Innovation of Novel Antibiotics: An Economic Perspective

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Despite the public attention to antibiotic overuse and the specter of antimicrobial-resistant pathogens, current infections necessitate the use of antibiotics. Yet, patients and providers may not fully consider the societal cost associated with inappropriate antimicrobial use and subsequent resistance. Policies intended to limit use to minimize resistance must be balanced with the competing concern of underutilization. It is difficult to determine whether research and development incentives or reducing the costs of bringing new antibiotics through expedited review will be sufficient. Likely, the most effective method would be allowing higher prices for use deemed to be clinically appropriate. The ultimate policy goal is to ensure that antibiotics are used appropriately, with the right patients receiving the right medication at the right time, and that the world has a steady stream of future antibiotics to effectively treat the resistant organisms that will inevitably emerge.

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Despite the public attention on antibiotic overuse and the specter of antimicrobial-resistant pathogens, current infections necessitate the use of antibiotics. Unlike other clinical services, however, the development of antimicrobial resistance impacts not only the patient who receives the antibiotic but also society at large, because of the potential for transmission of resistant organisms. Individual patients and providers may not fully consider the costs to society associated with inappropriate antimicrobial use and subsequent resistance.

Common definitions of appropriate use include consideration of clinical appropriateness (clinical benefit exceeds clinical risk) and economic appropriateness (clinical benefit exceeds clinical risk and cost). From a societal perspective, clinical risk would include the impact of use on future resistance. For this reason, the greater the impact of use on future resistance, the lower optimal utilization should be. Conversely, as the likelihood of the development of future effective therapies increases, the definition of optimal use expands accordingly.

In some instances, utilization may be greater than optimal, with key contributors including diagnostic uncertainty and demand from consumers. A 2013 Centers for Disease Control and Prevention report states that perhaps half of all antibiotics used in humans are unnecessary, with other research suggesting that around a quarter of antibiotics are prescribed for conditions that rarely indicate their use, such as viral upper respiratory tract infections [1, 2]. Providers’ ill-defined criteria for selecting which patients receive antibiotics are likely exacerbated by consumers pressuring caregivers for antibiotics (or other pharmaceutical solutions), with an expectation that if someone shows up sick at a doctor’s office, they should leave with a prescription [3].

Because the development of resistance is a reality, yet is imprecisely predicted, we must continuously innovate. In fact, the history of antibiotic discovery has mimicked a cat-and-mouse game, with more powerful drugs developed to treat the mutated pathogen that a previous antibiotic precipitated. An example of this progression is demonstrated by the development of methicillin-resistant Staphylococcus aureus, an organism that was effectively treated by vancomycin until vancomycin-resistant S. aureus emerged. Now, multidrug-resistant pathogens, particularly gram-negative

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bacteria, are rendering even powerful antibiotic combinations ineffective.

However, overuse is the not the only problem with antibiotic prescribing—there are also substantial clinical and economic costs associated with underuse of appropriate antibiotic therapy. A large body of research substantiates that when an appropriate antibiotic regimen is delayed or not started at all, negative clinical consequences, including preventable death, result [4–7]. Much of this underutilization is likely due to clinical uncertainty of a case, although some evidence suggests that cost concerns play a large part in drug choices when treating infectious diseases, with 87% of hospital providers citing cost reduction as a major driver of antibiotic stewardship programs [8]. This restriction of appropriate antimicrobial therapy not only has detrimental consequences on patient outcomes, but it also creates a unique and somewhat paradoxical circumstance, as this restraint reduces the financial incentives for the development of novel agents.

Policies intended to limit use to minimize resistance, preserve antibiotics for future use, and/or contain antibiotic expenditures, such as those restricting the most effective agents until after other agents fail to bring cure, must be balanced with the competing concern of underutilization. Two extremes demonstrate this balance. One extreme would be to ignore resistance and assume that innovation will always develop effective new agents. The other extreme is to fully incorporate the impact of utilization on resistance and presume no future innovations. The first case fails to recognize the possibility that future development will not keep pace with resistance, whereas the second case ignores future innovations. Thus, determining “appropriate use” of antibiotics will always be controversial because 2 critical variables—the contribution of use to resistance and the development of agents to overcome that resistance—are impossible to precisely estimate.

Paradoxically, at the same time that the clinical and economic impact of resistance is rising, the approval of new antibiotics has decreased precipitously over the past 30 years. Although the scientific difficulty in developing new antibiotics may be increasing, as microbes become resistant to an ever-increasing array of treatments and identification of novel targets is challenging, the most commonly cited explanation of the decrease in approval is that the market lacks sufficient economic incentives [9]. As of 2013, several major pharmaceutical companies have either discontinued or scaled back their antibiotic research and development (R&D) efforts. Among those drugs that are in the pipeline, very few seem likely to target resistant pathogens specifically [10–15]. The reduction in financial incentives to innovate stems, in part, from efforts to restrict utilization of novel antibiotics. As a result, new drugs must compete for a relatively small slice of the total antibiotic market. In addition, antibiotics may face a shorter market life span because of resistance, rendering the drug less effective over time. Because the current market is dominated by generics that are currently effective at treating many pathogens, a manufacturer must also consider that there is substantial competitive price pressure for any new entrant. The relatively short prescription length of 4–6 days also poses a problem, as patients (and payers) may balk at the relatively high price of a single antibiotic dose in comparison to the price of a single dose of a chronic medication.

Policies aimed at addressing the gap in innovation for rare “orphan” disorders over the past 30 years are a useful case to compare with the current antibiotic situation. Drugs that treat orphan disorders, such as enzyme replacement therapy for Gaucher disease, face a substantial quantity restraint. Prior to the 1980s, drug manufacturers saw orphan disorders as offering a comparatively low potential return on investment when the alternative was investing in a drug with a larger user population. Acknowledging the gap in innovation for orphan disorders, the United States passed the Orphan Drug Act of 1983, which conferred several benefits on manufacturers conducting research in qualified diseases, including tax advantages and enhanced patent protection.

**CHANGING THE INCENTIVES FOR INNOVATION**

Incentives to innovate depend on profit relative to R&D cost. Several policy options should be considered to ensure access to effective antibiotic therapies.

**Research Subsidies**

One approach would be to subsidize R&D for antibiotic innovation. There are several drawbacks to this strategy, most notably that research subsidies are difficult to target. Simple cost-based subsidies (eg, paying a percentage of R&D cost) would encourage inefficiency in research, just as cost-based reimbursement in healthcare encouraged inefficiencies in care delivery. Subsidies would need to be targeted toward the most promising areas, yet such targeting is difficult, given the uncertainty of R&D. Despite these concerns, many policies have been aimed at reducing the costs associated with drug discovery by trying to expedite the regulatory approval process and will likely encourage more focus on this area. Whether these current incentives are enough to stimulate innovation remains to be seen.

**Extended Market Exclusivity**

An alternative approach is to encourage innovation by offering extended market exclusivity, thus allowing manufacturers to command a higher price for a longer period to gain a greater return on the R&D investment. The Generating Antibiotic Incentives Now Act, for instance, extends the market exclusivity period from 5 years to 10 years for certain antibiotics [16]. However, the extension of exclusivity may not be enough to overcome the downward pressure on utilization and prices, especially if the effective life span of these new antibiotics is shortened by the development of resistant pathogens.
Increase Reimbursement

Given the concern over resistance, expanding the market by increasing utilization is not an appropriate strategy to improve innovation incentives. In fact, because of the relatively small pipeline of antibiotics and the increase in resistant pathogens, there is great concern that new drugs will not keep up with developing pathogens. If this becomes the case, it will put even more burden on policy makers and practitioners to reduce utilization of newer antibiotics. Under the assumption that policies will continue to put downward pressure on the utilization of novel antibiotics, the only remaining mechanism to increase innovation incentives is to increase price. Smaller markets of higher-priced drugs have been successful in certain specialty medications, and the current trend toward biologics points to the willingness of developers to enter smaller markets. Although the price per treatment is significant, the total number of patients needing treatment is small, and thus total expenditure would not increase significantly across the whole population. Moreover, given the cost-effectiveness of these agents when used appropriately—even when priced very high—a strategy of limited use at a higher price would increase the value generated by the healthcare system.

There are already a few examples of policies aimed at increasing the reimbursement for new antibiotics. In the United States, the New Technology Add-on Payment program introduced in 2001 provides a mechanism for new medical developments to be paid separately to inpatient diagnosis-related groups (DRGs) [17]. Because DRGs bundle payments for an admission into 1 prospective payment, the introduction of new (and expensive) technologies is discouraged, even if the services provide substantial value. Carving out an additional payment reduces a hospital’s incentive to minimize costs associated with new technologies, thereby reducing the price pressure on manufacturers of the technology. Other US federal programs could work in a similar way. For example, new antibiotics could be excluded from 340B pricing. The 340B Drug Pricing Program requires drug manufacturers to provide outpatient drugs to certain health facilities, particularly those that provide care to underserved populations such as critical access hospitals, at significantly reduced prices. Excluding novel antibiotics from this requirement would decrease the price pressure on manufacturers and create more economic incentive for potential developers to see a promising return on investment, although any such initiative must be balanced with the distributional concerns of raising prices for underserved populations.

CONCLUSIONS

There is no magic bullet to guarantee innovation in antibiotic development. It is difficult to determine whether R&D incentives or reducing the costs of bringing new antibiotics through expedited review will be sufficient. Likely, the most effective method would be allowing higher prices for use deemed clinically appropriate. While this strategy may increase the total costs to payers, a strategy of limited use at a higher price could increase the value generated by the healthcare system. Furthermore, an increase in price must be coupled with antimicrobial stewardship to protect against overutilization and reduce selective pressure for resistance. Simultaneously, strategies to reduce underutilization, which could lead to adverse health outcomes for patients, will be important. Quality measures that capture both overuse and underuse will be necessary to promote the optimal utilization of these highly valuable medications. The ultimate policy goal is to ensure both that antibiotics are used appropriately, with the right patients receiving the right medication at the right time, and that the world has a steady stream of future antibiotics to effectively treat the resistant organisms that will inevitably emerge.

Notes

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