

How Misaligned Incentives Influence Antibiotic Prescribing and Resistance

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Summary

Antibiotic resistance is a significant threat to public and patient health. Its emergence has significantly reduced a physician's ability to treat infections and increases the probability of mortality for patients. It also threatens to reverse significant medical gains, particularly the ability to perform transplants and other surgical procedures that are dependent on antibiotic effectiveness. Drug-resistant infections cause significant morbidity and mortality: Approximately 2 million Americans are infected with hospital-acquired infections annually, the vast majority of which are resistant to antibiotics, resulting in about 99,000 deaths each year. Emergence and spread of antibiotic resistance is engendered by inappropriate use of antibiotics, which occurs largely because of the misalignment of incentives for using and producing antibiotics. Problems with resistant bacteria are compounded by the fact that there are also impediments to the development of new antibiotics that could be effective against these resistant organisms. All these problems are systemic and require interventions at both the consumer and producer level to ensure the long-term efficacy of antibiotics.

Current realities

Studies have continually shown that the rate at which resistance emerges and spreads is strongly related to the total amount of drug usage. Thus, in this respect, antibiotics are similar to natural resources such as oil, water, fish, and forests: Usage “uses up” their effectiveness, diminishing them for future use. The greater the usage, the faster the resource is “depleted” (though antibiotics can be “renewed” through the introduction of new drug classes). Thinking about antibiotics in this manner provides a framework for considering the incentives that result in the overuse of antibiotics as well as under-investment in new drugs, and how to align incentives to improve the judicious use of antibiotics.

Most antibiotics in use today were invented decades ago. The rate at which new antibacterial agents have been introduced has fallen steadily for the last 40 years (see figure). One of the reasons for this is the high cost of bringing a new drug to market, a number that can exceed \$100 million. However, this figure only includes the cost of clinical trials, and does not include the cost to discover new compounds, which can be highly variable and is often more the result of luck than a targeted investigation. In addition, regulatory hurdles cause additional expense, not least of which is that antibiotics can be approved only for specific infections, not for the organism they treat (e.g. treating skin infections rather than *Staphylococcus* infections generally). In addition to the cost and uncertainty of bringing a drug to market, revenues from antibiotics are generally less than “blockbuster” drugs. For example, in 2005 Pfizer reported revenue of more than \$12 billion for Lipitor and revenue of only about \$2 billion for Zithromax (generic name azithromycin), which at the time was one of the most highly prescribed antibiotics. This disparity is largely because antibiotics are generally only taken for 7-10 days while a drug such as Lipitor is taken for months to years. In recent years this has been further impacted by the emergence of resistance, as doctors reserve new antibiotics for when they are necessary. This reduces the gains that a pharmaceutical company can make before the patent on its drug expires, further reducing their incentive to invest.

There is also a lack of incentives for pharmaceutical companies to preserve the efficacy of their drugs. One reason for this is that the categorization of drugs into classes (and thus patents) is based on the chemical structure of the active molecule of the antibiotic rather than the mechanism that engenders resistance. Thus, newly patented antibiotics may be functionally similar in terms of resistance even if

they are “different” as defined by intellectual property law. Because the resource embodied in the effectiveness of an antibiotic “class” is available to several pharmaceutical firms, no single firm has an incentive to take into full consideration the effect of its sales of antibiotics on future antibiotic effectiveness (an example of the economic theory of the tragedy of the commons). Patent expiration also plays a large role, as pharmaceutical companies have an incentive to sell as much of a drug as possible before their patent expires and generics enter the market.

Scientific opportunities and challenges

While pharmaceutical companies have incentives to push antibiotic sales, in theory doctors should only be prescribing antibiotics when they are clearly indicated. Unfortunately, we know this is not true. Despite the significant morbidity and mortality associated with antibiotic-resistant infections, and the link between increased antibiotic use and resistance, a large fraction of antibiotic use in medicine continues to be inappropriate. Inappropriate treatment results from a number of factors: (i) patient expectations/demand for antibiotics; (ii) possibility of malpractice lawsuits for not prescribing an antibiotic; (iii) time pressure on visit length (e.g., it is easier and faster to write a prescription than to explain to a patient why they do not need antibiotics); and (iv) uncertainty of diagnosis (i.e., it can be difficult to diagnose the cause of an infection).

All these factors are generally the result of not accounting for the negative externality associated with antibiotic usage. An externality occurs when an individual’s action(s) results in costs or benefits to others that are not taken into consideration by the individual. For antibiotics, there are both positive and negative externalities. The positive externality is that an infected individual will not transmit the infection once they are cured. The negative externality is that every individual that takes antibiotics produces some resistant bacteria, though this does not necessarily mean pathogenic bacteria. However, the use of antibiotics will produce some resistant bacteria (at least transiently). These resistant bacteria are transmitted to other individuals, or are excreted from the body and enter the environment, spreading resistance genes to other bacteria, including pathogenic bacteria. Despite the importance of antibiotics to medicine, patients and physicians rarely consider these externalities of antibiotic use. Thus, policy options that increase the “costs” of antibiotics to take account of these externalities will be the ones most likely to have a significant impact on antibiotic resistance.

The scientific challenges facing the health care community regarding antibiotic resistance revolve around both finding new antibiotics and preserving the ones that we currently have. With respect to new drug discovery, it is likely that much of the low hanging fruit has already been harvested. However, while drug discovery has become more expensive and more time-consuming, revolutions in computation allow for much faster discovery and testing of new antibiotics *in silico*. Challenges, though, are largely cost-based. It is expensive to develop new drugs, and regulatory hurdles can increase the challenges. On the other side of the equation is the need to increase the longevity of existing drugs. One primary means of doing this is through a reduction in the use of medically relevant antibiotics (particularly ones that are not needed for therapy). However, reducing drug use may impact the development of new drugs by reducing the incentives for production. Additional strategies, such as cycling and combination therapy, should also be explored as a means of increasing the lifespan of drugs.

Policy issues

- The dramatic decline in new antibiotics requires new strategies for encouraging investment in the discovery of new antibiotics, but these strategies need to avoid creating new disincentives. Policies that just encourage investment in new antibiotics without worrying about resistance will not fully address the long-term challenge of antibiotic resistance. For instance, financial incentives that just result in development of “me-too” antibiotics or that encourage pharmaceutical companies

to promote overuse of already approved antibiotics for fear of competition do not fully address the problem. Financial policies should thus be focused on the more difficult discovery component of research, through promotion of basic research. Additionally, public-private partnerships, which have been successful in the development of other antimicrobials in the past (e.g., antimalarials), may also be effective.

- In addition to new drugs, policies should also encourage pharmaceutical companies to care about the long-term efficacy of their drugs. Incentives such as tying patent expiration to disease incidence and resistance levels, patent consolidation (to avoid competition between drugs with the same mode of action), approval of drugs targeted at organisms rather than specific infections, or restrictions on the ability of other companies to create copy-cat drugs, present possible means of changing behavior. Conversely, fining companies or reducing their patent length due to rising rates of resistance, could present alternative (and quite formidable) mechanisms to increase a company's incentive to preserve the efficacy of a drug.
- Increasing vaccination coverage, especially for the influenza vaccine, could reduce the number of individuals becoming sick in the winter, and thus reduce the rate of inappropriate prescribing of antibiotics. Increased investment in other vaccines, such as a *Staphylococcus* vaccine, could also significantly reduce antibiotic usage rates.
- Many drug-resistant infections are the result of in-hospital transmission, thus, improving infection control could reduce the spread of antibiotic resistant infections. New technologies to track when clinicians/nurses wash their hands can help improve hand-washing compliance and may be cost-effective. Tying hospital reimbursement rates to resistance rates or not reimbursing for hospital-acquired infections (as the government has stopped doing for some infections in Medicare patients) could impact the spread of resistance. Increasing coordination among hospitals on antibiotic resistance could also help. As people move back and forth among hospitals, hospitals have less incentive to spend on infection control if other hospitals are not also spending on infection control.
- Lastly, policies to discourage inappropriate antibiotic use need to be implemented. Both through education, as well as by increasing the "cost" of antibiotics, which can be done either through higher co-pays, or by making it more difficult for doctors to prescribe. Laws to insulate doctors from lawsuits for the nonprescription of an antibiotic should also be written.

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New Antibacterial Agents Approved by FDA, 1983-2012

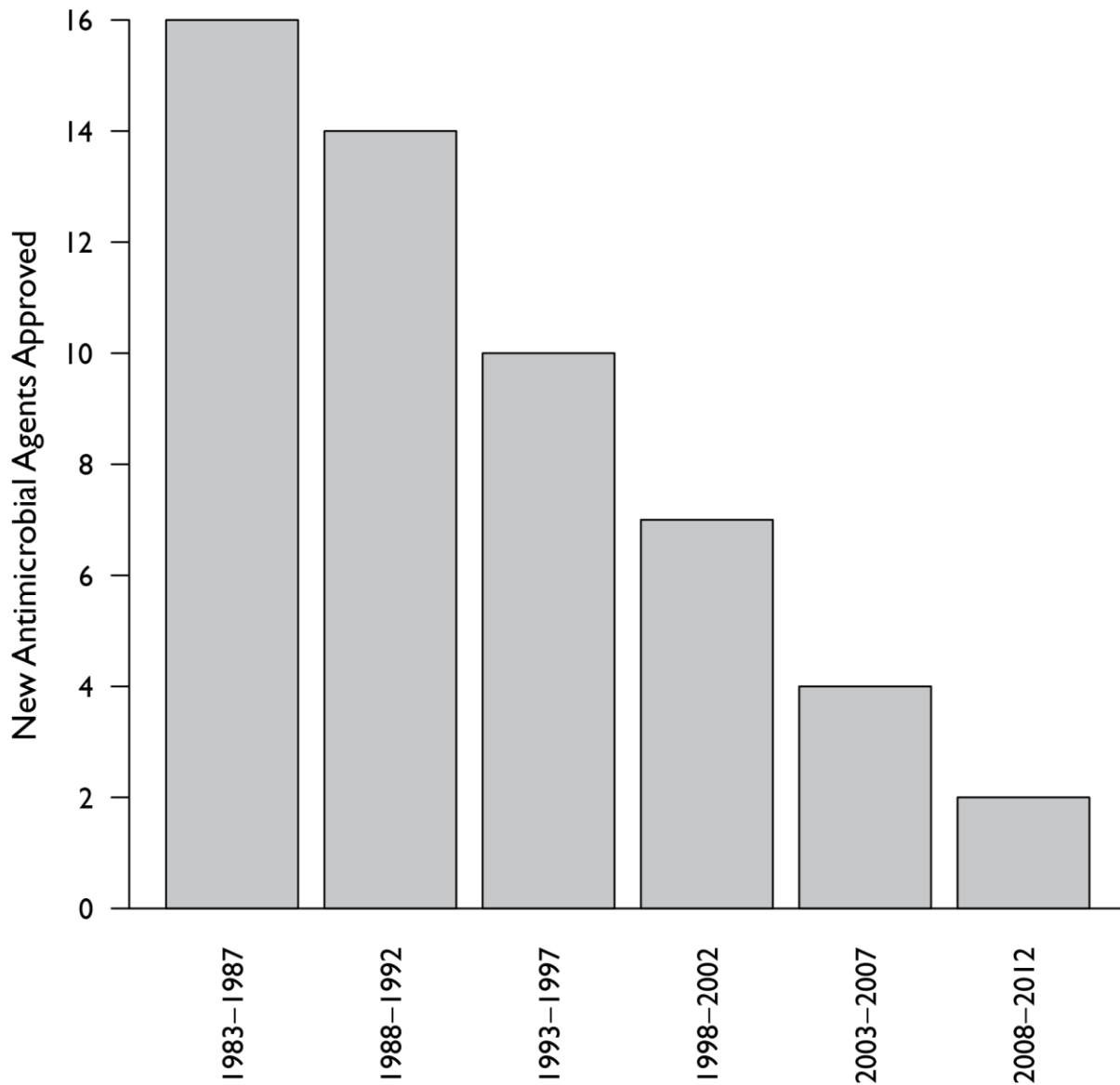


Figure: Fewer new antibiotics are being brought to market due to cost and regulatory hurdles, as well as relatively lower revenue opportunities.