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Evidence at time of regulatory approval and cost of new antibiotics in 2016-19: cohort study of FDA approved drugs

Mayookha Mitra-Majumdar [1], John H Powers III,[2] Beatrice L Brown,[1] Aaron S Kesselheim [1]

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[1]Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA
[2]Department of Medicine, George Washington University School of Medicine, Rockville, MD, USA
Correspondence to: Dr Aaron S Kesselheim, Program On Regulation, Therapeutics, And Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA; akesselheim@bwh.harvard.edu

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ABSTRACT

OBJECTIVE To review the clinical evidence, regulatory background, and cost of antibiotics approved by the US Food and Drug Administration (FDA), 2016-19.

DESIGN Cohort study of FDA approved drugs.

DATA SOURCES FDA databases, ClinicalTrials.gov, and drug labelling. Launch prices were extracted from IBM Micromedex Red Book.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Antibiotics approved by the FDA from October 2016 to December 2019 were identified, and key features of their clinical development were extracted from publicly available FDA databases, ClinicalTrials.gov, and drug labelling. Launch prices were extracted from IBM Micromedex Red Book to evaluate the cost of treatment against comparators.

RESULTS 15 new antibiotics received at least one special regulatory designation and were supported by a median of two pivotal trials. More than half of the pivotal trials used an active control non-inferiority design. All drugs were approved based on surrogate outcome measures. 52 postmarketing requirements and commitments were included across the cohort (median 3 for each drug). From January 2021, 27 postmarketing requirements and commitments were listed as pending, seven as ongoing, three as delayed, one as submitted, eight as released, and four as fulfilled. The most expensive new antibiotic was pretomanid at $36 399 (£29 618; €34 582) for a course of treatment, and the least expensive was rifamycin ($176). Cost ratios between study drugs and comparators ranged from 0.48 to 134.

CONCLUSIONS New antibiotics have been approved by the FDA in recent years mostly based on fewer, smaller, and non-inferiority pivotal trials that often used surrogate outcome measures but were commonly more costly. Efforts to incentivise the development of antibiotics should balance growing the antibiotic development pipeline with ensuring that clinical trials provide clinically relevant evidence of effectiveness in showing added benefits for the patient.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antibiotic resistance, associated with more than 35 000 deaths annually, is a public health problem, particularly for infections caused by Gram negative bacteria.

⇒ A vibrant development pipeline of new antibiotics to treat antibiotic resistant infections and improve patient outcomes is needed.

WHAT THIS STUDY ADDS

⇒ Most antibiotics introduced in the US in 2016-19 were approved by the Food and Drug Administration based on trials with a non-inferiority design that evaluated changes in surrogate outcome measures.

⇒ Postmarketing commitments and requirements were common.

⇒ These new antibiotics were often found to be non-inferior and more costly than the older effective comparator drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These trends should be taken into account by policymakers considering new incentives for the development of antibiotics.

⇒ Incentives for the development of new antibiotics should balance the need for a strong antibiotic development pipeline with ensuring that new drugs show added value for patients by, for example, improving patient outcomes in patient with antimicrobial resistant infections.

Introduction

Since the discovery of antibiotics almost a century ago, bacteria have acquired antibiotic resistance by various means.[1] According to the Centers for Disease Control and Prevention (CDC), every year at least 2.8 million people in the US are infected with bacteria resistant to at least one antibiotic.[1] Antibiotic resistance, associated with more than 35 000 deaths annually, is a public health problem, particularly for infections caused by Gram negative bacteria. A vibrant development pipeline of new interventions to treat infections and improve patient outcomes is needed.

In recent years, however, antibiotic development has slowed.[2] Between 1990 and 2000, the US Food and Drug Administration approved 21 new antibiotics compared with six in 2000-10.[3] Some have criticised the substantial testing required of new antibiotics to justify regulatory approval by the FDA.[4] Large pharmaceutical manufacturers have left antibiotic development, citing the high cost of development and the limited returns on drugs, at least compared with other disciplines, such as cancer treatments.[5] Also, when new antibiotics are approved, low uptake has been reported.

Legislators in the US have enacted multiple approaches to enhance the antibiotic development pipeline. The Generating Antibiotic Incentives Now (GAIN) Act of 2012 provided a five-year extension on guaranteed protection from entry of generic drugs for new antibiotics that treat multidrug resistant bacterial infections.[6] The act also made antibacterial and antifungal drugs with in vitro activity against resistant or other qualifying pathogens but without requiring added patient benefits automatically eligible for special FDA pathways intended to

streamline development and regulatory review. The 21st Century Cures Act of 2016 authorised a new expedited regulatory pathway, the limited population antimicrobial drug pathway, for studies conducted in populations with limited or no options.[7] Other policies are being developed, including a plan to provide more payments for new antibiotics used in hospitals. Other initiatives, like the Pioneering Antimicrobial Subscriptions To End Upsurging Resistance (PASTEUR) Act, which allows Congress to authorise large upfront payments for new antibiotics potentially again without requiring added patient benefits, are under discussion.[8]

To evaluate the recent output from the antibiotic development pipeline and explore the potential effect of new proposals, we reviewed a cohort of antibiotics approved from 2016 to 2019. Our goal was to understand the regulatory history of the new antibiotics, the evidence on which they were approved, and their cost.

Methods

From Drugs@FDA, we identified antibiotics that received their first FDA approval between October 2016 and December 2019. Drugs approved based solely on animal testing were not included in our cohort.

Data sources and extraction

Regulatory information

We used regulatory review documents from Drugs@FDA to extract the clinical characteristics of each drug: approved indications, target enrolled populations, method of administration, susceptible pathogens, and in vitro activity against ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp) pathogens.[9 10] We also identified the in vitro activity of each drug against bacteria included in the CDC's urgent threat pathogens list: carbapenem resistant *Acinetobacter*, *Clostridiodes difficile*, carbapenem resistant *Enterobacteriaceae*, and drug resistant *Neisseria gonorrhoeae*.[1]

We then extracted characteristics relevant to each drug's regulatory review process: date of investigational new drug filing, indicating the start of human clinical trials; date of new drug application filing, indicating the start of the FDA review; date of FDA approval; manufacturer; and any special regulatory designations that were assigned to the antibiotic during its development or FDA review periods.[11] We used this information to determine each drug's development time, defined as the time between investigational new drug filing and new drug application filing. Special regulatory designations included fast track, breakthrough treatment, accelerated approval, Orphan Drug Act, and priority review. We also tracked limited population antibacterial drug status and qualified infectious disease product status, the special designation created by the GAIN Act for antibacterials and antifungals with in vitro activity against a list of pathogens. Press releases from drug sponsors and other public sources provided confirmatory information on each drug's FDA designations.

Pivotal trials

The FDA often designates some clinical trials as pivotal trials when a drug is approved. These trials provide the main body of clinical evidence in support of the drug's efficacy and form the basis for FDA approval. For each pivotal trial, we extracted the indication or indications studied, study population, comparator regimen, primary end points, trial size and arms, and statistical hypothesis and analysis plan. These details were confirmed in ClinicalTrials.gov.[12] FDA law and regulations define a direct outcome used as a primary endpoint as a measure of how patients feel, function, or survive.[13] Direct endpoints, also referred to as true or clinically significant endpoints, look at outcomes directly relevant to patients, clinicians, and payers. These include survival and patient reported symptoms or function in their daily lives.[14] Indirect endpoints do not directly measure how a patient feels, functions, or survives, but are believed to reflect changes in a direct patient outcome and thus serve as surrogate measures of that effect. Clinician reported outcomes of signs of disease or clinician decisions (eg, prescribing more drug treatments), observer reported outcomes, and biomarkers (ie, objective measures of biological processes) are indirect endpoints.[15] We classified the primary endpoints as direct versus indirect endpoints. Indirect endpoints were further categorised into survival, patient reported outcomes of signs of disease, clinician reported outcomes, observer reported outcomes, and biomarkers.

Postmarketing requirements and commitments

We extracted postmarketing commitments or postmarketing requirements for each of our study drugs. Postmarketing requirements are studies and trials that manufacturers are required to complete under statutes and regulations, such as the Animal Efficacy Rule, Pediatric Research Equity Act, or the Food and Drug Administration Amendments Act (FDAAA). Postmarketing commitments are studies and trials that the manufacturer agrees to conduct, but which are not mandated by statute or regulation.[16] We recorded postmarketing commitments reportable under section 506B of the federal Food, Drug, and Cosmetic Act, but excluded non-reportable postmarketing commitments listed in the original approval letters. These details were identified in the drug's original approval letter listed in the Drugs@FDA database, and their statuses were identified from

the FDA's online database of postmarketing requirements and postmarketing commitments.

The FDA database categorises postmarketing requirements and postmarketing commitments into several different open or closed status categories. Open status includes pending, ongoing, delayed, terminated, and submitted postmarketing requirements or commitments. Pending studies have not yet started, but also do not meet the criteria to be listed as delayed. Ongoing studies are proceeding according to or ahead of schedule. Delayed studies are behind schedule. Terminated studies were ended by the manufacturer before completion and the FDA has not yet received a report. Submitted studies have been completed and a final report submitted to the FDA, but the FDA has not yet notified the applicant that the postmarketing commitment has been satisfied.[17] Closed status includes fulfilled and released postmarketing commitments and postmarketing requirements. Fulfilled studies have been completed; the FDA has received the final report and notified the applicant that the postmarketing commitment has been satisfied. The FDA lists some postmarketing commitments as released when they determine that the study is no longer feasible or would not provide meaningful information.

Cost of treatment

We extracted the dose, method of administration, and course of treatment of each drug from its FDA labelling. We then used the 2020 wholesale acquisition unit cost listed in IBM Micromedex Red Book to calculate the cost of treatment.[18] If a study drug was indicated for use in combination with other drugs, we included their cost in our calculation of the total cost of treatment. For all study drugs other than pretomanid for tuberculosis and secnidazole for bacterial vaginosis, we used the comparator regimen in their pivotal trials as the comparison point for our analysis. Where a pivotal trial did not use an active comparator, we relied on input from providers, professional guidelines, and recommendations from authorities, such as the CDC, to identify the most appropriate comparator treatment. For pretomanid, we used the World Health Organization's guidelines to select the comparator regimen.[19] Metronidazole was recommended as the best comparator for secnidazole. Our cost calculations did not account for optional step-downs to oral drug treatment if included as an option in pivotal trials.

We similarly used IBM Micromedex Red Book to extract the wholesale acquisition cost price of the comparator drugs, but we calculated the cost of treatment for comparator regimens mainly based on the dose and method of administration used in pivotal trials, rather than their labels. We used discretion in selecting the particular National Drug Code used to calculate the cost of a comparator regimen. Factors considered included the method of administration, dose, wholesale acquisition unit cost, and the last date when the wholesale acquisition cost price was updated. We matched the method of administration used in pivotal trials, and selected the least costly National Drug Code (in terms of unit wholesale acquisition cost) that came in a dose that most aligned with the course of treatment. If necessary, we chose a more expensive National Drug Code to reflect a more current price or a more appropriate dose option. Online supplemental appendix 1 shows the full calculations and methodology (cost analysis).

Patient and public involvement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of this research, because the study involved a review of publicly available data from regulatory and other sources relating to antibiotic drugs. The work will be disseminated to policymakers and patient groups focusing on antibiotic innovation.

Results

Our cohort had 15 new antibiotics: pretomanid, imipenem-cilastatin-relebactam, lefamulin, rifamycin, omadacycline, eravacycline, plazomicin, delafloxacin, secnidazole, meropenem-vaborbactam, ozenoxacin, bezlotoxumab, amikacin liposome inhalation suspension, cefiderocol, and omeprazole magnesium-amoxicillin-rifabutin (table 1). Online supplemental appendix 2 has a full list of data sources for each drug.

Approved indications and other regulatory characteristics

Four drugs were approved for complicated urinary tract infections, two for complicated intra-abdominal infections, two for community acquired bacterial pneumonia, and two for acute bacterial skin and skin structure infections. One drug each was approved for multidrug resistant tuberculosis, traveller's diarrhoea, bacterial vaginosis, impetigo, prevention of *Clostridodiodes difficile* recurrence, *Mycobacterium avium* complex lung disease, and *Helicobacter pylori* infection. Two drugs were simultaneously approved for two indications each, omadacycline for acute bacterial skin and skin structure infections and community acquired bacterial pneumonia, and imipenem-cilastatin-relebactam for complicated urinary tract infections and complicated intra-abdominal infections. Nine drugs showed in vitro activity against ESKAPE pathogens. Omadacycline and delafloxacin had an FDA approved indication for disease due to methicillin resistant *Staphylococcus aureus*. Bezlotoxumab, a human monoclonal antibody, was the only drug to target a CDC urgent threat pathogen (*C difficile*), and the only drug with a new mechanism of action (binding to *C difficile* toxin B).

Table 1 | Clinical characteristics of antibiotics approved by US Food and Drug Administration, 2016-19

Drug	Indications*	FDA approved target population	Susceptible pathogens†	Method of administration	New mechanism of action	In vitro activity *v* ESKAPE‡ pathogens
Bezlotoxumab	Prevention of recurrence of *Clostridodiodes difficile* infection	Adults with *C difficile* infection on treatment and high risk for recurrence	*C difficile*	Intravenous	Yes	No
Delafloxacin	ABSSSI	Adults with ABSSSI from susceptible bacteria	*Staphylococcus aureus (MSSA/MRSA), Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus, Staphylococcus intermedius, Streptococcus constellatus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa*	Oral, intravenous	No	Yes
Meropenem-vaborbactam	Complicated urinary tract infections	Adults with complicated urinary tract infections from susceptible bacteria	*E coli, K pneumoniae, E cloacae* spp complex	Intravenous	No	Yes
Secnidazole	Bacterial vaginosis	Adult women with bacterial vaginosis	Most isolates of *Bacteroides, Gardnerella vaginalis, Prevotella, Mobiluncus, Megasphaera* like type I/II	Oral	No	No
Ozenoxacin	Impetigo	Adults and children (aged ≥2 months) with impetigo caused by *S aureus* or *S pyogenes*	*S aureus, S pyogenes*	Topical	No	Yes
Plazomicin	Complicated urinary tract infections	Adults with complicated urinary tract infection from susceptible organisms with limited alternatives, including pyelonephritis	*E coli, K pneumoniae, Proteus mirabilis, E cloacae*	Intravenous	No	Yes
Eravacycline	Complicated intra-abdominal infections	Adults with complicated intra-abdominal infections	*E coli, K pneumoniae, Citrobacter freundii, E cloacae, Klebsiella oxytoca, E faecalis, Enterococcus faecium, S aureus, S anginosus, S intermedius, S constellatus, Clostridium perfringens, Bacteroides* sp, *Parabacteroides distasonis*	Intravenous	No	Yes
Amikacin liposome inhalation suspension	*Mycobacterium avium* complex lung disease	Adults with *M avium* complex who do not achieve negative sputum after at least 6 months of treatment, and limited alternative options (in combination with antibacterial drug)	*M avium*	Inhaled	No	No
Omadacycline	ABSSSI, CABP	Adult patients with CABP or ABSSSI caused by susceptible microorganisms	CABP: *Streptococcus pneumoniae, S aureus* (MSSA), *Haemophilus influenzae, Haemophilus parainfluenzae, K pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae* ABSSSI: *S aureus* (MRSA/MSSA), *S lugdunensis, S pyogenes, S anginosus, S intermedius, S constellatus, E faecalis, E cloacae, K pneumoniae*	Oral, intravenous	No	Yes

Continued

Table 1 Continued

Drug	Indications*	FDA approved target population	Susceptible pathogens†	Method of administration	New mechanism of action	In vitro activity *v* ESKAPE‡ pathogens
Rifamycin	Traveller's diarrhoea	Adults with traveller's diarrhoea caused by non-invasive strains of *E coli*	*E coli*	Oral	No	No
Imipenem-cilastatin-relebactam	Complicated urinary tract infections, complicated intra-abdominal infections	Adults with limited or no alternative treatment options for complicated urinary tract infections and complicated intra-abdominal infections	(All Gram negative bacteria) complicated urinary tract infections: *E cloacae*, *E coli*, *Klebsiella aerogenes*, *K pneumoniae*, *P aeruginosa*. Complicated intra-abdominal infections: *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *C freundii*, *E cloacae*, *E coli*, *Fusobacterium nucleatum*, *K aerogenes*, *Klebsiella oxytoca*, *K pneumoniae*, *Parabacteroides distasonis*, *P aeruginosa*	Intravenous	No	Yes
Pretomanid	Tuberculosis	Adults with pulmonary Extensively drug resistant, treatment intolerant, or non-responsive multidrug resistance (combination with bedaquiline and linezolid)	*M tuberculosis*	Oral	No	No
Lefamulin	CABP	Adults with CABP caused by susceptible organisms	*S pneumoniae*, *S aureus* (MSSA), *H influenzae*, *L pneumophila*, *M pneumoniae*, *C pneumoniae*	Oral, intravenous	No	Yes
Omeprazole magnesium-amoxicillin-rifabutin	*H pylori*	Adults with infections	*H pylori*	Oral	No	No
Cefiderocol	Complicated urinary tract infections	Adults with complicated urinary tract infections from susceptible organisms with limited or no alternative treatment options	*E coli*, *K pneumoniae*, *P mirabilis*, *P aeruginosa*, *E cloacae* complex	Intravenous	No	Yes

ABSSSI=acute bacterial skin and skin structure infections; CABP=community acquired bacterial pneumonia; MSSA=methicillin sensitive *Staphylococcus aureus*; MRSA=methicillin resistant *Staphylococcus aureus*.

*All information for indications covered by the first FDA approval.

†As listed in the FDA label.

‡ESKAPE=*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp, determined by identifying susceptible pathogens on the FDA label, and fact checked through FDA press releases.

Four drugs were approved for oral administration, six for intravenous administration, one for topical application, one for inhalation, and three in both oral and intravenous formulations.

Among 14 drugs with available data, the median development time was 8.2 years (interquartile range 5.9-9.1), defined as the time between investigational new drug filing and submission of new drug application. Meropenem-vaborbactam had the shortest total development time of 3.0 years and delafloxacin the longest at 15.3 years. All drugs received at least one special regulatory designation intended to speed up development or regulatory review. Eleven drugs received priority review designation, eight received fast track, two received Orphan Drug Act, two received breakthrough, and one received accelerated approval. Thirteen of the 15 drugs in our cohort received a qualified infectious disease product designation. Two drugs, pretomanid and amikacin liposome inhalation suspension, formally received limited population antibacterial drug approval (table 2) whereas three other drugs (plazomicin, imipenem-cilastatin-relebactam, and cefiderocol) were labelled for populations with limited or no treatment options.

Design and evidence from pivotal trials

The drugs in our cohort were supported by 28 total pivotal trials (median 2, range 1-3). The median number of patients enrolled in a trial was 388 (interquartile range 270.5-690, range 31-1446). The only pivotal trial with no comparison with an active or placebo control was the Nix-TB trial, a single arm multicentre study that compared pretomanid in combination with bedaquiline and linezolid with a putative historical control based on a literature review of surrogate outcomes of sputum culture in patients with a new diagnosis of extensively drug resistant tuberculosis not treated with pretomanid, delamanid, bedaquiline, or linezolid.[20] Of the 27 other trials, 17 compared the drug with an active comparator and 10 with placebo.

Fifteen trials used active-controlled non-inferiority hypotheses. Non-inferiority margins were 10% (in 7/15 trials), 12.5% (2/15), 15% (4/15), and 20% (1/15). One pivotal trial for rifamycin specified a non-inferiority margin in the form of a hazard ratio. To determine if a new treatment is non-inferior, researchers use a non-inferiority margin, defined as the maximum acceptable loss of effectiveness compared with an effective older agent. Ten studies used a superiority approach to show that the new drug was more efficacious than an existing one (one historical control and eight concurrent placebo control groups, and one comparison with a standard of care plus placebo add-on). Two trials had no specified hypothesis and used descriptive statistics to evaluate results. All drugs were approved on the basis of indirect outcome assessments as endpoints.

Most pivotal trials focused on composite primary endpoints that incorporated more than one of the endpoint categories of survival, patient reported outcomes, observer reported outcomes, clinician reported outcomes, and biomarkers. Patient reported outcomes were used in four pivotal trials but evaluated signs of disease rather than patients' symptoms, clinician reported outcomes in 19, and biomarkers in 14. No observer reported outcomes were used in the pivotal trials for our drug cohort. None of the trials used patient reported outcomes to evaluate patients' symptoms or function (online supplemental appendix 3).

All trials with superiority hypotheses showed significantly superior results. Of trials with non-inferiority hypotheses, 11 met that trial's statistical criteria for non-inferiority, one trial did not show non-inferiority (imipenem-relebactam-cilastatin in complicated urinary tract infections) whereas three trials (all in complicated urinary tract infections) showed significantly superior results. The results of the three superiority trials were driven by surrogate outcomes of urine culture without superiority for patient outcomes. The two trials with no hypotheses enrolled patients with resistant pathogens and the results were uninterpretable or showed worse outcomes with the new agent (cefiderocol showed a 16% increase in mortality).

Postmarketing requirements and commitments

We found 52 postmarketing requirements and postmarketing commitments (median 3) (online supplemental appendix 4). Pretomanid and lefamulin had the most at seven each; ozenoxacin and omeprazole magnesium-amoxicillin-rifabutin had none. Nearly half of these (25, 48%) were postmarketing requirements required under FDAAA section 505 (o), 21 (40%) under the Pediatric Research Equity Act, and one (2%) under accelerated approval; we found five postmarketing commitments under section 506B (10%). For nine drugs, the FDA required their sponsors to conduct US surveillance studies over five years after approval to monitor development of bacterial resistance based on in vitro data rather than patient outcomes. For 10 drugs, testing of efficacy and safety in children was required. As of January 2021, 27 postmarketing commitments were listed as pending, six as ongoing, three as delayed, one as submitted, eight as released (one was replaced with another postmarketing requirement), four as fulfilled, and three were no longer listed in the online database. No study drug had submitted or fulfilled all of its postmarketing commitments.

Drug prices and total cost of treatment

Comparative cost information was available for 13 study drugs, and the most expensive was pretomanid at $36 399 (£29 618; €34 582). The least expensive was rifamycin for traveller's diarrhoea ($176). The

Table 2 | Regulatory characteristics of new antibiotics approved by US Food and Drug Administration, 2016-2019

Drug (brand name)	Filed to start clinical trials	New drug application filed	Approval date	Sponsor (current manufacturer, if different)	LPAD designation	QIDP designation	Other FDA special programmes or designations
Bezlotoxumab (Zinplava)	November 2005	November 2015	October 2016	Merck Sharp & Dohme (N/A)	▶ No	▶ No	▶ Fast track ▶ Priority review
Delafloxacin (Baxdela)	June 2001, March 2007	October 2016	June 2017	Melinta Therapeutics (N/A	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Meropenem-vaborbactam (Vabomere)	December 2013	December 2016	August 2017	Rempex Pharmaceuticals (N/A)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Secnidazole (Solosec)	December 2013	January 2017	September 2017	Symbiomix Therapeutics (Lupin Pharmaceuticals)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Ozenoxacin (Xepi)	February 2010	June 2016	December 2017	Ferrer Internacional (N/A)	▶ No	▶ No	▶ None
Plazomicin (Zemdri)	December 2008	October 2017	June 2018	Achaogen (Cipla)	▶ No ▶ Labelled for limited population	▶ Yes	▶ Priority review
Eravacycline (Xerava)	August 2009	December 2017	August 2018	Tetraphase Pharmaceuticals (N/A)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Amikacin liposome inhalation suspension (Arikayce)	February 2011	March 2018	September 2018	Insmed Incorporated (N/A)	▶ Yes	▶ Yes	▶ Accelerated approval ▶ Fast track ▶ Breakthrough treatment ▶ Priority review ▶ Orphan drug
Omadacycline (Nuzyra)	Not found	February 2018	October 2018	Paratek Pharmaceuticals (N/A)	▶ No	▶ Yes	▶ Fast track ▶ Priority review
Rifamycin (Aemcolo)	December 2009	March 2018	November 2018	Cosmo Technologies (Redhill Biopharma)	▶ No	▶ Yes	▶ Priority review ▶ Fast track
Imipenem-cilastatin-relebactam (Recarbrio)	September 2010	November 2018	July 2019	Merck Sharp & Dohme (N/A)	▶ No ▶ Labelled for limited population	▶ Yes	▶ Priority review ▶ Fast track
Pretomanid (Pretomanid)	April 2005	December 2018	August 2019	The Global Alliance for TB Drug Development (Mylan)	▶ Yes	▶ Yes	▶ Priority review ▶ Orphan drug ▶ Fast track
Lefamulin (Xenleta)	October 2009, January 2015	December 2018	August 2019	Nabriva Therapeutics Ireland DAC (N/A)	▶ No	▶ Yes	▶ Priority review ▶ Fast track
Omeprazole magnesium-amoxicillin-rifabutin (Talicia)	October 2013	May 2019	November 2019	Redhill Biopharma (N/A)	▶ No	▶ Yes	▶ Priority review ▶ Fast track
Cefiderocol (Fetroja)	March 2013	December 2018	November 2019	Shionogi (N/A)	▶ No ▶ Labelled for limited population	▶ Yes (for Gram negative infections)	▶ Fast track

LPAD=limited population antibacterial drug; QIDP=qualified infectious disease product; N/A=not available.

QIDP, LPAD, and FDA regulatory designations apply to the indications and formulations listed on the original approval, and exclude indications that failed to gain approval or have subsequently gained approval.

*Drugs not designated as going through LPAD pathway but labelling claim based on approval for population with limited or no options.

cost ratios between study drugs and comparator regimens ranged from 0.48, for ozenoxacin for impetigo compared with topical retapamulin, to 134 for intravenous omadacycline for community acquired bacterial pneumonia compared with oral moxifloxacin. The study drugs that were less expensive than their comparators (giving a cost ratio of <1) were ozenoxacin for impetigo compared with topical retapamulin, and oral delafloxacin compared with intravenous vancomycin and aztreonam, with cost ratios of 0.48 and 0.84, respectively. Table 3 provides a summary of the results of the cost analysis.

Bezlotoxumab and amikacin liposome inhalation suspension required special calculation in the cost analysis. Bezlotoxumab, indicated for the prevention of recurrence of *C difficile*, did not have a comparator treatment on the market. The cost of treatment with weight based bezlotoxumab is $2850 (for a patient weighing 75 kg), but without a comparator, calculating a cost ratio was not possible. Amikacin liposome inhalation suspension, for *Mycobacterium avium* complex lung disease, was the only study drug intended for chronic use, and no comparator regimen exists. A month's supply of amikacin liposome inhalation suspension costs $12 381, with only one supporting pivotal trial in patients treated for 8-16 months. Treatment across this time period would cost $161 394-$215 192, making amikacin liposome inhalation suspension the most expensive drug by course of treatment in our cohort.

Discussion

Principal findings

The number of new antibiotics on the market has grown in line with policy incentives designed to increase the quantity of approved drug treatments. Our previous study examined a cohort of eight antibiotics approved between January 2010 and December 2015. In this study, we examined 15 new antibiotics approved in a shorter timeframe (October 2016-November 2019). This more recent cohort of new antibiotics had similar regulatory and pivotal trial characteristics to the cohort of antibiotics approved in 2009-15. In both cohorts, all drugs received at least one special regulatory designation intended to speed up development or review, but the application of these designations was inconsistent. Most pivotal trials had non-inferiority hypotheses; and reliance on surrogate endpoints was found (none used patient reported outcomes to directly evaluate patient symptoms or function, or both).

The limited number of pivotal trials, small numbers of patients enrolled in the trials, wider non-inferiority margins allowing greater losses of efficacy than the 2009-15 cohort, and limited postmarketing evidence because of incomplete postmarketing requirements and postmarketing commitments make it difficult to determine the real world value of improved patient outcomes with these new drug treatments. More than half of the 28 pivotal trials, and all trials for common infections like urinary tract infections and pneumonia, were non-inferiority trials. Non-inferiority trials are most appropriate when the need for more treatment options with improved adverse effects might justify a trade-off for slightly reduced efficacy, and also do not result in irreparable patient harm. We found non-inferiority trials allowing worse effectiveness of 10-20%, a wider range than in a similar study of antibiotics approved in 2010-15 (10-15%).[21] Non-inferiority hypotheses can be used to prioritise non-efficacy benefits.[22] These same trials are designed to exclude patients who lack current treatment options, however, and thus are less likely to provide evidence that the drug provides meaningful efficacy benefits above existing treatments, especially given their higher costs.[23] One non-inferiority trial failed to show non-inferiority, with the new drug 18.3% less effective than the older agent. The FDA review found that this trial was not adequate or well controlled (as required by law), but still used the trial as the basis for regulatory approval, also relying on in vitro data and animal models. These trial results were not prominently described in the drug's labelling.

Three non-inferiority trials showed significant superiority, mainly from the results of urine culture, a surrogate measure of unclear validity, without superiority for direct patient outcomes. Two trials were designed with no hypotheses and used only descriptive statistics, two design choices not classically associated with the adequate and well controlled investigations described in FDA regulations as being needed for new drugs to be approve. These two studies enrolled patients with resistant pathogens and the results were uninterpretable because of the small numbers of patients or showed increased mortality with the new agent. We found three drugs labelled for patients with limited or no treatment options despite a lack of substantial evidence from studies enrolling these patients.

All of the study drugs in our cohort were approved on the basis of at least one indirect outcome assessment as an endpoint, including many of the trials with superiority hypotheses. Indirect endpoints, also called surrogate endpoints, have become increasingly common in clinical trials since their introduction in the early 1990s to speed up HIV drugs coming to market.[24] Indirect endpoints are appropriate when clinical outcomes take years or longer to emerge, such as in oncology or other chronic conditions where physical changes accumulate over time. Indirect endpoints are also useful when the surrogate strongly reflects patient benefit. Use of indirect endpoints can accelerate clinical trials, decrease development costs, and get drugs to market quicker.[25] We found an average development time of about eight years, similar to results from other reviews of the development of antibiotics.[2]

Table 3 | Dose, duration, and cost of antibiotics recently approved by US Food and Drug Administration (2016-19) and comparator regimens

Recently approved antibiotic			Comparator			
Drug (brand name)	Dose	Cost (WAC, $)	Drug	Dose	Cost range (WAC, $)	Cost factor
Pretomanid (Pretomanid)	200 mg daily for 26 weeks plus linezolid 1200 mg daily orally and bedaquiline 400 mg daily orally for 2 weeks then 200 mg 3 times a week for 24 weeks	36 399	Isoniazid, rifampin, pyrazinamide, ethambutol	Intensive phase: 300 mg isoniazid, 600 mg rifampin, 1500 mg pyrazinamide, and 1200 ethambutol daily for 8 weeks. Continuation phase: 300 mg isoniazid and 600 mg rifampin daily for 18 weeks	1380	26.37
Imipenem-cilastatin-relebactam (Recarbrio)	1.25 g intravenously over 30 min, every 6 hours, for 4-14 days	4280-14 980	Imipenem-cilastatin	500 mg intravenously four times a day for 4-14 days	104-364	41.15
			Imipenem-cilastatin and colistimethate sodium	Cilastatin and colistimethate sodium (300 mg) ×1 followed by 300 mg cilastatin and colistimethate sodium every 12 hours and 500 mg imipenem intravenously four times a day for 4-14 days	536-1756	7.99-8.53
Lefamulin (Xenleta)	150 mg every 12 hours intravenously for 5-7 days or 600 mg tablets every 12 hours for 5 days	Intravenously: 1025-1435. Orally: 1375	Moxifloxacin	(For CABP) 400 mg moxifloxacin orally or intravenously daily for 7-14 days	Intravenously: 315-630. Orally: 21-41	Intravenously: 3.25-2.28 Orally: 66.81-33.41
Rifamycin (Aemcolo)	388 mg every 12 hours for 3 days	176	Ciprofloxacin	(For Traveller's diarrhoea) 500 mg orally every 12 hours for 5-7 days	2-3	92.65-66.18
Omadacycline (Nuzyra)	Loading: 200 mg intravenously over 60 min or 100 mg intravenously over 30 min, twice on day 1, then 100 mg intravenously daily or 300 mg tablets daily. Total 7-14 days	(All Indications, intravenously) 2760-5175	ABSSSI: Linezolid CABP: Moxifloxacin	(ABSSSI, Linezolid) 600 mg intravenously or tablets twice daily for 10-14 days (CABP, Moxifloxacin) 400 mg moxifloxacin orally or intravenously daily for 7-14 days	(ABSSSI, Linezolid) intravenously: 720-1440. Orally: 69-137. (CABP, Moxifloxacin) intravenously: 315-630. Orally: 21-41	ABSSS: Omadacycline intravenously, linezolid intravenously =3.83-3.59. Omadacycline intravenously, linezolid orally =40.23-37.72. CABP: Omadacycline intravenously, moxifloxacin intravenously =8.76-8.21. Omacadycline intravenously, moxifloxacin orally =134.11-125.73
Eravacycline (Xerava)	1 mg/kg intravenously twice daily for 4-14 days	588-2058	Ertapenem	1.0 g intravenously daily for 4-14 days	400-1400	1.47
			Meropenem	1.0 g intravenously three times a day for 4-14 days	85-149	6.89-13.78

Continued

Table 3 Continued

Recently approved antibiotic			Comparator			
Drug (brand name)	Dose	Cost (WAC, $)	Drug	Dose	Cost range (WAC, $)	Cost factor
Plazomicin (Zemdri)	15 mg/kg intravenously daily for 4-7 days	283-496	Meropenem	1 g intravenously three times a day for 4-7 days	85-149	3.32
Delafloxacin (Baxdela)	300 mg intravenously over 60 min twice daily for 5-14 days or 450 mg tablet twice daily for 5-14 days	Intravenously: 1325-3710. Orally: 744-2083	Vancomycin and aztreonam	15 mg/kg intravenously vancomycin and 2 g intravenously aztreonam twice daily for 5-14 days	884-2474	Delafloxacin intravenously 1.50-1.10. Delafloxacin orally 0.84
Secnidazole (Solosec)	2 g of granules once orally	282	Metronidazole	(Bacterial vaginosis) 750 mg orally daily for 7 days	6	48.00
Meropenem-vaborbactam Vabomere)	4 g intravenously three times a day for up to 14 days	29 938	Piperacillin-tazobactam	4 g/0.5 g intravenously three times a day for up to 10 days	754	39.72
Ozenoxacin (Xepi)	Apply thin layer to affected area twice daily for up to 5 days (dose unspecified)	297 (one 30 g tube ozenoxacin)	Retapamulin	Apply thin layer to the affected area twice a day for 5 days (dose unspecified)	623	0.48
Bezlotoxumab (Zinplava)	One time intravenously 10 mg/kg	2850 (for patient weighing 75 kg)	None available	-	-	-
Amikacin lipsosome inhalation suspension (Arikayce)	Daily oral inhalation of one 590 mg/8.4 mL vial, for indefinite use	12 380 (28 day supply) 1 61 394-2 15 192 (8-16 months)	Rifampin, ethambutol, and azithromycin	Azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg) three times a week for 8-16 months	111 (28 day supply) 1438-1918 (8-16 months)	(28 day supply) 111.90. (8-16 months) 112.21
Cefiderocol (Fetroja)	2 g intravenously three times a day for 7-14 days	7700-15 400	Imipenem/cilastatin	Imipenem/cilastatin (1 g:1 g) intravenously three times a day for 7-14 days	397-794	19.6-19.4
Omeprazole magnesium-amoxicillin-rifabutin (Talicia)	Four capsules three times a day for 14 days	669	Amoxicillin and omeprazole	1000 mg amoxicillin and 10 mg omeprazole three times a day for 14 days	9	77.21

$1 (£0.81; €0.95).

The use of indirect endpoints is questionable in acute diseases when direct outcomes can be measured rapidly. Also, indirect measures in acute diseases do not always reflect clinical benefit. For example, use of indirect assessment or biomarker of urine culture gives misleading superior results in trials when no added benefit is shown for the patient centred outcomes of survival or symptoms.[26] The expectation is that changes in indirect measures reflect changes in direct endpoints, but this validation is not always performed.[25] The efficacy of drugs approved based on unvalidated indirect measures is unclear. We have seen in this analysis that drugs approved on validated or unvalidated indirect outcomes are often priced as if they have already shown direct benefit to the patient. Our analysis showed that many of these drugs obtain full FDA approval (rather than accelerated approval) despite doubts on whether the indirect outcomes reflect benefit to the patient.

Nearly all of the trials in our cohort of drugs involved comparison with a placebo or active comparator. Pretomanid, however, was approved based on one single-arm study analysing 45 participants that compared pretomanid with a historical control and used a biomarker endpoint. (Inhaled amikacin was similarly based on a single-arm study with a biomarker endpoint.) Guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use recommend not using historical controls when patient and disease factors can affect outcomes (eg, in tuberculosis).[27] Pretomanid was approved based on limited evidence of questionable rigour, and was also the most expensive drug in our cohort. Furthermore, pretomanid along with inhaled amikacin was granted an Orphan Drug Act designation. Tuberculosis is a rare disease in the US, but is the main cause of mortality from infectious diseases globally, suggesting the need for further discussion of the correct application of special regulatory pathways.[28] These regulatory pathways allow new antibiotics to get regulatory approval with limited clinical data supporting their efficacy. Approval of new antibiotics based on smaller, fewer, and less rigorous pivotal trials that enrol patients who might not have unmet needs, produce new antibiotics with unclear evidence of effectiveness.[29] But these new antibiotics are often more costly: the study drugs were up to 134 times more expensive than the comparator regimen used in pivotal trials. In this context of evidentiary questions, small numbers of prescriptions for some of the new drugs leading to limited revenue for their manufacturers is not surprising. Rationale for use of other special regulatory designations was similarly questionable in certain cases; for example, secnidazole received QIDP status and five additional years of regulatory exclusivity despite bacterial vaginosis not being a serious, life-threatening disease as intended by law to receive this designation.

Limitations

The drugs in our cohort are often indicated for use (although often not tested) in patient populations with multidrug resistant or extensively drug resistant infections. Studies have shown that these patients are often excluded from trials of antibiotics.[30] Because these drugs are often marketed for use in multidrug resistant or extensively drug resistant infections, clinicians might use them for these indications. The new antibiotic might not be a direct substitute for the comparator in the pivotal trials, which we used in our cost analyses. Another limitation is that we did not conduct a systematic analysis of the safety profiles for each of our study drugs compared with other drugs for the same indication, or compared with evidence of benefit. These non-efficacy benefits might include lower toxicity, fewer adverse events, and greater potential for adherence (which might result in greater real world efficacy), and justify approving the drug based on slightly reduced efficacy.[31] Some drugs in our cohort had greater safety concerns than their predecessors. Plazomicin, for example, increased harms of renal insufficiency in patients, as noted in the drug's labeling.

Thirdly, in our cost analysis, we used the comparator in the drug's pivotal trials. The comparator chosen by the drug sponsor might not be the regimen recommended by professional guidelines or the most cost effective option for the indication studied. Some of the comparator regimens were more expensive than generic regimens currently recommended for clinical use. For example, ozenoxacin for impetigo was compared with retapumulin in its pivotal trials and had the lowest cost ratio in our cohort. Retapumulin is a similarly new expensive antibiotic, however, which likely skews the cost ratio towards a more favourable lower number. Generic mupirocin, by contrast, can also treat impetigo, and is available as a low cost over-the-counter treatment. Also, because we used discretion in choosing the comparator National Drug Code, small variations in the cost of treatment with comparator regimens might exist. Fourthly, our cost analysis was also based on wholesale acquisition unit prices that do not account for rebates, which are typically confidential, and so the cost of treatment for each drug does not always reflect the cost to a payer. Finally, all of the postmarketing commitments and postmarketing requirements had not been completed for any of the drugs in our cohort, which limited the scope of our analysis. Hence we could not draw associations between evidence of effectiveness shown in the pivotal trials and any confirmatory evidence provided by a drug's postmarketing requirements and postmarketing commitments.

Conclusions

This study of antibiotic innovation in the past five years showed that new antibiotics meant to fill unmet medical needs for improved efficacy lacked evidence that they do so on real clinical endpoints before approval by the FDA. These trends should be taken into account by policymakers considering new incentives for the development of antibiotics. For example, the PASTEUR bill would provide large government payments based on contracts for new antibiotics considered high priority.[8] Contracts under the PASTEUR Act are intended to determine payment on public health value rather than the quantity of an antibiotic, but the version of the Act introduced in the US Senate in 2021, like the preceding GAIN Act of 2012, did not require added benefits to be shown in patients with unmet needs to qualify for a contract. We have shown in this study that the value of a new antibiotic drug is not always clear based on testing before approval by the FDA. Efforts like the PASTEUR Act deal with the barrier of low sales potential to new antibiotic development but might not account for whether these drugs provide sufficient added benefit to the patient to justify payment. Increasing the number of agents coming to market should balance the robustness of evidence of improved direct patient outcomes compared with current standards of care, therefore meeting the needs of patients.

Contributors MM-M, JHP, and ASK conceptualised the study. MM-M and BLB were responsible for data collection and analysis. MM-M drafted the manuscript. BLB, JHP, and ASK reviewed the manuscript and provided substantial textual edits. MM-M is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

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ORCID iDs

Mayookha Mitra-Majumdar http://orcid.org/0000-0002-9385-2821
Aaron S Kesselheim http://orcid.org/0000-0002-8867-2666

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