



Antibiotics in the pipeline: a literature review (2017–2020)

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Abstract

Introduction Antimicrobial resistance (AMR) is an emerging global threat. It increases mortality and morbidity and strains healthcare systems. Health care professionals can counter the rising AMR by promoting antibiotic stewardship and facilitating new drug development. Even with the economic and scientific challenges, it is reassuring that new agents continue to be developed.

Methods This review addresses new antibiotics in the pipeline. We conducted a review of the literature including Medline, Clinicaltrials.org, and relevant pharmaceutical companies for approved and in pipeline antibiotics in phase 3 or new drug application (NDA).

Results We found a number of new antibiotics and reviewed their current development status, mode of action, spectra of activity, and indications for which they have been approved. The included studies from phase 3 clinical trials were mainly utilized for the treatment of acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, and pneumonia acquired in the healthcare settings. The number of these agents is limited against high priority organisms. The identified antibiotics were based mainly on previously known molecules or pre-existing antimicrobial agents.

Conclusion There are a limited number of antibiotics against high priority organisms such as multi-drug-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant Enterobacteriaceae. New antimicrobial agents directed against the top priority organisms as classified by the World Health Organization are urgently needed.

Keywords Antibiotics · Pipeline · Novel antibiotics · New antibiotics

Introduction

Antibiotics have provided protection against life-threatening bacterial infections for more than a century. However, indiscriminate use of antibiotics and organism evolution have led to the emergence of multi-drug-resistant organisms (MDRO), and at times resistant to most or even all currently available antibiotic classes, extensively drug-resistant or pan-resistant organisms (XDRO, PDRO). Antibiotic resistance is a serious emerging global health threat [1] and certain geographic areas might be affected more than others due to the pattern of antibiotic usage [2]. Thus, there is a great demand to search for novel antibiotics that are effective and safe. Antibiotic development has had several scientific

and economic challenges over the years. A major hindrance for industrial support for new antimicrobial development is the low return of investment [3]. That said, antibiotics are indispensable for global health. This paper reviews the antibacterial agents launched worldwide since 2017 and details their development status, mode of action, spectra of activity and the indications for which these antibiotics have been approved.

Methodology

Search strategy

Two investigators initially reviewed the listed databases and then additional two investigators did a follow-up search to identify new antibiotics in development by searching the FDA, WHO, European medicine agency, and Central Drugs

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Standard Control Organization (India) platforms. Using the 25 new antibiotics identified between January 1st, 2017 and January 31, 2021, we formulated keywords and a search strategy for further databases. Two investigators independently searched electronic databases MEDLINE, NIH U. S. National Library of Medicine (clinicaltrial.gov), and Science Direct for articles as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the period January 2017 to November 30th, 2020. When necessary, websites of pharmaceutical companies responsible for the development of the drug were accessed for further relevant information. Only English language articles were selected.

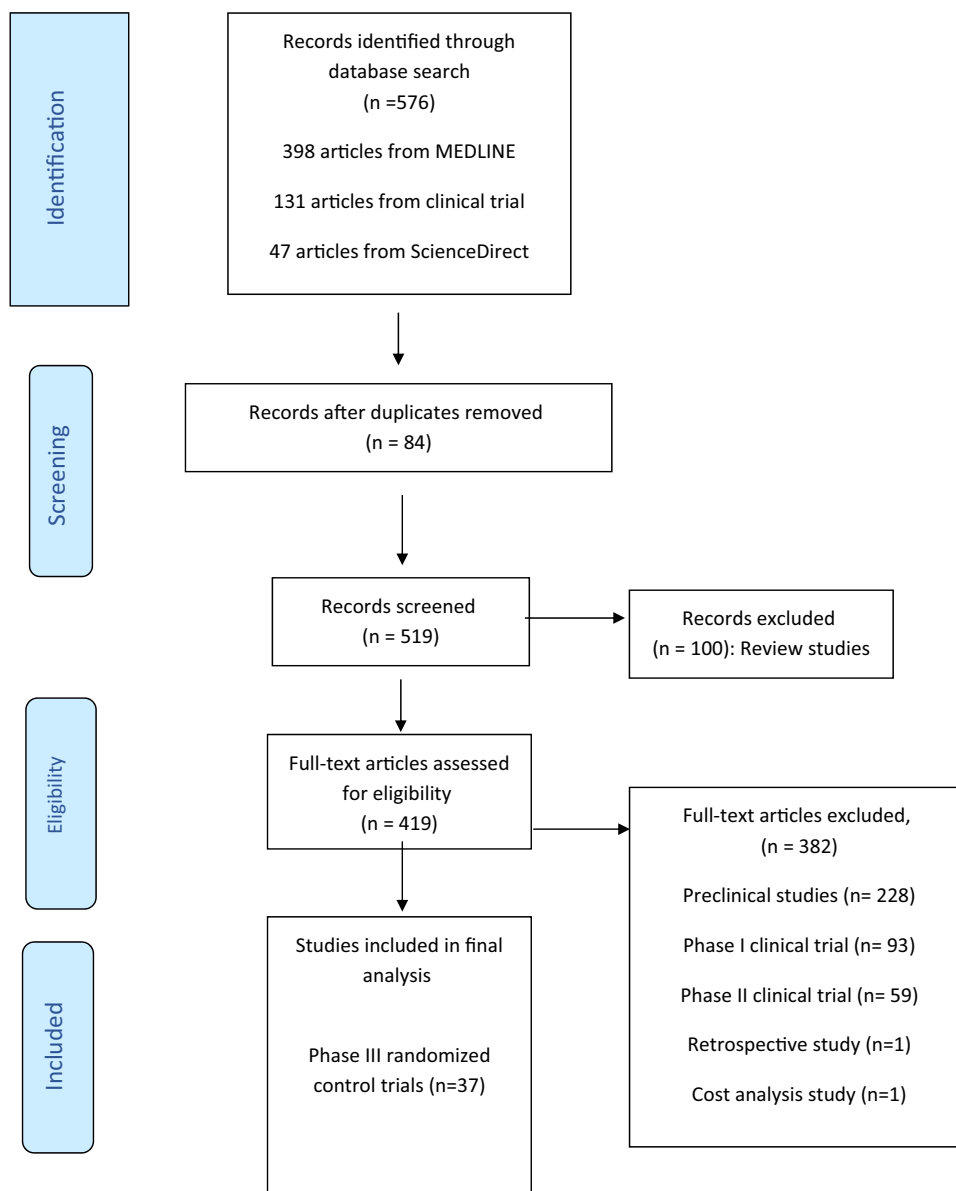
We used the following search terms (Fig. 1): Delafloxacin, Ridinilazole, Afabycin, Gepotidacin,

Meropenem–Vaborbactam, Imipenem–Relebactam, Cefepime “AAI101”, Sulbactam–Diazabicyclooctane, Plazomicin, Cefiderocol, Cefilavacin, Nafithromycin, Eravacycline, Lefamulin, Sulopenem Zoliflodacin, Omadacycline, Iclaprim, Solithromycin, Levonadifloxacin, Contezolid, Pretomanid, Taniborbactam, DprE1 inhibitor, Lascufloxacin and the umbrella term “novel antibiotics”.

Selection criteria

Four investigators independently extracted the data from the full text of the selected literature. We selected antibiotics currently in phase III new drug application (NDA), or were FDA approved. We also included drug trials and NDA in China, India, and Japan. We excluded phase I and phase II

Fig. 1 A flow diagram of the search strategy according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines



clinical trials, observational studies, case reports, cost analysis studies, and animal models. In the data extraction form, we included method-of-action, spectrum of activity, data from clinical trials, and the included antibiotics' adverse event profiles. Two reviewers assessed the quality of the included literature independently. The information extracted was compared to information provided on the drug manufacturer's website to confirm its development phase. We relied on data published in databases to confirm the spectrum of activity and adverse events.

Results

Of the 576 articles identified from database searching, 37 phase III clinical trials were included. Table 1 shows a summary of the reviewed antibiotics in the pipeline and their spectrum of activities.

Delafloxacin

Delafloxacin is a novel anionic fluoroquinolone antibiotic approved by the FDA on June 19th, 2017 [4]. It has the European Medicines Agency's (EMA) approval for the treatment of acute bacterial skin and skin structure infections (ABSSSI) [5]. Delafloxacin inhibits DNA replication, transcription, repair, and recombination by inhibiting the two primary enzymes: DNA gyrase (topoisomerase II) and topoisomerase IV enzymes [6]. Delafloxacin, as other fluoroquinolones, has a high pulmonary concentration of 13:1 compared to plasma and is primarily (65%) excreted as unchanged in the urine. Delafloxacin does not seem to prolong the QTc interval on ECG or cause phototoxicity [6]. Similar to other fluoroquinolones, delafloxacin has concentration-dependent antimicrobial activity. It has a low minimum inhibitory concentration (MIC) against *Streptococcus pneumoniae* and *Staphylococcus aureus* (including MRSA). Some levofloxacin-resistant *S. pneumoniae* strains are susceptible to delafloxacin. Delafloxacin is also active against *Pseudomonas aeruginosa*, anaerobes, and atypical organisms [6].

Delafloxacin was shown to be non-inferior to vancomycin plus aztreonam in the treatment of ABSSSI [7, 8]. In the PROCEED study, 660 adult patients received either delafloxacin 300 mg IV every 12 h or vancomycin IV 15 mg/kg every 12 h plus aztreonam IV 2 g every 12 h [7]. In an intent-to-treat (ITT) analysis, the response was similar in both arms (78.2% in delafloxacin versus 80.9% in vancomycin + aztreonam arm). Adverse event incidence was higher in the vancomycin plus aztreonam arm (4.5% versus 0.9%) [7]. In the second trial, delafloxacin was compared with vancomycin plus aztreonam in 850 adults [8]. In ITT analysis, response was similar in both arms (83.7% in delafloxacin

arm versus 80.6% in vancomycin + aztreonam arm) [8]. Vancomycin plus aztreonam had a higher adverse events than delafloxacin (1.2% versus 2.4%) [8]. The efficacy and safety of delafloxacin in community-acquired bacterial pneumonia (CABP) was compared with moxifloxacin in a phase III, multi-center, randomized trial (DEFINE-CABP) [9]. The study showed similar early clinical response of about 89% in each arm [9].

Meropenem/vaborbactam

Meropenem/vaborbactam is a fixed combination of meropenem and vaborbactam and was approved by FDA on August 29th, 2017 for treatment of complicated urinary tract infection (cUTI) including pyelonephritis [4] and by EMA on September 20th, 2018 for treatment of cUTI including pyelonephritis, complicated intra-abdominal infection (cIAI), and hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP) [10]. Vaborbactam does not have any anti-bacterial activity and its main function is to protect meropenem from degradation by β -lactamases especially *Klebsiella pneumoniae* carbapenemase (KPC). However, vaborbactam has no activity against OXA-48 and Metallo- β -lactamases (MBL) carbapenemases or carbapenem-resistant *P. aeruginosa* [10].

The TANGO I is a phase III randomized clinical trial and it compared meropenem–vaborbactam and piperacillin–tazobactam for 10 days in 550 adult patients with cUTI [11]. The overall success rate was higher in the meropenem/vaborbactam arm (98.4% versus 94%) in a non-inferiority trial. Microbial eradication in the modified ITT analysis occurred in 66.7% of the meropenem–vaborbactam arm compared with 57.7% in the piperacillin–tazobactam group [11]. Subsequently, in the TANGO II phase 3 randomized clinical trial, the study evaluated the efficacy and safety of meropenem–vaborbactam in 77 adults with carbapenem-resistant Enterobacteriaceae (CRE) confirmed or suspected infections versus best available therapy (BAT) [12]. In microbiologic CRE-modified ITT, meropenem–vaborbactam achieved a higher clinical cure with no difference in microbiologic cure at the end of therapy [12]. There was no significant difference in the mortality at day 28 (15.6% versus 33.3% $P=0.20$). Meropenem–vaborbactam had fewer adverse events (84% versus 92%) and fewer renal adverse event (4% versus 24%) [12]. The efficacy and safety evaluations of meropenem–vaborbactam in adults with HABP or VABP are expected to be completed in December 2020 in a phase IIIb TANGO III randomized clinical trial [13].

Imipenem–cilastatin + relebactam

Imipenem–cilastatin + relebactam is a fixed combination of imipenem, cilastatin, an imipenem renal metabolism

Table 1 Summary of antibiotics in the pipeline and their spectrum of activities

Name	FDA approved	EMA Approved	Antibiotic class	Indication/usage	CRAB	CRPA	CRE	KPC	MRSA	VRE	ESBL
2017											
1. Delafloxacin	✓	✓	Fluoroquinolone	ABSSSI	X	X	X	X	✓	X	X
2. Meropenem/vaborbactam	✓	✓	Carbapenem/ β -lactamases inhibitor	cUTI; cIAI	X	X	X	✓	X	X	X
2018											
1. Plazomicin	✓	✓	Aminoglycoside	cUTI	X	X	✓	X	✓	X	✓
2. Eravacycline	✓	✓	Tetracycline	cIAI	✓	X	X	X	✓	✓	✓
3. Omadacycline	✓	X	Tetracycline	CAP; ABSSSI		X	X	X	✓	✓	✓
2019											
1. Lefamulin ^a	X	X	Pleuromutilin	CABP	X	X	X	X	✓	✓	X
2. Cefiderocol	✓	✓	Cephalosporin	cUTI, HAP/VAP, blood-stream infection, and sepsis	✓	✓	✓	✓	X	X	✓
3. Pretomanid	✓	✓	Nitroimidazooxazine	XDR-TB; MDR-TB							
2020											
1. Levonadifloxacin(EMROK)/alalevonadifloxacin; (approved by DCGI for use in India)	X	X	Fluoroquinolone	ABSSSI				✓			
2. Iclaprim ^a	X	Withdrawn	DHFR inhibitors	ABSSSI	X	X	X	X	✓	X	X
3. Impipenem/cilastatin + relebactam	✓	✓	Carbapenem/ β -lactamases inhibitor	cUTI, AP, cIAI, HAP, VAP	X	✓ Except MBL Producer	✓	✓	X		
Phase III trial											
1. Solithromycin	(Phase III)		4th Generation macrolide	CAP	X	X	X	X	X	X	X
2. Sulopenem	(Phase III)		Thiopenem b-lactam	UTI; cIAI	X	X	X	X	X	X	✓
3. Ceflavlacin	(Phase III)		Glycopeptide- β -lactam (Cephalosporin) hybrid	ABSSSI	X	X	X	X	✓	✓	X
4. Cefepime + AAI101	(Phase III)		4th generation cephalosporin/ β -lactamases inhibitor	cUTI	X	X	✓	X	X	X	✓
5. Ridinilazole	(Phase III)		Inhibition of cell division, inhibition of toxin production	CDI	X	X	X	X	X	X	X
6. Cepotidacin	(Phase III)		Triazaacenaphthylene	ABSSSI; Uncomplicated urogenital gonorrhoea	X	X	X	X	✓	X	X
7. Sulbactam/diazabicyclotane	(Phase III)		β -Lactam/ β -lactamases inhibitor	cUTI	✓	X	✓	X	X	X	✓
8. Zoliflodacin	(Phase III)		Spiropyrimidinetrione	Uncomplicated gonorrhoea	X	X	X	X	X	X	X

Table 1 (continued)

Name	FDA approved	EMA Approved	Antibiotic class	Indication/usage	CRAB	CRPA	CRE	KPC	MRSA	VRE	ESBL
9. Taniborbactam	(Phase III)		β -Lactam/ β -lactamases inhibitor	cUTI	X		✓				
11. Contezolid	(Phase III in china whereas phase II in USA)		Oxazolidinone	ABSSSI							✓

CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRE, carbapenem-resistant Enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococcus; ESBL, extended-spectrum beta-lactamases; ABSSSI, acute bacterial skin and skin structure infections; cUTI, complicated urinary-tract infections; cIAI, complicated intra-abdominal infections; CAP, community-acquired pneumonia; CABP, community-acquired bacterial pneumonia; HAP/VAP, hospital-acquired pneumonia (nosocomial pneumonia) and ventilator-associated pneumonia; XDR-TB, extensively drug-resistant tuberculosis; MDR-TB, multi-drug-resistant tuberculosis; CDI, *Clostridium difficile* infection

^aNew drug application (NDA)

inhibitor, and relebactam, a β -lactamase inhibitor. Relebactam is active against Class A (including ESBL and KPC) and Class C (AmpC) β -lactamases, has activity against ESBL-producing Enterobacteriaceae, KPC, CRE, and possibly carbapenem-resistant *P. aeruginosa*. It has no activity against MBL and OXA-48 producers, *Acinetobacter baumannii*, or *Stenotrophomonas maltophilia* [14].

RESTORE-IMI 1 was a phase III randomized trial in 47 adults with HAP/VAP, cIAI, and cUTI caused by Gram-negative imipenem-resistant organisms [15–17]. The treated patients received either imipenem + cilastatin + relebactam or colistin base activity (CBA) plus imipenem + cilastatin. In supplemental microbiological modified ITT, the overall response was 75% in imipenem/relebactam group compared with 76.9% in colistin/imipenem group (difference – 4.5; 95% CI – 24.2 to 20.7). All-cause 28-day mortality in imipenem/relebactam compared with colistin/imipenem was 10.7% versus 23.1%, respectively [15].

RESTORE-IMI 2 trial was completed on April 3rd, 2019 and was a phase III clinical trial comparing imipenem + cilastatin + relebactam with piperacillin + tazobactam in 536 adults with HAP/VAP and all patients also received linezolid. Imipenem/cilastatin/relebactam was non-inferior ($P < 0.001$) to piperacillin/tazobactam when comparing 28-day all-cause mortality (15.9% vs. 21.3%) and showed a favorable clinical response (61.0% and 55.8%) at early follow-up [18].

Plazomicin

Plazomicin is a novel aminoglycoside antibiotic approved by the FDA on June 25th, 2018 and by the EMA on March 19th, 2018 to treat cUTI. Plazomicin binds to the 30S ribosomal subunit and inhibits protein synthesis in a concentration-dependent manner. It has activity against ESBL-producing Enterobacteriaceae, CRE, MRSA, and organisms producing aminoglycoside-modified enzymes. Like other aminoglycosides, plazomicin is associated with nephrotoxicity, ototoxicity and fetal harm in pregnant women [19].

A phase III randomized trial compared plazomicin with meropenem in 609 adults with cUTI or acute pyelonephritis followed by optional oral therapy. The microbiologic eradication rate at test-of-cure (TOC) visit was higher in plazomicin group vs. meropenem group (81.7% vs 70.1%; 95% CI 2.7–20.3) [20]. In Phase III open-label, non-inferiority (CARE) trial, 39 adults with bloodstream infection, HAPB, or VABP due to CRE were treated with plazomicin and all-cause mortality at day 28 or significant complications was 23.5% in the plazomicin arm compared with 50% of the patients in colistin arm [21].

Eravacycline

Eravacycline is a novel fluorocycline of the tetracyclines group and as such inhibits bacterial protein synthesis by binding to 30S ribosomal subunit. Eravacycline overcomes tetracycline-efflux and ribosomal protection mechanism. Eravacycline has activity against MRSA, VRE, ESBL Enterobacteriaceae, *A. baumannii*, and CRE, but has no activity against *P. aeruginosa* and *Burkholderia cenocepacia* [22, 23]. In a phase III, randomized, double-blind (IGNITE 1) clinical trial, an MITT showed a clinical cure of 87% in the eravacycline arm compared to 88.8% in the ertapenem arm [23]. Microbiological cure was 91.4% in the eravacycline group versus 95% in ertapenem group [23]. In the IGNITE4, a second phase III clinical trial, the clinical cure was 90.8% compared to 91.2% in the eravacycline and meropenem groups, respectively [24].

Omadacycline

Omadacycline is a tetracycline antibiotic and was approved in 2018 for treatment of CABP and ABSSSI. It overcomes the resistance by tetracycline-efflux and ribosomal protection mechanisms and has activity against *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* [25–27]. Thus, it can be used as a single agent to treat CABP as an alternative to the empirical combination of beta-lactam and macrolide.

The efficacy and safety of omadacycline were tested on a phase III randomized control trial (OPTIC) comparing omadacycline in 388 patients with moxifloxacin in 386 patients with CABP followed by oral omadacycline or Moxifloxacin [28]. The early clinical response was 81.1% in omadacycline group compared with 82.7% in the comparator group [28]. In the post-treatment evaluation, clinical response rate was 87.6% in omadacycline compared with 85.1% in moxifloxacin arm [28]. The rate of adverse events leading to treatment discontinuation was 5.5% in omadacycline compared with 7% in moxifloxacin [28].

Omadacycline had been tested in 316 patients and linezolid in 311 patients with ABSSSI in phase 3 randomized controlled (OASIS-1) trial of either omadacycline or linezolid followed by oral omadacycline or linezolid [29]. In the MITT, the early response rate was 84.8% vs. 85.5%, respectively, compared with linezolid. [29]. The clinical response of omadacycline was 83% for MRSA compared with 86% in the linezolid arm. Treatment-related adverse events were 18% in omadacycline arm versus 18.3% with linezolid [29].

Lefamulin

Lefamulin is a novel pleuromutilin antibiotic and was approved in August 2019 by U.S. FDA for use in CABP.

Lefamulin inhibits protein synthesis by inhibition of 50S bacterial ribosome. It has activity against *S. pneumoniae*, MRSA, VRE, MDR *Neisseria gonorrhoeae*, *Chlamydomydia pneumoniae*, *L. pneumophila*, *M. pneumoniae*, and *Haemophilus influenzae*. Lefamulin has a time-dependent killing with higher concentrations in epithelial lining fluid than in plasma [30]. Lefamulin was non-inferior to moxifloxacin in 551 adults with CABP in a phase III (LEAP-1) clinical trial [31]. Early clinical response was 87.3% versus 90.2% [31]. The rate of drug discontinuation was 2.9% in the lefamulin arm and 4.4% in the moxifloxacin arm [31]. In the second phase III clinical trial (LEAP-2), oral lefamulin was compared to moxifloxacin in 738 patients with CABP [32]. Lefamulin was non-inferior to moxifloxacin for CABP (90.8% versus 90.8%), clinical response (87.5% versus 89.1%), and clinically evaluable population (89.7% versus 93.6%) [32].

Cefiderocol

Cefiderocol is the first in a class of siderophore cephalosporins with activity against carbapenemase-producing Gram-negative bacteria (CRE, CRPA, and CRAB), MDR *S. maltophilia*, and *Burkholderia cepacia*, and ESBL- and MBL-producing organisms. Potential indications include cUTI, HAP/VAP, bloodstream infection, and sepsis caused by MDR Gram-negative isolate [33, 34]. A phase III trial compared cefiderocol in APEKS-NP trial with meropenem in 300 adults with health-care-associated pneumonia (HCAP), HABP, or VABP with all-cause mortality at day 14 of 12.4% vs. 11.6%, respectively [35]. The second Phase III clinical trial (CREDIBLE-CR) will compare cefiderocol with best available therapy in 150 adults with HAP, VAP, HCAP, cUTI, or BSI/Sepsis caused by carbapenem-resistant Gram-negative pathogens [36].

Levonadifloxacin/alalevonadifloxacin

Levonadifloxacin and its prodrug, alalevonadifloxacin, are broad-spectrum benzoquinolizone sub-class of quinolones and are active against multi-drug-resistant Gram-positive pathogens including MRSA, hVISA, VRSA, and quinolone-resistant strains [36, 37]. A phase III clinical trial compared oral/IV levonadifloxacin to oral/IV Linezolid in a multicenter, randomized, open-label trial [38]. Clinical cure rates for levonadifloxacin were higher compared to linezolid in the IV sub-group (91.0% versus 87.8%) and in the oral sub-group (95.2% versus 93.6%) [38].

Pretomanid

Pretomanid is a nitroimidazooxazine antibiotic [37] and is being proposed for use in a combination regimen to treat adults with pulmonary XDR-TB, or treatment-intolerant or nonresponsive MDR-TB [39]. It exhibits both

mycobactericidal activity against replicating and static *M. tuberculosis* [39]. In a phase III trial, 11 patients (10%) from 109 had an unfavorable outcome (7 deaths, 2 relapses, 1 lost to follow-up, and 1 withdrawal of treatment) [40].

Iclaprim

Iclaprim is a dihydrofolate reductase inhibitor (DHFR) which inhibits bacterial nucleic acid and protein synthesis and has superior activity to trimethoprim and overcomes trimethoprim resistance. It is bactericidal against Gram-positive MDR bacteria. Two phase III trials (ASSIST 1 and 2) compared IV iclaprim and IV linezolid in the treatment of complicated ABSSSI. These studies failed to show non-inferiority of iclaprim and caused QT-prolongation [41, 42]. A two-phase III clinical trial (REVIVE-1 and 2) assessed iclaprim non-inferiority against vancomycin in ABSSSI [43, 44]. In REVIVE-1, early clinical response was 83.5% and 79.7% to iclaprim and vancomycin, respectively. In REVIVE-2, the clinical response was 82.7% in the iclaprim arm and 76.3% in the vancomycin arm [43, 44].

Sulopenem

Sulopenem is a novel thiopenem B-lactam antibiotic, developed as a prodrug of sulopenem-etzadroxil for therapy of UTI and cIAI. It has good activity against ESBL-producing Enterobacteriaceae [45, 46]. The first Phase III clinical trial (SURE 1) will evaluate the efficacy and safety of PO sulopenem-etzadroxil/probenecid versus ciprofloxacin PO in women with uncomplicated UTI [47]. The second ongoing phase III (SURE 2) clinical trial is comparing sulopenem IV followed by sulopenem-etzadroxil/probenecid PO versus ertapenem IV followed by ciprofloxacin PO or amoxicillin-clavulanate PO in adults with cUTI [48]. The SURE 3 trial is the third, ongoing, phase III clinical trial comparing sulopenem IV followed by sulopenem-etzadroxil/probenecid PO to ertapenem IV followed by ciprofloxacin PO or amoxicillin-clavulanate PO in adults with cIAI [49].

Contezolid

Contezolid (MRX-I) is an oxazolidinone and is being considered for the treatment of complicated skin and soft tissue infections (cSSTI) caused by resistant Gram-positive bacteria [50]. It has activity against MRSA, vancomycin-resistant *E. faecium*, and resistant *S. pneumoniae*. A Phase II trial of contezolid acefosamil in patients with ABSSSI has been completed (NCT02269319) in the United States by MicuRx, and compared MRX-I (Contezolid) with vancomycin [50]. In a phase III clinical trial, contezolid was non-inferior (93.0%) compared to linezolid (93.4%) for the clinical cure rate of patients with cSSSIs [51].

Solithromycin

Solithromycin is a novel, fourth-generation macrolide, known as fluoroketolide, which inhibits protein synthesis by binding to bacterial ribosome. It has activity against macrolide-resistant *S. pneumoniae*, *H. Influenzae*, and atypical pathogens with potential indication for use in CABP [52, 53]. Oral solithromycin was non-inferior to oral moxifloxacin in 860 adults with CABP in a phase III trial (SOLITAIRE-ORAL) [54]. Early clinical response was 78.2% versus 77.9%. Elevation of ALT was observed in 5.4% of the solithromycin group compared with 3.3% in moxifloxacin group and elevated AST in 2.5% of solithromycin group compared with 1.9% in the comparator group [54]. Solithromycin (IV to PO) was non-inferior to moxifloxacin (IV to PO) in 863 adults with CABP in a phase III clinical trial (SOLITAIRE-IV) [55]. The early clinical response in ITT was 79.3% in solithromycin arm compared with 79.7% in moxifloxacin arm with a higher rate of adverse drug reactions in the solithromycin arm [55]. The efficacy of PO solithromycin compared with standard treatment (IV ceftriaxone with oral azithromycin) in 264 adults with uncomplicated gonorrhea has been tested in a phase III clinical trial (SOLITAIRE-U) [56]. The cure rate was 80.5% in solithromycin arm compared with 84.5% in ceftriaxone/azithromycin arm [56].

Cefepime + AAI101 (Enmetazobactam)

Cefepime + AAI101 is a B-lactam and B-lactamase inhibitor [57]. AAI101 is a novel inhibitor of ESBL, and classes A and D carbapenemases [57, 58]. The addition of AAI101 to cefepime resulted in a significant in vivo reduction in the MIC₅₀ against *Enterobacteriaceae* isolates [57]. Cefepime/AAI101 is being studied in a phase III randomized clinical trial in cUTI adults in comparison with piperacillin/tazobactam. The study was started on September 24, 2018 and completed on January 30th, 2020 (Clinical registration NCT03687255) [59].

Ridinilazole

Ridinilazole is a novel, non-absorbable, oral antimicrobial and is restricted to the gastrointestinal tract. An in vitro study showed that ridinilazole is a potent inhibitor of *C. difficile* by inhibiting cell division and reducing toxin production [60, 61]. Ridinilazole is being studied in a phase III randomized, controlled trial in comparison with fidaxomicin in one study (Clinical registration NCT02784002) [62] and with vancomycin (Clinical registration NCT03595566) in another study [63] for the treatment of *C. difficile* infection.

Gepotidacin

Gepotidacin (GSK2140944) is a novel triazaacenaphthylene antimicrobial agent and is an inhibitor of bacterial type II topoisomerase [64]. It shows excellent activity against MDR *N. gonorrhoeae* and Gram-positive bacteria including MRSA [65]. It had undergone phase II trial for the treatment of uncomplicated urogenital gonorrhea (Clinical registration NCT02294682) [66] and in treatment of ABSSSI caused by Gram-positive bacteria (Clinical registration NCT02045797) [67]. It is currently being used in a phase III, randomized study comparing efficacy and safety of Gepotidacin to Nitrofurantoin in uncomplicated urinary tract infection (Clinical registration—NCT04020341) [68].

Sulbactam/Diazabicyclooctane

Sulbactam/Diazabicyclooctane is a combination of B-lactam/B-lactamase inhibitors with a wide range of B-lactamases inhibition, including class A, C, D, CRE, and CRAB [69]. A Phase III randomized study will evaluate efficacy and safety of intravenous Sulbactam-ETX2514 in treating patients with *A. baumannii-calcoaceticus* Complex infection (Clinical registration NCT03894046) [70].

Zoliflodacin

Zoliflodacin is a novel Spiropyrimidinetrione is a type II topoisomerase inhibitor with a good activity against MDR *N. gonorrhoea* [71]. Another non-inferiority phase III clinical trial is evaluating the safety and efficacy of zoliflodacin vs. a combination of ceftriaxone and azithromycin for the treatment of uncomplicated gonorrhea (Clinical registration NCT03959527) [72].

Taniborbactam

Taniborbactam is an injectable, beta-lactamase inhibitor. Taniborbactam (VNRX-5133) can inhibit metallo-beta-lactamase and serine-beta-lactamases and has a broad-spectrum inhibitory activity against Ambler Class A (ESBLs), B (NDM and VIM), C (AmpC from *P. aeruginosa*) and, to a lesser extent, D (OXA) β -lactamase [72]. It is currently undergoing phase III clinical trial (ClinicalTrials.gov—NCT03840148) comparing cefepime–taniborbactam to meropenem in adults with cUTI [73].

Discussion

The current review details the clinical outcome of the use of the novel antibiotics in the pipeline. We found that the “novel” antibiotics were often based on previously known

molecules or pre-existing antimicrobial agents. With regard to the spectra of activity, there are a limited number of new antibiotics against high priority organisms such as multi-drug-resistant *P. aeruginosa*, and carbapenem-resistant Enterobacteriaceae. These antibiotics include: plazomicin [21], eravacycline [22, 23], imipenem–cilastatin + relebactam [14–18], Sulbactam/Diazabicyclooctane [70] and Cefiderocol [33–36]. This is an important deficit as the acute shortage is particularly challenging for the “priority organisms”. The issue of the need for new antimicrobial agents for priority organisms had been on the radar of the World Health Organization (WHO) for some time. The WHO priority list includes: 1) three “critical” organisms (*A. baumannii*, carbapenem-resistant *P. aeruginosa*, carbapenem-resistant and 3rd-generation cephalosporin-resistant Enterobacteriaceae); 2) six “high priority” organisms (*Enterococcus faecium*, *S. aureus* (vancomycin-resistant, methicillin-resistant, vancomycin intermediate and resistant), clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter*, fluoroquinolone-resistant *Salmonella* spp., 3rd-generation cephalosporin-resistant fluoroquinolone-resistant *N. gonorrhoeae*; and 3) three “medium priority” organisms (penicillin-non-susceptible *S. pneumoniae*, ampicillin-resistant *H. influenzae*, fluoroquinolone-resistant *Shigella* spp.) [74]. There is still a need to have further studies addressing these priority organisms as suggested by the WHO especially multi-drug-resistant tuberculosis and Gram-negative bacteria [75]. Of the included studies, few studies addressed healthcare-associated pneumonia. However, the burden of drug-resistant bacteria is high among these types of infections. This is an added issue to the clinical trial for the therapy of MDRO or pan-drug-resistant organism therapy. One of the issues of such trials is the use of strict definitions and the need to include one source of infection such as bloodstream infection [76]. Another difficulty is the difficulty in recruiting patients with MDRO. One study showed that out of the 2100 screened patients only 37 patients were randomized [77]. It had been suggested that such trials should include observational studies that are planned and executed in a way to reduce bias in the search of therapy for MDRO [76]. How scientists could run such observational studies giving the different predictors of mortality including the site of infection, gender, comorbidities and the implicated organism is an important question to address [78].

The strength of our review is the thorough and comprehensive searches of platforms, clinical trial registries, databases and pharmaceutical company websites. The review is limited by the heterogeneity of included studies and difficulties in the quantification of comparator arms. The regulatory requirements for the registration of antibiotics vary between the US and the EU and some of the drug approval status may quickly change. However, the review highlights a pipeline paucity of these essential drugs. This problem

may be further enhanced by the current COVID-19 pandemic where there may be lack of economic support for developing new agents reinforcing the need for international cooperation and coordination [79]. There is also a concern regarding the increased costs of these new antimicrobial agents for the treatment of MDR-organisms. In one study, the estimated cost for the treatment of methicillin-resistant *S. aureus* bacteremia is 6–60 times the cost of older antibiotics and that for carbapenem-resistant Enterobacterales or MDR *P. aeruginosa* or carbapenem-resistant *A. baumannii* is 2–20 times that of the older medications [80]. Clearly, there must be incentives for the industry to develop novel antibiotics and R&D incentive strategies ranging from single rewards to complex international models are needed to push future development. There is no alternative—when the pipeline runs dry, MDR-organisms will rule the world.

Declarations

Conflict of interest All the authors have no conflicts of interest.

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