The discovery of antibiotics in the 20th century to treat infections that had previously been lethal or severely debilitating ushered in a new era in medicine, enabling people to live longer and healthier lives. Antibiotics also brought about a shift in public health measures as chronic diseases replaced infectious diseases as the greatest contributor to morbidity and mortality. The initial success of antibiotics was so great that Surgeon General William Stewart pre-emptively declared victory against infectious diseases by 1967.1

The last several decades have demonstrated the opposite: powerful infectious diseases resistant to available antibiotics were emerging at an alarming rate. In 1992, the Institute of Medicine’s (IOM) Committee on Emerging Microbial Threats warned, ‘humankind is beset by a greater variety of microbial pathogens than ever before.’2 In recent years, antibiotic resistance has emerged, thought to be due to many factors, including the overuse and misuse of antibiotics in human patients, poor infection control efforts, and the widespread use of antibiotics in animal feeds.

Despite the need for new antibiotics with improved effectiveness to address the rising tide of resistance, the antibiotic pipeline has often been described as weak.3,4 Most antibiotics in use today originate from discoveries made in the mid-twentieth century, and critical gaps remain in our understanding of antibiotics and their targets.5 These issues simultaneously contribute to and are exacerbated by the fact that numerous large, for-profit pharmaceutical companies have abandoned active antibiotic development groups due to concerns about returns on investment.6 According to a review commissioned by the US government in 2014, social returns from antibiotic development can far exceed private returns.7 Antibiotics can be a poor value proposition due to limitations on use to avoid resistance and the high level of competition from established (and cheaper) generic products for the vast majority of patients infected with susceptible organisms. Thus, policymakers have sought to offer incentives to alter the ratio.8

Antibiotic incentive proposals have emerged from numerous sources.9,10 Some have suggested enhancements related to early research and development, including grants, fellowships, and other funding for investigational and translational research, research tax incentives and credits, and systems of open access research to allow investigators to better share promising research results. Others have advocated for incentives that accrue later and reward successful antibiotic development, such as monetary awards or prizes and early purchasing commitments upon successful development. The Infectious Diseases Society of America, for example, advocates for a combination of push and pull incentives, in addition to expansion of private–public partnerships (PPPs).11 Others have suggested harmonizing regulatory approval processes between FDA and EMA, noting differences in approval processes between the U.S. and Europe.12

Among the most controversial incentive programs for antibiotics are ones that affect the regulatory approval process and ones that target antibiotics’ market exclusivity periods to attempt to encourage private investment in research and development. In this...
review, we examine proposals intended to enhance new antibiotic availability by changing Food and Drug Administration (FDA) review to expedite antibiotic approval and offering enhanced possibilities for market exclusivity. We explore the practical, ethical, and legal parameters of these options.

1. Regulatory approval of antibiotics

Before prescription drugs can be administered to patients in the US, they must be approved by the FDA, a process through which the manufacturer gathers data on the investigational product that is subsequently reviewed by expert regulators to determine whether the benefits of the drug outweigh the risks for the intended indication. The clinical trials necessary to demonstrate substantial evidence of a drug’s efficacy and sufficient safety take about 5–7 years on average and, large, Phase 3 comparative trials can cost sponsors tens of millions of dollars. Evidence from the past decade of antibiotic approvals suggests that most antibiotics are studied in two pivotal Phase 3 trials. The number of patients enrolled in each trial is similar to the number of patients enrolled in trials of other drugs, like cancer drugs, and even fewer on average than the number of patients enrolled in new trials of antivirals. Data also indicate that, compared to drugs for other diseases, antibiotics are significantly more likely to progress from one phase of clinical trial testing to the next, and in particular are about 20% more likely to be approved after reaching Phase 3 than non-antibiotics.

Despite the advantages in likelihood of FDA approval that antibiotics have demonstrated over other drugs, the pharmaceutical industry and some patient representatives have pushed to further expedite the drug development and FDA review processes to encourage the study of antibiotics for multidrug resistant organisms. These include reliance on surrogate endpoints such as biomarkers, use of noninferiority hypothesis designs for key pre-approval clinical trials, and most recently, development of an expedited development track specific for antibiotics called the Limited Population pathway.

1.1. Testing investigational antibiotics in noninferiority trials

Clinical trials with a noninferiority hypothesis are designed to show that the drug is not worse than existing active drugs by an acceptable degree of inferiority (the margin), usually set at 10%. The goal, according to FDA regulatory guidance, is to demonstrate that any difference between the two treatments is small enough—that the effect is not too much smaller than the active control. Three criteria are required for the noninferiority trials: (1) the control drug must be effective; (2) a small decrease in effectiveness would not be detrimental to patients; and (3) the new intervention has ancillary benefits such as decreased side effects or improved dosing convenience that would help overcome any small decrease in effectiveness. One review of a decade of antibiotic approval found that most pivotal antibiotic trials used a non-inferiority design (78%). Another study found that seven of the eight antibiotics approved between 2010 and 2015 were approved using noninferiority hypotheses; only one of the eight—the one tested in a superiority design—had a novel mechanism of action.

One explanation for this reliance on noninferiority studies is that some scientists and policymakers consider superiority trials for antibiotics to be particularly challenging in terms of accruing new patients. Indeed, noninferiority trials may be useful in approving new antibiotics in certain circumstances. For example, tedizolid (Sivextro) was approved on the basis of trials using a non-inferiority hypothesis for multidrug resistant skin infections, but offered the possibility of decreased adverse effects compared to the previously-approved antibiotic linezolid (Zyvox).

But noninferiority trials are also problematic for multiple reasons. Technically, demonstration of noninferiority does not necessarily mean that the new drug is as good as its comparator, but this nuance is not usually communicated to physicians and patients. In addition, when successive drugs are all tested in noninferiority trials against each other, there can be a downward trajectory in effectiveness, which is also called “biocreep.” Finally, noninferiority testing may show that new products work at least almost as well as existing products for treatable conditions, but that approach does not address the essential policy issue that has led to greater attention to the area of antibiotic development—the need for new treatments for emerging threats from multidrug resistant bacteria.

1.2. The Limited Population pathway

In 2015, the US House of Representatives passed the 21st Century Cures Act, which contained a provision called the Limited Population pathway. A similar provision regarding limited population antibacterial drugs, with support from the Infectious Diseases Society of America (IDSA), multiple professional societies, and pharmaceutical companies, was to be included in the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. However, IDSA added an important clarification: “[t]he mechanism will not be used to approve drugs to treat more common infections or those for which sufficient alternative options exist.” When the proposal was not included in the final version of FDASIA, the concept was expanded upon in a 2013 Lancet Infectious Diseases article from an author team led by John Rex, the Chief Strategy Officer of the Infection Business Unit at AstraZeneca.

The stated purpose of the most recent iteration of the pathway, as described in the 21st Century Cures Act, is to expedite the development and availability of treatments for serious or life-threatening bacterial or fungal infections in patients with unmet needs, while maintaining safety and effectiveness standards for such treatments. Antibiotic manufacturers would be able to base applications for market approval on data including traditional endpoints, alternate endpoints, or a combination of the two, as well as datasets of a limited size. Types of acceptable data would include (1) pre-clinical, pharmacologic, or pathophysiologic evidence; (2) nonclinical susceptibility and pharmacokinetic data; (3) data from phase 2 clinical trials; and (4) “such other confirmatory evidence as the Secretary determines appropriate to approve the drug.” Approved antibiotics would have to carry a disclaimer on their labels, with data obtained in the post-approval period intended to replace traditional pre-approval studies.

By permitting approval for new antibiotics based on studies in limited patient populations rather than full clinical trials, the pathway would allow antibiotics to reach the market more quickly. This would obviously be attractive to companies thinking about investing in antibiotic development, since they would have to spend less on preapproval studies before they could start earning revenue on the drug. There may also be some clinical benefits from the pathway, in that the sooner new antibiotics are brought to market, the sooner they can be used, which may be useful for a drug for a rare or multidrug resistant infection.

However, the proposed pathway also has important negative public health implications. The data quality and rigor supporting the product would naturally fall far short of the well-controlled investigations required of most FDA-approved drugs. Though patients with life-threatening infections may be willing to accept the risks associated with being prescribed untested products, there are not sufficient systems in place to ensure that prescribing of...
pathway-approved drugs would be limited to such a very narrow set of patients. The company marketing the drug will face substantial pressure from its investors to increase revenues by maximizing its use for infections in which only in vitro activity has been demonstrated or for other off-label uses. In recent years, pharmaceutical manufacturers’ freedom to make off-label claims about their products has been supported by certain courts as a type of right to unfettered commercial speech, so it is not hard to imagine drugs with ‘Limited Population’ designations being subject to substantial off-label promotion.27

In addition, the proposed 21st Century Cures bill in the House and the companion DISARM Act in the Senate propose to strengthen antibiotic payments under the new technology add-on program (NTAP) that compensates hospitals for using newly-approved drugs.23,28 The NTAP option has existed since 2001, but between 2001 and 2015, CMS approved only 19 of 53 requests for inclusion,29 and the program has had limited impact on upstream research and development.30 Using the NTAP to extend coverage for new antibiotics developed under the proposed limited population pathway might have the unintended consequence of incentivizing off-label use by providers and institutions, with important patient safety implications.

1.3. Types of trial endpoints

Surrogate endpoints (including biomarkers) are markers of disease, such as laboratory tests or imaging studies, rather than actual clinical endpoints. Surrogate endpoints are a more convenient and cost-effective approach to studying investigational drugs because they can shorten trial duration and the number of patients that need to be enrolled to show a significant effect. In the antibiotic context, surrogate endpoints have been employed to help accelerate development. For example, in pre-approval studies for bedaquiline (Sirturo), a novel agent for multidrug resistant tuberculosis, the surrogate marker of disease response used was sputum clearance of mycobacteria after 8 and 24 weeks; bedaquiline demonstrated significantly faster sputum clearance, although by later study dates, total clearance was statistically comparable to the placebo control group.31 Though sputum clearance has practical significance for isolation protocols, its use as a surrogate marker for antibiotic approval is problematic in the context of the substantial risks that also emerged in the trials. In two phase IIb trials of bedaquiline, those taking the trial drug had a 5-fold increased risk of death compared to patients in the placebo arm.32

Surrogate endpoints are more appropriate for use in pivotal clinical trials supporting approval of new antibiotics when they have been previously validated. For example, the 2015 report of the Biomarkers Consortium for the Foundation of the National Institutes of Health has validated early-response endpoint measures for community-acquired bacterial pneumonia (improvement in 4 symptoms—cough, dyspnea, chest pain, and sputum production—after 4 days) and acute bacterial skin and skin structure infections (control of lesion spread within 2–3 days).33

If surrogate endpoints are not validated, they may not reliably predict important health benefits for patients, and it becomes harder for patients and physicians to weigh the benefits and risks of a drug when the known benefits only include markers of disease rather than actual patient endpoints such as morbidity or mortality.34 Despite the risks associated with use of surrogate endpoints in pre-FDA-approval clinical trials, their enhanced use features prominently in some proposals intended to enhance antibiotic development. The 21st Century Cures legislation, for example, allows antibiotics to qualify for the limited population pathway by virtue of their effect on surrogate (‘alternate’) endpoints along with other supporting data.23,35

1.4. Priority review vouchers

Priority review vouchers were created by legislation in 2007 and applied to drugs treating certain qualifying neglected tropical diseases, most of which were infectious diseases potentially susceptible to antibiotic therapy.36 The goal of the program was to incentivize development of treatments for conditions most prevalent in underdeveloped countries with poor and marginalized populations, where limited possibility for commercial success has not attracted sufficient private investment. Priority review vouchers are earned when a qualifying drug is FDA-approved, and the sponsoring company can either use the voucher to obtain priority regulatory review (a decision within a 6-month time window) of a different compound in its portfolio that had qualified for standard (10-month) review, or sell the voucher to another company. The FDA has awarded 4 tropical disease PRVs as of July 2016, and vouchers have sold for amounts ranging between $67.5 million and $350 million.37

There is little evidence that the program’s primary intention of spurring novel drug development for tropical diseases has been met in the first 8 years of its existence; on the contrary, two companies have earned windfalls for bringing antimicrobial products through FDA regulatory review that were already widely used around the world without conducting any additional research. Recently, FDA officials have criticized the program because they believe it does not provide sufficient resources to support shifting products on the review queue.38

1.5. The role of post-market surveillance

Increased postmarket surveillance of new antibiotics could greatly aid detection of adverse events and increase patients’ confidence in drugs approved based on less rigorous pre-approval testing data. The growth of large claims databases in recent years has permitted gains in researchers’ ability to conduct postmarket surveillance, and these have been leveraged by the FDA in its Sentinel system. Since 2007, the FDA has been authorized to impose risk evaluation and mitigation strategies (REMS) on new drugs exhibiting signals of safety risks, including requirements for enrolling in registries that can be used to clarify drug safety concerns.39

While post-approval surveillance may be useful to address safety questions, it is very challenging to use observational studies to evaluate a drug’s efficacy. The essential question regulators face when approving new antibiotics—tested via noninferiority trials, on the basis of surrogate endpoints, or via a limited population or some other expedited regulatory pathway—is whether these drugs will work in patients with resistant infections. Ultimately, early approval and reliance on postmarket surveillance imposes heightened risks on the public, and should thus be employed judiciously.

2. Regulatory exclusivity

Another strategy intended to encourage new antibiotic development has been to provide additional market exclusivity incentives based on regulatory approval. The period of market exclusivity after a new drug’s approval allows a company to charge high prices and earn revenues on its product in order to recoup costs associated with research and development. At baseline, all new drugs receive a minimum of 5–7 years of market exclusivity as a consequence of regulatory approval, while the maximum length of market exclusivity depends on how much time remains on a drug’s 20-year patents at the time of approval. The median length of time of market exclusivity for top-selling infectious disease products was
recently found to be 14.4 years (interquartile range 11.6–16.0 years), with antibiotics (and antifungals) specifically coming in at 14.0 years.40

Policymakers have long considered altering one or more of the factors contributing to a drug’s market exclusivity period to encourage greater investment in the field. For example, in 2006 the US Government Accountability Office suggested that patents for drug treating multidrug resistant bacteria could last 25–30 years.41 Other scholars have proposed even longer patent lengths for antibiotics that target resistant organisms.42,43 Two such strategies for extending market exclusivity have been taken up by Congress in recent years.

2.1. The GAIN Act of 2012

The FDA Safety and Innovation Act of 2012 contained a section called Generating Antibiotic Incentives Now (GAIN), which authorized the designation of new antibiotics as Qualified Infectious Disease Products (QIDPs). A QIDP designation provides the sponsor with 5 additional years of regulatory exclusivity for antibiotics, for a total of 10–12 years.44 The FDA has generated a list of more than 20 ‘qualifying pathogens’ for which QIDP applications can be based.45 As of December 2015, 58 drugs have received the QIDP designation, and of those, 6 are now FDA-approved.46

While the QIDP designation may help provide additional financial guarantees for drugs that reach the market, the designation does not help differentiate important new antibiotics from those with only minor incremental advantages; the designation can be awarded regardless of novelty of drug or severity of infection. Also, given that most antibiotics already receive more than 10–12 years of market exclusivity, it is unclear whether this designation provides a strong enough incentive to stimulate innovation. One analysis using time discounting suggests limited value to a 5-year extension of market exclusivity; the authors suggest lengthening the duration of market exclusivity to 10 years, in addition to extending push incentives for antibiotic development.47 QIDP designation and market exclusivity provisions will likely need to be combined with other incentives in order to persuade companies to engage in pre-clinical testing of antibiotics, given the long lag time between pre-clinical testing and the market exclusivity extensions.48

2.2. Wildcard exclusivity/antibiotic vouchers

Over the past decade, there have also been proposals to offer sponsors of new antibiotics benefits that could be transferred to other products. For example, in 2005, legislators proposed to award, in exchange for receiving approval for a new antibiotic, a wildcard exclusivity voucher of up to 2 years that could then be applied to extend the patent of any blockbuster drug already on the market.49 An earlier draft of the 21st Century Cures Act had a similar provision that would amend GAIN to allow one of the five years of exclusivity to be applied to one or more other drugs.49

In exchange, the rights–holder of the recipient drug was to donate up to 5% of sales of the blockbuster drug during that year to the NIH. A similar-sized donation was to be given to a ‘bona fide, independent patient assistance program.’ This wildcard proposal did not make it into the final bill passed by the U.S. House of Representatives.

Though certainly appealing to pharmaceutical companies, wildcard exclusivities could have astonishing cost implications. The cost of conducting an antibiotic trial would be in the tens of millions of dollars; the net profit from a wildcard voucher could be in the tens of billions.40 Proposed use of wildcard vouchers to antibiotics has recently been resurrected, although one analysis highlighted several flaws: (1) the duration of market exclusivity can potentially have tremendous costs (in terms of both patient access and affordability); (2) a significant mismatch between financial value and effort may result; (3) no clear method of rewarding transformative drugs exists; and (4) if vouchers are granted for antibiotics, other interest groups will lobby for inclusion.40 Proponents assert that meaningful limits, such as caps on financial value, can be placed on such vouchers to protect societal interests.41

3. Conclusions

With emerging infectious diseases and multi-drug resistant bacteria, US policymakers have understandably prioritized strategies intended to encourage antibiotic development (see Table 1). Two of the most contentious types of these policies include: (1) expediting development of new antibiotics by lowering evidentiary standards traditionally applied by the FDA, reducing time to market and lowering costs for drug sponsors; and (2) extending market exclusivity for that product (or a more successful drug).

Although well-intentioned, these proposals have numerous flaws. First, changing regulatory standards assumes that FDA rules have been the bottleneck in slowing the development of new antibiotics over the last 2 decades, despite lack of evidence regarding this principle. Moreover, the expedited pathways proposed have numerous risks to patients that have not been fully accounted for in their design. For example, while it is reasonable to expedite development of promising products to treat unmet medical needs, the testing of many antibiotics in non-inferiority trials means that the drugs are not being directed against multidrug resistant infections, and the lack of meaningful central controls on prescribing after approval opens these products up to widespread off-label use. A better solution would be to restrict expedited pathways to drugs tested in patients with resistant infections, and though we recognize the limitations discussed by FDA senior staff regarding superiority studies, 19 they should continue to be encouraged to facilitate development of antibiotics directed at patients with unmet medical needs, including resistant organisms. We also recognize a need for controls on physicians’ abilities to prescribe these antibiotics off-label, perhaps through attachment of Risk Evaluation and Mitigation Strategies, in which the FDA can require central registration of patients or physicians prior to use of the drug.

A second major assumption is that pull incentives extending market exclusivity periods are the best way to stimulate investment in new antibiotic development. While effective market exclusivity periods are of course essential to the pharmaceutical market, there is no evidence that market exclusivity periods are too short for antibiotics. In addition, such incentives are not optimally directed, since revenues related to approved drugs are more likely to accrue to the large pharmaceutical manufacturers that tend to acquire successful products, while there is evidence that original innovation in the antibiotic market occurs primarily in publicly-funded institutions and is continued by small- and moderate-sized companies. Success may drive acquisition of those companies or product lines by larger companies. Nonetheless, effective antibiotic innovation will largely need to be targeted at the scientists and institutions most likely to develop the breakthroughs that will help contribute to the public health fight against growing antibiotic resistance. When incentivizing research and development of new antibiotics, we must also carefully weigh the benefit of shorter, lower-cost trials if it means continued development of follow-on antibiotics with limited societal benefit, as opposed to the truly transformative drugs we need to address the most lethal pathogens of our time.
## Summary of some prominent regulatory policy interventions to promote antibiotic research and development

<table>
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<tr>
<th>Policy intervention</th>
<th>Status</th>
<th>Details</th>
<th>Benefits and Risks</th>
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<tr>
<td><strong>Policies affecting the way antibiotics are approved</strong></td>
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<td>Surrogate/composite endpoints in clinical trials</td>
<td>SurAlready in common use</td>
<td>Shortens duration and reduces number of enrollees needed to show efficacy in pivotal trial of investigational drug. Currently prevalent in pivotal trials of antibiotics</td>
<td>• Validated surrogate endpoints can predict clinical outcomes, although few surrogates used in antibiotic trials have been rigorously validated&lt;br&gt;• Drugs reach market and target populations sooner&lt;br&gt;• Non-validated surrogate markers do not necessarily correlate with patient-centered outcomes such as mortality</td>
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<td>Clinical trials with a noninferiority hypothesis</td>
<td>Already in common use</td>
<td>Study design that allows investigational drug to be tested in situation when a highly effective drug already exists, and a small decrease in effectiveness would not be of detriment to patients. Current basis for nearly all pivotal trials of antibiotics</td>
<td>• Permits approval of wider diversity of antibiotics based on testing in common clinical scenarios&lt;br&gt;• New drugs could have ancillary benefits such as decreased side effects or improved dosing convenience&lt;br&gt;• Successive noninferiority studies can lead to biocreep, hampering ability to independently evaluate risks and benefits of subsequent drugs&lt;br&gt;• Antibiotic is tested in population of patients with treatable condition, not in setting of multidrug resistant</td>
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<tr>
<td><strong>Priority Review Vouchers (PRVs)</strong></td>
<td>Enacted in 2007, extended in 2012</td>
<td>In exchange for obtaining FDA approval for drugs treating neglected tropical diseases (2007), most of which are infectious diseases necessitating antibiotic therapeutic options, the sponsoring company receives a voucher allowing it to obtain ‘priority review’ by the FDA of another drug (a 6-month time frame rather than the standard 10-month time frame)</td>
<td>• Commercial value of PRV adds financial incentive for antibiotic development&lt;br&gt;• Only one of eight PRVs has been used; the others have been sold for millions of dollars&lt;br&gt;• Sale of vouchers decreases incentive to market and sell the new antibiotic&lt;br&gt;• No clear evidence that PRV program has stimulated production of new tropical disease drugs&lt;br&gt;• Cost-benefit analysis suggests corporate windfalls for comparatively small investments in research and development&lt;br&gt;• Patients with life-threatening conditions may be willing to absorb greater risk (and cost) in exchange for getting drugs sooner&lt;br&gt;• A limited population label is supposed to limit use of the drug to its target population, but there is no evidence that off-label use could be prevented&lt;br&gt;• Substantially increased risk that the drugs are later shown to be ineffective or unsafe, and use the drugs could induce resistance to related products&lt;br&gt;• Postmarket surveillance of drugs is not currently optimized despite recent innovations like the Sentinel system</td>
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<td>Limited Population pathway</td>
<td>Passed by U.S. House of Representatives in 2015, proposed in U.S. Senate in 2016</td>
<td>Expedited pathway specific for new antibiotics based on the principle that the more essential the new antibiotic is for a given population, the less rigorous the data collected prior to approval</td>
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<td><strong>Policies affecting market exclusivity periods for approved antibiotics</strong></td>
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<tr>
<td>Qualified Infectious Disease Products (QIDPs)</td>
<td>Enacted via Generating Antibiotic Incentives Now Act of 2012; 58 compounds currently have QIDP status</td>
<td>Extends guaranteed minimum exclusivity period for QIDPs based on FDA approval from 5–7 years to 10–12 years</td>
<td>• Provides additional period of reimbursement particularly relevant to antibiotics with no patent protection or only a few years remaining on their patents&lt;br&gt;• Promise of additional market exclusivity might encourage private investment in antibiotic development&lt;br&gt;• Median exclusivity period for top-selling products is already 12–14 years so unclear whether additional 5 years offered will have real effect&lt;br&gt;• Disconnect between early development (often in academic centers and by small- and medium-sized companies) and market exclusivity (often awarded to large pharmaceutical company that bought rights to the drug)</td>
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References and notes