Elsevier Editorial System(tm) for The Lancet Infectious Diseases

Manuscript Draft

Manuscript Number: THELANCETID-D-18-00394R1

Title: WHO`s analysis of the clinical antibacterial and antituberculosis pipeline

Article Type: Invited Review

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World Health Organization

Electronic Publishing

ePub Summary

IP Planning Clearance **ePub Number: ePub-IP-00170258-PC**

Responsible Officer
PAULIN Sarah

Office/Region
HQ

Cluster/Department/Unit
HIS/EMP/IAU

Provisional Title (in English)
WHO`s analysis of the clinical antibacterial and antituberculosis pipeline

Product Type
External Publication

Product Subtype
External Publication

Category
Journal Article

Subjects (Level 1)
Infectious/parasitic diseases, Medicines

Subjects (Level 2)
Drug resistance, Essential medicines

Attribution of authorship
Attribution to individuals or groups

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Type of collaboration

[X] Content development	[ ] Translation	[ ] Financial
[ ] Distribution	[ ] Other	[ ] None

Name of partner(s) and type of collaboration
The experts from the clinical pipeline advisory group were involved in the content development based on the WHO publication and the discussions that took place at the advisory group meeting 12 -13 June 2017 in Geneva. Ursula Theuretzbacher was the main author of the publication through an agreement for performance of work with WHO.

Category of partner
Other

Will the IP include recommendations?
No

Decision regarding the use of the logos of external partners
Yes

Specify the logos of external partners to be used
To be confirmed by the orinigator.

Comment Log (Can be empty)

Date	User	ID	Note
13-March-2018	KRECH Ruediger	24	Approved on behalf of Director EMP.
9-March-2018	HILL Suzanne Rose	19	Approve - director EMP

WHO`s analysis of the clinical antibacterial and antituberculosis pipeline

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Keywords: Antibiotics, clinical development, pipeline, antibacterial, antituberculosis, antibiotic resistance

Key points

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

Summary

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

Funding

Funding was provided by the German government.

Background

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

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

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

Methods

We performed a systematic review of the antibacterial drugs currently in the clinical pipeline with exhaustive efforts to identify all antibacterial drugs actually under study. We carefully evaluated evidence to identify limitations on specific antibacterial effects. All identified molecules and detailed assessment were transparently reported to inform decision making. Publicly available information concerning antibacterial drugs in clinical development were identified scrutinizing existing pipeline reviews,[6-9] international trial registry platforms (ClinicalTrials.gov,[10] WHO trial registry platform[11]), the commercial database Adis Insight,[12] a patent database (the Lens),[13] conference abstracts, publications, and press releases. This was supplemented by searches through PubMed for peer-reviewed journal articles in all languages and Google for grey literature. The search cut-off date was 1 July 2018. Additional details about the search strategy and selection criteria are described in the Appendix and WHO report.[14]

For some agents, some data sources reported different phases of development in different countries. In that situation, both or the most advanced development phase reported has been listed. The data set retrieved through the above-mentioned searches was shared with relevant stakeholders, including industry associations, and verified feedback was included in the data set. Companies that sponsor research were not contacted. Whenever possible, the pipeline evaluation was based on peer-reviewed literature searching known names and synonyms of each drug to build a dedicated dossier (Appendix, page 1). In the assessment of early clinical development stage agents, publicly available presentations and posters from scientific conferences and information published by the developers was also evaluated and included if considered scientifically sound. The resulting data documentation was provided to an advisory group of international experts with expertise in drug discovery, drug development, microbiology, chemistry, pharmacokinetics/pharmacodynamics (PK/PD), infectious diseases, and global health. The advisory group was selected according to complementary expertise taking into account geographical representation and gender balance (Appendix, page 2). The experts assessed each agent for activity against the WHO priority pathogens and the innovation criteria at a face-to-face advisory group meeting on 12–13 June 2017 in Geneva. A new cycle of evaluation evolved through several iterations, over a period of 12 months, including an additional virtual advisory group meeting on 12 July 2018. Consensus agreement of the advisory board was reached during the advisory group meetings. Potential conflicts of interests were managed following the World Health Organization Guideline Handbook. [14, 15] Members of the advisory group who had conflicts of interest with respect to a particular drug were excluded from the discussion on that drug. Experts' feedback informed all evaluation steps and final decisions was incorporated into the pipeline evaluation.

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

development but did not progress through the pipeline since 1 January 2015 were excluded from this analysis.

The advisory group classified each included drug based on its expected activity against WHO priority pathogens (carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacteriaceae or others) and its innovative potential assessing whether cross-resistance to other used antibacterial drugs was documented or suspected. The expanded biological definition of innovation as "no cross-resistance" was applied based on the overarching requirement that a drug shall not be affected by known cross-resistance to existing drugs in the organisms and indications for which it is intended to be used. Additionally, the three traditional criteria for innovation - a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site) and a novel mode of action were applied. The basics for these criteria of innovation have been laid out in a recent publication.[16] The assessment of activity and innovation was based on peer-reviewed publications when available and additional information from presentations and posters at scientific conferences. In vitro activity of drugs that are currently not being developed for relevant indications was not considered in the evaluation. A specific focus was placed on the assessment of *in vitro* and *in vivo* or clinical characteristics (when available). Additionally, minimum inhibitory concentrations (MICs), *in vivo* models and if available, data on pharmacokinetics/pharmacodynamics were analysed. Based on these critical evaluations, the antibacterial activity of the drugs was classified according to the categories "active", "not or insufficiently active", or "possibly active" in case of inconclusive or insufficient data. For modified compounds of a known class with few or no data on their activity against specific pathogens, the advisory group made assumptions based on the properties of the known antibiotic class to classify the agents as "possibly active" based on the activity of similar drugs with activity against the respective pathogen. Pathogen-focused drugs against *M. tuberculosis* and *C. difficile* developed specifically against these pathogens were therefore not assessed for their activity against PPL pathogens. The same applied to the species-specific biological products.

Results

Three antibiotics were approved by the U.S. Food and Drug Administration (FDA) since the first WHO report in September 2017[14]: delafloxacin, meropenem/vaborbactam and plazomicin (Appendix, Table 1). By the cut-off date of 1 July 2018, 30 new chemical entity (NCE) antibacterial drugs against PPL pathogens (Table 2), ten biologics (Table 3), ten NCEs against *M. tuberculosis* (Table 4), and four NCEs against *C. difficile* (Appendix, Table 5) were identified. Additionally, four combinations of antibiotics and potentiators or enablers that do not contain new chemical entities were included.

Antibacterial drugs with activity against Gram-negative bacilli

Of the 30 NCEs, four have been submitted for review at FDA and/or the European Medicines Agency (EMA) or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA): eravacycline, iclaprim omadacycline and lascufloxacin. Eleven are expected to have some activity against at least one of the WHO critical priority pathogens that are resistant to carbapenems, and thus mostly extensively-drug resistant (XDR) according to the ECDC definition.[17] From these 11 drugs, only the siderophore-conjugated cephalosporin cefiderocol provides coverage against all three critical priority pathogens: carbapenem-resistant *A. baumannii* (CRAB), carbapenem-resistant *P. aeruginosa* (CRPA), and carbapenem-resistant Enterobacteriaceae (CRE). Additionally, two other drugs have activity against CRAB (ETX2514/sulbactam, TP-6076) and only one against CRPA (murepavadin). Altogether, eight drugs have at least partial coverage of CRE.

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

mechanisms beyond the production of β-lactamases with mechanisms such as a decreased permeability of the outer membrane, upregulated efflux pumps, and modified penicillin-binding proteins.[18-20] The inconsistent inhibitory activity against OXA enzymes and the prominence of non-β-lactamase mediated resistance mechanisms explain why most new BLI combinations add no benefit in case of *A. baumannii* and only limited benefits for *P. aeruginosa*.

BL-BLI combinations: A new aspect of BLIs in the clinical pipeline is the evolution of the chemical class of diazabicyclooctanes (DBOs) which are non-β-lactam BLIs with avibactam as the first representative.[21] Although BLIs have historically lacked intrinsic antimicrobial activity, the new sub-group of DBO-based molecules now includes development BLI candidates with intrinsic antibacterial activity. Antibacterial activity through binding to Penicillin Binding Protein 2 (PBP) becomes in some more recent compounds (nacubactam, ETX2514 and zidebactam) an important or even dominating factor in the combination and provides synergistic activity.[22-24]

New BLs: Cefiderocol, a cephem, is intrinsically more stable to β-lactamases and hence not dependent upon a BLI partner. In addition, cefiderocol's uptake is enhanced by siderophore-mediated use of the bacterial iron transport mechanism.[25] Based on data currently available, this compound has the broadest Gram-negative spectrum of any agent in the pipeline. [26]

Tetracyclines: Not surprisingly, pre-existing resistance is also seen in other derivatives of known classes. Tetracyclines are a good example, with more than 1000 resistance genes reported.[27] New tetracyclines in the clinical pipeline address some of the class-specific resistance mechanisms and improve coverage in a given species. In general, new tetracyclines have been optimised either against Gram-negative or Gram-positive bacteria.

Combination products with approved drugs: Due to their potential clinical benefit, four combinations using pairs of already approved entities were additionally analysed. Aztreonam/avibactam combines an old monobactam with intrinsic stability against class B β-lactamases (metallo-β-lactamases, MBL) and the recently registered DBO BLI avibactam with inhibitory activity of class A and C β-lactamases.[28] Expanding of the spectrum is specifically expected for metallo-β-lactamase-producing Enterobacteriaceae due to the intrinsic stability of monobactams to these enzymes.[29] The combination of cefepime/tazobactam is expected to improve on piperacillin/tazobactam through better protection against ESBLs, as cefepime is easier to potentiate than piperacillin with an optimised tazobactam dose.[30] Zidovudine is active against carbapenem and colistin resistant (mcr positive) Enterobacteriaceae and a fixed combination of zidovudine with colistin is in clinical development. [31] A new oral fixed combination of ceftibuten and clavulanic acid will target urinary tract infections caused by ESBL-producing Enterobacteriaceae.

Innovation: All the mentioned drugs are derivatives of extensively-used antibacterial classes and pre-existing resistance is likely to occur quickly. Of the anti-Gram-negative antibacterial drugs included in the current pipeline, only murepavidin is classified as being innovative as it belongs to a new chemical class.[32] It also has a new target and mode of action with no currently known cross-resistance mechanism to approved antibacterial drugs and is thus classified in this analysis as meeting the innovative criteria. It is active only against *P. aeruginosa*. [33]

Routes of administration: Most anti-Gram-negative NCEs in the pipeline will be available only as parenteral (IV) formulations with the exceptions of sulopenem, which is administered as a prodrug. This synthetic penem described in the 1980s has activity against both Gram-positive bacteria and ESBL-producing Enterobacteriaceae but no activity against carbapenem-resistant organisms. Data on its absorption and urinary recovery were not identified in the public domain. The oral carbapenem in clinical development, tebipenem, was not included in this analysis as it is an approved drug in Japan. A new addition to potential oral treatments is the BLI-cephalosporin combination, ETX0282/cefpodoxime, which entered clinical development and is active against CRE except MBL producers. [34]

Antibacterial drugs with activity against Gram-positive and Gram-negative cocci

Most drugs with focus on Gram-positive cocci are derivatives of known fluoroquinolones, tetracyclines, macrolides, dihydrofolate reductase (DHFR) inhibitors (trimethoprim) and oxazolidinone classes (Table 2). The FABI inhibitor afabicin and potentially lefamulin (pleuromutilin) were classified as innovative for human use, although pleuromutilins have been used before in a topical formulation and in the animal sector.[35]

The functional class of bacterial topoisomerase inhibitors is not new but comprises new chemical structures and distinct but overlapping binding sites with fluoroquinolones without demonstrated cross-resistance to date.[36] Both of the new bacterial topoisomerase inhibitors (NBTIs) in development are orally available and their spectrum targets Gram-positive pathogens, respiratory tract infection pathogens and *N. gonorrhoeae*.[37] No cross-resistance of zoliflodacin with fluoroquinolones has been described to date in *N. gonorrhoeae*.[38] Although several antibacterial drugs in the pipeline have *in vitro* activity against *N. gonorrhoeae*, only the two NBTIs are currently being developed for this indication.

Biologics

Biologics comprise of monoclonal and polyclonal antibodies, and phage-derived products (Table 3). So far, only one biologic, a monoclonal antibody against *C. difficile* toxin B (bezlotoxumab), has been approved by EMA and FDA. Three monoclonal antibodies against *P. aeruginosa*, four monoclonal antibodies against *S. aureus* (including one that is linked to an antibiotic) and two polyclonal antibodies against *C. difficile* are currently in clinical development. One polyclonal antibody preparation against *C. difficile* acts systemically against the *C. difficile* toxin B, with the other active in the large intestine after oral application. Two engineered endolysins, which are enzymes used by bacteriophages to destroy the bacterial peptidoglycan cell wall, are being developed against *S. aureus* infections. Insufficient information is currently available yet regarding the potential for resistance development either by immune response to the product and target alterations. The potential place of biologics in the prevention or treatment of infections will require completion and careful evaluation in clinical trials.

M. tuberculosis

Ten drugs are being developed against *M. tuberculosis*. Six of the ten new drugs in development qualified as innovative or probably innovative (Table 4). Several new targets are pursued: DprE1 (cell wall synthesis), MmpL3 (membrane transporter), Leucyl-tRNA synthetase (protein synthesis), qcrB (subunit of the cytochrome bc1 complex), and enzymes of the respiratory electron transport chain. Three drugs in clinical development target DprE1. [38] As listed in Table 4 most drugs in the pipeline are in early clinical phases and more information is needed to assess the individual drugs, especially the contribution they may have on the activity of specific combination regimens. Further time is needed to assess of new anti-tuberculosis medicines for potential or acquired resistance as resistance patterns might not clearly emerge even in advanced development phases.

C. difficile

Four new drugs against *C. difficile* are in clinical development, with two of them representing new classes (Appendix, Table 5). Three of four small molecule drugs against *C. difficile* are oral formulations with an active ingredient not sufficiently absorbed to be systemically relevant. This fact mitigates two commonly encountered hurdles in antibacterial drug R&D: PK and toxicity. Hence treatment of *C. difficile* infection is a viable option to bring a new class of antibacterial drugs with such liabilities to the market. In addition to the small molecules in the clinical pipeline there are two polyclonal antibodies in development as previously described (Table 3). In comparison to other acute bacterial infectious diseases, there is more innovation in the *C. difficile* area despite the fact that demand for innovation related to resistance in *C. difficile* is lower.

Discussion

Innovation is of key interest for this pipeline analysis. In the context of bacterial resistance and the corresponding need for new antibacterial drugs, each of the three traditional criteria for innovation on its own - a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site) and a novel mode of action – may be confounded by complex drug-bacteria interactions. Each of these criteria may be insufficient to characterise innovation if the goal is to develop new antibacterial drugs against the most resistant priority pathogens. Therefore, the overarching criteria of "lack of known cross-resistance" as the most relevant criterion when assessing innovation in the context of antibiotic resistance was used as reasonable predictor of a drug's activity against XDR or pan-drug resistant (PDR) bacteria.[16]

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

Efforts focusing on Gram-negatives began to emerge as MDR and XDR resistance rose globally and concern increased substantially, but progress translating these discoveries has been slow, partly due to the difficulty overcoming two lipid bilayer membranes and associated efflux pumps in Gram-negative bacteria.[40] The Gram-negative clinical pipeline has little innovation and gaps remain with respect to critical PPL pathogens. Based on the long R&D timelines of 10 or more years for any discovery project, we currently have a pipeline in which anti-Gram-positive projects are sufficient in response to the medical need though innovation is also neglected in the Gram-positive space.

What are the implications of low innovation in the Gram-negative category? We predict significant gaps in coverage, especially for CRAB and CRPA, but also CRE in some geographical areas. The anti-Gram-negative R&D has focused on the β-lactam class and BLIs, as these are very well validated starting points for improving efforts. So far, BLIs that inhibit classes A, C, D of β-lactamases predominate. The epidemiology of β-lactamases determines the usefulness of new BLI-combinations in different geographic regions in pathogens with BLs as main resistance mechanism in β-lactam antibiotics. CRE are an important example as the production of a variety of carbapenemases is the major resistance mechanism.[2] Most new BLIs inhibit KPC enzymes (prevailing in North America, Latin America and in some European countries), whereas the metallo-β-lactamases (class B) are not inhibited (dominant in Asia, South Pacific region and important in some European countries and Africa).[41] Similarly, OXA carbapenemases are mostly not covered (dominate in African countries and are important in the Middle East and some European countries).[41, 42] In countries with especially high rates of carbapenem resistance in Enterobacteriaceae and a high prevalence of BLs other than KPC, the gaps in coverage (MBLs and OXAs) of the new BLIs is most relevant.[41] Whether the new BLI VNRX-5133 with expanded coverage of the MBLs NDM and VIM enzymes holds its promise can't be assessed due to limited information.[43] The next generation cephalosporin cefiderocol has improved β-lactamase stability and its structure incorporates a siderophore to facilitate penetration into the bacterial cell wall. These features may provide improved coverage of all three WHO critical priority pathogens.[44] The potential for cross-resistance to known resistance mechanisms and its relevance is not known so far.

Another concern is the lack of orally available innovative antibacterial drugs in the clinical pipeline. These are valuable in many settings but are especially needed for the treatment of common community-acquired infection, such as UTIs caused by ESBL-producing and fluoroquinolone-resistant Enterobacteriaceae. In the community, non-judicious use of modified derivatives of existing antibiotic classes will increase selection pressure and the risk of even faster spread of resistance in

Gram-negative bacteria in the community and healthcare settings. This situation is especially risky in drugs with cross-resistance to carbapenems. Future oral penems or carbapenems (e.g. sulopenem or tebipenem) might aggravate the selection pressure for carbapenem resistance if used widely. New antibacterial classes without co-selection pressure that are orally available, optimised for UTIs, and restricted for targeted use are urgently needed.

It has been proposed that positive results in animal disease models have limited value in the field of antibacterial biologics as they can be followed by clinical failure.[45] To date, only two monoclonal antibodies have been approved for infectious diseases outside the biothreat field: palivizumab, for the prevention of respiratory syncytial virus, and bezlotoxumab, which targets the *C. difficile* toxin B to reduce recurrence risk. Technological advances in the field, moving to multi-specific, multi-functional strategies, and improved definition of patient groups at risk as well as commercial reasons have attracted multiple specialised companies to push their biologics into clinical trials.[46, 47] Antibodies are usually studied as preventive or adjunctive therapy. A potential clinical impact of antibody use as adjunctive therapy has not yet been shown.

For *C. difficile* infections, two new chemical classes are in Phase 1 and 2 clinical development and it is not known yet if they will demonstrate an additional benefit over vancomycin or metronidazole.[48] Though the burden of disease may be high, it is usually not associated with acquired resistance to antibiotics.[49]

The development of new anti-tuberculosis drugs faces specific challenges, including the need to treat tuberculosis with a combination of at least three different antibacterial drugs. Unlike the large majority of TB patients worldwide who can expect a relapse-free cure with a 6-month course of first-line medication, patients with drug-resistant TB (usually including resistance to at least rifampicin, commonly combined with isoniazid resistance, or with further resistance to fluoroquinolones and/or aminoglycosides) require treatment regimens which are longer, less effective and less accessible than first-line regimens, but more costly, toxic and complicated to deliver. Most second-line MDR-TB regimens are currently designed to last 9 to 24 months, presenting a formidable challenge to health service providers to ensure patient adherence and obtain sustainable cure.[50,51] New drugs and drug regimens are needed to shorten and simplify therapy for both drug-sensitive and drug-resistant *M. tuberculosis*.[52] Intracellular environment, dormant forms and complex PK conditions add to the challenges of drug R&D in the TB arena. Although some new targets and new classes are listed in the pipeline, there were only ten drugs in clinical development. Given the high anticipated attrition rates that have been seen with other molecules, and the remaining challenge of identifying the optimal drug combination, the clinical pipeline for TB drugs is still insufficient.[53, 54]

The limitations of our analysis are mainly grounded around information variability due to limited publicly available data. While strong effort was undertaken to make this analysis as complete as possible and base assessments on peer-reviewed publications, the availability and quality of data varied significantly between clinical candidates. Despite WHO's requirements on clinical trial transparency, some of the trials with products in this pipeline are not listed in any clinical trial registry. Lack of key information especially impeded the assessment of expected activity against PPL pathogens. While for some agents peer-reviewed activity assessments were available, for others we had to rely on limited company information, or the comparison to other agents with a similar structure, if no data had been published. Furthermore, for some agents the assessment was made purely based on *in vitro* activities, while for others it was on clinical and PK/PD.

The assessment of innovation was also subject to limitations. Lack of cross-resistance is the most relevant criterion when assessing innovation in the context of antibiotic resistance.[16] In early stages of development sufficient information may not be available yet. Novel chemical scaffolds, binding sites and modes of action are reasonable predictors for a lack of cross-resistance. For these reasons, all four aspects were separately assessed. However, in some instances a question mark indicates where information was insufficient (e.g. structure not published) or the experts could not reach a final agreement on novelty. This pipeline analysis should be regarded as a snapshot at the time of its

creation. The field moves quickly as shown by the rapid changes captured by our analysis over a time period of 12 months: as more information becomes available the innovation and spectrum of activity assessments may change.

Conclusion

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

Contributors

UT, SG, SH, PB designed the study protocol, SG and UT did the search for the drugs to be included, SG managed the data, UT provided the data for the 2018 update and scientific assessment of individual drugs. MS and CL contributed information about tuberculosis. SH chaired the first advisory board meeting 2017 and PB the second in 2018. All members of the advisory group provided input and contributed to the final consensus. UT wrote the first draft of the article and all authors provided feedback, commented on, and reviewed the manuscript. PB and SP supported overall project coordination, setup and review. The overall study was overseen by the WHO Secretariat. The contribution of WHO employees has been prepared strictly in a personal capacity and reflects the view of the authors. The views expressed must not be attributed to the WHO, its Secretariat, or its Member States.

Conflicts of interests

UT, SG, MP, MB, GT, JPP, LC, PB, SP, CL, LM declare no conflicts of interest.
MS: is employed by TB alliance, is Member of the Board of Directors at The Medicines Company; LS reports personal fees from Acidophil, Appili, Debiopharm, DesignMedix, Melinta, Merck, Nabriva, Taisho, Taxis, Vertex, X-Chem, Grey Healthcare, Innovacorp, PureTech, TPG, CARB-X, Uppsala University, NIH, University of Washington, IMI-Enable, Forge Therapeutics outside the submitted work; JR reports holding a position as Chief Medical Officer & Director at F2G, Non-Executive Director & Consultant at Adenium Biotech, Operating Partner & Consultant at Advent Life Sciences and Expert-in-Residence at Wellcome Trust, member of the Scientific advisory Boards of Macrolide Pharmaceuticals, Bugworks Research, Basilea Pharmaceutica, Forge Therapeutics, and Novo Holdings, he reports personal fees from Phico Therapeutics, ABAC Therapeutics, Polyphor, Heptares Therapeutics, Gangagen, Meiji Seika Pharma, Basilea Pharmaceutica International, Allecra Therapeutics, Forge Therapeutics, SinSa Labs, AtoxBio, Peptilogics, F. Hoffmann-LaRoche, and Novo Holdings, he is shareholder in AstraZeneca, F2G, Adenium Biotech, Advent Life Sciences, Macrolide Pharmaceuticals, and Bugworks Research; SH reports grants from IMI Brussels, during the conduct of

the study; grants from Pfizer, personal fees from Novartis, personal fees from DNA Electronics, personal fees from Bayer, personal fees from GSK, outside the submitted work.

For all experts, advice was provided in their personal capacity. The views in this report do not necessarily reflect, and should not be interpreted as, the official position of any agency or institution. The declaration of interests of the advisory board members can be found in the appendix.

Acknowledgments

We thank Enrico Tognana and Marco Cavaleri (EMA) for conducting the search on the Adis Insight database, and Jiangdong Jiang (Chinese Academy of Medical Sciences) for conducting the search on antibacterial products in China.

Advisory group

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Table

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

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Eravacycline (Xerava)	NDA[1] MAA[1]	Tetracycline	iv (Tetraphase)	?	○	●	/	–	–	–	–
Omadacycline	NDA[2]	Tetracycline	iv & oral (Paratek)	○	○	○	●	–	–	–	–
Iclaprim	NDA[3]	DHFR inhibitor	iv (Motif Bio)	/	/	/	●	–	–	–	–
Lascufloxacin	NDA[4]	Fluoroquinolone	iv & oral (Kyorin)	○	○	○	?	–	–	–	–
Relebactam + imipenem/cilastatin	3	DBO-BLI + carbapenem/ degradation inhibitor	iv (MSD)	○	?	●[5]	/	–	–	–	–
Cefiderocol	3	Siderophore-cephalosporin	iv (Shionogi)	●	●	●	/	?	–	–	–
Lefamulin	3	Pleuromutilin[6]	iv & oral (Nabriva)	/	/	/	●	?	✓[6]	–	✓
Sulopenem, sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○[7]	/	–	–	–	–
Murepavadin (POL-7080)	3	Novel membrane targeting antibiotic	iv & inhaled (Polyphor)	/	●	/	/	✓	✓	✓	✓
Solithromycin	3[8]	Macrolide	iv & oral (Cempra/Melinta)	/	/	/	●	–	–	–	–
Levonadifloxacin Alalevonadifloxacin	3[9]	Fluoroquinolone	iv (Wockhardt) oral (Wockhardt)	○	○	○	?	–	–	–	–
Cefilavancin (TD-1792)	3[10]	Glycopeptide-cephalosporine conjugate	iv (Theravance/R-Pharm)	/	/	/	●	–	–	–	–
AAI101 + Cefepime	3	β-lactam BLI + cephalosporin	iv (Allecra)	○	○	○[11]	/	–	–	–	–
Contezolid Contezolid acefosamil	2/3[12]	Oxazolidinone	oral (MicuRx) iv (MicuRx)	/	/	/	●	–	–	–	–
Gepotidacin	2	NBTI (Triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●	✓	✓	–	✓
Zoliflodacin	2	NBTI (Spiropyrimidenetrione)	Oral (Entasis/GARDP)	/	/	/	●	✓	✓	–	✓
ETX2514+sulbactam[13]	2	DBO-BLI /PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	–	–	–	–
Nafithromycin (WCK-4873)	2	Macrolide	Oral (Wockhardt)	/	/	/	●	–	–	–	–
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
LYS-228	2	Monobactam	iv (Novartis)	○	○	●	/	–	–	–	–
Zidebactam + Cefepime	1	DBO-BLI/ PBP2 binder + cephalosporin	iv (Wockhardt)	○	?	●	/	–	–	–	–
Nacubactam + meropenem	1	DBO-BLI/ PBP2 binder + meropenem	iv (Roche)	○	?	●[5]	/	–	–	–	–
VNRX-5133 + cefepime	1	Boronate-BLI + cephalosporin	iv (VenatoRX)	?	?	●	/	?	–	–	?
ETX0282+cefpodoxime	1	DBO-BLI + cephalosporin	Oral (Entasis)	○	○	●[5]	/	–	–	–	–
SPR-741 + β-lactam	1	Polymyxin + β-lactam	iv (Spero)	?	?	?	/	–	–	–	–
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	○	○	○	●	–	–	–	–
TP-271	1	Tetracycline	iv & oral (Tetraphase)	?	○	○	●	–	–	–	–
TP-6076	1	Tetracycline	iv (Tetraphase)	●	○	?	/	–	–	–	–
TNP-2092	1	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?	–	–	–	–
AIC-499 + unknown BLI	1	β-lactam + BLI	iv (AiCuris)	?	?	?	/	–	–	–	–

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

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data or no agreement among the advisory group; – criterion not fulfilled; NCR, no cross-resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action;

BLI, β-lactamase inhibitor; E, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; AB, *A. baumannii*, carbapenem-resistant; PA, *P. aeruginosa*-, carbapenem-resistant; DBO, diazabicyclooctane; DHFR, dihydrofolate reductase; iv, intravenous;

NBTI, novel bacterial topoisomerase II inhibitor; NDA, new drug application (FDA), MAA, Marketing Authorization Application (EMA). OPP, other priority pathogens on the WHO PPL ("high" and "medium" priority); PBP, penicillin-binding protein

Underlined agents: New chemical class

[1] MAA submitted on 17 August 2017, CHMP has adopted positive opinion for approval.; NDA submitted on 2 January 2018 for the iv form only for cIAI, PDUFA date August 28, 2018
[2] NDA submitted on 5 February 2018, PDUFA date October 2018
[3] Completed NDA submission 14 June 2018
[4] NDA in Japan only
[5] Active against *K. pneumoniae* carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae
[6] First systemic formulation of this class, which has been used topically and in animals previously
[7] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae
[8] withdrawn MAA, FDA complete response letter, currently no development activities outside of Japan
[9] Phase-3 trial ongoing only in India, phase-1 oral studies in the USA in 2014 (alalevonadifloxacin)
[10] Developed only for Russia
[11] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant and some KPC producing carbapenem-resistant Enterobacteriaceae
[12] Contezolid acefosamil: Phase 2 in USA not yet recruiting. Contezolid: NDA in China expected end of 2018
[13] Combination of ETX2514 with imipenem/cilastatin planned

Table 3. Biological antibacterial agents in clinical development

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

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

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

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
Pretomanid (PA-824)	3	Nitroimidazole	Oral (TB Alliance)	?	–	–	?
SQ-109[1]	2/3	Diamine	Oral (Sequella/Infectex)	?	–	✓	✓
Delpazolid (LCB01-0371)[2]	2	Oxazolidinone	Oral (LegoChem)	–	–	–	–
Sutezolid[3]	2	Oxazolidinone	Oral (TB Alliance/Sequella)	–	–	–	–
Telacebec (Q-203)	2	Imidazopyridine amide	Oral (Qurient/Infectex)	✓	✓	✓	✓
Macozinone (PBTZ-169)	1 (2)	DprE1 inhibitor (benzothiazinone)	Oral (Innovative Medicines For Tuberculosis Foundation)[4]	✓	✓	✓	✓
GSK070 (GSK-3036656)	1	Leu RS inhibitor (oxaborole)	Oral (GlaxoSmithKline)	✓	✓	✓	✓
OPC-167832	1	DprE1 inhibitor	Oral (Otsuka)	?	✓	✓	✓
TBA-7371	1	DprE1 inhibitor	Oral (TB Alliance)	✓	✓	✓	✓
TBI-166[5]	1	Riminophenazine (Clofazimine-analogue)	Oral (Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College)	–	–	–	–

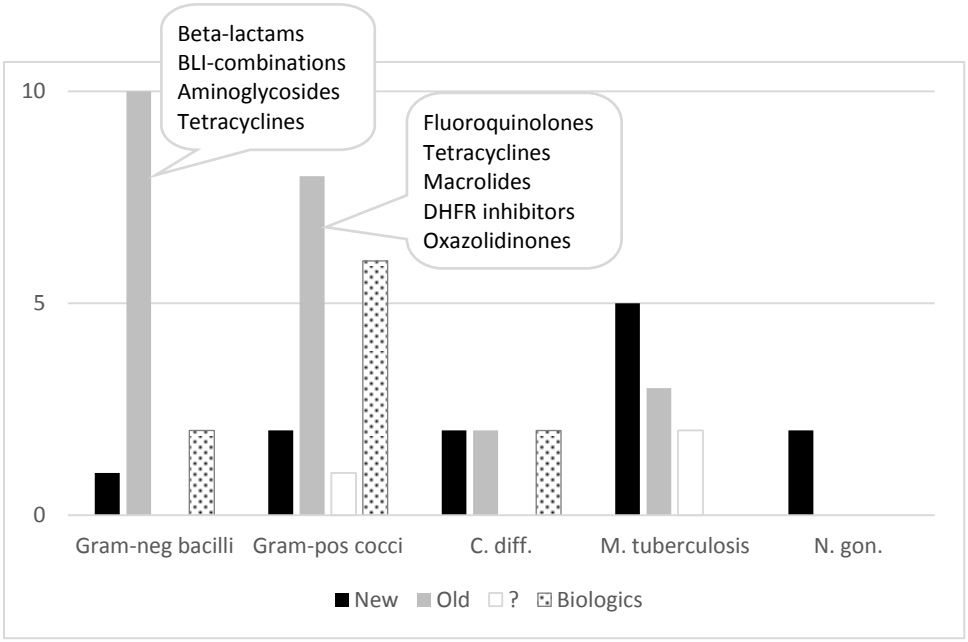
Innovation assessment: ✓ criterion fulfilled; **?** Inconclusive data; – criterion not fulfilled

NCR, no cross resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action; DprE1, decaprenylphosphoryl-β-D-ribose 2-epimerase. Underlined agents: New chemical class. These agents are being developed for use against TB; their activity against other priority pathogens was not assessed.

[1] Chemically close to ethambutol
[2] Delpazolid also completed a phase-1 trial as injectable for MRSA and vancomycin-resistant *Enterococcus* spp. infections
[3] Developed by Sequella and independently by the Global Alliance for TB Drug Development, non-exclusive patent held by Sequella and by The Medicines Patent Pool
[4] In Russia developed by Nearmedic Plus
[5] Clofazimine is approved for leprosy and used for TB

Figure

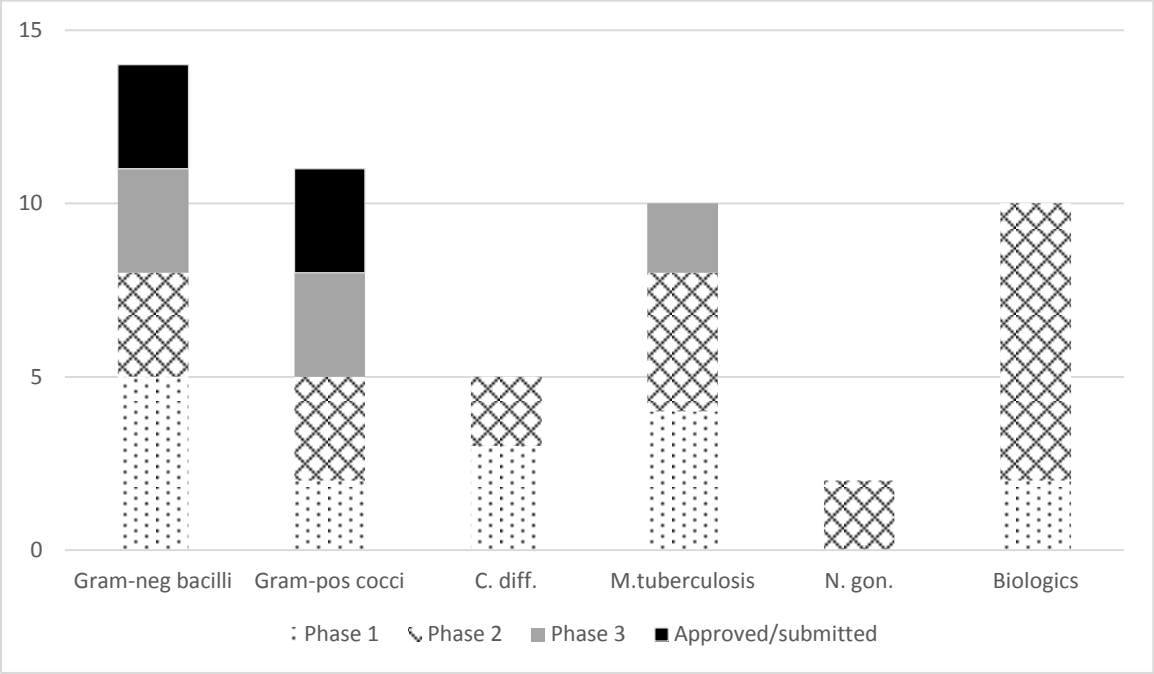
Figure 1. Number of antibiotics in clinical development according to focus of activity*



* Gram-neg bacilli: CRAB, CRPA, CRE; Gram-pos cocci: Staphylococci, Streptococci; C. diff., *Clostridium difficile*; M. tuberculosis, *Mycobacterium tuberculosis*; N. gon, *Neisseria gonorrhoeae*; BLI, β-lactamase inhibitor

new, new chemical class small molecule; old, modified class small molecule including combinations with BLIs;
?: innovation status inconclusive or unknown
Gepotidacin was counted in the category Gram-positive cocci and *Neisseria gonorrhoeae*
Drugs with inconclusive or unknown activity were not included

Figure 2. Number of antibiotics in clinical development phases and recent approvals according to focus of activity*



*Gram-neg bacilli: CRAB, CRPA, CRE; Gram-pos cocci: Staphylococci, Streptococci; C. diff., *Clostridium difficile*; M. tuberculosis, *Mycobacterium tuberculosis*; N. gon, *Neisseria gonorrhoeae*

Drugs with inconclusive or unknown activity were not counted
Drugs approved after June 2017 were included

Re: THELANCETID-D-18-00394 - WHO`s analysis of the clinical antibacterial and antituberculosis pipeline

Dear Dr. De Ambrogi,
Thank you for reviewing our manuscript and forwarding the comments of the four reviewers. The revised draft is submitted in a highlighted and clean version. We have responded below to each comment and revised the manuscript accordingly. In order to improve the readability, we have only highlighted major changes and not minor changes to wording.

Editor's comments:

1- Please be aware that the limit for the word count in Reviews is 4500 words (maximum 5000). You are within that limit but if after the revision you struggle to fit, there is always the option to move something to the Appendix where there is no word count limit. You can keep the sections Introduction, Methods, Results, and Discussion or restructure the paper as you see fit. The methodology for the search needs to be clearly explained.
The word count is below 4500 words.

2- Please be aware that the limit for the number of references is 150.
The number of references is below 150 and citations to posters and websites have been limited.

3- A 150-word unstructured summary should be included.
The summary has been included.

4- Reviews should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages.
A brief section entitled "Search strategy and selection criteria" has been included and moved to the appendix.

5- Please add a panel called "Key points" where you list the key points of the article.
Key points have been included.

6- Systematic reviews that do not include meta-analysis will be considered under the Review heading and must be reported according to the PRISMA guidelines.
The PRISMA guidelines were followed as applicable and meaningful.

7- A review can include about five illustrations to aid the reader. If you have more non-text items (figures/tables), you will need to move something to the Appendix (that should be a single PDF file with page numbers). In the text, any reference to the Appendix (including tables and figures) must be something like "Appendix, page X".
The manuscript includes 2 figures and 5 tables. Table 1 and 5 were moved to the Appendix though it would be easier for readers to keep at least Table 1 in the manuscript.

8- Please ensure that you provide your figures in an editable format and as separate files. For trial profiles a word file made of editable text boxes is the preferred format. For any statistical images (histograms, survival or time-to-even curves, line graphs, scatter graphs, forest plots, etc) you should provide editable vector files (ie, the original artwork generated by the statistical package used to

make the image). Our preferred formats for these files are .ai, .eps, or .pdf. We cannot guarantee accurate reproduction of images without these files.
The figures are in an editable format in a Word file.

9- Please also include written consent of any cited individual(s) noted in acknowledgments or cited as personal communications.
As we couldn't organise a written consent of every cited individual we removed most acknowledgments and included only persons who were involved in the update of the study.

10- All authors are required to provide a Conflict of Interest Statement and should complete a standard form, which is available at http://download.thelancet.com/flatcontentassets/authors/icmje-coi-form.pdf. This form can be uploaded with the manuscript at submission. The form has been modified by the ICMJE following consultation with authors and editors. Further information is available in a joint ICMJE statement published on July 1, 2010. For more information see Lancet 2009; 374: 1395-96.
Most COI Statements have been uploaded. One missing statement (Simon Gottwalt) will be sent as soon as possible.

11- All authors should complete and sign the author statement form and upload the signed copy. The form can be downloaded from the page (http://www.thelancet.com/lancet-infectious-diseases-information-for-authors/statements-permissions-signatures#conflicts-of-interest) from the fourth line of "Authors and contributions". The corresponding author must countersign manually the forms at the bottom of the page and send us the scanned version; electronic signatures are not accepted.
Most Authors Statement Forms have been uploaded. One missing form will be sent as soon as possible.

12- It is very important that despite the change of type of article the presentation of the methods is improved. Who did the search? What was done if there was disagreement? How was the advisory board created and selected? In what the decisions at the advisory board meeting were taken (did expert vote or fill a questionnaire or was there another form of agreement?).
The methods have been described in the manuscript:

- Who did the search? This information is given in the section contributors: "SG and UT did the search for the drugs to be included, SG managed the data, UT provided the data for the 2018 update and scientific assessment of individual drugs."
- What was done if there was disagreement? This information was added: "Consensus agreement of the advisory board was reached during the advisory group meetings."
- How was the advisory board created and selected? This information is included in the methods section: "… advisory group of international experts with expertise in drug discovery, drug development, microbiology, chemistry, pharmacokinetics/pharmacodynamics (PK/PD), infectious diseases, and global health. The advisory group was selected according to complementary expertise taking into account geographical representation and gender balance. The bios can be found on the WHO website: http://www.who.int/phi/news/analysis_clinical_dev_pipeline_antibacterial_t/en/index1.html . This information is included in the Appendix.
- In what the decisions at the advisory board meeting were taken? This information was added: "Consensus agreement of the advisory board was reached during the advisory group meetings." As the experts group was small the consent was based on discussions and expressed verbally.

13- At the end of the Executive Summary, please indicate the name of the funding source.
The funding source has been included.

14- In order to avoid incurring again in the attempted blockage of publication from WHO that we have had for the paper on the Priority Pathogen List and since there are coauthors who work for WHO, I exceptionally ask you to include a signed copy from a WHO employee that WHO approves the revised version of the paper that you will submit. I know that that is already a standard procedure but I definitely do not want to have you and your coauthors in the unpleasant situation that we had back in December.
This sentence was added: "The contribution of WHO employees has been prepared strictly in a personal capacity and reflects the view of the authors. The views expressed must not be attributed to the WHO, its Secretariat, or its Member States."
A signed approval by WHO has been submitted.

Reviewers' comments:

Reviewer #1:
This is a well written comprehensive descriptive study of state of the art analysis of the clinical antibacterial and anti tuberculosis pipeline. The conclusion is reasonable that the clinical pipeline analysis confirms the urgent need for innovative antibacterial drugs against the WHO critical priority pathogens. There are some minor edits required.

On the top of page 8 the expression that "lack of know cross-resistance" should be "lack of known cross-resistance".
The footnote in Table 3, 'C, new chemical class' should be 'CC, new chemical class'.
The error has been corrected.

Reviewer #2:
The authors present a substantial body of data to support this thorough approach to assessing the 2017-2018 antibacterial and antimycobacterial pipeline. The paper may benefit from some further expansion which may be more appropriate for the follow up analysis.
1- Although language may be a potential challenge but the team neglected Asian activities in this field. Kyorin, Daiichi-Sankyo and Otsuka are exceptions. However, a substantial level of investment occurs in Japan, Korea and elsewhere in Asia and as the WHO team I think this should be included or at least stated why these efforts were not included.
Indeed, language is a problem but also the non-availability of information. The first WHO clinical pipeline report published data that was available in the public domain and collected through the methods described in the manuscript. No clinical trials by other Asian companies were registered in any of the public registers nor in the commercial database that was also consulted. To attempt to fill in the presumed gaps primarily in Asia WHO increased its efforts in the 2018 update of the clinical pipeline report through multiple methods including contractual agreements with local speaking experts from the Chinese Academy of Medical Sciences to support data gathering in China (see acknowledgment) and collaborating with organisations to gather information in Japan. Additional Asian companies that we found through these efforts had no programs in clinical development. We also researched the companies that were analyzed in a comprehensive recent analysis of Indian companies (doi: 10.1002/cmdc.201700043)

2- A number of these Phase I programs have been in on-going for more than 3-4 years thus I think some acknowledgement of some of the substantive pre-clinical programs or the platforms they are based on. The reason for raising this topic is that it will require investment in these much earlier stage programs to feed the pipeline and hopefully the significant academic and industry effort will be recognized. I would like to suggest that a slightly optimistic perspective may be provided in a table of NCEs such as LpxC inhibitors or other novel approaches to providing fodder for the development pipeline. The reader could benefit from seeing further than the current Phase I agents a number of

which are not novel but will still cost several millions of pounds or dollars to move to Phase II and beyond.
We acknowledge the value of an analysis of the global preclinical pipeline to highlight the entire R&D chain including the risks and efforts to bring a programme to the clinical stage. Therefore, WHO started already the project of a preclinical pipeline analysis that will link all necessary efforts to get a drug to patients. The preclinical activities are so complex and extensive that we think it would go beyond the scope of this publication.

3- I do not wish to be picky but a couple of compounds were omitted, namely tebipenem and zabofloxacin. Both are approved in Asia but are undergoing R&D in the US. I raise tebipenem as sulopenem was mentioned and both are in clinical development in the US.
One of our exclusion criteria was approval anywhere in the world. We mentioned tebipenem only in connection with stewardship and selection pressure of oral penems. To the best of our knowledge sulopenem has not been approved anywhere in the world. We currently see several development activities in the US of drugs that have been approved and used for a long time in Asia or Europe.

4- Page 9 discusses C difficile agents however closes with the comment "Though the burden may be high, it is not associated with acquired resistance to antibiotics" which is true but several of the new drugs clearly have an adverse effect on the microbiome and new and better agents against CDI may be needed thus Table 4 provides useful information.
We agree that new drugs may have more benefits than responding to a resistance issue. This is specifically true for C. difficile. Unfortunately, the topic of medical challenges for C. difficile and detailed benefits of new drugs that are rarely confirmed in RCTs could not be expanded though very interesting and important.

5- A quick fact-check, page 5, paragraph 2, line 6 was tetracycline correct or is it omadacycline?
We referred to derivatives of known classes, with tetracyclines one of them.

6- Having checked the WHO PPL Neisseria gonorrheae seems to have been missed in the list of target agents and yet recent publicity seems to make this multi drug resistant species a major public health hazard. I am aware that several early stage agents are purportedly being studied for GC alone. This is a brave approach as from a commercial viewpoint this is a poor choice as single dose or at best very short course therapy is mandatory, preferably orally and to be "inexpensive or cheap".
N. gonorrheae was included in this analysis (text, figures). As we wanted to keep the main table manageable and not too overloaded N. gonorrheae is included in the OPP column (see legend). Only 2 drugs are currently being developed for gonococcal disease. We agree that it would be interesting to discuss this field in more detail but tried to follow the instructions and stay within the suggested word limit.

7- Market forces- recent swings in pharmaceutical and biotech values are having a major impact on R&D choices in companies and programs which focus on more likely successes with good returns. However, the potential numbers of CRAB CRPA CRKP etc are likely to reduce as some of the imminent agents are approved and prescribed.
To visualise this potential effect, we introduced table 1 (Appendix) to show the drugs approved since 2017. They are not available yet in most countries.

8- Finally, this process is very relevant and provides a great deal of information and would make a useful "snapshot" of a highly changeable field. Do the authors know if this will be maintained in an on-going manner on the WHO site?
Updates will continue. This manuscript has a cut-off date of July 1 2018 and provides a snapshot of this field. As abridged development pathways will speed up the time to NDA the pipeline will change rapidly. An update of this publication in 2019 is already planned and will be posted on the WHO site.

Reviewer #3:
The manuscript is very well written, structured, laid out and proof read. The content is authoritative as well as of great interest and timely.

A large part of the content produced by the submitting authors was already known to me from the WHO publication: Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). Licence: CC BY-NC-SA 3.0 IGO. Available on http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf
The revised manuscript was updated with a cut-off date of July 1 2018 to reflect the changes in the pipeline and provide the newest analysis. Since the first WHO report three antibiotics have been approved and more information became available that impacted the analysis.

The German government funded the initial WHO report, it would appear favourable to acknowledge them for funding the original WHO report.
The acknowledgment was added.

The methodology is a search of the literature was made and then each identified molecule was then assessed by the group in a meeting. "The experts assessed each agent for activity against the WHO priority pathogens and the innovation criteria at an advisory group meeting on 12-13 June 2017 in Geneva." Which is table 1 and it reports whether the agent is a new agent from a different class, acts on a different target or has a new mode of action. it therefore sumarises new information with a useful table. Perhaps the search appendix 1 (very useful) of the WHO report can be given as an appendix in LID?
We expanded the methods section, additionally referred to the first WHO report and provided the search criteria in the Appendix.

Table 2 amalgamates several agents based on the fact they are biologicals however the biologicals are aimed against three groups of diffeernt bacteria/mycobacteria.
We were not sure if this comment suggests a modification.

References appear quite selected from the original 170 with some new ones, there are several from some groups and the authors, certain arguments are cited many times others much less. The conclusion only talks about gram negatives (important but VRE, TB are still priorities).
Though this manuscript specifically highlights the critical priority pathogens VRE and other pathogens are mentioned (…despite potential *in vitro* activity of some current candidates, no antibiotic in development is specifically studied for infections caused by *Enterococcus faecium*.) The manuscript includes drugs against TB underlining its priority. This important disease deserves a much more detailed analysis which has been undertaken by specialised experts and can be found on the website of WHO or other organisations. VRE was mentioned and TB is included. As the field of TB has huge challenges that go beyond resistance and short treatment we could not focus on this area but included more references. We agree with the reviewer that several topics would have been worth describing in more detail but would have been gone beyond the allowed word count.

Appendix 2 in WHO report regarding conflicts of interests should be reflected in the paper in the declaration of interests.
This section has been expanded.

Reviewer #4:

In the Abstract please add for which priority bacteria the new drugs are not adequate The background is absolutely scarse of information about current epidemiological landscape for resistant bacteria worldwide.

The abstract was completely rewritten due to the format change and the lower word count.

Please cite recent interesting paper on this topic published in ICM (Bassetti et al. Intensive Care Med. 2017 Oct;43 and De Waele J et al. Intensive Care Med. 2018 Feb;44(2):189-196)

Due to the space limit we couldn't include an overview of the current epidemiology but added the reference by Bassetti et al. Though stewardship in ICUs is of utmost importance we couldn't discuss all these aspects due to the limited word count. Therefore, this topic and reference (De Waele et al) could not be included in the manuscript.

In the methodology please explain the criteria for inclusion of the "experts" in the advisory board Please clearly state what is their background

This information was added in the expanded methods section (…advisory group of international experts with expertise in drug discovery, drug development, microbiology, chemistry, pharmacokinetics/pharmacodynamics (PK/PD), infectious diseases, and global health. The advisory group was selected according to complementary expertise taking into account geographical representation and gender balance). Additionally, a link is provided in the Appendix that summarises the experiences of the members of the advisory group.

The description of the antibiotics doesn't reflect "an expert opinion", but it appears a simply list of drugs. I would suggest to add more comments on the different antibiotics and what it will be their place in therapy when commercialized, if any.

Placing antibiotics in different categories, especially in the innovation category was based on available evidence that was presented to the experts. In some cases, the special knowledge of an expert, e.g. medicinal chemist or PK/PD expert was needed to interpret the available information. Though more comments on the different antibiotics and their place in therapy would be of high importance these aspects would have gone beyond the scope of this topic and the allowed word count. It will be covered by a separate publication.

Add a table or figure about advantages and limitations of the drugs in pipeline, at least for the ones in phase 2/3 of development.

We agree that this information would be valuable. It was included in the first draft but had to be omitted due to the space limitation.

Please report the conflict of interests of the authors, If any.

A detailed list of conflicts of interest is included in the manuscript.

Supplemental items

Click here to download Supplemental items: Appendix.docx

WHO`s analysis of the clinical antibacterial and antituberculosis pipeline

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Keywords: Antibiotics, clinical development, pipeline, antibacterial, antituberculosis, antibiotic resistance

Key points

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

Summary

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

Funding

Funding was provided by the German government.

Background

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

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

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

Methods

We performed a systematic review of the antibacterial drugs currently in the clinical pipeline with exhaustive efforts to identify all antibacterial drugs actually under study. We carefully evaluated evidence to identify limitations on specific antibacterial effects. All identified molecules and detailed assessment were transparently reported to inform decision making. Publicly available information concerning antibacterial drugs in clinical development were identified scrutinizing existing pipeline reviews,[6-9] international trial registry platforms (ClinicalTrials.gov,[10] WHO trial registry platform[11]), the commercial database Adis Insight,[12] a patent database (the Lens),[13] conference abstracts, publications, and press releases. This was supplemented by searches through PubMed for peer-reviewed journal articles in all languages and Google for grey literature. The search cut-off date was 1 July 2018. Additional details about the search strategy and selection criteria are described in the Appendix and WHO report.[14]

For some agents, some data sources reported different phases of development in different countries. In that situation, both or the most advanced development phase reported has been listed. The data set retrieved through the above-mentioned searches was shared with relevant stakeholders, including industry associations, and verified feedback was included in the data set. Companies that sponsor research were not contacted. Whenever possible, the pipeline evaluation was based on peer-reviewed literature searching known names and synonyms of each drug to build a dedicated dossier (Appendix, page 1). In the assessment of early clinical development stage agents, publicly available presentations and posters from scientific conferences and information published by the developers was also evaluated and included if considered scientifically sound. The resulting data documentation was provided to an advisory group of international experts with expertise in drug discovery, drug development, microbiology, chemistry, pharmacokinetics/pharmacodynamics (PK/PD), infectious diseases, and global health. The advisory group was selected according to complementary expertise taking into account geographical representation and gender balance (Appendix, page 2). The experts assessed each agent for activity against the WHO priority pathogens and the innovation criteria at a face-to-face advisory group meeting on 12–13 June 2017 in Geneva. A new cycle of evaluation evolved through several iterations, over a period of 12 months, including an additional virtual advisory group meeting on 12 July 2018. Consensus agreement of the advisory board was reached during the advisory group meetings. Potential conflicts of interests were managed following the World Health Organization Guideline Handbook.[14, 15] Members of the advisory group who had conflicts of interest with respect to a particular drug were excluded from the discussion on that drug. Experts' feedback informed all evaluation steps and final decisions was incorporated into the pipeline evaluation.

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

development but did not progress through the pipeline since 1 January 2015 were excluded from this analysis.

The advisory group classified each included drug based on its expected activity against WHO priority pathogens (carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacteriaceae or others) and its innovative potential assessing whether cross-resistance to other used antibacterial drugs was documented or suspected. The expanded biological definition of innovation as "no cross-resistance" was applied based on the overarching requirement that a drug shall not be affected by known cross-resistance to existing drugs in the organisms and indications for which it is intended to be used. Additionally, the three traditional criteria for innovation - a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site) and a novel mode of action were applied. The basics for these criteria of innovation have been laid out in a recent publication.[16] The assessment of activity and innovation was based on peer-reviewed publications when available and additional information from presentations and posters at scientific conferences. In vitro activity of drugs that are currently not being developed for relevant indications was not considered in the evaluation. A specific focus was placed on the assessment of *in vitro* and *in vivo* or clinical characteristics (when available). Additionally, minimum inhibitory concentrations (MICs), *in vivo* models and if available, data on pharmacokinetics/pharmacodynamics were analysed. Based on these critical evaluations, the antibacterial activity of the drugs was classified according to the categories "active", "not or insufficiently active", or "possibly active" in case of inconclusive or insufficient data. For modified compounds of a known class with few or no data on their activity against specific pathogens, the advisory group made assumptions based on the properties of the known antibiotic class to classify the agents as "possibly active" based on the activity of similar drugs with activity against the respective pathogen. Pathogen-focused drugs against *M. tuberculosis* and *C. difficile* developed specifically against these pathogens were therefore not assessed for their activity against PPL pathogens. The same applied to the species-specific biological products.

Results

Three antibiotics were approved by the U.S. Food and Drug Administration (FDA) since the first WHO report in September 2017[14]: delafloxacin, meropenem/vaborbactam and plazomicin (Appendix, Table 1). By the cut-off date of 1 July 2018, 30 new chemical entity (NCE) antibacterial drugs against PPL pathogens (Table 2), ten biologics (Table 3), ten NCEs against *M. tuberculosis* (Table 4), and four NCEs against *C. difficile* (Appendix, Table 5) were identified. Additionally, four combinations of antibiotics and potentiators or enablers that do not contain new chemical entities were included.

Antibacterial drugs with activity against Gram-negative bacilli

Of the 30 NCEs, four have been submitted for review at FDA and/or the European Medicines Agency (EMA) or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA): eravacycline, iclaprim omadacycline and lascufloxacin. Eleven are expected to have some activity against at least one of the WHO critical priority pathogens that are resistant to carbapenems, and thus mostly extensively-drug resistant (XDR) according to the ECDC definition.[17] From these 11 drugs, only the siderophore-conjugated cephalosporin cefiderocol provides coverage against all three critical priority pathogens: carbapenem-resistant *A. baumannii* (CRAB), carbapenem-resistant *P. aeruginosa* (CRPA), and carbapenem-resistant Enterobacteriaceae (CRE). Additionally, two other drugs have activity against CRAB (ETX2514/sulbactam, TP-6076) and only one against CRPA (murepavadin). Altogether, eight drugs have at least partial coverage of CRE.

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

mechanisms beyond the production of β-lactamases with mechanisms such as a decreased permeability of the outer membrane, upregulated efflux pumps, and modified penicillin-binding proteins.[18-20] The inconsistent inhibitory activity against OXA enzymes and the prominence of non-β-lactamase mediated resistance mechanisms explain why most new BLI combinations add no benefit in case of *A. baumannii* and only limited benefits for *P. aeruginosa*.

BL-BLI combinations: A new aspect of BLIs in the clinical pipeline is the evolution of the chemical class of diazabicyclooctanes (DBOs) which are non-β-lactam BLIs with avibactam as the first representative.[21] Although BLIs have historically lacked intrinsic antimicrobial activity, the new sub-group of DBO-based molecules now includes development BLI candidates with intrinsic antibacterial activity. Antibacterial activity through binding to Penicillin Binding Protein 2 (PBP) becomes in some more recent compounds (nacubactam, ETX2514 and zidebactam) an important or even dominating factor in the combination and provides synergistic activity.[22-24]

New BLs: Cefiderocol, a cephem, is intrinsically more stable to β-lactamases and hence not dependent upon a BLI partner. In addition, cefiderocol's uptake is enhanced by siderophore-mediated use of the bacterial iron transport mechanism.[25] Based on data currently available, this compound has the broadest Gram-negative spectrum of any agent in the pipeline. [26]

Tetracyclines: Not surprisingly, pre-existing resistance is also seen in other derivatives of known classes. Tetracyclines are a good example, with more than 1000 resistance genes reported.[27] New tetracyclines in the clinical pipeline address some of the class-specific resistance mechanisms and improve coverage in a given species. In general, new tetracyclines have been optimised either against Gram-negative or Gram-positive bacteria.

Combination products with approved drugs: Due to their potential clinical benefit, four combinations using pairs of already approved entities were additionally analysed. Aztreonam/avibactam combines an old monobactam with intrinsic stability against class B β-lactamases (metallo-β-lactamases, MBL) and the recently registered DBO BLI avibactam with inhibitory activity of class A and C β-lactamases.[28] Expanding of the spectrum is specifically expected for metallo-β-lactamase-producing Enterobacteriaceae due to the intrinsic stability of monobactams to these enzymes.[29] The combination of cefepime/tazobactam is expected to improve on piperacillin/tazobactam through better protection against ESBLs, as cefepime is easier to potentiate than piperacillin with an optimised tazobactam dose.[30] Zidovudine is active against carbapenem and colistin resistant (mcr positive) Enterobacteriaceae and a fixed combination of zidovudine with colistin is in clinical development. [31] A new oral fixed combination of ceftibuten and clavulanic acid will target urinary tract infections caused by ESBL-producing Enterobacteriaceae.

Innovation: All the mentioned drugs are derivatives of extensively-used antibacterial classes and pre-existing resistance is likely to occur quickly. Of the anti-Gram-negative antibacterial drugs included in the current pipeline, only murepavidin is classified as being innovative as it belongs to a new chemical class.[32] It also has a new target and mode of action with no currently known cross-resistance mechanism to approved antibacterial drugs and is thus classified in this analysis as meeting the innovative criteria. It is active only against *P. aeruginosa*. [33]

Routes of administration: Most anti-Gram-negative NCEs in the pipeline will be available only as parenteral (IV) formulations with the exceptions of sulopenem, which is administered as a prodrug. This synthetic penem described in the 1980s has activity against both Gram-positive bacteria and ESBL-producing Enterobacteriaceae but no activity against carbapenem-resistant organisms. Data on its absorption and urinary recovery were not identified in the public domain. ~~Some concern has been expressed that an oral penem may exert strong selection pressure for carbapenem resistance, especially if widely used.~~ The oral carbapenem in clinical development, tebipenem, was not included in this analysis as it is an approved drug in Japan. A new addition to potential oral treatments is the BLI-cephalosporin combination, ETX0282/cefpodoxime, which entered clinical development and is active against CRE except MBL producers. [34]

Antibacterial drugs with activity against Gram-positive and Gram-negative cocci

Most drugs with focus on Gram-positive cocci are derivatives of known fluoroquinolones, tetracyclines, macrolides, dihydrofolate reductase (DHFR) inhibitors (trimethoprim) and oxazolidinone classes (Table 2). The FABI inhibitor afabicin and potentially ~~brilacidin~~ lefamulin (pleuromutilin) were classified as innovative for human use, although pleuromutilins have been used before in a topical formulation and in the animal sector.[35]

The functional class of bacterial topoisomerase inhibitors is not new but comprises new chemical structures and distinct but overlapping binding sites with fluoroquinolones without demonstrated cross-resistance to date.[36] Both of the new bacterial topoisomerase inhibitors (NBTIs) in development are orally available and their spectrum targets Gram-positive pathogens, respiratory tract infection pathogens and *N. gonorrhoeae*.[37] No cross-resistance of zoliflodacin with fluoroquinolones has been described to date in *N. gonorrhoeae*.[38] Although several antibacterial drugs in the pipeline have *in vitro* activity against *N. gonorrhoeae*, only the two NBTIs are currently being developed for this indication.

Biologics

Biologics comprise of monoclonal and polyclonal antibodies, and phage-derived products (Table 3). So far, only one biologic, a monoclonal antibody against *C. difficile* toxin B (bezlotoxumab), has been approved by EMA and FDA. Three monoclonal antibodies against *P. aeruginosa*, four monoclonal antibodies against *S. aureus* (including one that is linked to an antibiotic) and two polyclonal antibodies against *C. difficile* are currently in clinical development. One polyclonal antibody preparation against *C. difficile* acts systemically against the *C. difficile* toxin B, with the other active in the large intestine after oral application. Two engineered endolysins, which are enzymes used by bacteriophages to destroy the bacterial peptidoglycan cell wall, are being developed against *S. aureus* infections. Insufficient information is currently available yet regarding the potential for resistance development either by immune response to the product and target alterations. The potential place of biologics in the prevention or treatment of infections will require completion and careful evaluation in clinical trials.

M. tuberculosis

Ten drugs are being developed against *M. tuberculosis*. Six of the ten new drugs in development qualified as innovative or probably innovative (Table 4). Several new targets are pursued: DprE1 (cell wall synthesis), MmpL3 (membrane transporter), Leucyl-tRNA synthetase (protein synthesis), qcrB (subunit of the cytochrome bc1 complex), and enzymes of the respiratory electron transport chain. Three drugs in clinical development ~~(TBA-7371 entered Phase 1 shortly after the cut-off date)~~ target DprE1. [38] As listed in Table 4 most drugs in the pipeline are in early clinical phases and more information is needed to assess the individual drugs, especially the contribution they may have on the activity of specific combination regimens. Further time is needed to assess of new anti-tuberculosis medicines for potential or acquired resistance as resistance patterns might not clearly emerge even in advanced development phases.

C. difficile

Four new drugs against *C. difficile* are in clinical development, with two of them representing new classes (Appendix, Table 5). Three of four small molecule drugs against *C. difficile* are oral formulations with an active ingredient not sufficiently absorbed to be systemically relevant. This fact mitigates two commonly encountered hurdles in antibacterial drug R&D: PK and toxicity. Hence treatment of *C. difficile* infection is a viable option to bring a new class of antibacterial drugs with such liabilities to the market. In addition to the small molecules in the clinical pipeline there are two polyclonal antibodies in development as previously described (Table 3). In comparison to other acute bacterial infectious diseases, there is more innovation in the *C. difficile* area despite the fact that demand for innovation related to resistance in *C. difficile* is lower.

Discussion

Innovation is of key interest for this pipeline analysis. In the context of bacterial resistance and the corresponding need for new antibacterial drugs, each of the three traditional criteria for innovation on its own - a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site) and a novel mode of action – may be confounded by complex drug-bacteria interactions. Each of these criteria may be insufficient to characterise innovation if the goal is to develop new antibacterial drugs against the most resistant priority pathogens. Therefore, the overarching criteria of "lack of known cross-resistance" as the most relevant criterion when assessing innovation in the context of antibiotic resistance was used as reasonable predictor of a drug's activity against XDR or pan-drug resistant (PDR) bacteria.[16]

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

Efforts focusing on Gram-negatives began to emerge as MDR and XDR resistance rose globally and concern increased substantially, but progress translating these discoveries has been slow, partly due to the difficulty overcoming two lipid bilayer membranes and associated efflux pumps in Gram-negative bacteria.[40] The Gram-negative clinical pipeline has little innovation and gaps remain with respect to critical PPL pathogens. Based on the long R&D timelines of 10 or more years for any discovery project, we currently have a pipeline in which anti-Gram-positive projects are sufficient in response to the medical need though innovation is also neglected in the Gram-positive space.

What are the implications of low innovation in the Gram-negative category? We predict significant gaps in coverage, especially for CRAB and CRPA, but also CRE in some geographical areas. The anti-Gram-negative R&D has focused on the β-lactam class and BLIs, as these are very well validated starting points for improving efforts. So far, BLIs that inhibit classes A, C, D of β-lactamases predominate. The epidemiology of β-lactamases determines the usefulness of new BLI-combinations in different geographic regions in pathogens with BLs as main resistance mechanism in β-lactam antibiotics. CRE are an important example as the production of a variety of carbapenemases is the major resistance mechanism.[2] Most new BLIs inhibit KPC enzymes (prevailing in North America, Latin America and in some European countries), whereas the metallo-β-lactamases (class B) are not inhibited (dominant in Asia, South Pacific region and important in some European countries and Africa).[41] Similarly, OXA carbapenemases are mostly not covered (dominate in African countries and are important in the Middle East and some European countries).[41, 42] In countries with especially high rates of carbapenem resistance in Enterobacteriaceae and a high prevalence of BLs other than KPC, the gaps in coverage (MBLs and OXAs) of the new BLIs is most relevant.[41] Whether the new BLI VNRX-5133 with expanded coverage of the MBLs NDM and VIM enzymes holds its promise can't be assessed due to limited information.[43] The next generation cephalosporin cefiderocol has improved β-lactamase stability and its structure incorporates a siderophore to facilitate penetration into the bacterial cell wall. These features may provide improved coverage of all three WHO critical priority pathogens.[44] The potential for cross-resistance to known resistance mechanisms and its relevance is not known so far.

Another concern is the lack of orally available innovative antibacterial drugs in the clinical pipeline. These are valuable in many settings but are especially needed for the treatment of common community-acquired infection, such as UTIs caused by ESBL-producing and fluoroquinolone-resistant Enterobacteriaceae. In the community, non-judicious use of modified derivatives of existing antibiotic classes will increase selection pressure and the risk of even faster spread of resistance in

Gram-negative bacteria in the community and healthcare settings. This situation is especially risky in drugs with cross-resistance to carbapenems. Future oral penems or carbapenems (e.g. sulopenem or tebipenem) might aggravate the selection pressure for carbapenem resistance if used widely. New antibacterial classes without co-selection pressure that are orally available, optimised for UTIs, and restricted for targeted use are urgently needed.

It has been proposed that positive results in animal disease models have limited value in the field of antibacterial biologics as they can be followed by clinical failure.[45] To date, only two monoclonal antibodies have been approved for infectious diseases outside the biothreat field: palivizumab, for the prevention of respiratory syncytial virus, and bezlotoxumab, which targets the *C. difficile* toxin B to reduce recurrence risk. Technological advances in the field, moving to multi-specific, multi-functional strategies, and improved definition of patient groups at risk as well as commercial reasons have attracted multiple specialised companies to push their biologics into clinical trials.[46, 47] Antibodies are usually studied as preventive or adjunctive therapy. A potential clinical impact of antibody use as adjunctive therapy has not yet been shown.

For *C. difficile* infections, two new chemical classes are in Phase 1 and 2 clinical development and it is not known yet if they will demonstrate an additional benefit over vancomycin or metronidazole.[48] Though the burden of disease may be high, it is usually not associated with acquired resistance to antibiotics.[49]

The development of new anti-tuberculosis drugs faces specific challenges, including the need to treat tuberculosis with a combination of at least three different antibacterial drugs. Unlike the large majority of TB patients worldwide who can expect a relapse-free cure with a 6-month course of first-line medication, patients with drug-resistant TB (usually including resistance to at least rifampicin, commonly combined with isoniazid resistance, or with further resistance to fluoroquinolones and/or aminoglycosides) require treatment regimens which are longer, less effective and less accessible than first-line regimens, but more costly, toxic and complicated to deliver. Most second-line MDR-TB regimens are currently designed to last 9 to 24 months, presenting a formidable challenge to health service providers to ensure patient adherence and obtain sustainable cure.[50,51] New drugs and drug regimens are needed to shorten and simplify therapy for both drug-sensitive and drug-resistant *M. tuberculosis*.[52] Intracellular environment, dormant forms and complex PK conditions add to the challenges of drug R&D in the TB arena. Although some new targets and new classes are listed in the pipeline, there were only ten drugs in clinical development. Given the high anticipated attrition rates that have been seen with other molecules, and the remaining challenge of identifying the optimal drug combination, the clinical pipeline for TB drugs is still insufficient.[53, 54]

The limitations of our analysis are mainly grounded around information variability due to limited publicly available data. While strong effort was undertaken to make this analysis as complete as possible and base assessments on peer-reviewed publications, the availability and quality of data varied significantly between clinical candidates. Despite WHO's requirements on clinical trial transparency, some of the trials with products in this pipeline are not listed in any clinical trial registry. Lack of key information especially impeded the assessment of expected activity against PPL pathogens. While for some agents peer-reviewed activity assessments were available, for others we had to rely on limited company information, or the comparison to other agents with a similar structure, if no data had been published. Furthermore, for some agents the assessment was made purely based on *in vitro* activities, while for others it was on clinical and PK/PD.

The assessment of innovation was also subject to limitations. Lack of cross-resistance is the most relevant criterion when assessing innovation in the context of antibiotic resistance.[16] In early stages of development sufficient information may not be available yet. Novel chemical scaffolds, binding sites and modes of action are reasonable predictors for a lack of cross-resistance. For these reasons, all four aspects were separately assessed. However, in some instances a question mark indicates where information was insufficient (e.g. structure not published) or the experts could not reach a final agreement on novelty. This pipeline analysis should be regarded as a snapshot at the time of its

creation. The field moves quickly as shown by the rapid changes captured by our analysis over a time period of 12 months: as more information becomes available the innovation and spectrum of activity assessments may change.

Conclusion

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

Contributors

UT, SG, SH, PB designed the study protocol, SG and UT did the search for the drugs to be included, SG managed the data, UT provided the data for the 2018 update and scientific assessment of individual drugs. MS and CL contributed information about tuberculosis. SH chaired the first advisory board meeting 2017 and PB the second in 2018. All members of the advisory group provided input and contributed to the final consensus. UT wrote the first draft of the article and all authors provided feedback, commented on, and reviewed the manuscript. PB and SP supported overall project coordination, setup and review. The overall study was overseen by the WHO Secretariat. The contribution of WHO employees has been prepared strictly in a personal capacity and reflects the view of the authors. The views expressed must not be attributed to the WHO, its Secretariat, or its Member States.

Conflicts of interests

UT, SG, MP, MB, GT, JPP, LC, PB, SP, CL, LM declare no conflicts of interest.
MS: is employed by TB alliance, is Member of the Board of Directors at The Medicines Company; LS reports personal fees from Acidophil, Appili, Debiopharm, DesignMedix, Melinta, Merck, Nabriva, Taisho, Taxis, Vertex, X-Chem, Grey Healthcare, Innovacorp, PureTech, TPG, CARB-X, Uppsala University, NIH, University of Washington, IMI-Enable, Forge Therapeutics outside the submitted work; JR reports holding a position as Chief Medical Officer & Director at F2G, Non-Executive Director & Consultant at Adenium Biotech, Operating Partner & Consultant at Advent Life Sciences and Expert-in-Residence at Wellcome Trust, member of the Scientific advisory Boards of Macrolide Pharmaceuticals, Bugworks Research, Basilea Pharmaceutica, Forge Therapeutics, and Novo Holdings, he reports personal fees from Phico Therapeutics, ABAC Therapeutics, Polyphor, Heptares Therapeutics, Gangagen, Meiji Seika Pharma, Basilea Pharmaceutica International, Allecra Therapeutics, Forge Therapeutics, SinSa Labs, AtoxBio, Peptilogics, F. Hoffmann-LaRoche, and Novo Holdings, he is shareholder in AstraZeneca, F2G, Adenium Biotech, Advent Life Sciences, Macrolide Pharmaceuticals, and Bugworks Research; SH reports grants from IMI Brussels, during the conduct of

the study; grants from Pfizer, personal fees from Novartis, personal fees from DNA Electronics, personal fees from Bayer, personal fees from GSK, outside the submitted work.

For all experts, advice was provided in their personal capacity. The views in this report do not necessarily reflect, and should not be interpreted as, the official position of any agency or institution. The declaration of interests of the advisory board members can be found in the appendix.

Acknowledgments

We thank Enrico Tognana and Marco Cavaleri (EMA) for conducting the search on the Adis Insight database, and Jiangdong Jiang (Chinese Academy of Medical Sciences) for conducting the search on antibacterial products in China. ~~We also thank, Clarke Cole, Damiano de Felice (Access to Medicines Foundation), Kevin Outterson (CARB-X), Manica Balasegaram, Gabrielle Landry (GARDP), Laura Marin (JPIAMR), Els Toreele, Monica Garcia (MSF Access Campaign), Dennis M. Dixon (NIAID/NIH), Christine Årdal (Norwegian Public Health Institute), Anthony So (ReAct group), Grania Brigden (TB Union), David Visi, Joe Thomas (The PEW Charitable Trusts), Erica Lessem, Mike Frick (Treatment Action Group), Nina Grundmann (IFPMA), Arthur Phyllis (Bio), Marie Petit (BEAM Alliance) for reviewing pipeline data.~~

Advisory group

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***Manuscript with revisions highlighted**

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

Name (trade name)	Approved by	Antibiotic class	Route of administration ()	Indication	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP	NCR	CG	T	MoA
Delafloxacin (Baxdela)	FDA	Fluoroquinolone	iv & oral (Melinta)	ABSSSI (CAP, Ph3)	⊖	⊖	⊖	●	–	–	–	–
Vaborbactam + meropenem	FDA	Boronate BLI + carbapenem	iv ()	cUTI (*E.coli, K. pneumoniae, Enterobacter cloacae*)	⊖	⊖	●‡	/	?	✓	–	–
Plazomicin	FDA	Aminoglycoside	iv (Achaogen)	cUTI	⊖	⊖	●	/	–	–	–	–

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

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

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Eravacycline (Xerava)	NDA[1] MAA[1]	Tetracycline	iv (Tetraphase)	?	○	●	/	–	–	–	–
Omadacycline	NDA[2]	Tetracycline	iv & oral (Paratek)	○	○	○	●	–	–	–	–
Iclaprim	NDA[3]	DHFR inhibitor	iv (Motif Bio)	/	/	/	●	–	–	–	–
Lascufloxacin	NDA[4]	Fluoroquinolone	iv & oral (Kyorin)	○	○	○	?	–	–	–	–
Relebactam + imipenem/cilastatin	3	DBO-BLI + carbapenem/ degradation inhibitor	iv (MSD)	○	?	●[5]	/	–	–	–	–
Cefiderocol	3	Siderophore-cephalosporin	iv (Shionogi)	●	●	●	/	?	–	–	–
Lefamulin	3	Pleuromutilin[6]	iv & oral (Nabriva)	/	/	/	●	?	✓[6]	–	✓
Sulopenem, sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○[7]	/	–	–	–	–
Murepavadin (POL-7080)	3	Novel membrane targeting antibiotic	iv & inhaled (Polyphor)	/	●	/	/	✓	✓	✓	✓
Solithromycin	3[8]	Macrolide	iv & oral (Cempra/Melinta)	/	/	/	●	–	–	–	–
Levonadifloxacin Alalevonadifloxacin	3[9]	Fluoroquinolone	iv (Wockhardt) oral (Wockhardt)	○	○	○	?	–	–	–	–
Cefilavancin (TD-1792)	3[10]	Glycopeptide-cephalosporine conjugate	iv (Theravance/R-Pharm)	/	/	/	●	–	–	–	–
AAI101 + Cefepime	3	β-lactam BLI + cephalosporin	iv (Allecra)	○	○	○[11]	/	–	–	–	–
Contezolid Contezolid acefosamil	2/3[12]	Oxazolidinone	oral (MicuRx) iv (MicuRx)	/	/	/	●	–	–	–	–
Gepotidacin	2	NBTI (Triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●	✓	✓	–	✓
Zoliflodacin	2	NBTI (Spiropyrimidenetrione)	Oral (Entasis/GARDP)	/	/	/	●	✓	✓	–	✓
ETX2514+sulbactam[13]	2	DBO-BLI /PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	–	–	–	–
Nafithromycin (WCK-4873)	2	Macrolide	Oral (Wockhardt)	/	/	/	●	–	–	–	–
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
LYS-228	2	Monobactam	iv (Novartis)	○	○	●	/	–	–	–	–
Zidebactam + Cefepime	1	DBO-BLI/ PBP2 binder + cephalosporin	iv (Wockhardt)	○	?	●	/	–	–	–	–
Nacubactam + meropenem	1	DBO-BLI/ PBP2 binder + meropenem	iv (Roche)	○	?	●[5]	/	–	–	–	–
VNRX-5133 + cefepime	1	Boronate-BLI + cephalosporin	iv (VenatoRX)	?	?	●	/	?	–	–	?
ETX0282+cefpodoxime	1	DBO-BLI + cephalosporin	Oral (Entasis)	○	○	●[5]	/	–	–	–	–
SPR-741 + β-lactam	1	Polymyxin + β-lactam	iv (Spero)	?	?	?	/	–	–	–	–
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	○	○	○	●	–	–	–	–
TP-271	1	Tetracycline	iv & oral (Tetraphase)	?	○	○	●	–	–	–	–
TP-6076	1	Tetracycline	iv (Tetraphase)	●	○	?	/	–	–	–	–
TNP-2092	1	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?	–	–	–	–
AIC-499 + unknown BLI	1	β-lactam + BLI	iv (AiCuris)	?	?	?	/	–	–	–	–

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

Innovation assessment: ✓ criterion fulfilled; ? Inconclusive data or no agreement among the advisory group; - criterion not fulfilled; NCR, no cross-resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action;

BLI, β-lactamase inhibitor; E, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; AB, *A. baumannii*, carbapenem-resistant; PA, *P. aeruginosa*-, carbapenem-resistant; DBO, diazabicyclooctane; DHFR, dihydrofolate reductase; iv, intravenous;

NBTI, novel bacterial topoisomerase II inhibitor; NDA, new drug application (FDA), MAA, Marketing Authorization Application (EMA). OPP, other priority pathogens on the WHO PPL ("high" and "medium" priority); PBP, penicillin-binding protein

Underlined agents: New chemical class

[1] MAA submitted on 17 August 2017, CHMP has adopted positive opinion for approval.; NDA submitted on 2 January 2018 for the iv form only for cIAI, PDUFA date August 28, 2018

[2] NDA submitted on 5 February 2018, PDUFA date October 2018

[3] Completed NDA submission 14 June 2018

[4] NDA in Japan only

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

[6] First systemic formulation of this class, which has been used topically and in animals previously

[7] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant but not carbapenem-resistant Enterobacteriaceae

[8] withdrawn MAA, FDA complete response letter, currently no development activities outside of Japan

[9] Phase-3 trial ongoing only in India, phase-1 oral studies in the USA in 2014 (alalevonadifloxacin)

[10] Developed only for Russia

[11] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant and some KPC producing carbapenem-resistant Enterobacteriaceae

[12] Contezolid acefosamil: Phase 2 in USA not yet recruiting. Contezolid: NDA in China expected end of 2018

[13] Combination of ETX2514 with imipenem/cilastatin planned

~~[10] Phase-trial in Indiaphase-1 studies in the USA~~

Table 3. Biological antibacterial agents in clinical development

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens		
				PA	SA	CD
DSTA-4637S	1	Anti-*S. aureus* IgG monoclonal antibody/rifamycin	iv (Genentech/Roche)	/	●	/
PolyCab	1	*C. difficile* polyclonal antibody	iv (MicroPharm)	/	/	●
IMM-529	1/2	*C. difficile* polyclonal antibody	Oral (Immuron)	/	/	●
AR-301 (tosatoxumab)	1/2	Anti-*S. aureus* IgM monoclonal antibody	iv (Aridis)	/	●	/
514G3	1/2	Anti-*S. aureus* IgG monoclonal antibody	iv (XBiotech)	/	●	/
SAL-200	2	Phage endolysin	iv (Intron)	/	●	/
CF-301	2	Phage endolysin	iv (Contrafect)	/	●	/
~~ASN-100[1]~~	~~2~~	~~Anti-*S. aureus* IgG monoclonal antibody~~	~~iv (Arsanis)~~	~~/~~	~~●~~	~~/~~
Suvratoxumab[1]	2	Anti-*S. aureus* IgG monoclonal antibody	iv (MedImmune)	/	●	/
MEDI-3902[1]	2	Anti-*P. aeruginosa* IgG monoclonal antibody	iv (MedImmune)	●	/	/
AR-105 (Aerucin)	2	Anti-*P. aeruginosa* IgG monoclonal antibody	iv (Aridis)	●	/	/

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

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

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
Pretomanid (PA-824)	3	Nitroimidazole	Oral (TB Alliance)	?	–	–	?
SQ-109[1]	2/3	Diamine	Oral (Sequella/Infectex)	?	–	✓	✓
Delpazolid (LCB01-0371)[2]	2	Oxazolidinone	Oral (LegoChem)	–	–	–	–
Sutezolid[3]	2	Oxazolidinone	Oral (TB Alliance/Sequella)	–	–	–	–
~~SQ-109[2]~~	~~2~~	~~Diamine~~	~~Oral (Sequella/Infectex)~~	~~?~~	–	~~✓~~	~~✓~~
Telacebec (Q-203)	2	Imidazopyridine amide	Oral (Qurient/Infectex)	✓	✓	✓	✓
Macozinone (PBTZ-169)	1 (2)	DprE1 inhibitor (benzothiazinone)	Oral (Innovative Medicines For Tuberculosis Foundation)[4]	✓	✓	✓	✓
GSK070 (GSK-3036656)	1	Leu RS inhibitor (oxaborole)	Oral (GlaxoSmithKline)	✓	✓	✓	✓
OPC-167832	1	DprE1 inhibitor	Oral (Otsuka)	?	✓	✓	✓
TBA-7371	1	DprE1 inhibitor	Oral (TB Alliance)	✓	✓	✓	✓
TBI-166[5]	1	Riminophenazine (Clofazimine-analogue)	Oral (Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College)	–	–	–	–

Innovation assessment: ✓ criterion fulfilled; **?** Inconclusive data; – criterion not fulfilled

NCR, no cross resistance to other antibiotic classes; CC, new chemical class; T, new target; MoA, new mode of action; DprE1, decaprenylphosphoryl-β-D-ribose 2-epimerase. Underlined agents: New chemical class. These agents are being developed for use against TB; their activity against other priority pathogens was not assessed.

[1] Chemically close to ethambutol~~Delpazolid also completed a phase-1 trial as injectable for MRSA and vancomycin-resistant *Enterococcus* spp. infections.~~

[2] Delpazolid also completed a phase-1 trial as injectable for MRSA and vancomycin-resistant *Enterococcus* spp. infections ~~Developed by Sequella and independently by the Global Alliance for TB Drug Development, non-exclusive patent by Johns Hopkins University~~

[3] Developed by Sequella and independently by the Global Alliance for TB Drug Development, non-exclusive patent held by Sequella and by The Medicines Patent Pool ~~SQ-109 is also being tested for use in the treatment of *H. pylori* infections. It is an ethambutol derivative.~~

[4] In Russia developed by Nearmedic Plus

[5] Clofazimine is approved for leprosy and used for TB

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

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Innovation			
				NCR	CC	T	MoA
Cadazolid	3	Oxazolidinone-quinolone hybrid	Oral, not absorbed (Actelion, now J&J)	–	–	–	–
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)	✓	✓	✓	✓
DS-2969	1	GyrB inhibitor[‡]	Oral, not absorbed (Daiichi Sankyo)	?	?	?	?

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

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

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

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