus aureus*
NBTI	novel bacterial topoisomerase II inhibitor
NDA	new drug application
NDM	New Delhi metallo-β-lactamase
OPP	other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority)
PBP	penicillin-binding protein
PDF	peptide deformylase
PK/PD	pharmacokinetics/pharmacodynamics
PPL	priority pathogens list
R&D	research and development
TB	tuberculosis
tet	tetracycline resistance encoding gene
VIM	Verona integron-encoded metallo-β-lactamase

Executive summary

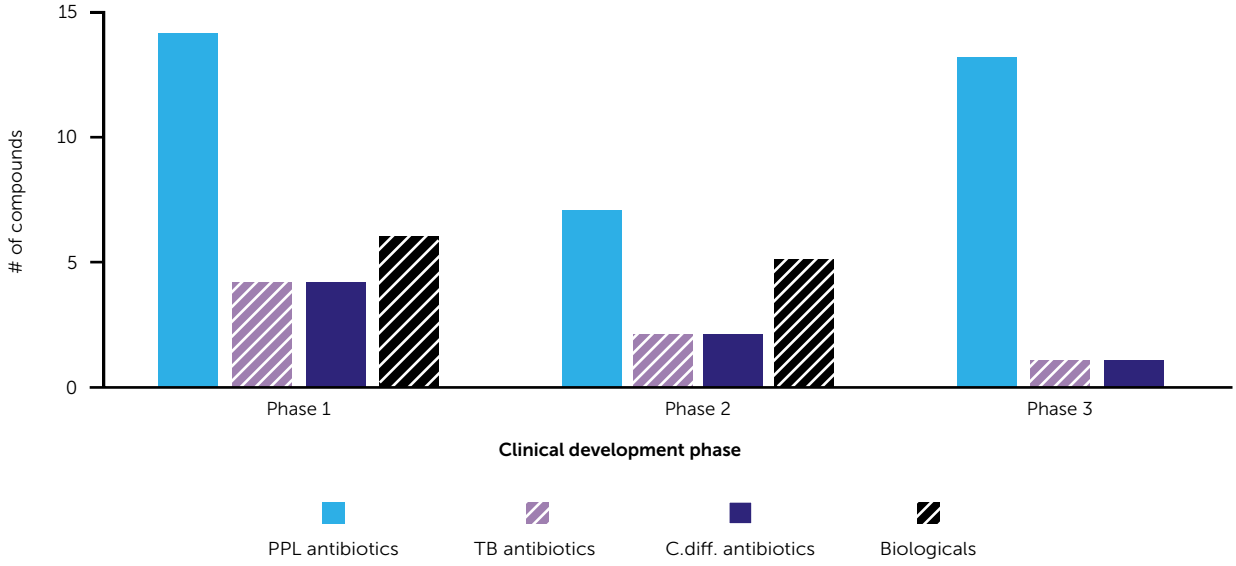
As part of implementation of the Global Action Plan on Antimicrobial Resistance, WHO drew up a list of priority antibiotic-resistant pathogens (priority pathogens list; PPL) to guide research into and the discovery and development of new antibiotics. As a further step, WHO reviewed the publically available information on the current clinical development pipeline of antibacterial agents to assess the extent to which the drug candidates act against these priority pathogens, *Mycobacterium tuberculosis*, and *Clostridium difficile*.

The review shows that the current clinical pipeline is still insufficient to mitigate the threat of antimicrobial resistance:

- More investment is needed in basic science, drug discovery and clinical development, especially for *Mycobacterium tuberculosis* and the critical priority Gram-negative carbapenem-resistant pathogens *Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae*.
- Most of the agents in the pipeline are modifications of existing antibiotic classes. They are only short term solutions as they usually cannot overcome multiple existing resistance mechanisms and do not control the growing number of pan-resistant pathogens.
- More innovative products are required against pathogens with no cross- or co-resistance to existing classes.
- Although oral formulations for community diseases associated with high morbidity are essential globally, few oral antibiotics for infections caused by Gram-negative pathogens are in the pipeline.

As of May 2017, a total of 51 antibiotics (including combinations) and 11 biologicals were in the clinical pipeline with 42 new therapeutic entities (33 antibiotics and nine biologicals) that target priority pathogens, seven products for tuberculosis (TB) and nine for C. difficile infections (seven antibiotics and two biologicals) (Fig. 1). The qualitative analysis shows a lack of potential treatment options for priority resistant bacteria, especially for multidrug- and extensively drug-resistant Gram-negative pathogens.

Fig 1. Antibacterial agents currently in phases 1–3 of clinical development[a]



[a] This figure does not include bedaquiline and delamanid, two new drugs to treat MDR-TB that are currently in Phase 3 trials, but have already received conditional marketing approval.

Innovativeness: Among the 33 antibiotics that are being developed for priority pathogens, eight belong to five distinct new antibiotic classes, and they fulfil at least one of the four criteria that were used to assess the extent to which agents in the pipeline can be classified as innovative:

- absence of cross-resistance to existing antibiotics
- new chemical class
- new target or
- new mechanism of action.

Gram-positive pathogens: Marketing approval of new antibiotic classes, such as oxazolidinones and cyclic lipopeptides, has increased therapeutic options for multidrug-resistant Gram-positive pathogens, but new treatments for those pathogens are still required to keep up with the anticipated evolution of resistance. Sixteen products in the current pipeline show activity against one or more Gram-positive priority pathogens. Among them are two new antibiotic classes, and seven of the products are biological agents (monoclonal antibodies and endolysins). Most of the antibiotics and all the anti-Gram-positive biologicals specifically target methicillin-resistant *Staphylococcus aureus*, while another highly important pathogen, vancomycin-resistant *Enterococcus* spp., has received little attention.

Gram-negative pathogens: The situation is worse for Gram-negative bacterial infections. These bacteria have been assessed as the most critical priority for antibiotic research and development (R&D), as strains are emerging worldwide that cannot be treated with any of the antibiotics currently on the market. While recent entries in the clinical pipeline (clinical phase 1) show an increased focus on Gram-negative bacteria, almost all the agents are modifications of existing antibiotic classes and address specific resistance mechanisms. They are active only against specific pathogens or a limited subset of resistant strains.

Tuberculosis: Another neglected area in new product development is treatment against drug-resistant TB. Only seven new agents for TB are currently in clinical trials. Of these, four are in phase-1, and only one compound is in phase-3. This is especially problematic because treatment of TB infections requires a combination of at least three antibiotics. Novel treatment regimens of short duration that are assembling non-toxic drugs are desperately needed.

Biologicals: Of the 11 biological treatments in phase -1 and -2, nine target the priority pathogens *S. aureus and P. aeruginosa*. Whether such biological treatments could serve as real alternatives to antibiotics is not yet clear; they are being developed to complement antibiotics as adjunctive or pre-emptive treatment. The higher costs of monoclonal antibodies than of regular antibiotics may also limit their potential use as alternative treatments, especially in low- and middle-income countries.

What is to be expected to come to the market: Given the average success rates and development times (average development time from phase-1 until approval is about seven years), the current pipeline of antibiotics and biologicals could lead to around 10 new approvals over the next five years. However, these potential new treatments will add little to the already existing arsenal and will not be sufficient to tackle the impending AMR threat. It needs to be kept in mind that the likelihood of future approvals of antibiotics that are in phase-1 has been estimated to be 14%. Hence, of the 10 anti-Gram-negative products in phase-1, only one to two could probably make it to the market.

Public funding: Many of the products in the clinical pipeline are already co-funded by research grants from public and philanthropic institutions, especially for TB, for which most development is undertaken by not-for-profit entities. Furthermore, universities and other publicly funded research institutions are often the source of the technology that is the starting point for R&D projects in small and medium-sized enterprises. The contribution of the pharmaceutical industry remains a key success factor and essential in bringing new therapeutic products to the market.

Infection control and stewardship: New antibiotics alone will not be sufficient to mitigate the threat of antimicrobial resistance. Their development should go hand in hand with infection prevention and control activities and fostering of appropriate use of existing and future antibiotics through stewardship measures. The draft *WHO Global Development and Stewardship Framework to Combat Antimicrobial Resistance* should provide the necessary guidance for using antibiotics more responsibly in the human, animal and agricultural sectors.

This report is a vital contribution to WHO's work on setting priorities for combatting antimicrobial resistance. It represents the first steps in understanding the developments in the clinical pipeline for priority pathogens and TB and to identify gaps. The aim is to develop the process and methodology further with input from stakeholders. The WHO Secretariat welcomes any additional information and/or feedback

on the data presented in this document, which should be sent to iauinfo@who.int. Additional analysis is needed to identify future R&D gaps and to assess clinical outcomes of candidate drugs. In moving forward greater collaboration is needed between all stakeholders in addition to more transparency of clinical trials. All individuals and/or companies are encouraged to register clinical trials in line with the WHO policy through the WHO International Standards for Clinical Trial Registries. WHO aims to repeat the analysis annually making the data available through the WHO Global Observatory on Health R&D.

All the data contained in this report can be downloaded from the WHO Global Observatory on Health R&D: http://www.who.int/research-observatory/en/

1. Introduction

The discovery of antibiotics has long been regarded as one of the most significant medical achievements of the twentieth century. Antibiotics have saved millions of lives (1) and enabled important medical procedures, including surgery and cancer chemotherapy (2). The emergence and spread of antibacterial resistance in all geographical areas, including in bacteria that cause hospital- and community-acquired infections, is, however, jeopardizing the effectiveness of these potentially life-saving treatments (3). The threat includes the spread of multidrug-resistant bacteria, and infections with no therapeutic options have been reported (4). The rise in resistance not only impedes the ability to treat bacterial infections in humans and animals but has broader societal and economic effects that ultimately threaten achievement of the Sustainable Development Goals. This situation requires urgent, coordinated action at global, regional and national levels (5,6).

Resistance is a natural phenomenon, and it is inevitable that it will develop to all antibiotics at some time. As misuse and overuse of antibiotics accelerate the development of resistance (4), antibiotics should be used more responsibly and new antibacterial treatments should be developed to counteract emerging resistance. However, there are challenges, which are both scientific – for the discovery of new antibiotics – and economic –for ensuring investment into research and development (7).

Following the discovery of Salvarsan in 1907 and of penicillin in 1928, there was a flurry of discovery of new antibiotics in the 1950s and 1960s, with the approval of several distinct classes of antibiotics. Since that "golden age", however, few new classes have been successfully brought to market. Since the 1980s, the total number of antibiotics approved has fallen significantly, increasing only slightly between 2011 and 2016 (8). After several lean decades, some "first-in-class" antibiotics have been approved (1,9).

Most of the new antibiotic classes, however, target Gram-positive bacteria, while the major challenge is to find new antibiotics against Gram-negative bacteria, which are identified as a critical priority by WHO on its priority pathogens list (PPL) for R&D of new antibiotics (10)(Box 1.). Because of the complexity of the Gram-negative cell wall, discovery of novel antibiotics that can permeate this barrier and stay inside the bacterium is very challenging (11). The lack of new, quality lead chemicals to test against Gram-negative bacteria is another major impediment to discovery (7).

In recent years, political commitment to combat antimicrobial resistance has increased significantly at global, regional and national levels. In 2015, the Sixty-eighth World Health Assembly endorsed the Global Action Plan on antimicrobial resistance (12), whereby Member States committed themselves to prepare national action plans and, inter alia, to promote the development of new antibiotics. These commitments were reinforced by the United Nations General Assembly at its Seventy-first Session in 2016 at a high-level meeting on antimicrobial resistance (13). The meeting of the Group of 20 in 2017 highlighted the importance of fostering R&D, in particular for agents against priority pathogens and TB, and called for an international R&D collaboration hub to maximize the impact of existing and new R&D initiatives (14). Continued commitment and collaboration are required to increase containment of antimicrobial resistance in human and animal health, the environment and other relevant sectors.

The aim of the Global Action Plan prepared by WHO with the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health is to ensure the continued availability of treatment options. To achieve this goal, the Plan sets out five strategic objectives. Objective 5 is to increase R&D for new antibacterial treatments. In May 2016, WHO and the Drugs for Neglected Diseases initiative launched the Global Antibiotic Research and Development Partnership (GARDP) for the development of new antibiotic treatments and to ensure access and appropriate use. Recent initiatives such as GARDP and CARB-X, a collaborative commitment of the Wellcome Trust and the Government of the USA, as well as a number of existing initiatives such as the Innovative Medicines Initiative and the Joint Programming Initiative on Antimicrobial Resistance have started to indicate a way forward for R&D of new antibiotics and other interventions to combat antimicrobial resistance. In 2016, more than 90 pharmaceutical, diagnostics and biotechnology companies, and industry associations from different countries recognized the need to increase research into new antibiotics. They committed to engage in

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

TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEARCH AND DEVELOPMENT

FIVE REASONS WHY

1

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

2

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

3

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

4

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

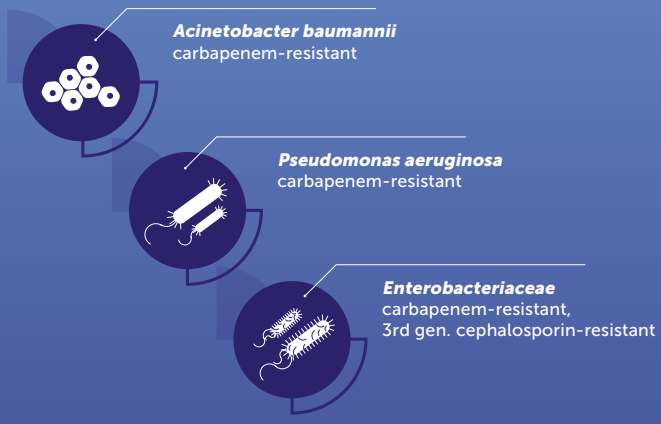
5

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

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

OTHER PRIORITY PATHOGENS

CRITICAL PRIORITY

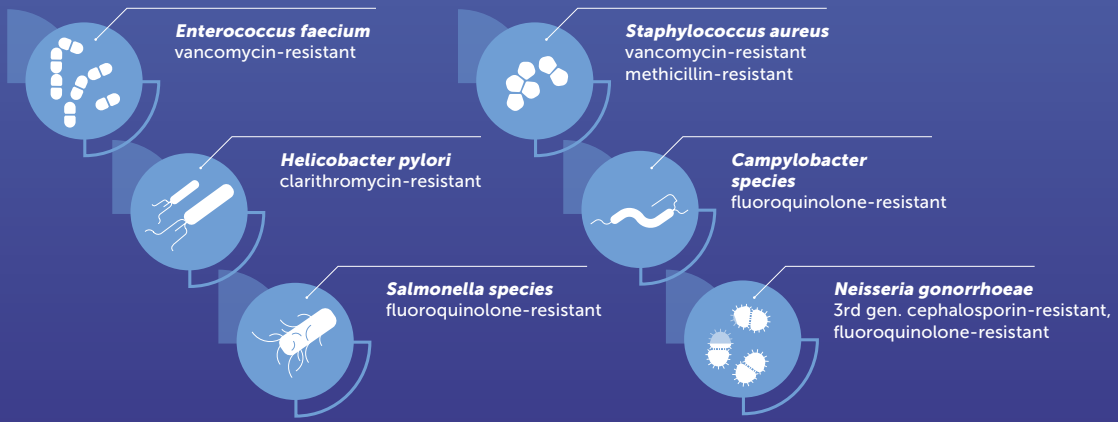


Acinetobacter baumannii
carbapenem-resistant

Pseudomonas aeruginosa
carbapenem-resistant

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

HIGH PRIORITY



Enterococcus faecium
vancomycin-resistant

Staphylococcus aureus
vancomycin-resistant
methicillin-resistant

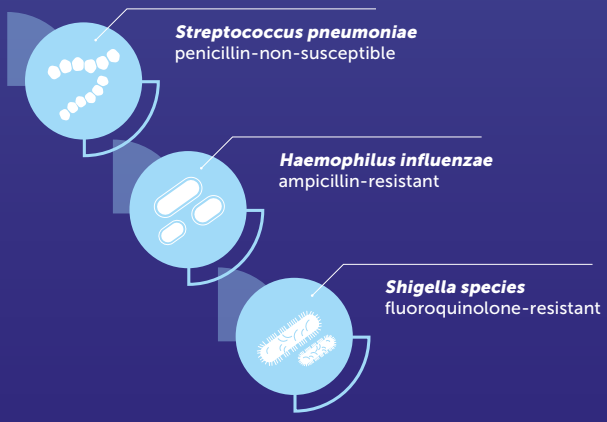
Helicobacter pylori
clarithromycin-resistant

Campylobacter species
fluoroquinolone-resistant

Salmonella species
fluoroquinolone-resistant

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

MEDIUM PRIORITY



Streptococcus pneumoniae
penicillin-non-susceptible

Haemophilus influenzae
ampicillin-resistant

Shigella species
fluoroquinolone-resistant

collaborative initiatives with academia and public bodies to enhance antibiotic discovery and agreed on a roadmap to reach this aim (15,16).

While antimicrobial resistance comprises resistance not only of bacteria but also of viruses, fungi and parasites, this analysis addresses only new treatments against bacteria. These were classified as of critical, high or medium priority on the WHO PPL. TB and C. difficile were also included in this review. This clinical pipeline analysis should facilitate further setting of priorities for R&D. Going beyond existing analyses (1,17–19), it covers drug development worldwide and biological drugs. It is also the first review of the publicly available information of the current antibacterial clinical development pipeline to assess the extent to which candidate drugs correspond to the priorities on the PPL and for TB. It will be repeated annually to reflect changes in the clinical pipeline. Both the PPL and this clinical pipeline analysis are critical elements of the future WHO Global Development and Stewardship Framework to Combat Antimicrobial Resistance (20).

2. Methodology and search results

2.1 Scope and inclusion criteria

This review is limited to new therapeutic entities (NTEs) that are in phase 1-3 clinical trials that have publicly available information and do not have market authorization anywhere in the world for human use. It is restricted to agents that have the potential to treat serious bacterial infections and have a specifically antibacterial effect. This analysis does not include:

- preventive interventions, such as vaccines or topical decolonizing agents;
- immunomodulating or microbiome modulating agents;
- nonspecific inorganic substances;
- biodefence agents;
- agents not developed for systemic use (injectable or oral formulations) but only for topical application (e.g. creams or eye drops);
- new formulations of existing treatments; nor
- an analysis of clinical outcomes.

Fixed-dose combinations of potentiators (molecules that enhance the effectiveness of antibiotics but are not antibacterial themselves) and antibiotics are included, even if they do not contain a new therapeutic entity. Agents developed for use against TB were identified from published reviews of the TB pipeline (22,23), complemented by the review for this analysis. Oral, non-systemic agents for *C. difficile* infections are also included in a separate section.

Only agents that are in active development are included. Agents that concluded their last clinical trials prior to 1 January 2015 and for which there was no other sign of further development are listed in table 6. Agents that no longer appear on the respective company's online development pipeline have been excluded. Greater transparency is needed of clinical trials and all individuals are encouraged to register clinical trials in light with the WHO policy through the WHO International Standards for Clinical Trial Registries. The search strategy is detailed in Annex 1.

2.2 Assessment of activity against priority pathogens and innovation

The evaluation of the antibacterial clinical development pipeline was based on an in-depth analysis conducted by an advisory group comprised of clinicians, microbiologists and leading experts in antibiotics R&D, pharmacokinetics/pharmacodynamics (PK/PD) and antibiotic resistance. The experts reviewed the quality criteria and assessed each agent against those criteria at a 2-day meeting. The group was assisted by members of the WHO Secretariat, who were in charge of retrieving data and screening them initially for inclusion or exclusion of products for the review and for synthesizing the evidence. The data set was shared before the advisory group meeting with relevant stakeholders, including associations of pharmaceutical companies active in the area (see Acknowledgements), to ensure the most complete data set. Feedback received was verified and included in the data set. Individual companies that are sponsoring research were not contacted.

Evidence for activity against priority pathogens and innovativeness was retrieved from the peer-reviewed literature (when available) and summarized. For agents in the early stages of development, information from presentations and posters at scientific conferences and information published by the developers was

also used. Information was considered only if it was publicly available and after an internal quality review. Members of the advisory group who had conflicts of interest (Annex 2) with respect to a particular agent were excluded from the discussion of that agent. The draft evaluation of all antibiotics was circulated to all members of the advisory group, and feedback from the group on the content and format was incorporated.

2.2.1 Expected activity against priority pathogens

Data obtained both in vitro and in vivo (when available) were reviewed for the assessment of activity against priority pathogens. In assessing activity, the advisory group made judgements about whether the agent was potentially clinically active against the selected bacteria on the basis of published minimum inhibitory concentrations (MICs) and their pharmacokinetics. When available, data on PK/PD and information on nonclinical or clinical efficacy were taken into account in the assessment. Drugs that have shown activity in vitro but are currently not being developed for relevant indications were not assessed against the respective pathogens.

The advisory group classified agents for which there were inconclusive data as "possibly active". For agents for which there were few or no data on their activity against specific pathogens, the advisory group made assumptions based on the properties of the known antibiotic class to classify the agents as "possibly active", if similar drugs are known to be active against the respective pathogen (24).

The existence of clinical trials that examined the clinical outcomes against the infections caused by the pathogens were noted. The data has not been included as it requires systematic review.

2.2.2 Innovativeness

An agent was considered innovative if it fulfilled one of the following innovativeness criteria:

- absence of cross-resistance to existing antibiotics;
- new chemical class;
- new target; or
- new mechanism of action.

Ultimately, the concept of antibacterial innovation implies that the agent is different enough from existing molecules to obviate cross-resistance. Cross-resistance can be measured by systematic susceptibility testing in vitro of a diverse panel of genetically defined pathogens, combined with genetic characterization of mutants and molecular structural analysis. When such an assessment was available, "no cross-resistance" was used as a determinant of innovativeness (25).

3. Agents in clinical development

3.1 Antibiotics potentially active against pathogens on the WHO priority pathogens list

Table 2. Antibiotics and combinations containing an NCE that are developed for PPL pathogens

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Delafloxacin[a]	NDA[1]	Fluoroquinolone	IV & oral (Melinta)	■	■	■	■	✗	✗	✗	✗
Vaborbactam + meropenem (Carbavance)	NDA	Boronate BLI + carbapenem	IV (The Medicines Co)	■	■	■	[b]	✓	✗	✗	/
Cefiderocol	3	Siderophore-cephalosporin	IV (Shionogi)	■	■	■		✗	✗	✗	/
Relebactam + imipenem/ cilastatin	3	DBO-BLI + carbapenem/ degradation inhibitor	IV (Merck & Co)	■	■	■	[b]	✗	✗	✗	✗
Sulopenem	3	Carbapenem	IV & oral (Iterum)	■	■	■	[c]	✗	✗	✗	✗
Plazomicin	3	Aminoglycoside	IV (Achaogen)	■	■	■		✗	✗	✗	✗
Lascufloxacin	3	Fluoroquinolone	IV & oral (Kyorin)	■	■	■	■	✗	✗	✗	✗
Eravacycline	3	Tetracycline	IV & oral (Tetraphase)	■	■	■		✗	✗	✗	✗
Omadacycline	3	Tetracycline	IV & oral (Paratek)	■	■	■	■	✗	✗	✗	✗
Solithromycin	3	Macrolide	IV & oral (Cempra)	■	■	■	■	✗	✗	✗	✗
Iclaprim	3	DHFR-inhibitor	IV (Motif Bio)	■	■	■	■	✗	✗	✗	✗
Lefamulin	3	Pleuromutilin[4]	IV & oral (Nabriva)	■	■	■	■	✓[d]	✗	✓	/
MRX-I/MRX-4	2/3[e]	Oxazolidinone	IV & oral (MicuRx)	■	■	■	■	✗	✗	✗	✗
Gepotidacin	2	NBTI (Triazaacenaphthylene)	IV & oral	■	■	■	■	✓	✗	✓	✓
Zoliflodacin	2	NBTI (Spiropyrimidenetrione)	Oral (Entasis)	■	■	■	■	✓	✗	✓	✓
Murepavidin (POL-7080)	2	Novel membrane targeting AB	IV (Polyphor)	■	■	■		✓	✓	✓	✓
Brilacidin	2	Novel membrane targeting antibiotic	IV (Innovation Pharmaceuticals)	■	■	■	■	✓	✓	/	/
Nafithromycin (WCK-4873)	2	Macrolide	Oral (Wockhardt)	■	■	■	■	✗	✗	✗	✗
Afabicin (Debio-1450)	2	FabI inhibitor	IV & oral (Debiopharm)	■	■	■	■	✓	✓	✓	✓
Finafloxacin	2	Fluoroquinolone	IV (MerLion)	■	■	■	■	✗	✗	✗	✗
LYS-228	1	Monobactam	IV (Novartis)	■	■	■		✗	✗	✗	✗
GSK-3342830	1	Siderophore-cephalosporin	IV (GlaxoSmithKline)	■	■	■		✗	✗	✗	/
AIC-499 + unknown BLI	1	β-lactam+BLI	IV (AiCuris)	■	■	■		✗	✗	✗	✗
Zidebactam + Cefepime	1	DBO-BLI/ PBP2 binder + cephalosporin	IV (Wockhardt)	■	■	■		✗	✗	✗	✗

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Nacubactam + unknown antibiotic	1	DBO-BLI/ PBP2 binder + unknown antibiotic	IV (Roche)	■	■	■		✖	✖	✖	✖
AAI101 + cefepime or piperacillin	1	β-lactam BLI + cephalosporin or penicillin	IV (Allecra)	■	■	■		✖	✖	✖	✖
VNRX-5133 + unknown antibiotic	1	Boronate-BLI + unknown class	IV (VenatoRX)	■	■	■		✓	✓	/	✖
ETX2514 + sulbactam	1	DBO-BLI /PBP2 binder + β-lactam-BLI/PBP1,3 binder	IV (Entasis)	■	■	■		✖	✖	✖	✖
SPR-741 + unknown antibiotic	1	Polymixin + unknown class	IV (Spero)	■	■	■		✖	✖	/	/
TP-271	1	Tetracycline	IV & oral (Tetraphase)	■	■	■	■	✖	✖	✖	✖
TP-6076	1	Tetracycline	IV (Tetraphase)	■	■	■		✖	✖	✖	✖
KBP-7072	1	Tetracycline	IV & oral (KBP BioSciences)	■	■	■	■	✖	✖	✖	✖
TNP-2092	1	Rifamycin-quinolone hybrid	Oral (Tennor)	■	■	■	■	✖	✖	✖	✖
Alalevonadifloxacin	1[f]	Fluoroquinolone	Oral (Wockhardt)	■	■	■	■	✖	✖	✖	✖

Pathogen activity: ■ active, ■ possibly active, ■ not or insufficiently active. Agents against critical priority pathogens were assessed only against these (three barst) but might be active against other priority pathogens (OPP). The only agents assessed against OPP (fourth bars) were those that are not active against critical priority pathogens. **Innovativeness assessment:** ✓ criterion fulfilled; / Inconclusive data or no agreement by the advisory group; ✖ criterion not fulfilled

Abbreviations: BLI, β-lactamase inhibitor; C, new chemical class; CRE, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; CRAB, A. baumannii, carbapenem-resistant; CRPA, P. aeruginosa-, carbapenem-resistant; DBO, diazabicyclooctane; DHFR, dihydrofolate reductase; 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 filed. OPP, other priority pathogens on the WHO PPL ("high" and "medium" priority); PBP, penicillin-binding protein; T, new target

Underlined agents: New class

a. Delafloxacin was approved by the US Food and Drug Administration on 21 June 2017, after the assessment by the advisory group; the agent is therefore still listed.

b. Active against *K. pneumoniae* carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae

c. Active against extended-spectrum β-lactamase-producing cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae

d. First systemic formulation of this class, which is currently used topically and in animals previously

e. A phase-3 trial has been announced but not registered. MRX-4 is the injectable version of MRX-I and is in phase-1 trials.

f. Phase-2 trials completed in India in 2012, but phase-1 studies subsequently initiated in the USA

g. Vaborbactam + meropenem was approved by the US Food and Drug Administration on 30 August 2017, after the assessment by the advisory group; agent is therefore still listed.

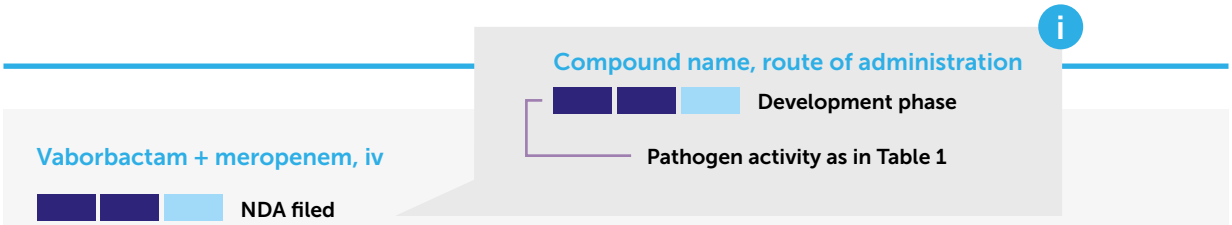
3.1.1 Beta-lactams

β-Lactams are a well-established group of antibiotics that includes penicillins, cephalosporins, carbapenems and monobactams. Numerous analogues have been developed and used in clinical practice, but the emergence of bacteria that produce β-lactamases, enzymes that destroy β-lactams, can render them ineffective (26). Combining a β-lactam with a β-lactamase inhibitor (BLI) can restore effectiveness and has resulted in several new combinations with carbapenems or cephalosporins (27).

There are four classes of β-lactamases, known as A, B, C and D, with many subclasses. Traditional BLIs (clavulanic acid, tazobactam, sulbactam) inhibit extended-spectrum β-lactamases (ESBLs) but do not inhibit carbapenemases (β-lactamases that are able to destroy carbapenems) of the same class. The recently introduced BLI avibactam has an extended class A inhibitory spectrum and includes the *KPC*. All new BLIs that inhibit class A carbapenemases also inhibit ESBLs.

Other carbapenemases belong to class B (metallo-β-lactamases (MBLs)) and class D. There is no universal inhibitor of all clinically relevant β-lactamases, and the BLIs in development show different patterns and rates of restoration of susceptibility. In addition, the distribution of β-lactamases varies regionally, and the susceptibility patterns depend on the geographical distribution of enzyme types (28). Despite inhibition of β-lactamases, other resistance mechanisms may still confer resistance to BLI combinations (29–32).

Some new BLIs have strong, independent antibacterial activity of their own that is based on inhibiting the same target as β-lactams, the penicillin-binding proteins (PBPs). This may result in synergistic antibacterial activity. Resistance mechanisms other than β-lactamase production are not influenced by BLIs. Four new β-lactam antibiotics for monotherapy and seven β-lactam + BLI combinations containing a new chemical entity are in development. In addition, three companies are developing fixed-dose formulations of already approved β-lactams and BLIs.



Vaborbactam + meropenem, iv

NDA filed

- Boronate-based BLI: Although it represents a new chemical structure, modifications of β-lactamases may result in cross-resistance with known BLIs.
- Mainly inhibits class A β-lactamases. Vaborbactam restores susceptibility to meropenem in *K. pneumoniae carbapenemase* (KPC)-producing Enterobacteriaceae but not in MBL producers(33,34).
- NDA submitted and approved by the US Food and Drug Administration on 30 August 2017 based on NCT02166476
- Additional trial on hospital-acquired and ventilator-associated pneumonia vs piperacillin + tazobactam (NCT03006679) and a small open-label trial of carbapenem-resistant pathogens vs best available therapy (NCT02168946)

Relebactam + imipenem/cilastatin, iv

Phase 3

- Relebactam is a BLI of the diazabicyclooctane (DBO) type: synthetic non-β-lactam-based BLIs (like avibactam).
- Inhibits class A and C β-lactamases.
- Combination partly effective against CRPA and CRE (only class A, but not MBL producers), not better in CRAB than imipenem alone (35,36)
- Clinical trials in hospital-acquired or ventilator-associated pneumonia vs piperacillin/tazobactam (NCT02493764) and imipenem-resistant pathogens vs colistin (NCT02452047)

Zidebactam + cefepime, iv

Phase 1

- Zidebactam is a DBO-type BLI with relevant antibacterial activity against wild-type Enterobacteriaceae and probably CRPA due to penicillin-binding protein 2 inhibition (37).
- Synergistic activity in β-lactamases class A, including ESBL, KPC producer activity, but elevated MICs in MBL producers (38,39)
- Possible toxicological risk indicated by chemical structural alert
- Phase-1 in development (NCT02532140, NCT02942810, NCT02707107)

Nacubactam + unknown antibiotic, iv

Phase 1

- Nacubactam is a BLI of the DBO type with some intrinsic antibacterial activity due to PBP 2 inhibition (weaker than zidebactam).
- Inhibits class A and C β-lactamases (39,40).
- Combination partner probably meropenem; synergistic activity with various partners in Enterobacteriaceae; only BLI activity in CRPA; no added benefit against CRAB
- Phase-1 pharmacokinetics study with meropenem (NCT03174795)

AAI-101 + cefepime or piperacillin, iv

Phase 1

- AAI-101 is a BLI β-lactam scaffold; combination partner not clear
- Slightly improved inhibitory activity against KPCs, some added benefit over cefepime alone in bacteria producing β-lactamases class A and ESBLs (42,43)
- Phase 1 studies not registered; entering phase 2

VNRX-5133 + unknown antibiotic, iv

Phase 1

- Boronate-based BLI with activity against several MBLs, especially New Delhi metallo-β-lactamase (NDM) and Verona integron-encoded metallo-β-lactamase (VIM).
- May be active in combination with meropenem or a cephalosporin against some MBL-producing strains of Gram-negative bacteria, but other resistance mechanisms often co-carried by MBL producers might limit this activity.
- Limited data available (44); phase-1 study (NCT02955459)

ETX2514 + sulbactam,iv

Phase 1

- ETX2514 is a BLI of the DBO type targeting serine β-lactamases (including OXA); has intrinsic antibacterial activity against Enterobacteriaceae
- Restores the activity of sulbactam (penicillanic acid sulfone); combination developed for *A. baumannii* infections (45–47)
- Phase-1 study (NCT02971423)
- Further combinations with ETX2514 are planned.

AIC-499 + unknown BLI, iv

Phase 1

- Limited data available: no information on structure, activity or the partner BLI has been published.
- A phase-1 trial started in January 2017 but is not registered.

Cefiderocol, iv GSK-3342830, iv

Phase 3

Phase 1

- These two agents are cephalosporins linked to a siderophore and make use of the bacterial iron transport mechanism to facilitate uptake of the agent through the outer membrane of Gram-negative bacteria (48–54). Although the siderophore can overcome many resistance types, the mechanism itself has been shown to be prone to the emergence of resistance (55). The agents are stable against most β-lactamases, including MBLs, but have partly elevated MICs in CRPA and KPC overproducers. Susceptibility rates are comparable to those of colistin and tigecycline (56); pharmacokinetics and pharmacodynamics are similar to those of other cephalosporins.
- Cefiderocol: Phase-3 clinical trials for hospital-acquired and ventilator-associated pneumonia vs meropenem (NCT03032380) and critical Gram-negative pathogens vs best available therapy (NCT02714595)
- GSK-3342830: Good activity against CRAB; activity against CRPA, but strains with elevated MICs identified; activity against CRE, but higher MICs than wild type. A phase-1 trial was suspended in March 2017 (NCT02751424).

Sulopenem, iv/oral

Phase 2

- Synthetic penem; oral prodrug sulopenem etzadroxil
- Activity against Enterobacteriaceae, including ESBL producers; Gram-positive activity similar to that of carbapenems; complete cross-resistance with existing carbapenems (57)

LYS-228, iv

Phase 1

- Monobactam with improved stability to serine β-lactamases (classes A, C and D), including ESBL and KPC; retains stability of the monobactam class to MBLs
- Limited data on activity against Enterobacteriaceae in vitro (58)
- Phase-1 trial announced but not registered

3.1.2 *Aminoglycosides*

Commonly used aminoglycosides such as gentamicin, netilmicin, tobramycin and amikacin show different resistance rates globally. The most common resistance mechanism is the production of aminoglycoside-modifying enzymes. A newer resistance mechanism is the production of bacterial ribosome-modifying enzymes (16S rRNA methylases), which often occurs in NDM-producing Enterobacteriaceae (59).

Plazomcin, iv

Phase 3

- Sisomicin derivative with improved stability against aminoglycoside-modifying enzymes but vulnerability to 16S rRNA methylases, causing cross-resistance with other aminoglycosides
- Activity against wild-type Enterobacteriaceae and aminoglycoside-modifying enzyme-producing strains that are often resistant to carbapenem. Not active in case of resistance due to 16S rRNA methylases, which are often found in NDM-producing strains (60–63)
- Class-specific pharmacokinetics, pharmacodynamics and safety (no clinical comparison available)
- Phase-3 programme (NCT02486627)
- Small open-label trial against carbapenem-resistant Enterobacteriaceae vs colistin: improved outcome and safety (NCT01970371) with plazomicin

3.1.3 *Tetracyclines*

More than 1000 tetracycline resistance genes have been reported, including efflux pumps, ribosomal protection proteins, tetracycline inactivating enzymes (tet) and mosaic genes (64,65). New tetracyclines address some of these class-specific resistance mechanisms. Five new tetracycline derivatives are in clinical development, two against Gram-negative bacteria and three against Gram-positive and community-acquired pneumonia pathogens.

Eravacycline, iv/oral

Phase 3

- Synthetic tetracycline, unaffected by *tet*(M), tet(K) and *tet*(B), but elevated MICs in the presence of *tet*(A) and *tet*(X); MICs similar to those of tigecycline (66)
- Activity against Enterobacteriaceae and *A. baumannii* similar to that of tigecycline but with lower MICs. Higher MICs in resistant strains (CRE and CRAB), depending on breakpoints of partial or complete cross-resistance with tigecycline (67–69).
- Pharmacokinetics similar to that of tigecycline (non-linear, concentration-dependent protein binding, low serum concentrations, mainly biliary elimination); oral bioavailability about 30% (70,71)
- Phase-3 programme: non-inferiority trial design vs ertapenem (NCT01844856) and meropenem (NCT02784704)

Omadacycline, iv/oral

Phase 3

- Modified minocycline, optimized for Gram-positive pathogens (72)
- Overcomes some minocycline resistance mechanisms in Gram-positive pathogens (including enterococci), especially ribosomal protection and efflux pumps (*tet*(K), *tet*(L), *tet*(O))
- MICs comparable to those of tigecycline in MRSA and resistant *S. pneumoniae*; higher MICs in Gram-negative organisms, with little activity in CRE, CRAB and *Neisseria gonorrhoeae* (relatively high MICs) (73,74)
- Better pharmacokinetics than eravacycline and tigecycline: linear; plasma protein binding: 20–30%, concentration-independent; oral bioavailability 35% depending on food intake; mean half-life about 17 h; large volume of distribution; primarily biliary elimination, 14% renal (75)
- Clinical trials vs linezolid (NCT02877927) and vs moxifloxacin (NCT02531438)

TP-6076, iv/oral

Phase 1

- Synthetic, optimized for Gram-negative pathogens; little influence of *tet*(M, Q, K, A, B and D); elevated MICs in A. baumannii overexpressing adeAB (76)
- MICs lower than those of tigecycline in Enterobacteriaceae and *A. baumannii*. Higher MICs in cases of carbapenem resistance, especially in tigecycline co-resistant strains (77)
- No pharmacokinetics data available; phase-1 trial ongoing but not registered

TP-271, iv/oral

Phase 1

- Synthetic; activity similar to that of tigecycline; vulnerable to *tet*(A) and *tet*(X)
- Activity similar to that of tigecycline against *Haemophilus influenzae* and Gram-positive pathogens, including vancomycin-resistant *Enterococcus faecium* (78).
- Phase-1 clinical trials ongoing (NCT03024034, NCT02724085)

KBP-7072, iv/oral

Phase 1

- Omadacycline derivative, optimized for Gram-positive respiratory pathogens
- Limited information available (79)
- Phase-1 clinical trials completed (NCT02454361, NCT02654626)

3.1.4 *Topoisomerase inhibitors*

Quinolones are synthetic antibiotics that were discovered in the 1960s. The drugs in use today are fluoroquinolones. They target two essential type II topoisomerases: DNA gyrase and topoisomerase IV. They bind preferentially to the gyrase subunit GyrA and to the topoisomerase IV subunit ParC (80). Six new agents in this group are in clinical development, optimized for Gram-positive bacteria and pathogens that cause respiratory tract infections (*S. pneumoniae, H. influenzae, Moraxella spp., Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumoniae*).

Two agents, novel bacterial topoisomerase II inhibitors, have new chemical structures, which have distinct but overlapping binding sites with fluoroquinolones (81). Their spectrum targets Gram-positive pathogens, respiratory tract infection pathogens and *N. gonorrhoeae*. Two agents being developed against *C. difficile* infections are described in section 3.4.

Delafloxacin, iv/oral

NDA filed

- Fluoroquinolone optimized for Gram-positive and respiratory tract infection pathogens (82–85)
- Very low MICs against pneumococci (elevated MICs in levofloxacin-resistant strains but still susceptible) and *S. aureus* (MICs elevated against MRSA but still susceptible; some cross-resistance with moxifloxacin)
- Activity against Gram-negative bacteria similar to that of levofloxacin, with complete cross-resistance; lower MICs in acidic environments
- Pharmacokinetics not linear; renal elimination 65%; oral bioavailability about 60%; plasma protein binding 84%
- Approval by the US Food and Drug Administration in July 2017 based on two phase-3 trials (NCT01811732, NCT01984684); one phase-3 trial is under way (NCT02679573).

Lascufloxacin, iv/oral

Phase 3

- Fluoroquinolone optimized for Gram-positive and respiratory tract infection spectrum (86)
- Spectrum and activity similar to those of levofloxacin except very low MICs against wild-type *S. aureus* and elevated MICs against MRSA due to cross-resistance. Depending on breakpoints, probably limited efficacy against MRSA; complete cross-resistance in Gram-negative bacteria
- Developed in Japan; five phase-3 trials registered in the Japanese clinical trial registry

Alalevonadifloxacin, oral

Phase 1

- luoroquinolone; oral prodrug of levonadifloxacin, which is the arginine salt of S-(–)-nadifloxacin. Nadifloxacin has been available since 1993 as a topical drug for acne (87).
- Optimized for Gram-positive activity
- Same activity spectrum as that of lascufloxacin
- Underwent phase-2 trial in India in 2012, now in phase-1 studies in the USA (NCT02253342, NCT02244827, NCT01875939, NCT02217930).

Finafloxacin, iv/oral

Phase 2

- Fluoroquinolone; already approved as otic suspension
- Activity comparable to that of ciprofloxacin; complete cross-resistance; lower MICs in acidic environments (88)
- Trial in *Helicobacter pylori* (NCT00723502); phase 2 vs ciprofloxacin (NCT00722735, NCT01928433)

Zoliflodacin, oral

Phase 2

- Novel bacterial topoisomerase II inhibitors with similar spectrum but different structure from gepotidacin (spiropyrimidenetrione scaffold)
- No cross-resistance has been described (92,93).
- Phase-2 trial for treatment of gonorrhoea (NCT02257918)
- Phase-3 trials for treatment of gonorrhoea announced with Global Antibiotic Research and Development Partnership

Gepotidacin, iv/oral

Phase 2

- Novel bacterial topoisomerase II inhibitors active against Gram-positive and Gram-negative cocci; slower killing than fluoroquinolones
- No cross-resistance has been described (89–91).
- Two phase-2 studies for treatment of gonorrhoea (NCT02294682) and acute bacterial skin and skin-structure infections caused by Gram-positive bacteria (NCT02045797). No phase-3 trial has been announced so far.

TNP-2092, oral

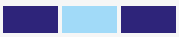
Phase 1

- Hybrid molecule linking a rifamycin and a quinolone pharmacophore to prevent fast emergence of resistance to the rifamycin antibiotic (94)
- Activity comparable to that of rifamycin; limited information on clinical development; plans for development against gastrointestinal pathogens including *H. pylori* and *C. difficile* announced (95)
- Was in clinical development in 2008; development now revived, with phase-1 trials in China (not registered)

3.1.5 *Novel membrane-targeting antibiotics*

Natural antimicrobial peptides and many (semi) synthetic non-peptide antibiotics target specific components and functions of the bacterial membrane and can affect both the inner and the outer membrane (96–98). Membrane-targeting antibiotics may target Gram-negative and/or Gram-positive pathogens.

Murepavidin, iv



Phase 2

- Synthetic macrocyclic protegrin mimetic; inhibits the lipopolysaccharide-assembly protein (99–101)
- Specific activity against *Pseudomonas aeruginosa* (including resistant strains) (100)
- Two completed phase-2 studies (NCT02096315, NCT02096328)

Brilacidin, iv/topical

Phase 2

- Non-peptide defensin mimetic, optimized for *S. aureus* activity (102–104)
- Although the chemical structure and mode of action are different from those of daptomycin, the cellular effects in *S. aureus* are similar: abrogation of cell wall and membrane functions and cytoplasmic protein misfolding stress.
- Little activity against Gram-negative bacteria
- Phase-2 study (NCT02052388, NCT01211470

3.1.6 *Pleuromutilins*

Pleuromutilins are natural products that were discovered in 1950. They inhibit bacterial protein synthesis by binding at two sites to the peptidyl-transferase centre of the ribosomal 50S subunit of the bacterial ribosome. Drugs of this class are used in veterinary medicine and, since 2007, as topical drugs in humans (retapamulin). Resistance is common in animal infections but rare in human infections. In MRSA, some cross-resistance was observed to the phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A group of antibiotics through the *cfr* gene and to clindamycin through the *vga* genes.

Lefamulin, iv/oral

Phase 3

- First pleuromutilin in development for systemic use. Low MICs against pneumococci and staphylococci, higher MICs against *H. influenzae* (105–108).
- High non-linear plasma protein binding, low unbound concentrations, higher concentrations in epithelial lining fluid than in plasma, half-life about 10 h (109)
- Phase-3 studies of iv/oral vs moxifloxacin iv/oral ± linezolid (NCT02559310) and oral vs moxifloxacin oral (NCT02813694)

3.1.7 *FabI inhibitors*

FabI (enoyl-acyl carrier protein reductase) is critical to fatty acid biosynthesis in many bacteria. FabI inhibitors have been known since the 1950s and are represented by isoniazid and ethionamide for TB treatment and the non-specific biocide and slow-binding FabI inhibitor triclosan. These agents have different binding characteristics (108). It is not known whether they exert selection pressure on staphylococci, which could lead to cross-resistance (111,112).

Afabicin, iv/oral

Phase 2

- Afabicin is a staphylococcus-specific antibiotic developed for *S. aureus* infections as iv and oral forms (prodrug) (113).
- Activity in vitro is comparable to that of rifampicin; active against extra- and intracellular *S. aureus*, independently of resistance patterns. Slow reduction of bacterial load. Risk for emergence of high-level resistance may be offset by high affinity to the target (112,114,115).
- Phase-2 study (NCT02426918)

3.1.8 *Oxazolidinones*

Oxazolidinones have been in clinical use since 2000; linezolid was the first drug approved, followed by tedizolid. Modifications of the scaffold may address class-specific resistance mechanisms. Some agents in this class have been developed for *C. difficile* infections and TB.

MRX-I/MRX-4, iv/oral

Phase 2/3

- Activity against MRSA, vancomycin-resistant *Enterococcus faecium* and resistant *S. pneumoniae*
- Little information published, and potential differences from linezolid are unclear (116).
- A phase-2 trial has been completed (NCT02269319). The company announced that it had started a phase-3 trial in China in late 2016, but this trial is not registered.

3.1.9 *Macrolides and ketolides*

Ketolides are a subclass of the macrolides and are structural analogues of erythromycin, a 14-membered macrolide. They have higher affinity than macrolides to domain V and domain II of the 23S ribosomal RNA and retain activity against the main resistance mechanisms of erythromycin. The ketolide telithromycin is rarely used because of a restricted label and liver toxicity warnings.

Solithromycin, iv/oral

Phase 3

- Activity in vitro similar to that of telithromycin (117–119)
- Cross-resistance with telithromycin not known; no cross-resistance with macrolides in pneumococci or A streptococci, but cross-resistance reported in staphylococci
- An NDA was filed but was rejected by the US Food and Drug Administration because liver toxicity had not been adequately characterized. The application to European Medicines Agency has been withdrawn and future development plans are not clear yet after the merger with Melinta (121).
- The NDA was based on two phase-3 trials for community-acquired pneumonia (NCT01756339, NCT01968733); trial in treatment of gonorrhoea (NCT02210325) (122,123)

Nafithromycin, iv/oral

Phase 2

- Activity in vitro similar to that of telithromycin
- Active against some macrolide- and ketolide-resistant pneumococci, but cross-resistance in ermB-induced pneumococci, staphylococci and group A streptococci. High MICs to *H. influenzae* (124–126)
- Safety and potential liver toxicity unknown
- Phase-2 clinical trial (NCT02903836)

3.1.10 *Dihydrofolate reductase inhibitors*

Dihydrofolate reductase (DHFR) inhibitors disturb the folate metabolism of microorganisms that is required for the production of DNA and RNA. Trimethoprim has been available since 1962 and has been combined with sulfonamides to slow the emergence of resistance. Nonetheless, high resistance rates have reduced its usefulness.

Iclaprim, iv

Phase 3

- DHFR inhibitor designed for use against MRSA infections more than 20 years ago
- Greater affinity to DHFR than trimethoprim (127)
- Some activity against trimethoprim-resistant isolates of MRSA, but mutations in the *dfr* gene can lead to rapid emergence of resistance.
- Previous NDAs to the US Food and Drug Administration and the European Medicines Agency were rejected because of concern about efficacy (failed to show non-inferiority against linezolid) and safety (cardiac and hepatic safety, three possibly related deaths).
- Development continued, with two new phase-3 studies (NCT02600611, NCT02600611) under a US Food and Drug Administration fast-track designation. Two studies against hospital-acquired or ventilator-associated pneumonia are planned.

3.1.11 *Potentiators*

These molecules do not have intrinsic antibacterial activity but can enhance the activity of other antibiotics. Several strategies for the use of potentiators to enhance or enable the activity of antibiotics clinically are being pursued, and one agent has entered clinical trials.

SPR-741, iv

Phase 1

- Polycationic polymyxin derivative that interacts with the negatively charged outer membrane of Gram-negative bacteria and enables penetration of antibiotics that are usually restricted to Gram-positive bacteria (128)
- Expected to be less toxic than other polymyxins
- Combination partner not announced; SPR-741 potentiates the activity of rifampicin, clarithromycin and fusidic acid (129).
- Phase-1 trial started in 2017 (NCT03022175)

3.2 Combinations without new chemical entities

There are four combinations of antibiotics and potentiators or enablers that do not contain new chemical entities. As their spectra are different from those of existing combinations of these molecules, they might provide some benefit over current antibiotic combinations.

Aztreonam + avibactam

Phase 2

- The monobactam aztreonam is not hydrolysed by MBLs, and avibactam protects the antibiotic from ESBLs and KPCs (130,131).
- Active against CRE but not CRPA or CRAB
- Phase-2 study (NCT02655419)

Cefepime + Tazobactam, iv

Phase 1

- Slightly more effective against ESBL-producing Enterobacteriaceae than cefepime alone.

C-Scape, oral

Phase 1

- Combination of oral β-lactam and oral BLI, both off-patent but not disclosed
- Potential drug for community urinary tract infections with ESBL-producing Enterobacteriaceae (especially CTX-M β-lactamase producers); however, a benefit over amoxicillin + clavulanic acid remains to be shown.
- Hyperproduction or combination of β-lactamases that are not inhibited could lead to resistance.

ARB-002 + colistin, iv

Phase 1

- Combination of colistin and an off-patent non-antibiotic drug (not disclosed) that covers colistin-resistant strains
- Phase-1 trial in development; no trials registered

Table 2. New antibiotic combinations that do not contain a new chemical entity currently in clinical development

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens			
				CRAB	CRPA	CRE	OPP
Aztreonam + avibactamt	2	Monobactam + DBO-BLI	iv (Pfizer)	■	■	□	■
Cefepime + tazobactam	1	Cephalosporin + β-lactam BLI	iv (Wockhardt)	■	■	□[a]	■
C-Scape	1	β-lactam + BLI	oral (Achaogen)	■	■	■	■
ARB-002+colistin	1	Unknown (approved) potentiator + polymyxin	iv (Helperby)	▒	▒	▒[a]	■

Pathogen activity: □ active, ▒ possibly active, ■ not or insufficiently active.

Abbreviations: CRAB, *A. baumannii*, carbapenem-resistant; CRPA, *P. aeruginosa*, carbapenem-resistant; CRE, Enterobacteriaceae, carbapenem- and third-generation cephalosporin-resistant; OPP, other priority pathogens on the WHO list ("high" and "medium" priority). Innovativeness assessment is not shown for these non-new chemical entity agents, as none of the four criteria is met.

[a] Active against cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae

3.3 Agents in development for treating tuberculosis

Human TB is caused by *M. tuberculosis*. Among the estimated 10.4 million new TB cases occurring worldwide in 2015, an estimated 580,000 new cases (5.6%) were resistant to rifampicin or rifampicin and isoniazid, two of the most important first-line TB drugs, with an estimated 30% fatality rate (132). Innovative new treatments thus are urgently needed. The following agents are being developed specifically for treatment of TB. This list does not include bedaquiline and delamanid, two new drugs to treat MDR-TB that are currently in phase-3 trials, but have already received conditional marketing approval.

Pretomanid, oral

Phase 3

- Nitroimidazole analogue (nitroimidazo-oxazine)
- Prodrug activated by a deazoflavin (cofactor F_{420})-dependent nitroreductase
- Inhibits cell wall mycolic acid biosynthesis and also acts directly as a nitric oxide donor, with subsequent poisoning of the respiratory chain. The mechanism of action is complex and not completely understood.
- In phase-3 trials for both drug-sensitive and drug-resistant TB (NCT02333799, NCT02589782, NCT03086486)

Delpazolid (LCB01-0371), oral

Phase 2

- Belongs to the class of oxazolidinones; has also been in development for MRSA
- Presently in a phase-2 early bactericidal activity study (NCT02836483)

SQ-109, oral

Phase 2

- Structurally related to ethambutol
- Inhibits the mycobacterial membrane protein large 3 (MmpL3) transporters, which are involved in the export of mycolic acids for the synthesis of the mycobacterial cell wall.
- Two phase-2 trials for treatment of TB (NCT01785186, NCT01218217)
- Also in a phase-2 trial for treatment of *H. pylori* infection (NCT01252108)

GSK-3036656, oral

Phase 1

- Inhibits leucyl-tRNA synthetase (LeuRS)
- Chemical structure is an oxaborole.
- Presently in phase-1 clinical development (NCT03075410)

Q-203, oral

Phase 1

- Inhibits cytochrome bc1 in the respiratory chain.
- An imidazopyridine amide
- Completed a phase-1 trial (NCT02530710); another trial is under way (NCT02858973).

PBTZ-169, oral, OPC-167832, oral

Phase 1 **Phase 1**

- These two compounds inhibit decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1). which is a flavoenzyme that catalyses a key step in the synthesis of the complex cell wall of *M. tuberculosis*. The mechanism of action of many compounds discovered in TB phenotypic screening programmes appears to be through inhibition of this flavoenzyme.
- PBTZ-169: A benzothiazinone that binds DprE1 covalently, causing irreversible inhibition of the enzyme. Currently in phase-1 clinical development (NCT03036163)
- OPC-167832: Limited information available; phase-1 started, but no trials are registered.

Table 3. Agents for the treatment of tuberculosis currently in clinical development

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Innovation			
				C	T	MoA	NCR
Pretomanid	3	Nitroimidazole	Oral (Global Alliance for TB Drug Development)	✖	✖	✓	✓
Delpazolid (LCB01-0371)[a]	2	Oxazolidinone	Oral (LegoChem)	✖	✖	✖	✖
SQ-109[b]	2	Diamine	Oral (Sequella/Infectex)	✖	✓	✓	✓
GSK-3036656	1	Leu RS inhibitor (oxaborole)	Oral (GlaxoSmithKline)	✓	✓	✓	✓
Q-203	1	Imidazopyridine amide	Oral (Qurient/Infectex)	✓	✓	✓	✓
PBTZ-169	1	DprE1 inhibitor (benzothiazinone)	Oral (Innovative Medicines For Tuberculosis Foundation)	✓	✓	✓	✓
OPC-167832	1	DprE1 inhibitor	Oral (Otsuka)	✓	✓	✓	✓

Innovativeness assessment: ✓ criterion fulfilled; ✓ Inconclusive data or no agreement by the advisory group; ✖ criterion not fulfilled.

Abbreviations: C, 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 class. These agents are being developed for use against TB; their activity against other priority pathogens was not systematically assessed.

[a] elpazolid also completed a phase-1 trial as injectable for MRSA and vancomycin-resistant Enterococcus spp. infections.

[b] SQ-109 is also being tested for use in the treatment of H. pylori infections.

3.4 Agents in development for treating *Clostridium difficile* infections

Infections with *C. difficile* can cause severe enterocolitis and are a serious public health threat in developed countries. *C. difficile* infections are primarily managed by prevention, control and stewardship, and treatment options are still available. Therefore, it was not reviewed for inclusion in the PPL for R&D. Nonetheless, agents developed for *C. difficile* infections are listed here, although their activity against PPL pathogens was not assessed (133).

Cadazolid, oral

Phase 3

- Non-absorbable oxazolidinone-quinolonehybrid; most activity due to the oxazolidinone part
- Confirmed in-vitro and clinical activity against *C. difficile* (134–136)
- Two phase-3 studies (NCT01987895 andNCT01983683.
- Continuation of development is unclear after the acquisition of Actelion by Johnson & Johnson

Ridinilazole, oral

Phase 2

- Non-absorbable bis-benzimidazole, new structure with a new mode of action that is not yet clear. It might inhibit cell division by binding to the DNA minor groove (137–139).
- Phase-2 study completed (NCT02784002).

OPS-2071, oral

Phase 2

- Quinolone, no structure published
- Developed for enteric infections, including due to *C. difficile*
- Phase-2 trial ongoing (NCT02473393), although the study design is closer to that of a phase-1 trial.

MCB-3837, iv

Phase 1

- Oxazolidinone–quinolone hybrid for iv treatment (140)
- The company claims that a phase-2 trial is planned (141), but no trials are registered.

MGB-BP-3, oral

Phase 1

- Non-absorbable antibiotic with a novel chemical structure (distamycin derivative), a new target and mode of action (DNA minor groove binder). It acts on multiple binding sites and interferes with transcription (142,143).
- Active against Gram-positive bacteria; resistance in Gram-negative bacteria through efflux pumps
- Phase-1 study completed (NCT02518607) (144)

DS-2969, oral

Phase 1

- Gyr B inhibitor, chemical structure unclear
- Active against Gram-positive bacteria (except E. faecium) and H. influenzae; no activity against Enterobacteriaceae (147)
- Oral bioavailability about 70%; systemic exposure unclear
- Preclinical toxicology findings inconclusive

CRS-3123, oral

Phase 1

- New chemical class with a new target and a new mode of action: a diaryldiamine derivative that inhibits the Met-aminoacyl-tRNA synthetase (145)
- Active against Gram-positive bacteria, including ; inhibits toxin production in vitro (146)
- Little information about the propensity for emergence of single-step resistance due to target mutations
- Systemic absorption only at higher doses
- Phase-1 trial completed (NCT01551004, NCT02106338); phase-2 trial planned

Table 4. Agents for the treatment of C. *difficile* infections currently in clinical development

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Innovation			
				C	T	MoA	NCR
Cadazolid	3	Oxazolidinone-quinolone hybrid	Oral, not absorbed (Actelion)	✖	✖	✖	✖
Ridinilazole	2	Bis-benzimidazole	Oral, not absorbed (Summit)	✔	✔	✔	✔
OPS-2071	2	Quinolone	Oral (Otsuka)	✖	✖	✖	✖
MCB-3837	1	Oxazolidinone-quinolone hybrid	iv (Morphochem)	✖	✖	✖	✖
MGB-BP-3	1	DNA minor groove binder (Distamycin)	Oral, not absorbed (MGB Biopharma)	✔	✔	✔	✔
CRS-3123	1	Met-aminoacyl-tRNA synthetase inhibitor (Diaryldiamine)	Oral, not absorbed (Crestone)	✔	✔	✔	✔
DS-2969	1	GyrB inhibitor[a]	Oral, not absorbed (Daiichi Sankyo)	/	/	/	/

Innovativeness assessment: ✔ criterion fulfilled; / Inconclusive data or no agreement by the advisory group; ✖ criterion not fulfilled.

Abbreviations:C, new chemical class; T, new target; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes. Underlined agents: New class. These agents are being developed for C. *difficile* infections; their activity against PPL pathogens was not assessed.

[a] Novobiocin is also a GyrB inhibitor, but was withdrawn from the market.

3.5 Biological agents

Eleven products in the clinical pipeline are not classic small-molecule antibiotics but comprise monoclonal antibodies, polyclonal antibodies and phage endolysins. Treatment with living bacteriophages in principle falls within the scope of this clinical pipeline review, but the three products that are in clinical trials (NCT02116010, NCT02664740, NCT02757755) are being developed only in topical forms. Only one biological antibacterial that targets *C. difficile* toxins, Bezlotoxumab, is currently approved. Hence, all these products can in principle be considered innovative as they target new structures through new modes of action. So far, these non-traditional agents have been developed for pre-emptive or adjunctive therapy. Their potential use for single-agent therapy and a real "alternative" to traditional antibiotics remains to be proven (148), and there have been several clinical failures in the past (149). Though some of the monoclonal antibodies listed are being developed only for pre-emptive therapy, they were included in this clinical pipeline analysis, as their mode of action is similar to that of monoclonal antibodies developed for adjunctive treatment.

MEDI-3902, iv

Phase 2

- Anti-*P. aeruginosa* IgG monoclonal antibody, targets virulence factors Psl and PcrV, which are involved in the secretion of multiple virulence factors (150,151).
- Clinical trials for the prevention of ventilator-associated pneumonia in colonized patients
- Phase-2 trial under way (NCT02696902)

Aerubumab, iv

Phase 2

- Anti-*P. aeruginosa* IgG1 monoclonal antibody binds to surface polysaccharide alginate to enhance immune response.
- Half-life, 3-4 weeks
- Phase-2 trials under way (NCT03027609)

Suvratoxumab, iv

Phase 2

- Anti-*S. aureus* IgG monoclonal antibody targets virulence factors β-toxin and surface-localized clumping factor A (152,153).
- Long half-life, around 80 days
- Phase-2 development (NCT02296320)

ASN-100, iv

Phase 2

- Anti-*S. aureus* IgG monoclonal antibody targets virulence factors β-haemolysin and 4 leukocidins (154).
- Half-life, 24 days
- Phase-2 trial under way (NCT02940626)

514G3, iv

Phase 1/2

- Anti-*S. aureus* IgG3 monoclonal antibody targets virulence factor SpA (involved in immune evasion); cloned from the B cells of a healthy human donor with pre-existing antibodies against SpA
- Phase-1 and -2 trials for adjunct treatment of bacteraemia caused by *S. aureus* (NCT02357966)

AR-301, iv

Phase 1/2

- Anti-*S. aureus* IgG1 monoclonal antibody targets virulence factor β-toxin.
- Phase-1 and -2 proof-of-concept study (NCT01589185)

DSTA-46375, iv

Phase 1

- Thiomab-antibiotic conjugate: anti-*S. aureus* IgG monoclonal antibody bound to a rifamycin analogue
- Antibody binds to surface proteins of *S. aureus* and releases rifamycin to kill intracellular *S. aureus* (155)

SAL-200, iv

Phase 2

- Recombinant form of phage endolysin SAL-1, an enzyme that destroys the peptidoglycan cell wall of a bacterium to release new virus particles (156,157)
- Fast killing of *S. aureus*; synergistic with antibiotics
- Very short half-life (158)
- An immune response against the enzyme might limit its usefulness; antibodies were detected in 37% of volunteers, but it is not clear whether this is clinically relevant.
- Phase-2 trial (NCT03089697) for treatment of persistent *S. aureus* bacteraemia

CF-301, iv

Phase 2

- A phage endolysin similar to SAL-200 (159,160)
- No resistance appears to emerge in serial passages.
- Similar questions about immunogenicity as for SAL-200
- In phase-1 trials as adjunctive therapy for *S. aureus* bacteraemia (NCT02439359)

PolyCab, iv

Phase 1

- *C. difficile* polyclonal antibody against *C. difficile* toxins produced in sheep
- Phase-1 study (ISRCTN80902301)

IMM-529, oral

Phase 1/2

- Anti-*C. difficile* polyclonal antibody (IgG, IgA, IgM) against toxin A + B derived from vaccinated cow's colostrum
- Also targets *C. difficile* spores and vegetative cells
- 80% efficacy in prophylaxis and therapy in animal models
- Phase-1/2 trial (NCT03065374)

Table 5. Biological antibacterial agents for in clinical development

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens			
				CRAB	CRPA	CRE	OPP
DSTA-4637S	1	Anti-*S. aureus* IgG monoclonal antibody/ rifamycin	iv (Genentech/Roche)	■	■	■	▭
CF-301	1	Phage endolysin	iv (Contrafect)	■	■	■	▭
PolyCab	1	C. *difficile* polyclonal antibody	iv (Micropharma)	■	■	■	■
IMM-529	1/2	C. *difficile* polyclonal antibody	Oral (Immuron)	■	■	■	■
AR-301	1/2	Anti-*S. aureus* IgM monoclonal antibody	iv (Aridis)	■	■	■	▭
514G3	1/2	Anti-*S. aureus* IgG monoclonal antibody	iv (XBiotech)	■	■	■	▭
SAL-200	2a	Phage endolysin	iv (Intron)	■	■	■	▭
ASN-100[a]	2	Anti-*S. aureus* IgG monoclonal antibody	iv (Arsanis)	■	■	■	▭
Suvratoxumab[a]	2	Anti-*S. aureus* IgG monoclonal antibody	iv (MedImmune)	■	■	■	▭
MEDI-3902[a]	2	Anti-*P. aeruginosa* IgG monoclonal antibody	iv (MedImmune)	■	▭	■	■
Aerubumab	2	Anti-*P. aeruginosa* IgM monoclonal antibody	iv (Aridis)	■	▭	■	■

Pathogen activity: ▭ active, ▪ possibly active, ■ not or insufficiently active. Agents against critical priority pathogens were assessed only against these (three bars) but might be active against other priority pathogens (OPP). The only agents assessed against OPP (fourth bar) were those that are not active against critical priority pathogens.

Abbreviations: CRAB, *A. baumannii,* carbapenem-resistant; CRPA, *P. aeuruginosa,* carbapenem-resistant; CRE, Enterobacteriaceae, carbapenem- and third-generation cephalosporin-resistant; iv, intravenous; OPP, other priority pathogens on the WHO list ("high" and "medium" priority). Except for one monoclonal antibody against *C. difficile* (Bezlotoxumab), no biologicals to treat bacterial infections are approved. Hence, all the agents listed would fulfil the criteria for innovativeness used for antibiotics.

a. These products are in trials for pre-emptive indications only.

3.6 Agents that are not under active development or for which there is no recent information

Several products are listed in the online clinical development pipelines of various companies, but their development status has not been updated recently. Products were not included in the current clinical pipeline list if their last registered clinical trials were finalized before 1 January 2015 and for which there was no sign of further development (e.g. press releases) since that date. It is not uncommon in antibiotic development, however, for product development to be suspended for several years and for the product to be bought by another company to continue development. Therefore, these agents were tracked and are listed in Table 6.

Table 6. Agents the development of which was suspended or for which there is no recent information

Name	Phase	Antibiotic class	Developer
CB-618	1	DBO-BLI	Merck
IDP-73152	1	Peptide deformylase (PDF) inhibitor	IlDong
TD-1607	1	Glycopeptide-cephalosporin hybrid	Theravance
Benapenem	1	Carbapenem	Xuanzhu/KBP Bioscience
KBP-5081	1	Oxazolidinone	Xuanzhu/KBP Bioscience
KBP-0078	1	Oxazolidinone	Xuanzhu/KBP Bioscience
Ramoplanin	2	Lipodepsipeptide	Nanotherapeutics
Panobacumab	2	Anti-*P. aeruginosa* IgG monoclonal antibody	Aridis
CG-400549	2	FabI inhibitor	CrystalGenomics
Sutezolid[a]	2	Oxazolidinone (TB)	Sequella/Pfizer
Cefilavancin	3	Glycopeptide-cephalosporin hybrid	Theravance

Abbreviations:BLI, β-lactamase inhibitor; DBO, diazabicyclooctane

a. The development of sutezolid has been suspended for several years; however, Johns Hopkins University recently licensed related intellectual property to the Medicines Patent Pool (161).

4. Analysis of the clinical pipeline

As of May 2017, a total of 51 antibiotics (including combinations) and 11 biologicals were in the clinical pipeline to target priority pathogens, *M. tuberculosis* and *C. difficile*. There were 33 new chemical entity antibiotics and combinations for critical and high-priority pathogens in the pipeline. Of these, 12 are expected to be active against at least one of the three critical priority carbapenem-resistant pathogens, *P. aeruginosa*, *A. baumannii* and Enterobacteriaceae (Table 7) Seven antibiotics are in trials for *M. tuberculosis* and C. difficile infections. In addition, 11 biological treatments are in phase-1 and -2 development, targeting mainly *S. aureus*, but also *P. aeruginosa* and *C. difficile* infections.

Of the critical priority pathogens, CRE are those targeted by the most (nine) antibiotics, although they are not universally active. Three and four agents are expected to be active against CRPA and CRAB, respectively. Only two agents, GSK-3342830 (phase-1) and cefiderocol (phase-3), are expected to be active against all three critical priority pathogens.

Furthermore, two monoclonal antibodies are being developed against *P. aeruginosa*.

Sixteen agents are active against multiresistant Gram-positive pathogens, mainly against resistant *S. pneumoniae* and/or MRSA. Seven of the sixteen are biological agents against S. aureus (monoclonal antibodies and endolysins). Few of the agents have been tested for activity against vancomycin-resistant Enterococcus spp. Two agents of new chemical classes have completed phase-2 trials for gonococcal infections.

Of 14 PPL antibiotics in phase-1 trials, 10 target at least one of the Gram-negative critical priority pathogens,however, conclusive data on the activity of many of these drugs is still lacking, as they are only in clinical phase-1 and are thus categorized as "possibly active". Eight of these potential anti-Gram-negative agents are β-lactams or β-lactam + BLI combinations. Fifteen (excluding Sulopenem) of the PPL antibiotics are being developed as oral formulations, but only one is expected to be active against at least one critical priority pathogen.

Table 7. Analysis of the clinical development pipeline

	Number of compounds "active" and "possibly active" against the pathogen[b]								Assessed as innovative		
	Phase 1		Phase 2		Phase 3						
Pathogen	Active	Possibly active	Active	Possibly active	Active	Possibly active	Total compounds active	Total compounds possibly active	Active	Possibly active	Compounds developed as oral formulations [d]
PPL critical priority pathogens	**6**	**4**	**1**	**-**	**5**	**-**	**12**	**4**	**2**	**1**	**1**
A. baumannii carbapenem-resistant	3	3	-	-	1	1			0	1	1
P. aeruginosa carbapenem-resistant	1	5	1	-	1	1			1	1	0
CRE carbapenem-resistant	4	5	-	-	5	-			1	1	1
PPL other priorities	**2**	**2**	**4**	**2**	**5**	**2**	**11**	**6**	**4**	**0**	**14**
Gram-positive (MRSA, VRE, resistant S. pneumoniae)	2	1	2	1	5	2			2	0	11
H. pylori clarithromycin-resistant	-	1	-	1	-	-			-	-	1
N. gonorrhoea cephalosporin-resistant fluoroquinolone-resistant	-	-	2	-	-	-			2	-	2
Mycobacterium tuberculosis[a]	**4**	**-**	**2**	**-**	**1**	**-**	**7**	**-**	**5**	**0**	**7**
Clostridium difficile[a]	**4**	**-**	**2**	**-**	**1**	**-**	**7**	**-**	**3**	**0**	**6**

Combinations of antibiotics that do not contain a new therapeutic entity and biologicals were not included.

Sulopenem (oral formulation) was not included, since it is active against ESBL- but not carbapenemase-producing *Enterobacteriaceae*.

A, active; PA, possibly active; PPL, priority pathogens list; CRE, Enterobacteriaceae, carbapenem- and third-generation cephalosporin-resistant; ESBL, extended beta-lactamase; MRSA, methicillin-resistant *Staphyloccocus aureus*; VRE, vancomycin-resistant *Enterococcus*

[a] Only general activity against *C. difficile* and *M. tuberculosis* was assessed and not that against resistant strains.

[b] Some agents are active against more than one PPL pathogen and are counted more than once.

5. Outlook and discussion

5.1 The current clinical pipeline is insufficient against pathogens on the WHO priority pathogens list and TB.

As of May 2017, there were 42 new therapeutic entities (traditional antibiotics and biologicals) that target critical and high-priority pathogens in the clinical pipeline. While these include some innovative treatments, the clinical development pipeline is still insufficient to counter the rising resistance. Potential treatment options are lacking for the most critical resistant bacteria, especially for multidrug and extensively drug-resistant Gram-negative pathogens. Few of the treatments under development are likely to cover a broader range of resistant pathogens and are often active against only some and not all isolates of a certain pathogen.

Marketing approval of new antibiotic classes, such as oxazolidinones and cyclic lipopeptides, has improved the treatment options for multidrug-resistant Gram-positive pathogens, but new antibiotics against those pathogens are still required to keep up with the anticipated evolution of resistance. Sixteen products in the current pipeline show activity against one or more Gram-positive priority pathogens. Among them are two new antibiotic classes, and seven of the products are biological agents (monoclonal antibodies and endolysins). Whether such biological treatments could serve as real alternatives to antibiotics is not yet clear; they are being developed to complement antibiotics as adjunctive or pre-emptive treatment. Most of the antibiotics and all the Gram-positive biologicals specifically target MRSA, while another highly important pathogen, vancomycin-resistant *Enterococcus* spp., has received little attention from developers. This may be due to the scientific challenges and to the fact that that it is not a major cause of the indications usually chosen for drug development. Several agents in late clinical phases are being developed for less severe infections and for outpatient treatment, especially for MRSA and other respiratory pathogens. These agents include a new class against staphylococci. Additional innovative approaches should be encouraged to ensure that successful treatment options for Gram-positive organisms are available in the future.

The situation is worse for Gram-negative bacterial infections. These bacteria have been assessed as the most critical priority for antibiotic R&D, as strains are emerging worldwide that cannot be treated with any of the currently marketed antibiotics. While recent entries in the clinical pipeline show an increased focus on Gram-negative bacteria, almost all the agents are modifications of existing antibiotic classes and address specific resistance mechanisms. They are active only against specific pathogens or a limited subset of resistant strains.

Only two compounds of the same class show potential for sufficient activity against all three critical priority pathogens. These compounds are new cephalosporins combined with a siderophore, which use the bacterial iron uptake system for entry into the bacterial cell. Agents that are broadly active against more than one of the critical priority bacteria are required for empirical treatment of severe infections during the delay before the results of susceptibility testing become available, as this is the interval during which antibiotics have the greatest effect on survival. Only three anti-Gram-negative compounds are being developed as oral formulations, and only one is active against carbapenem-resistant strains. Oral drugs are required in countries with high resistance rates in community-treated infections such as urinary tract infections. This is especially important for low- and middle-income countries but is not addressed by the current pipeline.

Other high-priority Gram-negative bacteria on the PPL are hardly being addressed. Two new oral compounds of the novel class are being developed and tested for uncomplicated gonococcal disease. Others (solithromycin and delafloxacin) failed as single-dose treatments but may be revived in a two- or multiple-dose regimen. No agents are being developed against resistant *Salmonella* spp., especially S. Typhi, a specific problem in low- and middle-income countries. Two compounds in the pipeline are being tested for use in *H. pylori* infections.

Another neglected area in new product development is drug-resistant TB. The standard therapy today for drug-resistant TB is long (usually between nine and twenty months) and toxic, combining four to seven drugs, and the cure rates are relatively low (about 50% reported globally in 2015). Furthermore, only about 20% of all

patients are reported to receive treatment. Despite the estimated 10.4 million new TB cases occurring worldwide in 2015 and the widespread resistance to two of the most important first-line TB drugs (rifampicin and isoniazid), only seven new agents for TB are in clinical trials. Of these, four are in phase-1, and only one compound is in phase-3 (excluding bedaquiline and delamanid). This is especially problematic because TB treatment requires a combination of at least three antibiotics. Novel treatment regimens of short duration that are assembling non-toxic drugs are desperately needed (161). The development of sutezolid has been on hold for some years, but the recent license agreement between the Johns Hopkins University and the Medicines Patent Pool could reinvigorate its development (162).

Infections with *C. difficile* have been classified as an urgent public health threat by the US Centers for Disease Control. However, *C. difficile* is addressed primarily by infection prevention, control and stewardship. In addition, other treatment options are still available. Therefore, *C. difficile* is not on the WHO PPL for R&D. The analysis showed that nine products are in development for *C. difficile*, including three first-in-class antibiotics and two polyclonal antibodies. Non-absorbable antibiotics obviate the challenges of suitable systemic pharmacokinetics and associated potential toxicity. The *C. difficile* pipeline could result in additional treatment options in the near future.

5.2 More innovative approaches are required, but there are scientific challenges.

Five of the 32 new chemical entity antibiotics being developed for PPL pathogens are in distinct chemical classes that have not been used systemically in humans before. As some of the agents in development belong to the same new antibiotic class, eight products against the priority pathogens and 16 in total (including against TB and *C. difficile*) fulfil at least one of the four criteria used to assess the extent to which agents in the pipeline are based on innovative approaches: new chemical class, new target, new mechanism of action and no cross-resistance to existing antibiotics. The agents also include lefamulin, a pleuromutilin, although this class has been used before in animals and for topical treatment in humans, with unknown consequences for selection of resistance. Two drugs belong to the functional class of BLIs and are associated with liabilities similar to those of other BLIs. The two novel bacterial topoisomerase II inhibitors are chemically distinct but are in the same functional class, and there is no information on potential cross-resistance.

Of the 11 biological treatments in phase-1 and -2 development, nine target the priority pathogens *S. aureus* and *P. aeruginosa*. All of the biologicals, comprising seven monoclonal antibodies and two phage-derived endolysins, are currently being developed as pre-emptive or adjunctive treatment. Three monoclonal antibodies are in clinical trials for disease prevention in colonized patients, and the remaining products are being tested as adjuncts and not as replacements for antibiotics. While the biologicals can be considered innovative, their potential use as alternatives has yet to be proven, and it seems unlikely that they could be used to replace therapeutic antibiotics. The higher costs of monoclonal antibodies than of regular antibiotics may also limit their potential use as alternative treatments, especially in low- and middle-income countries (163). Additional interventions, such as vaccines, were not considered in this analysis.

Agents currently in the pipeline, especially for Gram-negative bacteria, are mainly improvements of existing classes. While this has the advantage that the risky discovery process is started with a well-characterized, validated lead, some level of cross-resistance and fast adaption of bacterial populations can be expected. Most searches for modified molecules of known classes focused on certain class-specific resistance mechanisms. This resulted in improvement but not in full restoration of susceptibility in a given pathogen. Ideally, R&D should result in entirely new classes, targets and modes of action in order to avoid cross-resistance to existing antibiotics (25).

Finding novel chemical structures with new binding sites and new modes of action is, however, genuinely difficult and less successful than drug discovery in other fields (164). The challenges include finding compounds with more than one binding site in order to avoid single-step resistance and that penetrate the outer layers of Gram-negative cell walls without being pumped out immediately. Other general hurdles are toxicity due to the high concentrations required to kill bacteria and appropriate pharmacokinetics. One reason for failure is the lack of diverse compounds suitable for bacterial treatment in the chemical libraries of pharmaceutical companies. The absence of new, suitable chemical matter to serve as leads for drug discovery is a main bottleneck in antibiotic discovery (165).

5.3 Outlook: More work is needed to fill the pipeline

Given the average success rates and development times in the past (18), the current pipeline of antibiotics and biologicals could lead to around 10 new approvals over the next 5 years. However, these new treatments will add little to the already existing arsenal and will not be sufficient to tackle the impending AMR threat. More investment is needed in basic science, drug discovery and clinical development, especially for the critical priority Gram-negative carbapenem-resistant pathogens *P. aeruginosa, A. baumannii* and *Enterobateriaceae.*

It also needs to kept in mind that likelihood of future approval of an antibiotic that is in phase-1 has been estimated to be 14%. Hence, of the 10 anti-Gram-negative products in phase-1, only one to two will probably make it to the market. The average time from phase-1 until approval is about seven years. The development time is even longer for TB treatment because of its many unique aspects, including the requirement for combination therapy, ideally consisting of multiple innovative new drugs.

Over the past three years, two new BLI combinations to which some Gram-negative pathogens have higher susceptibility rates have been approved, and one more is awaiting approval. Developers are close to submitting NDAs to the US Food and Drug Administration for four more improved members of old classes, which will increase coverage of CRE and some of the other critical priority pathogens. These agents do not, however, show universal activity against all strains of a specific pathogens. Adaptation of existing antibiotic classes is a valuable short-term approach, but innovative approaches to antibacterial treatment are required to overcome resistance in a sustainable manner. Therefore, focus on basic science should be increased to address scientific bottlenecks.

More support should be given for preclinical and clinical development of new products. The development of antibiotics is economically less attractive than other therapeutic areas for many reasons. There is a well-established market for efficacious generic substitutes, and antibiotics are often prescribed for only a brief time (166). For TB, a disease that affects mainly the poor, there is very little commercial incentive to invest in developing new treatments (167).

Many of the products in the pipeline are already co-funded by research grants from public and philanthropic institutions, especially for TB, for which most development is done by not-for-profit entities. Furthermore, universities and other publicly funded research institutions are often the source of the technology that is the starting-point for R&D projects in small and medium-sized enterprises. The pharmaceutical industry has a key role to play and in the Davos Declaration and the related Roadmap has committed to further engage in collaboration with academic and public partners to enhance the development of new antibiotics (15,16).

New antibiotics will not be sufficient to mitigate the threat of antimicrobial resistance. Antibiotic development must go hand in hand with efforts to foster appropriate use of existing and future antibiotics. The coming WHO Global Framework for Development and Stewardship to Combat Antimicrobial Resistance (20) should provide the necessary rules and guidance for more responsible use of antibiotics in the human, animal and agricultural sectors.

This report is part of WHO's work on setting priorities for antimicrobial resistance under the Global Action Plan and the Global Framework. The analysis shows the extent to which the priorities identified on the PPL along with TB and *C. difficile* infections are being addressed by current clinical development. It will be repeated annually, to monitor how the pipeline is developing and how it reacts to the PPL. Additional work is needed to define antimicrobial drug needs in more detail, taking into account not only pathogens but also the most urgent symptoms and patient populations. Hence, development of preferred product characteristics or target product profiles would be a next step in guiding R&D on antibiotics.

5.4 Methodological considerations

5.4.1 Variable data quality

The aim of this report is to provide a complete, accurate picture of current clinical development activities on the basis of publicly data. While every effort was made to ensure that the analysis was as complete as possible and assessments were based on peer-reviewed publications, the availability and quality of the data varied.

A range of sources was used to find information about products in development. None of the public databases searched (peer-reviewed literature, patents, clinical trials) covered all the products that were finally listed in this report. Knowledge of drug development projects, especially for early-stage products, relies to a certain extent on informal information from experts in the field, including from presentations and posters given at scientific conferences or business meetings. We considered such projects only when the information about them was publicly available.

Despite WHO's position on clinical trial transparency (168), some of the products in the pipeline are not listed in any clinical trial registry, and the results of most trials were not disclosed within the recommended 12 months after completion. The absence of critical data from earlier phases and from randomized controlled trials complicated the assessment of some agents in advanced development phases. It is essential that any public investment in antibiotic drug development include an obligation to adhere to clinical trial transparency standards and to publish both positive and negative results. Nineteen of the world's largest funders of medical research recently signed a joint statement on public disclosure of results from clinical trials (169) and have committed themselves to these principles.

Data inequality impeded assessment of expected activity against PPL pathogens. While peer-reviewed assessments of activity were available for some agents, for others we had to rely on publically available company information or comparisons with other agents with a similar structure if no data were published. Furthermore, the primary assessment was based on data obtained in vitro, with some secondary data on pharmacokinetics and pharmacodynamics and clinical information when available. This approach will be further refined in future pipeline analyses, and the WHO Secretariat welcomes suggestions for improving the method.

Assessments of innovativeness were also subject to certain limitations. Lack of cross-resistance is the most relevant criterion of innovativeness in the context of antibiotic resistance. A new chemical scaffold, a new binding site and a new mode of action are "surrogate markers" and good predictors of lack of cross-resistance. For these reasons, the four aspects were assessed separately. There is, however, no clear definition of "surrogate markers", and a "?" in some instances indicates that the experts could not agree whether a criterion had been fulfilled. For some compounds, lack of information (e.g. structure not published) made assessment impossible. Developers should make a special effort to define and characterize the cross-resistance of their agent with existing classes. When this information was available, it allowed categorization of a compound.

5.4.2 Differences from other pipeline reports

The antibacterial clinical pipeline has been assessed by others recently (1,17,170). While the products in these clinical pipelines are largely similar, there are some important differences:

- The Pew pipeline (17) is restricted to products developed for the market in the USA. Some of the products in the Pew pipeline were excluded because of the cut-off date for our analysis.
- The review by Butler et al. (1) includes topical treatments, which were excluded.
- This analysis focuses on products being developed for PPL pathogens. Agents in development for TB and *C. difficile* infections are nonetheless listed but in separate sections.
- For biologicals, this pipeline was limited to specific antibacterial treatments. Reviews by the Pew Charitable Trusts (19) and Czaplewski et al. (18) include several additional approaches for prevention of disease and reduction of antimicrobial resistance.

5.4.3 Limitations and next steps

The meeting of the advisory group and the review of the clinical antibacterial pipeline were undertaken with certain limitations, including restrictions on time and data inequality due to reliance on data available in the public domain and input from the advisory group, which led to a degree of publication bias. To strengthen future reviews, certain limitations will be addressed, including additional effort to capture drug candidates being developed in markets such as China and the Russian Federation to ensure a more comprehensive global analysis.

Building on this first review, the terms of reference of the advisory group, its membership and the method used for the review will be strengthened, including the criteria for inclusion and exclusion of products and classification of their activity and innovativeness in the absence of comparable data quality. In moving forward greater collaboration is needed between all stakeholders in addition to more transparency of

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

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Annex 1. Search strategy and results

Information on agents in development was sought from a variety of sources. The cut-off point was 1 May 2017, and no agents were added or removed after that date. Information that met the inclusion criteria was combined into one list. Publications were cross-checked by compound name and synonyms (research numbers and brand names) to remove duplicates. Some data sources reported different phases of development, in different countries or use for different indications. For these agents, the most advanced development phase was listed in this clinical pipeline. The sources searched are listed below.

- Journal articles (review articles published since 2015; search terms: antibacterial pipeline OR antibiotic pipeline) on the clinical antibacterial pipeline were retrieved from PubMed and grey literature from Google. Information on antibacterial agents that met the inclusion criteria was retrieved from recent publications and reports (1–5).
    - The list of antibiotics in clinical development of The Pew Charitable Trusts in December 2016 (2) was used as the basis. TD-1607, WCK-771, CG-400549, ramoplanin and ceftaroline + avibactam were removed from this list because their development appeared to be halted; fusidic acid and zabofloxacin were removed as they already have market approval in some countries. After addition of agents from the other sources (described below), we double-checked our list against the March 2017 update of the Pew pipeline (2).
    - AAI-101 + cefepime and lascufloxacin were added from the publication by Butler et al. (1). We did not consider agents for topical application or surotomycin, cefilavancin, radezolid and afabicin, which appear to have been discontinued.
    - The list of biologicals was based on a review on alternatives to antibiotics (3). Only direct therapeutic approaches that met the inclusion criteria were considered. Vaccines, probiotics and immunomodulators were excluded, as were phage therapies, which are currently being developed only as topical applications. Bezlotoxumab (now approved) and AR-101 (no recent update) were not included.
    - TNP-2092 was added from Bush et al. (4).
- To complement the list, the International Clinical Trials Registry Platform (6) and ClinicalTrials.gov (7) were searched for phases 1–3 trials of antibacterial agents registered between 1 January 2014 and 1 May 2017. Two separate searches were carried out, the data were combined, and duplicates (same trial ID) were removed:
    - ClinicalTrials.gov was searched for trials on the topic (intervention) "antibacterial agents" with the advanced search function; 1673 trials were retrieved.
    - The International Clinical Trials Registry Platform and ClinicalTrials.gov were searched for trials conducted under relevant conditions. To make this search as inclusive as possible, the search covered priority pathogens, relevant indications and some general terms related to bacterial infection and antibiotic resistance:

      cocc OR bact OR baumannii OR Klebsiella OR Escherichia OR Proteus OR Providencia OR aureus OR pylori OR Morganella OR Salmonella OR Haemophilus OR Shigella OR Clostridium OR difficile OR Pseudomonas OR aeruginosa OR E. coli OR Serratia OR Bloodstream infections OR urinary tract infections OR CUTI OR complicated intra-abdominal infections OR CIAI OR pneumonia OR VABP OR pyelonephritis OR ABSSSI OR cSSSI OR uSSSI OR cSSTI OR gonorrhea OR gonorrhoea OR skin and skin structure infection OR Sepsis OR Bone and joint infection OR meningitis OR endocarditis OR febrile neutropenia OR Carbapen OR ESBL OR MRSA

      These searches yielded 632 trials on the International Clinical Trials Registry Platform and 656 trials in ClinicalTrials.gov.

The combined dataset with duplicates removed comprised 2562 trials. Of these, 80 trials involved a product that fell into the scope of this study, including the following agents that were added to the list: VNRX-5133, ETX2514 + sulbactam, OPS-2071, SPR-741, cefepime + tazobactam and the biologicals ASN-100, DSTA-4637S, IMM-529 and PolyCAb.

- In collaboration with the European Medicines Agency, the commercial database Adis Insight (8) was searched with the terms antibacterials OR bacteriophages in the "drug class" filter. The search was limited to agents in clinical development (phases 1–3) that were not yet approved by any national regulatory agency. This search yielded 213 products, of which 43 met the inclusion criteria. All 43 agents were already on the list.
- The international patent database The Lens (9) was searched for patent families filed between 1 January 2007 and 1 May 2017 in the International Patent Classification A61P31/04 (A61: medical or veterinary science/hygiene; P: specific therapeutic activity of chemical compounds or medicinal preparations; 31/04: antibacterial agents). The 100 companies (applicants) that had filed the most applications were identified, and their online clinical development pipelines were screened for antibacterial products. In addition, the websites of all companies that had a product in the published clinical R&D pipelines (1–5) were searched for products in phases 1–3 clinical trials. The compounds benapenem, KBP-5081 and KBP-0078 made by the Chinese company Xuanzhu Pharma were found, and the WHO Representative in China was contacted to obtain additional information. As no additional information could be obtained to confirm active development, these compounds were not included in this clinical pipeline.
- The list of agents retrieved through the above-mentioned searches was sent to the advisory group of experts and further organizations and individuals active in the field of antibacterial drug development (see Acknowledgements) to obtain information about additional agents. A list of the individuals and organizations that received the data is included in the Acknowledgements. ARB-002, AIC-499, LYS-228 and C-Scape were added to the list after confirmation of their development status on the respective companies' websites.

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Annex 2. Declaration of interests of advisory group members

Management of conflicts of interest was a priority throughout the analysis and decision-making for the antibacterial clinical pipeline. In reviewing and assessing the declarations of interest (DOIs) of the experts at the first advisory group meeting on the analysis of the clinical development pipeline of antibacterial treatments, the WHO Essential Medicines and Health Products Department sought the advice of the Office of Compliance, Risk Management and Ethics.

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

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

The experts who declared no potential conflicts of interests were: Mical Paul, Ursula Theuretzbacher and Guy Thwaites. These experts were allowed full participation in the meeting.

The experts who disclosed insignificant or minimal conflicts of interest, listed below, were Mark Butler and Jean-Pierre Paccaud. These experts were allowed full participation in the meeting.

The experts who disclosed potentially significant conflicts of interest were Lloyd Czaplewski, Stephan Harbarth, John Rex, Lynn Silver and Melvin Spigelman. These participants were excluded from discussions of the relevant interests, listed below.

Mark Butler is Senior Research Officer at the Institute for Molecular Bioscience, University of Queensland, and Director (sole proprietor) of MSBChem Consulting. In his DOI, he reported having received remuneration for employment within the past 4 years with a commercial entity or organization with an interest related to the subject of the meeting. He receives a salary from the University of Queensland for discovery and pre-clinical drug development in the antibiotic area. He also reported that his salary has been partially funded by the Wellcome Trust during the past 4 years and that he has been the recipient of support from the Australian National Health and Medical Research Council for antibiotic research. After initial screening of the DOI and consultation with the Office of Compliance, Risk Management and Ethics, the technical unit requested further information regarding consulting services provided by MSBChem Consulting. Mr Butler reported that he started the company in late 2016 and has had only one client, which was not active in the area of antibiotics.

Lloyd Czaplewski is Director of Chemical Biology Ventures Ltd and Director and owner of Abgentis Ltd. In his DOI, he reported having provided consulting services through Chemical Biology Ventures Ltd. After initial screening of the DOI and consultation with the Office of Compliance, Risk Management and Ethics, the technical unit requested further information about the companies, organizations, institutions for which he has provided consulting services. He was recused from all discussions on products from companies for which he provided consulting services within the past 4 years: CARBX, Global Antibiotic Research and Development Partnership and Helperby Therapeutics. In his DOI, he also reported having been employed and commercial business interests in Abgentis Ltd and Persica Pharmaceuticals; however, these companies do not have products in the pipeline. In his DOI, he also reported that he has organized and spoken at conferences on the antibiotic pipeline and on alternatives to antibiotics, for which he received honoraria. The products discussed at the meeting from which he was recused are: ARB-002 + colistin, TP 6076, SPR-741 and Ridinilazole.

Stephan Harbarth is Head of the Antimicrobial Stewardship Programme at Geneva University Hospitals and Faculty of Medicine. In his DOI, he reported having provided consulting services to GSK, Janssen and Novartis within the past 4 years and was recused from all discussions of products from these companies. In his DOI, he also reported receiving financial support for research from Pfizer and BioMerieux within the past 4 years and was therefore recused from discussions of products from these companies. The products discussed at the meeting from which he was recused are: GSK-3342830, gepotidacin, GSK-3036656, LYS-228, aztreonam + avibactam and sutezolid.

Jean-Pierre Paccaud stated that, because of his affiliation with the not-for-profit Drugs for Neglected Diseases initiative organization, which hosts the Global Antibiotic Research and Development Partnership (GARDP), his participation in the meeting might be perceived as potentially providing the organization with information that could result in a "competitive advantage". As the organization is not for profit, this was not considered a significant conflict of interests, and he participated fully in the meeting.

John H. Rex is Chief Medical Officer and Director of F2G Ltd, Chief Strategy Officer of CARB-X, non-Executive Director and Consultant of Adenium Biotech ApS, Operating Partner and Consultant of Advent Life Sciences and Expert-in-Residence at the Wellcome Trust. In his DOI, he reported having provided consulting services to Polyphor Ltd, and he was recused from any discussion involving their products. He was also recused from discussions of products from CARB-X and AstraZeneca, by which he was employed within the past 4 years. He also reported having shareholdings in AstraZeneca Pharmaceuticals, F2G Ltd., Adenium Biotech ApS, Advent Life Sciences, Macrolide Pharmaceuticals and Bugworks Research Inc., but noted that no products from these companies were to be discussed in the advisory group meeting. He was recused from discussions of products from Spero Therapeutics, with which he reported having a commercial interest. The products discussed at the meeting from which he was recused are: ETX2514 + sulbactam, zoliflodacin, murepavadin, TP-6076 and SPR-741.

Lynn Silver is President of LL Silver Consulting LLC. In her DOI, she reported having provided consulting services for the following companies, and she was recused from any discussion involving their products: Achaogen, Debiopharm, Melinta, Merck and Nabriva. The products discussed at the meeting from which she was recused are: afabicin, delafloxacin, imipenem/cilastatin + relebactam, lefamulin and plazomicin.

Melvin Spigelman is President and Chief Executive Officer of the Global Alliance for TB Drug Development. In his DOI, he reported commercial business interests in The Medicines Company and Synergy Pharmaceuticals, and he was recused from discussions on their products. He was also recused from discussions of products from the Global Alliance for TB Drug Development, by which he was employed within the past 4 years. The products discussed at the meeting from which he was recused are: meropenem + vaborbactam and pretomanid.

After review of the DOIs and receipt of the additional information requested, the disclosed interests of the following individuals were considered insignificant or minimal with respect to the meeting, and they were allowed to participate fully: Mark Butler, Jean-Pierre Paccaud. The disclosed interests of the following participants were considered potentially significant, and they were thus excluded from the discussion at which the relevant interests were identified: Lloyd Czaplewski, Stephan Harbarth, John Rex, Lynn Silver and Melvin Spigelman. All the reported interests were disclosed to the Chair before the meeting and to other meeting participants by the technical unit in a slideshow presentation; they are also disclosed in this meeting report and will be disclosed in relevant publications.

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