/631/326/107 Biological sciences Microbiology Clinical microbiology

/631/326/22/1290 Biological sciences Microbiology Antimicrobials Antibiotics

/631/326/22/1434 Biological sciences Microbiology Antimicrobials Antimicrobial resistance

Critical analysis of antibacterial agents in clinical development

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Abstract

The antibacterial agents currently in clinical development are predominantly derivatives of well-established antibiotic classes and were selected to address class-specific resistance mechanisms and determinants that were known at the time of their discovery. Many of these agents aim to target the antibiotic-resistant priority pathogens listed by the WHO, including Gram-negative bacteria of the critical priority category, such as carbapenem-resistant *Acinetobacter*, *Pseudomonas* and *Enterobacterales.* Although some current compounds in the pipeline exhibit increased susceptibility rates in surveillance studies depending on geography, pre-existing cross-resistance both within and across antibacterial classes limits the activity of many of the new agents against the most extensively drug resistant (XDR) and pan drug resistant (PDR) Gram-negative pathogens. In particular, cross-resistance to unrelated classes may occur by co-selection of resistant strains, thus leading to the rapid emergence and subsequent spread of resistance. There is a continued need for innovation and new-class antibacterial agents to provide effective therapeutic options against infections specifically caused by XDR and PDR Gram-negative bacteria.

[H1] Introduction

There is a widely acknowledged need for new antibacterial agents to address the global increase in resistance, and the need for new agents is especially urgent for the treatment of antibiotic-resistant Gram-negative bacteria. In early 2017, the WHO convened a group of experts that used a multi-criteria decision analysis method to prioritise the need for new drugs to treat antibiotic-resistant bacteria[1]. The WHO assigned the highest priority for antibacterial drug research and development to the Gram-negative bacteria *Acinetobacter*, *Pseudomonas,* and species of the *Enterobacterales* that are resistant to carbapenems and are usually extensively drug resistant (XDR)[1]. The same year, the WHO released a clinical pipeline report, which was updated in 2018 and 2019 (Refs [2, 3]; WHO clinical pipeline report [https://apps.who.int/iris/bitstream/handle/10665/330420/9789240000193-eng.pdf) . The clinical pipeline reports analysed antibiotics and biologics according to their activity against the critical priority pathogens carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* (CRE). The level of innovation in the global clinical pipeline was assessed based on the absence of pre-existing cross-resistance to currently used antibacterial drugs[4].

In this Review, we summarise the current published literature and publicly available information on the antibacterial agents in all phases of clinical development based on the WHO pipeline report[3]. This Review is limited to antibacterial agents that were in clinical development for systemic human use and that did not yet have regulatory approval anywhere in the world for human use. Additionally, drugs against *Clostridioides difficile* infection are included though mostly not being systemically absorbed after oral administration. The principal focus is on the ability of new agents to treat infections caused by bacteria that are XDR or pan drug resistant (PDR), the main driver of research and development[5]. Thus, bacteriological information is an important basis for this analysis. We further analyse the gaps of the global clinical pipeline and need for future antibacterial agents. Although other therapeutic and preventative approaches have been developed, in this Review we focus on direct-acting small molecules for therapeutic purposes ('traditional antibiotics'). Non-traditional therapies[6, 7] and anti-tuberculosis treatments[8, 9] have been extensively reviewed elsewhere. Discussing economic challenges of antibacterial drug development was beyond the scope of this Review.

[H1] Top three resistant pathogens

[H2] Carbapenem-resistant *Acinetobacter baumannii*. The prevalence of carbapenem resistance among *Acinetobacter* spp. is extremely variable and ranges from <10% to >90% (Ref. [10]). XDR is common due to the diverse and extensive arsenal of chromosomally encoded and acquired resistance genes carried by this pathogen (Figure 1). Overexpression of the intrinsic chromosomally encoded β-lactamase ADC (class C β-lactamase in *A. baumannii*) and OXA-51-like enzymes, as well as diverse acquired β-lactamases such as OXA-23-, OXA-24/40-, OXA-58-like, and class A β-lactamases (for example, TEM and SHV) found on a range of mobile genetic elements are the main resistance mechanisms against β-lactam antibiotics[11]. Combinations of different β-lactamases and the accumulation of other resistance determinants such as aminoglycoside-modifying enzymes, porin deficiencies, efflux or target protein modification render CRAB resistant to most usually available antibacterial drugs and increasingly also to tigecycline and colistin. XDR and PDR isolates are routinely being reported in some countries[12, 13].

[H2] Carbapenem-resistant *Pseudomonas aeruginosa*. CRPA are genetically diverse and usually exhibit more than one resistance mechanism, including porin deficiency (OprD), hyperproduction of

the chromosomally encoded cephalosporinase AmpC, efflux pumps, and various class-specific resistance mechanisms (for example, mutations in quinolone resistance-determining regions)[14]. These chromosomally encoded resistance determinants alone or in combination affect carbapenems and other ß-lactams differently, and diverse combinations are prevalent in isolates from distinct countries[14]. Loss of porins is the most common mechanism leading to carbapenem resistance. Overexpression of one of the several efflux pumps (*mexB*, *mexY*) is a non-specific mechanism that affects especially cefepime, aminoglycosides, fluoroquinolones and meropenem[15]. Acquired resistance mechanisms such as ß-lactamases (for example, ESBLs or class B metallo-ß-lactamases (MBLs)) are often co-transferred with genes that encode aminoglycoside-modifying enzymes but are less frequent compared to resistance conferred by chromosomally encoded genes. The prevalence of MBLs, especially VIM and IMP, is highly variable in different countries, and they are increasingly widespread in some regions[14]. The accumulation of several resistance mechanisms to different antibacterial classes can lead to XDR or even PDR strains[16] (Figure 1).

[H2] Carbapenem-resistant *Enterobacterales*. Carbapenem resistance in *Enterobacterales* (mainly *Klebsiella pneumoniae*, but also *Enterobacter cloacae*, *Escherichia coli, Citrobacter* spp. and *Serratia marcescens*) is caused by the production and high diversity of all β-lactamase classes (class A, class B, class C and class D), which are often present in combination and confer resistance to almost all β-lactam antibiotics (Figure 1). The epidemiology of β-lactamases is complex, as exemplified by the production of MBLs (often NDM-type) that ranges from 1% in the United States to 100% in the Asia-Pacific region[17, 18], with a prevalence of NDM-producing *E. coli* of 83%, 13%, 1%, 1% and 2% in Asia, Europe, America, Africa and Oceania continents, respectively[19]. By contrast, the KPC class A carbapenemases are found more widely distributed in the Americas, Korea and China[20]. In Europe, the prevalence of carbapenem resistance also differs greatly, with the highest rates in Mediterranean and Balkan countries[21]. Even inter-hospital prevalence of CRE and individual resistance mechanisms can range from <10 to 90%. New β-lactamase variants with a range of amino acid substitutions, increased hydrolysis of the β-lactam antibiotic, or amplification of the *bla* gene are commonly described. In addition, a diversity of KPC-2 and KPC-3 variants conferring resistance to ceftazidime–avibactam are circulating in the United States and Europe[22-24]. The production of β-lactamases may be accompanied by other resistance mechanisms, such as porin deficiencies with a similar highly diverse epidemiology, with upregulated efflux pumps in *E. coli* and, rarely, insertions into *E.coli* penicillin-binding protein 3 (PBP3), that affect the microbiological activity of cephalosporins and monobactams[25, 26]. All these resistance mechanism-related factors explain the high variability of susceptibility rates to new β-lactam-based therapies against CRE. In addition, CRE are also often resistant to unrelated antibacterial classes such as fluoroquinolones, aminoglycosides, fosfomycin, tigecycline, thus being XDR and sometimes also PDR[27]. Associated resistance to colistin and tigecycline is linked to worse clinical outcome[28, 29]. In Greece, a prevalence of ~30% for XDR and ~5% for PDR has been reported[27]. The propensity of specific clones of *K. pneumoniae* to spread in hospital environments has been shown to correlate with the degree of resistance; distressingly, carbapenemase-producing isolates have the highest transmissibility[30, 31].

[H1] β-lactam-based clinical pipeline

As shown by the four recently approved ß-lactamase inhibitor (BLI) combinations (two approved since 2017) (Table 1), the clinical pipeline (Table 2) is characterised by new derivatives of the ß-lactam class or functional class of BLIs, most of them focused on improvements in the coverage of *Enterobacterales*[3]. The renaissance of β-lactam antibiotics in the beginning of the 21st century has enriched the therapy options and addressed the class-specific resistance due to the production of β-lactamases by either combining a β-lactam-containing molecule with a BLI or modifying it to prevent hydrolysis.

[H2] β-lactamase inhibitors and new combinations.

BLIs have seen a remarkable evolution from β-lactam-derived molecules to new chemical classes, the diazabicyclooctanes (DBOs) and boronate classes[32]. The DBO class has evolved from mostly functional BLIs with avibactam-ceftazidime as the first DBO combination to compounds with additional relevant intrinsic antibacterial activity through binding to PBP2 in enteric bacteria, one of the target proteins of β-lactam antibiotics (Table 3). This intrinsic antibacterial activity, albeit modest in some cases, contributes to a synergistic effect that may even extend the spectrum of the combination to some strains with MBL production, even if the MBLs are not inhibited. Boronate BLIs lack an intrinsic effect but have evolved to BLIs with a wider inhibitory spectrum to include some MBLs such as NDM and VIM (taniborbactam and the preclinical BLI QPX7728). Given that β-lactamases are mechanistically and structurally distinct, finding a BLI that is equally effective against all classes and relevant enzymes remains difficult[33, 34].

The BLIs vaborbactam (boronate) and relebactam (DBO) have been approved recently in combination with meropenem and imipenem, respectively (Table 1). Vaborbactam inhibits class A and class C β-lactamases, whereas meropenem is not hydrolysed by class C enzymes[37]. Relebactam is a DBO with similar inhibitory activity as avibactam against KPC[35]. Resistance against relebactam–imipenem in *K. pneumoniae* is mainly caused by MBLs, OXA-48, or GES carbapenemases or overexpression of the gene encoding KPC. The susceptibility rates in imipenem-non-susceptible *K. pneumoniae* and *P. aeruginosa* are 50% to 80% (Ref. [36]). Thus, considerable pre-existing cross-resistance is documented. BLIs cross the outer membrane of *K. pneumoniae* using OmpK35 and preferably OmpK36 (Refs. [37, 38]). In case of concomitant porin deficiencies (an as yet rare mechanism), the BLI combinations would be ineffective.

Currently, nine BLI combinations (one β-lactam, six DBOs and two boronates) are in clinical development. A tenth boronate BLI is ready for Phase 1 but not included yet in the clinical pipeline (Table 3). Aztreonam–avibactam is shown in Table 3 but not in Table 2 because it is a combination of registered components. This combination unites the activity of aztreonam against MBL-producing bacteria and the inhibitory activity of avibactam against class A, class C and some class D (OXA) enzymes, thus covering a broad spectrum of β-lactamases. Other than belonging to different chemical classes (but the same functional class), the BLIs differ in their extent to affect bacteria directly due to PBP2 binding (DBOs) and an extended inhibitory coverage that in some compounds includes at least some MBLs (taniborbactam and QPX7728 in preclinical development).

The most advanced DBO in clinical development is durlobactam (ETX2514; intravenous only) with inhibitory activity against class A and class C β-lactamases and a broad range of class D β-lactamases beyond OXA-48 (for example, OXA-23, OXA-24/40, OXA-51 and OXA-58 families). Because these β-lactamases are the most prevalent resistance determinants in CRAB, the company decided to develop this BLI in combination with sulbactam (β-lactam-based BLI and PBP3 inhibitor) for the therapy of *A. baumannii* infections. Resistance to the combination is currently rare and driven by the presence of MBLs (such as NDM-1) or mutations in PBP3, which is the target of sulbactam[39]. In countries with extremely high resistance prevalence in *Acinetobacter* species such as India, resistance to durlobactam–sulbactam is due to NDM-producing isolates[40]. On the basis of whole-genome sequencing analyses, changes in the expression of efflux pumps may additionally reduce susceptibility[41].

Nacubactam and zidebactam are DBOs with inhibitory activity against class A, class C and some class D β-lactamases, and they bind to PBP2, thus showing synergistic activity in *Enterobacterales*[33]. This effect arises when the PBP2-directed activity of nacubactam is combined with PBP3-targeted agents such as cefepime[42], whereas meropenem primarily binds to PBP2 in *E. coli*. Nacubactam, at lower

minimal inhibitory concentrations (MICs) (≤4 mg/L if tested alone), dominates the combination activity through PBP2 inhibition and may contribute to activity against MBL producers at high nacubactam concentrations[43]. At higher MICs (MIC >4 mg/L), nacubactam contributes to the combination activity against bacteria with class A or class C β-lactamases, contingent on β-lactamase inhibition[42]. Nacubactam has no intrinsic effect on non-fermenters [42, 44]. Similarly, zidebactam binds to PBP2 and has intrinsic activity against *E. coli* and *Klebsiella* spp. but insufficient activity against *Enterobacter* spp. and no activity against *Pseudomonas* and *Acinetobacter* spp.[45]. In combination with cefepime (which inhibits PBP3), zidebactam adds these PBP2-inhibiting potencies in *E. coli* and *Klebsiella* spp. As expected, the activity against CRPA is mediocre or insufficient (close to or above the clinical breakpoint for cefepime for 50% of the strains and absent in CRAB[45, 46]. Reduced susceptibility to cefepime–zidebactam is mostly associated with MBLs (IMP or VIM), or combinations of mechanisms such as overexpression of MexAB–OprM or MexXY efflux pumps, diminished OprD function and high-level AmpC production[46].

Taniborbactam is a bicyclic boronate and acts as a dual-action inhibitor of both serine-β-lactamases (SBLs) and MBLs[47, 48]. The broad inhibitory activity includes class A and class C enzymes as well as the MBLs NDM and VIM but not IMP, and moderately the OXA-48 carbapenemase (class D)[47]. In combination with cefepime, the MICs against NDM- and VIM-producing *Enterobacterales* are increased and 10% to 20% of strains are resistant[49]. Given the scant knowledge of boronate-modifying enzymes, it will be of particular interest to observe if unprecedented drug-modifying reactions emerge in response to clinical use[32]. Cefepime- or meropenem-non-susceptible *P. aeruginosa* show 20% to 30% resistance to taniborbactam–cefepime, and thus can only be used for confirmed susceptible strains[50]. Another similar boronate, QPX7728, is in preclinical studies. Although showing a similar inhibitory spectrum[51], the main difference is its potential for intravenous and oral formulations.

Three BLI combinations for oral use are in clinical development, thus far mainly focused on the development for treating urinary tract infections (UTIs): one boronate BLI and two DBOs. The boron BLI VNRX-7145 (prodrug, active compound VNRX-5236) is combined with the oral cephalosporin ceftibuten. Its spectrum encompasses ESBL-, KPC- and OXA-48-producing *Enterobacterales*[52]. Some weakness in the enzyme inhibitory activity is seen with selected OXA and class C enzymes[53]. VNRX-7145 restores the susceptibility of ceftibuten non-susceptible *Enterobacterales* in 87% of strains, most efficiently in ESBL- or KPC-producers[54]. The oral DBO ETX0282 (prodrug, active compound ETX1317) is combined with the oral cephalosporin cefpodoxime proxetil (prodrug) and is active against *Enterobacterales* strains producing ESBL, KPC or OXA-48-like β-lactamases. ETX0282 has intrinsic activity through PBP2 binding with useful activity against *Enterobacterales* and synergy depending on its concentration. Whether this synergistic effect will be sufficient for treating MBL-producing strains remains to be seen[55]. The second oral DBO is ARX-1796, an oral prodrug of avibactam that has mostly insufficient PBP2 inhibitory activity[56].

Finally, the penicillanic acid sulfone BLI enmetazobactam is similar to tazobactam with improved inhibitory activity of ESBL and OXA-48 enzymes in *Enterobacterales* and is being developed in combination with an optimised dosage regimen of cefepime[57]. Cefepime is easier to potentiate than piperacillin, therefore, achieving lower MICs of the combination in wild-type strains as well as in ESBL- and some KPC-2 and KPC-3-producers. Whether those theoretical advantages compared to piperacillin–tazobactam translate into improved clinical efficacy in the therapy of ESBL-producing *Enterobacterales* (not CRE) remains to be proven in randomized controlled clinical trials.

In general, the new BLI combinations contribute to improved options to treat KPC- and OXA-48-producing *Enterobacterales*, especially *Klebsiella* spp., in countries where these are the prevailing resistance mechanisms (Figure 2). In countries where other β-lactamases dominate, they hardly

make a difference to existing antibacterial drugs. Owing to at least some pre-existing cross-resistance all these new β-lactam antibiotics and BLI combinations should only be used with confirmed susceptibility results. This drug class has been and will continue to be heavily used and hence continued selection pressure through the new derivatives of this group will quickly lead to expected but also unexpected resistances. The first signs of new resistance developments in *Klebsiella* spp. are already visible: ceftazidime–avibactam is vulnerable to KPC β-lactamase mutants with increased hydrolytic capacity for ceftazidime. Such mutants can easily be obtained *in vitro*[29] and have been selected in patients treated with ceftazidime–avibactam[58]. For ceftolozane–tazobactam, there are reports of *in vivo* selection of *P. aeruginosa* mutants with sequence mutations in AmpC conferring resistance to both ceftolozane–tazobactam and ceftazidime–avibactam[31,32]. Many β-lactamase-encoding genes travel together on mobile elements with transmissible resistance factors for other antibacterial classes[59]. Selection pressure due to various antibiotic classes and spread of such resistant bacteria may leave the new BLI combinations a short period of useful activity. Though each of the BLIs has its own inhibitory pattern, they may not translate into phenotypic differences of the MIC values of the combinations. However, good regional surveillance of molecular information regarding the most common β-lactamases and non-enzymatic mechanisms (porin deficiency and efflux) and broad antibiotic knowledge will be essential to make informed decisions and best use of the new BLI combinations in specific healthcare environments[60].

[H2] New stand-alone β-lactam antibiotics.

Cefiderocol is a cephalosporin structurally related to ceftazidime and cefepime but more stable to various β-lactamases. The cephalosporin molecule is linked to a siderophore that can bind to iron which facilitates bacterial cell entry in addition to the usual entry via porin channels; this results in improved penetration of cefiderocol in the bacterial cell which is most relevant in non-fermenters[61,62]. In *Enterobacterales*, variations in iron transport channel expression, which varies by species and within species, may cause a wide distribution of MICs[63]. Compared to ceftazidime–avibactam, cefiderocol has similar in vitro microbiological activity against *Enterobacterales* and *P. aeruginosa* but is more active against *Acinetobacter*, *Stenotrophomonas*, and *Burkholderia* species. The resistance prevalence in CRE and CRPA is a little lower than ceftazidime–avibactam[64]. The main weakness of cefiderocol is its limited activity against NDM-producing *E. coli* as well as OXA-23-and OXA-24-producing *Acinetobacter* spp.[65]. MIC_{90} values are about 8 doubling dilutions higher in KPC-2-producing *Enterobacterales* compared with wild-type strains. Due to the very low MICs in wild-type strains, the reduction of activity may still keep cefiderocol MICs for many strains below the clinical breakpoint[63] (FDA breakpoints; [https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria] EUCAST breakpoints [https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria]). Similarly, the reduced susceptibility of ESBL-, carbapenemase- or AmpC-producing strains may not translate into immediate clinical resistance[63] but may be problematic in critically ill patients with altered pharmacokinetic profiles. However, the most problematic XDR or PDR strains have variable susceptibility with ~64% of NDM-producing pathogens testing susceptible[65]. MICs clustering around the breakpoint may be the beginning of a stepwise development of resistance, and reliable susceptibility testing will be essential.

Cefiderocol has been recently approved by the FDA for the treatment of complicated UTIs (including pyelonephritis) caused by susceptible Gram-negative bacteria in patients with limited or no alternative treatment options[66]. However, results from a small descriptive study in critically ill patients with XDR Gram-negative bacteria raised concerns as higher rates of infection-related deaths with treatment failure were seen for cefiderocol than for the comparator (best available therapy). In addition, the development of cefiderocol resistance during therapy was linked to poor outcomes. The results of this study with its inherent limitations of a small descriptive trial, leave clinicians with

little evidence to support its use in patients with XDR Gram-negative bacteria, especially *Acinetobacter* spp. and *Pseudomonas spp.*[67]. A better understanding of cefiderocol efficacy and the associated risk factors will require additional well-designed studies.

BOS-228 is a new monobactam in Phase 2 clinical development. As other monobactams, BOS-228 inhibits PBP3 and is stable to MBLs. Additionally, it has been modified to resist hydrolysis by most serine β-lactamases in *Enterobacteriaceae*[68]. Cross-resistance exists with aztreonam when non- β -lactamase mechanisms are involved (for example, upregulated efflux and/or porin downregulation, mutations in PBP3 and the envelope stress response system)[69].

Sulopenem and tebipenem in form of their bioavailable esters are both in Phase 3 clinical development and will provide new oral therapies for ESBL-producing (MDR) *Enterobacteriaceae* but also confront the medical community with specific challenges. Sulopenem is a thiopenem with intravenous and oral formulation (prodrug), whereas tebipenem is an orally available carbapenem (as a prodrug) that was approved in Japan in 2009 for the treatment of paediatric respiratory tract infections (therefore, not included in table 2). Both antibiotics have a similar spectrum against Gram-negative bacteria compared to ertapenem, which focuses on ESBL-producing *Enterobacteriaceae*. These agents show complete cross-resistance with ertapenem and other carbapenems[70]. Sulopenem failed to demonstrate non-inferiority compared with ertapenem for complicated intra-abdominal infections in a recent Phase 3 trial[71]. Sulopenem and tebipenem have been developed for community-acquired uncomplicated UTIs and oral follow-on after intravenous therapy for complicated UTIs[72, 73]. If used widely, they will most likely exert a strong selection pressure for carbapenem resistance, as any other carbapenem[74]. Antibiotic stewardship programs would need to be established in the community to mitigate this risk. From the public health perspective, oral carbapenem-sparing options for the treatment of MDR strains would be preferable.

[H1] Tetracycline derivatives

New semisynthetic and synthetic tetracycline derivatives based on new chemistry approaches have been recently approved or are in clinical development. Tetracyclines were discovered in the 1940s and have been widely used in human and veterinary medicine, and agricultural applications, which has contributed to the widespread dissemination of tetracycline resistance. Efflux pumps and ribosome protection proteins are the most common resistance mechanisms[75]. In Gram-negative bacteria target-site mutations have been described, recently even for tigecycline[76]. Lately, enzymatic degradation has gained more attention as new highly transferrable plasmid-mediated tetracycline-inactivating enzymes, Tet(X3) and Tet(X4), have been described and are globally present. They degrade all tetracyclines, including tigecycline and the recently approved eravacycline and omadacycline[77-79]. Such plasmids may carry other resistance determinants such as *mcr-1* (colistin-resistance) and genes encoding MBLs (for example, NDM), thus potentially rendering isolates XDR[78, 80]. The fully synthetic eravacycline (intravenous) has activity against CRE comparable to tigecycline and exhibits cross-resistance with tigecycline[79, 81]. The semisynthetic minocycline derivative omadacycline has been recently approved for the oral and intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired pneumonia (CAP). The activity against XDR *Enterobacterales* is insufficient[82].

Three more tetracyclines are in early clinical development: KBP-7022 with a spectrum similar to tigecycline[83],[84] but lower MICs in Acinetobacter spp.[85]. No information is available about cross-resistance with tigecycline. The second tetracycline is TP-6076 with activity against *Enterobacterales* and *Acinetobacter* spp. and lower MICs than tigecycline. The impact of these in vitro findings is not known yet pending pharmacokinetic-pharmacodynamic studies and breakpoint decisions. In tigecycline- and minocycline-non-susceptible *Acinetobacter* isolates the MICs of TP-6076 were

slightly increased[86]. In *K. pneumoniae,* tigecycline-resistant strains are mostly also resistant to TP-6076 (Ref [87]), and resistance to tigecycline in carbapenem-resistant strains is high in some areas[27]. Resistance in *K. pneumoniae* is due to overexpressed RamA, a transcriptional regulator that modulates efflux pump expression[88]. Such a resistance mechanism is increasingly found in CRE with porin deficiency, production of various β-lactamases and aminoglycoside-inactivating enzymes[28], thus reducing the value of this antibiotic as a treatment option for the most resistant bacteria. It is not yet known if the liabilities of tigecycline such as low plasma exposure, concentration-independent plasma protein binding and adverse event concerns will be mirrored by the new tetracyclines[89]. Preliminary information points to a similar adverse event profile of TP-6067 as tigecycline with dose-dependent gastrointestinal side effects, including nausea and vomiting as the most frequently reported adverse effects. The third tetracycline, TP-271, a synthetic tetracycline, is very similar to tigecycline and, active against respiratory pathogens. It is not affected by Tet(M) (ribosomal protection protein), but affected by Tet(A) (efflux) and Tet(X) (enzymatic inactivation)[90].

Similar to other derivatives of long-used classes, the new tetracyclines address some class-specific resistance mechanisms of the older representatives of this class such as doxycycline but have a high degree of cross-resistance to tigecycline. They do not represent reliable alternatives for XDR or PDR Gram-negative bacteria. A potential benefit regarding non-potency related characteristics over tigecycline, such as pharmacokinetics and safety have not been shown so far.

[H1] Other derivatives of old classes

In addition to β-lactams, β-lactamase inhibitors and tetracyclines, a few other old classes have been used as starting points to develop derivatives. The polymyxins are seeing a revival with SPR206, a polymyxin derivative with slightly improved potency that also reduces the magnitude of cross-resistance. The increasingly described plasmid-mediated mcr resistance is often associated with other resistance genes that encode for β-lactamases (including carbapenemase) and for resistances to other antibacterial classes that may include fluoroquinolones and aminoglycosides[91]. Thus, several antibiotic classes may select for XDR or even PDR strains. Carbapenem-resistant *K. pneumoniae* that also exhibit resistance to colistin in more than 30% of the strains have been described in a recent study[28]. It is not clear yet how polymyxin resistance and associated cross-resistance to unrelated classes will develop over the next years, whether SPR206 will be of any benefit in polymyxin-resistant strains, and whether the promise of lower class-specific toxicity will hold true in patients[92].

Another polymyxin derivative (SPR741) with limited intrinsic activity but improved safety is being studied for permeabilization of the outer membrane, thereby granting antibacterial agents access to their intracellular targets[93]. The most beneficial combinations of such a 'potentiator' strategy are not known yet and development is pending.

The aminoglycoside class has seen a recent addition, plazomicin, to reduce the impact of aminoglycoside-modifying enzymes. Although plazomicin has activity against many CRE isolates, organisms producing the NDM-1 MBL or OXA-48 enzymes are often resistant to plazomicin due to co-production of ribosomal methyl transferase[94, 95]. Another aminoglycoside has also entered first trials in humans. This aminoglycoside, apramycin, has been licensed since 1980 for oral use in veterinary medicine. It was active in 87% of carbapenem-resistant *Klebsiella* isolates from Greek hospitals, a similar susceptibility rate compared to plazomicin. Though apramycin is not affected by 16S rRNA methylases that cause resistance to plazomicin and all other aminoglycosides, it is ineffective against the acetyltransferase AAC(3)-IV producing strains[96, 97]. Resistance in human isolates was already described in 1993 (Ref [98]). Its usefulness against XDR Gram-negative strains will depend on the future epidemiology of aminoglycoside resistance, but rapid resistance development and spread can be anticipated if it is used clinically.

Derivatives of old classes with activity against Gram-positive bacteria are in clinical development. No information on their differentiation from drugs that are already available is published about the oxazolidinone contezolid with equal activity and non-inferiority compared with linezolid[99] and the ketolide nafithromycin that is comparable to telithromycin[100]. Two rifamycin conjugates, TNP-2092 (rifamycin-quinolizinone conjugate with rifampicin-like activity[101]) and TNP-2198 (rifamycin-nitroimidazole conjugate) are in clinical development. Insufficient information is published to assess their potential clinical usefulness.

[H1] Beyond old classes

[H2] New chemical scaffolds, new targets or binding sites, and a new mode of action.

Two new antibiotics that represent new chemical scaffolds with activity against Gram-positive bacteria are in clinical development. The target FabI, an enoyl-ACP reductase that is the rate-limiting enzyme in the last step for fatty acids biosynthesis, is known from existing FabI inhibitors (isoniazid, *Mycobacterium tuberculosis*) and triclosan (in some consumer products)[102]. Afabicin (Debio-1450) is a new intravenously and orally administered FabI inhibitor that exhibits selective antibacterial activity against staphylococcal species[103]. As expected, there is no cross-resistance with other antibacterial drugs used for staphylococcal infections[104]. Preliminary studies indicate that afabicin may not be prone to rapid emergence of resistance despite binding to a single target, possibly due to the high affinity binding of afabicin [102]. It is currently being developed for the treatment of bone and joint infections[105]. Other FabI inhibitors are in preclinical development (for example, MUT056399)[106].

The prodrug TXA709 is a benzamide compound and targets the bacterial protein FtsZ, which has an essential role in septum formation, and prevents bacterial cell division without an eukaryotic homolog[107]. Its activity is focused on *S. aureus* with no pre-existing cross-resistance to commonly used antibiotics due to its new chemical class, new target and new mode of action. As expected, this single target agent leads to a relatively high frequency of resistance that may be mitigated by using it in combination with other agents[108]. Though the immediate medical need for a new drug against multi-resistant *S. aureus* is low, a new-class antibacterial drug may be valuable in selected cases and on a broader basis in the future.

The topoisomerase inhibitors zoliflodacin (spiropyrimidinetrione) and gepotidacin (triazaacenaphthylene) are new chemical scaffolds and bind to gyrase, the same target as the fluoroquinolones but at distinct binding sites. They are developed for the treatment of uncomplicated urogenital gonorrhoea. Due to its different chemical structure and distinct binding site, zoliflodacin has so far not shown to be cross-resistant to fluoroquinolones[109]. For gepotidacin a Phase 2 study in uncomplicated urogenital gonorrhoea raised some questions regarding cross-resistance to ciprofloxacin and emergence of resistance. Three isolates with higher gepotidacin MICs were quinolone resistant and showed a mutation in the *parC* gene, which is known to affect gepotidacin binding. Two of these isolates developed high-level resistance to gepotidacin and were bacteriological failures in the clinical trial[110]. Due to overlapping binding sites, gepotidacin may show some cross-resistance to ciprofloxacin and emergence of resistance may soon arise once used in clinical practice. Gepotidacin is currently also developed for uncomplicated UTI. Its MICs against fluoroquinolone-susceptible *E. coli* are much higher than levofloxacin but cross-resistance to fluoroquinolones has not been described yet in *E. coli*[111, 112].

Although fluoroquinolones target both the DNA gyrase GyrA subunit and the topoisomerase IV ParC subunit, no inhibitor of GyrB and/or ParE is currently in clinical use[113]. The new GyrB inhibitor SPR-720 (aminobenzimidazole) inhibits the ATPase activity of gyrase in *M. tuberculosis* and non-tuberculous mycobacteria (NTM)[114]. It will be developed for these bacteria.

The development of intravenous murepavidin, a cyclic peptide that targets the lipopolysaccharide transport protein D (LptD) in *P. aeruginosa*, was terminated in July 2019 due to concerns about nephrotoxicity observed in Phase 3. The inhaled form of murepavidin is in preclinical development for *P. aeruginosa* infections in patients with cystic fibrosis. Therefore, it is not included in Table 2.

Lefamulin, a member of the pleuromutilin class has been approved by the FDA for the treatment of community-acquired bacterial pneumonia in 2019 (Ref [115]). Though pleuromutilins are an established class for systemic use in veterinary medicine and is used topically in humans (retapamulin has been approved in 2007), lefamulin represents a new scaffold for systemic use in humans. Whether the prior use and selection pressure of this class will accelerate the emergence of resistance against lefamulin remains to be seen. Caution should be exercised when prescribing this drug to patients with QT prolongation and ventricular arrhythmias. It has shown embryo-fetal toxicity in animals and should not be described to pregnant women and females of reproductive potential without effective contraception[115].

[H2] New antibacterial agents against *Clostridioides difficile*.

New antibacterial drugs against *C. difficile* infection are being developed with the goal to reduce recurrences. They are usually orally available and not absorbed, thus systemic pharmacokinetics and toxicity do not represent major challenges in the discovery process. This group of antibiotics has been included as they represent mainly new chemical classes with new targets and new mode of action. The most advanced compound is ridinilazole, a bis-benzimidazole that is suggested to inhibit cell division and is associated with reduction in spore and toxin production[116, 117]. Three new chemical structures with new targets and new mode of action are in early clinical development. MGB-BP-3 is a distamycin derivative and a binds to the DNA minor groove[118]. It acts on multiple binding sites and interferes with transcription. ACX-362E is a synthetic purine and targets DNA polymerase IIIC[119]. CRS-3123 is a diaryldiamine derivative that inhibits the Met-aminoacyl-tRNA synthetase[120]. Little information is available about the propensity for rapid emergence of single-step resistance due to mutations in the target of CRS-3123. The clinical value of these new drugs will depend on the proof that they can reliably reduce the rate of recurrence.

[H1] Conclusion

This narrative overview critically reviewed the antibacterial agents in clinical development and confirms the limited scope of these new antibacterial agents, especially against Gram-negative critical priority pathogens. In particular, all agents in development against the critical priority pathogens exhibit pre-existing cross-resistance.

The global clinical pipeline is dominated by derivatives of known chemical and functional classes. Though the experience with widely used antibacterial classes and the familiarity with class-specific safety profiles and pharmacokinetic and pharmacodynamic properties are good starting points for antibacterial research and development programmes, chemical modifications lead to improvements that are usually incremental and address only selected class-specific resistance mechanisms that are known at the time of lead optimisation, whereas others remain unaffected. Thus, a relatively high rate of pre-existing cross-resistance in XDR strains or substantially increased MICs compared to the wild-type strains may limit the benefit of such new therapies in many geographic regions and locations. They are unlikely to ease the global threat of XDR and PDR Gram-negative bacteria. Knowledge of the surveillance data on the distribution of molecular epidemiology and resistance mechanisms at the local level will be an absolute prerequisite for adequate therapy decisions. This fact and the focus on one or a few specific pathogens limit these antibacterial drugs for use in the

initial treatment phase of critically ill patients, before the pathogen and susceptibility profile is known.

Most new drugs in clinical development are not active against CRAB. The three compounds that are active (a BLI combination, a polymyxin derivative and a tetracycline derivative) are all affected by pre-existing cross-resistance or substantially increased MICs compared to wild-type strains that may reduce efficacy in critically ill patients due to pharmacokinetic and pharmacokinetic–pharmacodynamic variability [121]. In *Pseudomonas* spp., non-specific resistance mechanisms such as porin deficiency and overexpressed efflux pumps may lead to a high baseline resistance rate to new derivatives and reduce the usefulness both of new BLI combinations but also of other antibacterial classes.

In addition to pre-existing cross-resistance in all key bacterial pathogens, new resistance will emerge rapidly to newly introduced derivatives if used widely and replacing older empiric therapies without adequate stewardship. The emergence of new resistance determinants is also driven by all currently used antibiotics of the old class. Some of these examples are already described for ceftazidime–avibactam, other BLI combinations, new tetracyclines and plazomicin. Unpredictable components of the evolution of resistance to known antibacterial classes[122] may increase the risk of unacceptably high rates of resistance to a new derivative emerging during the development or soon thereafter. Though discovering and developing new chemical structures for new bacterial targets is extremely challenging, it is the most promising strategy to start with an effective antibacterial agent without pre-existing cross-resistance. Substantial efforts should be directed to this endeavour.

Antibacterial drugs currently in Phase 3 clinical development that target Gram-negative bacteria are usually evaluated for the treatment of complicated UTI, complicated intra-abdominal infections (cIAI) and sometimes hospital-acquired pneumonia and ventilator-associated pneumonia (HAP and VAP) caused by susceptible bacteria. They are compared to standard of care antibiotics in non-inferiority clinical design. Though complicated UTI and cIAI caused by susceptible bacteria are not a high unmet medical need, as several antibacterial alternatives exist, this development strategy is aligned with a streamlined regulatory pathway that ensures a more robust safety population. When a new antibacterial drug is approved, clinicians often have minimal information about the efficacy in patients infected with XDR or PDR bacteria where the medical need is highest, even when clinical trials are designed to include such patients. In addition to the streamlined pivotal studies to achieve approval, only company sponsored non-clinical information is available to provide some early indications of potential differentiations between similar drugs. After approval physicians are faced with the lack of independent critical analysis of data and evidence, lack of surveillance systems to detect rapidly new patterns of resistance, lack of updated therapeutic guidelines, and lack of rapid diagnostic capabilities in many institutions. Nevertheless, these new antibiotics may still be useful for individual patients or specific situations without the availability of needed evidence at the time of approval based on careful situation-specific evaluation of the new drug.

All new-class antibacterial agents focus on Gram-positive bacteria (especially *S. aureus* or *C. difficile*) or Gram-negative cocci (for example, *Neisseria gonorrhoeae*), thus highlighting the scientific barriers to antibiotic discovery in the field of Gram-negative rods. Overcoming barriers to drug penetration and efflux avoidance for Gram-negative bacteria is still a main hurdle that impedes innovation[122].

In conclusion, the need for research and development of new antibacterial drugs, especially against the WHO critical priority pathogens is still strong. Efforts should focus on innovation and antibacterial agents without pre-existing cross-resistance (new class or new target) to provide drugs for the most resistant pathogens and prepare for unpredictable resistance challenges in the future. The discovery of such new antibiotics requires sustained commitment over a long time period with substantial

levels of resources needed to solve the numerous challenges of new-class antibacterial agents and collective efforts to expand the science base.

Acknowledgements

The authors thank S. Paulin and P. Beyer (WHO) and the members of the advisory group of the WHO pipeline report M. Butler, L. Czaplewski, J. Hood, F. Franceschi, R. Kozlov, C. Lienhardt, N. Ohmagari, L. Silver, R. Alm for their support, advice and contributions.

Author contributions

U.T. wrote the article. U.T.; K.B., S.H., M.P., J.H.R., G.E.T. and E.T. reviewed and edited of manuscript before submission.

Competing interests

U.T., M.P., E.T., G.E.T. declare no financial relationships with any organisations that might have an interest in the submitted work. K. B. receives retirement compensation from Bristol-Myers Squibb, Johnson & Johnson and Pfizer, and is a shareholder for Entasis, Fedora and Johnson & Johnson. In the past year, she has served as a consultant or Scientific Advisory Board member for Allecra, Entasis, Fedora, Forma, Gladius, Mutabilis and VenatoRx. J.H.R. reports holding a position as Chief Medical Officer & Director at F2G, Non-Executive Director and Consultant at Adenium Biotech, Operating Partner and 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. S.H. 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, and personal fees from GSK, outside the submitted work.

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Table 1. Antibacterial agents that have been approved since 2017 by the FDA or EMA (modified according to the WHO clinical pipeline report[3]).

Name (trade name)	Approved by (date, indication)	Antibiotic class	Route of administration (market authorization holder)	Indication/s	Expected activity against				Characteristics			
					CRAB	CRPA	CRE	Other[a]	NCR	CC	T	MoA
Delafloxacin (USA: Baxdela, EU: Quofenix)	FDA (6/2017 ABSSSI, 10/2019 CAP) MAA	Fluoroquinolone	Intravenous and oral (Melinta, Menarini)	ABSSSI, CAP	○	○	○	●	-	-	-	-
Vaborbactam and meropenem (Vabomere)	FDA (8/2017) EMA (11/2018)	Boronate BLI and carbapenem	Intravenous (Melinta, Menarini)	cUTI	○	○	●[b]	/	?	✓	-	-
Plazomicin (Zemdri)	FDA (7/2018)	Aminoglycoside	Intravenous (Pliva)	cUTI	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	FDA (8/2018) EMA (9/2018)	Tetracycline	Intravenous (Tetraphase)	cIAI	?	○	●	/	-	-	-	-
Omadacycline (Nuzyra)	FDA (10/2018)	Tetracycline	Intravenous and oral (Paratek)	CAP (intravenous), ABSSSI (intravenous ,	○	○	○	●	-	-	-	-

				oral)								
Relebactam and imipenem and cilastatin (Recarbrio)	FDA (7/2019) MAA	DBO-BLI and carbapenem and degradation inhibitor	Intravenous (Merck Sharp and Dohme)	cUTI, cIAI	○	?	●[b]	/	-	-	-	-
Lefamulin (Xenleta)	FDA (8/2019) MAA	Pleuromutilin	Intravenous and oral (Nabriva)	CAP	/	/	/	●	?	✓[c]	-	-
Cefiderocol (Fetroja)	FDA (11/2019) MAA	Siderophore cephalosporin	Intravenous (Shionogi)	cUTI	●	●	●	/	?	-	-	-

ABSSI, acute bacterial skin and skin structure infections; BLI, β-lactamase inhibitor; CAP, community acquired pneumonia; CC, new chemical class; cIAI, complicated intraabdominal infections; CRAB, carbapenem-resistant *A. baumannii*; CRE, third-generation cephalosporin-resistant and carbapenem-resistant *Enterobacterales*; CRPA, carbapenem-resistant *P. aeruginosa*; cUTI, complicated urinary tract infection; DBO, diazabicyclooctane; EMA, European Medicines Agency; MAA, Marketing Authorization Application (EMA); MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; PBP, penicillin-binding protein; T, new target.

[a]Other pathogens, mostly Gram-positive and/or N. gonorrhoeae.

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

[c]First systemic formulation of this class in humans, still used in animals and topically in humans.

● active; ? possibly active; ○ not or insufficiently active; / activity not assessed; ✓ criterion fulfilled; ? Inconclusive data or no agreement among experts; - criterion not fulfilled.

Table 2. Antibacterial agents in clinical development (modified according to the WHO clinical pipeline report[3])

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against				Characteristics			
				CRAB	CRPA	CRE	Other[a]	NCR	CC	T	MoA
Sulopenem (intravenous), Sulopenem etzadroxil and Probenecid (oral)	3	Penem	Intravenous and oral (Iterum)	○	○	○[b]	/	-	-	-	-
Durlobactam (ETX2514) and sulbactam	3	DBO-BLI (PBP2 inhibitor) and β-lactam-BLI (PBP1 and PBP3 inhibitor)	Intravenous (Entasis)	●	/	/	/	-	-	-	-
Taniborbactam (VNRX-5133) and Cefepime	3	Boronate-BLI and cephalosporin	Intravenous (VenatoRx)	○	?	●	/	?	✓[c]	-	-
Enmetazobactam (AAI101) and Cefepime	3	β-lactam BLI and cephalo-sporin	Intravenous (Allecra)	○	○	○[d]	/	-	-	-	-
Zoliflodacin	3	Topoisomerase inhibitor (Spiropyrimidenetrione)	Oral (Entasis/GARDP)	/	/	/	●	✓	✓	-	✓
Gepotidacin	3	Topoisomerase inhibitor (Triazaacenaphthylene)	Intravenous and oral (GSK)	/	/	/	●	?	✓	-	✓
Contezolid Contezolid acefosamil	2/3[f]	Oxazolidinone	Oral (MicuRx) and intravenous Oral (MicuRx)	/	/	/	●	-	-	-	-
Afabicin (Debio-1450)	2	FabI inhibitor	Intravenous and oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
BOS-228 (LYS228)	2	Monobactam	Intravenous (Boston Pharmaceuticals)	○	○	●	/	-	-	-	-
Nafithromycin (WCK-4873)	2	Macrolide	Oral (Wockhardt)	/	/	/	●	-	-	-	-
TNP-2092	2	Rifamycin–quinolizinone conjugate	Intravenous and oral (TenNor)	/	/	/	?	-	-	-	-
Zidebactam and Cefepime	1	DBO-BLI (PBP2 inhibitor) and cephalosporin	Intravenous (Wockhardt)	○	?	●	/	-	-	-	-
Nacubactam and Meropenem	1	DBO-BLI (PBP2 inhibitor) and carbapenem	Intravenous (NacuGen Therapeutics)	○	○	●[e]	/	-	-	-	-
ETX0282 and Cefpodoxime	1	DBO-BLI (PBP2 inhibitor) and cephalosporin	Oral (Entasis)	○	○	●[e]	/	-	-	-	-
VNRX-7145 and Ceftibuten	1	Boronate-BLI and	Oral (VenatoRx)	○	○	●[e]	/	?	✓[c]	-	-

		cephalosporin									
SPR741 and β-lactam	1	Polymyxin (potentiator) and β-lactam	Intravenous (Spero)	?	?	?	/	-	-	-	-
SPR206	1	Polymyxin	Intravenous (Spero)	●	●	●	/	-	-	-	-
SPR720	1	GyrB inhibitor	Oral (Spero)	/	/	/	●[g]	?	✓	?	?
KBP-7072	1	Tetracycline	Oral (KBP BioSciences)	○	○	○	●	-	-	-	-
TP-271	1	Tetracycline	Intravenous and oral (Tetraphase)	?	○	○	●	-	-	-	-
TP-6076	1	Tetracycline	Intravenous (Tetraphase)	●	○	?	/	-	-	-	-
EBL-1003 (Apramycin)	1[h]	Aminoglycoside	Intravenous (Juvabis)	?	-	?	/	-	-	-	-
TNP-2198	1	Rifamycin-nitroimidazole conjugate	Oral (TenNor)	/	/	/	●	-	-	-	-
TXA709	1	FtsZ inhibitor	Oral and intravenous (Taxis)	○	○	○	●	✓	✓	✓	✓
ARX-1796 (oral Avibactam prodrug)	1	DBO-BLI and β-lactam	Oral (Arixa Pharmaceuticals)	○	○	●[e]	/	-	-	-	-

other pathogens, mostly Gram-positive and/or *N. gonorrhoeae*

BLI, β-lactamase inhibitor; CC, new chemical class; CRAB, carbapenem-resistant *A. baumannii*; CRE, third-generation cephalosporin-resistant and carbapenem-resistant *Enterobacterales*; CRPA, carbapenem-resistant *P. aeruginosa*; DBO, diazabicyclooctane; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; other, other pathogens, mostly Gram-positive and/or *N. gonorrhoeae*; PBP, penicillin-binding protein; T, new target.

[a] Other pathogens, mostly Gram-positive and/or *N. gonorrhoeae*

[b] Active against extended-spectrum β-lactamase (ESBL)-producing cephalosporin-resistant but not carpabepenem-resistant *Enterobacterales*.

[c] The first boronate-BLI is vaborbactam and has been approved 2017 in combination with meropenem

[d] Active against extended-spectrum β-lactamase-producing cephalosporin-resistant and some *K. pneumoniae* carbapenemase (KPC) producing carbapenem-resistant *Enterobacteriales*.

[e] Active against KPC but not metallo-β-lactamase-producing *Enterobacterales*.

[f] Contezolid acefosamil: Phase 2 in USA. Contezolid: Phase 3 in China, NDA in China expected in 2020.

[g] Developed against non-tuberculous mycobacteria and M. tuberculosis

[h] Currently used in animals.

● active; ? possibly active; ○ not or insufficiently active; / activity not assessed; ✓ criterion fulfilled; ? Inconclusive data or no agreement among experts; - criterion not fulfilled.

Table 3. Activity of β-lactamase inhibitors in combination[a] (modified according to the WHO clinical pipeline report[3]).

β-lactamase inhibitor (synonym, chemical class)	Combination partner	Development phase	ESBL-E	CRE				CRAB	CRPA
			Class A (ESBL)	Class A (KPC)	Class D (OXA-48)	Class B (NDM)	PBP2		
Durlobactam (ETX2514; (DBO)	Sulbactam	3	/	/	/	/	●	●	/
Enmetazobactam (AAI101; penicillanic acid sulfone)	Cefepime	3	●	?	○	○	-	○	○
Taniborbactam (VNRX-5133; boronate)	Cefepime	3	●	●	●	●	-	○	?
Avibactam (DBO)	Aztreonam	3	●	●	●	●	○	○	○
Zidebactam (DBO)	Cefepime	1	●	●	●	?	●	○	?
Nacubactam (DBO)	Meropenem	1	●	●	●	?	●	○	○
ETX0282 (DBO)	Cefpodoxime (oral application)	1	●	●	●	○	●	○	○
VNRX-7145 (boronate)	Ceftibuten (oral application)	1	●	●	●	○	-	○	○
ARX-1796 (DBO; oral avibactam prodrug)	To be determined (oral application)	1	?	?	?	○	○	○	○

CRAB, carbapenem-resistant *A. baumannii*; CRPA, carbapenem-resistant *P. aeruginosa*; CRE, carbapenem-resistant *Enterobacterales*; DBO, diazabicyclooctanes; ESBL-E, extended-spectrum β-lactamase producing third-generation cephalosporin-resistant *Enterobacterales*; PBP2, penicillin-binding protein 2.

a Against representative β-lactamases in *Enterobacterales*, binding to PBP2 in *Enterobacterales*, and antibacterial activity of the BLI combination against critical priority pathogens.

● active; ? possibly active; ○ not or insufficiently active; / activity not assessed.; - no inhibitory activity

Figure 1. **Relevance of resistance determinants.**

The resistance determinants in carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and carbapenem-resistant *Enterobacterales* (CRE) are diverse and mostly associated with non-specific or acquired resistance to other unrelated antibiotic classes. Carbapenem-resistance is frequently caused by the interplay between common (blue) and less common and variable resistance determinants (green). Chromosomally encoded resistance determinants are depicted inside the cell shape while acquired ones are shown outside the shape. In CRAB, the common resistance determinants are intrinsic chromosomally encoded β-lactamases and acquired enzymes that are usually not inhibited by ß-lactamase inhibitors (BLIs). CRPA strains are characterised by chromosomally encoded resistance determinants (OprD deficiency, overexpression of efflux pumps and AmpC). Mutations in penicillin-binding protein 3 (PBP3) are still rare and effect the combination partner of BLIs. In extensively drug resistant and pan drug resistant strains additional horizontally transferred resistance may accumulate. CRE are dominated by β-lactamases of all classes with high geographical variation. Porin deficiency may be combined with β-lactamases. In some areas carbapenem-resistance is associated with resistance to last-resort antibiotic options. MBL, metallo-ß-lactamases; ESBL, extended-spectrum β-lactamase.

Figure 2. **Number of antibiotics in clinical development or approved since 2017 with activity against the critical priority pathogens CRAB, CRPA, CRE.**

Most recently approved or currently developed new antibiotics focus on carbapenem-resistant *Enterobacteriales* (CRE) but cover them incompletely and dependent on the geographic distribution of resistance determinants. They cover either bacteria that produce only extended-spectrum β-lactamases (ESBL) or have added activity against KPC and OXA-48 enzymes or additional activity against some metallo-β-lactamases (MBL). Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has multiple intrinsic and acquired resistance mechanisms which cause a high rate of extensively drug resistance and pan drug resistance. The efficacy of the few new antibiotics with activity against *Acinetobacter* spp. is limited owing to pre-existing reduced susceptibility or non-susceptibility in the most resistant strains. The rate of pre-existing cross resistance in carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is high and no substantial solution is provided by new antibiotics.

Text Box 1: Antibacterial drugs in clinical development in 2019 and future perspectives.

- The clinical pipeline dominated by derivatives of most major known chemical and functional classes, especially β-lactams, ß-lactamase inhibitors (BLIs), but also tetracyclines.
- All antibiotic candidates currently under development to treat infections caused by the WHO critical priority bacteria have at least some cross-resistance with existing agents.
- Selected class-specific resistance mechanisms are addressed, others remain unaffected.
- Relatively high rate of cross-resistance in extensively drug resistant (XDR) strains and specifically in pan drug resistant (PDR).
- Pipeline focused on carbapenem-resistant *Enterobacterales* (CRE) has incomplete β-lactamase coverage, especially for β-lactamases prevalent in Asia, Africa, but also in some European countries.
- Susceptibility rates depend on the epidemiology of resistance mechanisms in different regions and locations.
- Best use of new drugs is achieved if regional molecular resistance epidemiology is known and if agents are selected according to susceptibility tests.
- Few innovative new antibiotics against *Staphylococcus aureus* as well as *Neisseria gonorrhoeae* and *Clostridioides difficile*.
- Continued high need for innovation, especially new-class antibiotics without pre-existing cross-resistance.

Related links

WHO clinical pipeline report:
https://apps.who.int/iris/bitstream/handle/10665/330420/9789240000193-eng.pdf

EUCAST breakpoints: https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria

FDA breakpoints: https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria

Table of content:

New antibacterial agents to address the global increase in resistance are urgently needed. In this Review, Theuretzbacher and colleagues critically review the current published literature and publicly available information on the antibacterial agents in all phases of clinical development.

Glossary:

β-lactamases.

Heterogenous group of enzymes produced by bacteria, which hydrolyse β-lactam antibiotics.

Porin.

Proteins that form nonspecific channels allowing the transport of molecules across the outer membranes of Gram-negative bacteria.

Penicillin-binding protein.

Bacterial enzymes involved in bacterial cell wall biosynthesis and the target of penicillin and all the other antibiotics of the β-lactam class.

Minimal inhibitory concentrations (MICs).

Lowest concentration of an antibacterial compound, which prevents visible growth of bacteria.

Non-fermenters.

Heterogenous group of bacteria which cannot use glucose and thus, are unable generate energy through fermentation of glucose. Important bacteria of this group are *Pseudomonas* and *Acinetobacter*.

Clinical breakpoint.

Chosen concentration of an antibiotic which defines whether a species of bacteria is susceptible or resistant to the antibiotic and is used to predict the clinical outcome.

Siderophore.

Small, high-affinity iron-chelating compounds that are secreted by microorganisms and serve primarily to transport iron across cell membranes.

FtsZ.

FtsZ is a protein encoded by the *ftsZ* gene that is essential for producing a new cell wall between the dividing bacterial cells.

DNA gyrase.

Enzyme within the class of topoisomerases that has multiple roles in DNA replication, recombination, and transcription.

Topoisomerase.

Enzymes that participate in the overwinding or underwinding of DNA.