Antibiotic effectiveness: Balancing conservation against innovation

Ramanan Laxminarayan

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PERSPECTIVE

Antibiotic effectiveness: Balancing conservation against innovation

Ramanan Laxminarayan*

Antibiotic effectiveness is a natural societal resource that is diminished by antibiotic use. As with other such assets, keeping it available requires both conservation and innovation. Conservation encompasses making the best use of current antibiotic effectiveness by reducing demand through vaccination, infection control, diagnostics, public education, incentives for clinicians to prescribe fewer antibiotics, and restrictions on access to newer, last-resort antibiotics. Innovation includes improving the efficacy of current drugs and replenishing effectiveness by developing new drugs. In this paper, I assess the relative benefits and costs of these two approaches to maintaining our ability to treat infections.

Since their introduction into modern medicine in 1941, antibiotics have saved millions of lives. Although access to antibiotics remains a problem—more than a million children with untreated pneumonia and sepsis die each year—the effectiveness of these drugs is declining globally, driven by ever-higher rates of antibiotic use and selection pressure for resistance (*1*). For example, gonorrhea, which was entirely susceptible to penicillin in the 1970s, is now becoming increasingly resistant to third-generation oral cephalosporins and is reemerging as a threat (*2*). Resistance elements, such as extended-spectrum β-lactamase (ESBL), NDM-1, and *Klebsiella pneumoniae* carbapenemase (KPC)–producing Enterobacteriaceae, have made many Gram-negative infections untreatable globally (*3*).

Antibiotic resistance is a problem of managing an open-access resource, such as fisheries or oil (*4*). Individual patients, doctors, pharmaceutical companies, hospitals, and even countries have little incentive to use antibiotics judiciously. Maintaining antibiotic effectiveness in the long term requires conservation, defined broadly as technological, medical, and incentive-based solutions to keep existing antibiotics working (Fig. 1); and innovation, defined as efforts to develop new antibiotics.

The two approaches are essentially linked: Just as incentives for finding new sources of oil reduce incentives to conserve oil, large public subsidies for new drug development discourage efforts to improve how existing antibiotics are used. And just as the cost of discovering new sources of oil becomes more expensive as the resource is depleted, new antibiotics are likely to cost more than existing ones—not only because the easiest-to-find resources may have been discovered but also because of higher regulatory costs (of clinical trials in the case of antibiotics and environmental protection in the case of oil) (*5*).

Conservation

Antibiotic use by humans is a significant driver of resistance. Global sales of antibiotics for human consumption increased 36% between 2000 and 2011, with Brazil, Russia, India, China, and South Africa accounting for 76% of the increase (*6*). Higher consumption was also noted for two "last-resort" classes of antibiotics, carbapenems (45%) and polymyxins (13%). Newer antibiotics tend to be more expensive but also used less frequently (Fig. 2). Reducing the need for antibiotics and reducing unnecessary antibiotic use will help keep existing antibiotics working. Reducing need is best achieved by reducing the burden of infections by: (i) improving public health and sanitation, especially in low-income countries where antibiotics are used to fill the gap created by unsafe water, poor sanitation, and deficient public health (approaches to deal with these problems are dealt with elsewhere in the special section); (ii) expanding the use of existing vaccines and investing in new vaccines; and (iii) improving hospital infection control.

The introduction of the pneumococcal conjugate vaccine has reduced the burden of pneumococcal disease, avoided many prescriptions for antibiotics, and lowered rates of invasive disease caused by strains not susceptible to penicillin. In the United States, resistant pneumococcal strains decreased by 59% between 1999 and 2004 to 1.7 cases per 100,000 (*7*). However, fewer than a quarter of the world's children are protected by pneumococcal conjugate vaccination, which is not yet part of the routine immunization programs in India and China. Furthermore, only 14 to 48% of health care workers in Europe reported being vaccinated against seasonal influenza (*8*), a common trigger for an inappropriate antibiotic prescription or for use against secondary infections. Unfortunately, a vaccine against *Staphylococcus aureus*, the most common cause of postoperative infection, has remained elusive, and recent trials have not been promising (*9*).

Reducing antibiotic overuse is the other part of conservation. In many low- and middle-income countries, nonprescription antibiotic use contributes to resistance (*10*). Even when prescriptions are needed to obtain antibiotics, physicians may not adequately screen for appropriate use. A potential solution is to allow over-the-counter access to first-generation antibiotics while more strictly regulating newer-generation antibiotics. Addressing fevers in low- and lower-middle–income countries through integrated management of childhood illnesses could reduce the burden of disease while also lowering antibiotic use (*11*, *12*). Improving hospital infection control through surgical infection prophylaxis, skin preparation, and preoperative

Fig. 1. Activists of the alliance My Agriculture protest against the use of antibiotics in intensive livestock farming in front of the Federal Chancellery in Berlin, Germany, on 18 January 2012. Several protesters dressed as chickens advertised another demonstration to take place on 21 January 2012. [Credit: EPA/Maurizio Gambarini]

Center for Disease Dynamics, Economics & Policy, Washington, DC, USA; Princeton Environmental Institute, Princeton, NJ, USA; Public Health Foundation of India, New Delhi, India. ***E-mail: ramanan@cddep.org**

screening and decolonization can reduce the need for antibiotics, particularly in resource-poor settings that have made less progress in limiting health care–associated infections (*1*).

In many high-income countries, patient norms drive expectations for antibiotic prescribing (*13*). Public education, such as the French effort that led to a 5% reduction in the number of antibiotic prescriptions over the first 5 years (*14*), or the annual mass media campaigns in Belgium that reduced antibiotic prescriptions by 36% between 1999–2000 and 2006–2007 (*15*), should be deployed in high-prescribing countries (*16*).

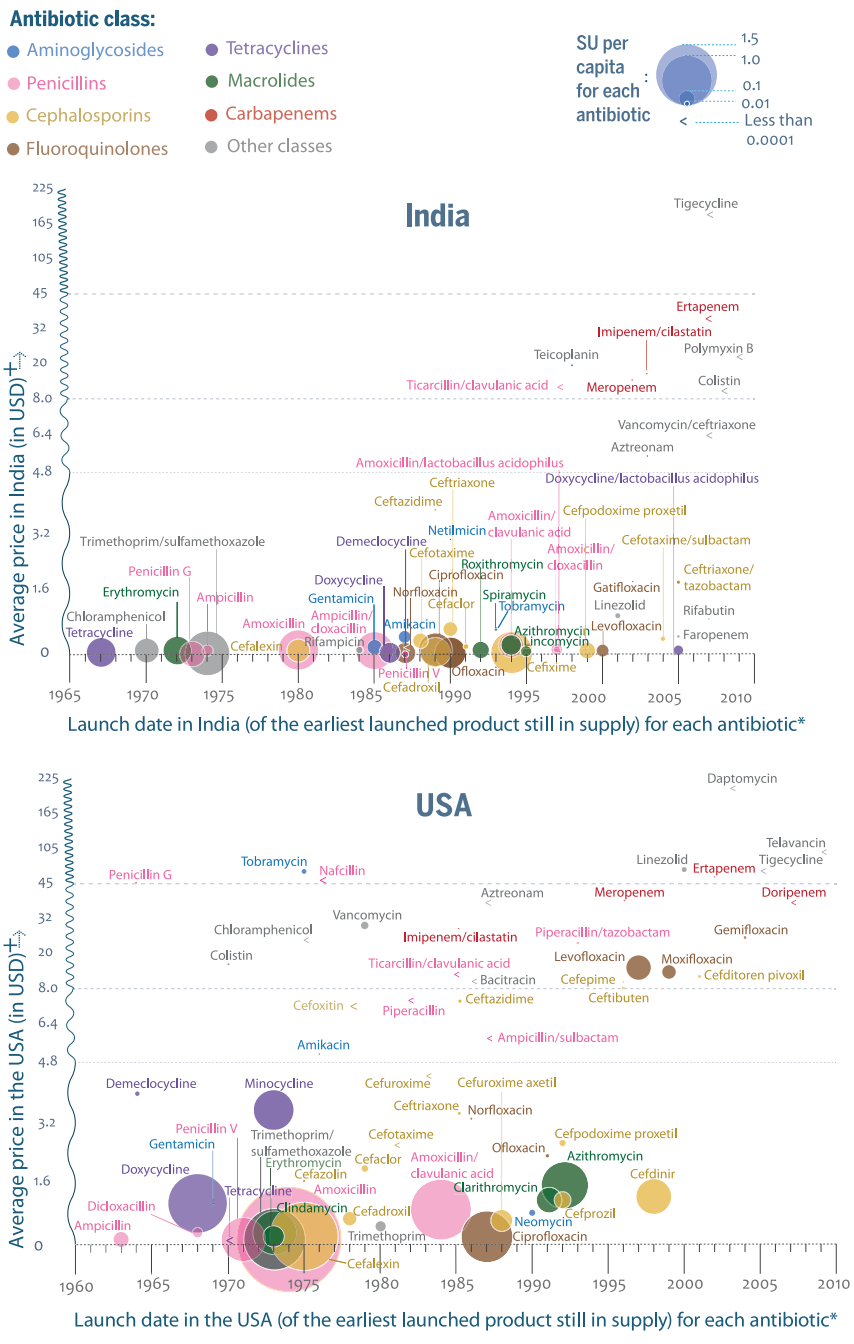

Fig. 2. Consumption of select key retail antibiotics in the United States and India in 2010, by year of market introduction and price. Bubble sizes correspond to the estimated quantity of standard units (SUs) per capita dispensed in the retail sector in 2010. Variable scaling is used on the y axis. Antibiotics that do not have sales data, revenue data, or the launch date reported are not shown. In the U.S. section, aztreonam/lysine, launched in 2010 with estimated sales of 318 SUs at an average price of $3750 USD during 2010, is not shown. *The date of market launch may differ from this measure. +The average price for each antibiotic is estimated by dividing total retail sales revenue by the number of SUs sold in the retail sector. [Data source: IMS MIDAS]

In China, hospitals that rely on pharmaceutical sales for income have an incentive to overprescribe; one study estimated that a quarter of the revenue in two hospitals came from antibiotic sales (*17*). In India, doctors routinely receive compensation from drug sellers in exchange for directing patients to their pharmacies (*18*). In Taiwan (*19*) and other parts of the world, antibiotic prescribing may also be influenced by competition between health care providers and from unsanctioned providers. Mass drug administration of antibiotics for the management of severe acute malnutrition (*20*) and trachoma control (*21*) could contribute to resistance at a mass scale if not monitored carefully (*22*).

Antibiotics are also used extensively in agriculture, in subtherapeutic concentrations, to promote growth and prevent disease in livestock. Associations have been reported between time spent on farms and colonization with multidrug-resistant *Staphylococcus aureus* (MRSA) (*23*, *24*). Medically important antibiotics have been withdrawn from subtherapeutic use for growth promotion in the European Union (by regulation) and in the United States (by nonbinding advisories).

Finally, genes for resistance to biocides, which include alcohols, phenols, and quaternary ammonium compounds, are often carried on the same multidrug resistance plasmid as antibiotic resistance genes (*25*). The widespread use of biocides coselects for antibiotic resistance genes and could promote the spread of multidrug resistance plasmids (*26*).

Innovation

Even if antibiotics are used appropriately, resistance is an inevitable consequence of drug selection pressure, necessitating the discovery, testing, and development of new antibiotics. The thin pipeline of new antibiotics reflects a declining trend in new drug development across all therapeutic areas, caused by the difficulty of innovation and the challenges of regulatory hurdles (*27*). Some new agents treat soft-tissue skin infections caused by MRSA and other conditions (*28*), but the newest antibiotics are at least two orders of magnitude more expensive than first-line antibiotics, putting them out of reach of many.

New antibiotics are given 5 years of additional market exclusivity under the Generating Antibiotic Incentives Now (GAIN) section of the 2012 Food and Drug Administration Safety and Innovation Act. Efforts to lower antibiotic development costs (such as by basing approval on more limited clinical evidence) are fruitful when they do not compromise safety and efficacy. Of the 61 new antibiotics approved between 1980 and 2009, 26 (43%) were withdrawn, compared with a 13% withdrawal rate for other therapeutic categories (*29*).

Pharmaceutical firms have little incentive to sell fewer antibiotics to reduce the likelihood of resistance. If anything, resistance makes existing antibiotics obsolete and creates demand for newer, more expensive antibiotics; market incentives may thus work against conservation's effectiveness.

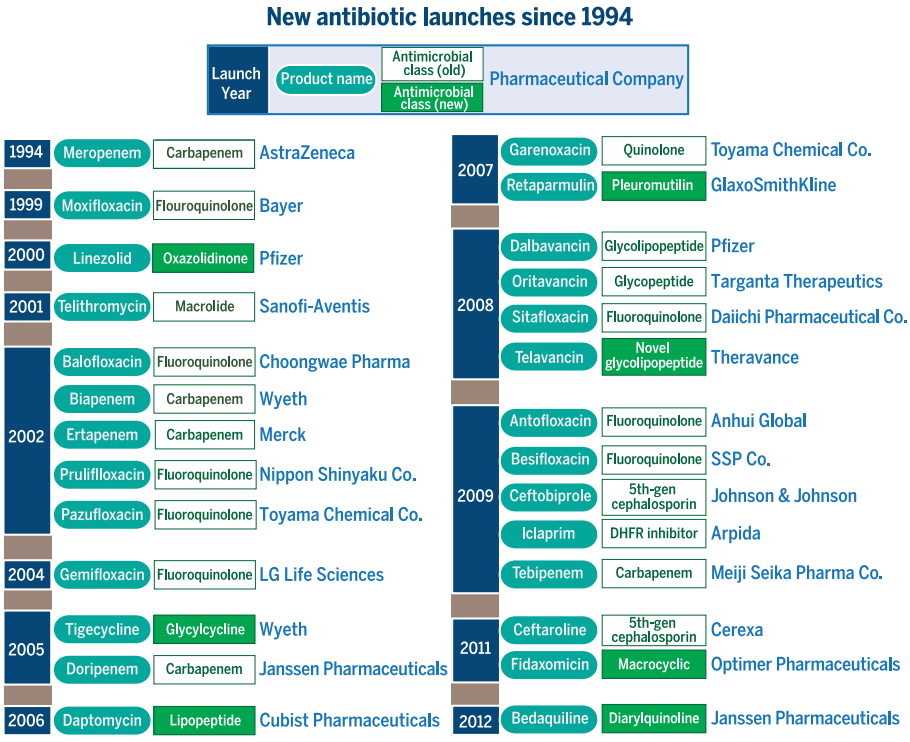

Fig. 3. Antibiotic pipeline for the past 20 years.

Insurers' and third-party payers' low reimbursement rates for antibiotics partly reflect value perceptions shaped by the low prices of older antibiotics; they discourage both conservation and new drug development.

Some have proposed delinkage as a solution to this problem: A different entity (such as the government) would purchase an antibiotic at a fixed price unrelated to the quantity sold and then ration it (*30*). However, it is unclear how a drug could be allocated to its highest-value use and whether government could perform this function any better than private markets.

What other kinds of innovation are most useful? Innovation could involve combination therapies, such as amoxicillin-clavulanate, that target both essential functions and resistance factors. Development efforts could repurpose old drugs to optimize dosing levels and the duration, and route of administration, and leverage pharmacokinetics and pharmacodynamics to identify promising combination drug therapies. For example, optimizing dosing of colistin, a drug first introduced in the 1950s, can reduce toxicity and improve efficacy (*31*).

Innovation could also aim at preventing the development of resistance and protecting nontarget gut bacterial flora during antibiotic treatments. For example, absorbents can prevent active antibiotic residues from reaching the gastrointestinal flora (*32*).

Innovation in point-of-care diagnostics to identify both the cause of an infection and its sensitivity to common antibiotics would be particularly appropriate for countries such as India, Brazil, and China, which need to preserve their ability to treat bacterial infections but are unlikely to be immediate markets for any new broad-spectrum antibiotics. More affordable diagnostics could significantly reduce unnecessary antibiotic prescriptions and ensure that the right antibiotic is prescribed.

Balancing conservation and innovation

The issue of antibiotic resistance has often been framed as a crisis in new drug development, but with little supporting evidence. The pharmaceutical industry has responded to the threat of soft-tissue MRSA infections by developing new antibiotics, including most recently a single-dose Oritavancin or a two-dose Dalbavancin for treatment in outpatient settings (*33*, *34*). Contrary to popular belief, many new antibiotics have been introduced during the past two decades (Fig. 3), but their cost is much greater than that of older antibiotics, and many have been pulled from the market. Direct public financing such as the recent $200 million grant to GlaxoSmithKline by the Biomedical Advanced Research and Development Authority to produce a new antibiotic (*35*) may increase the number of drugs in the pipeline but does not address issue of cost to consumers or of missing incentives for conservation.

The benefits of conserving existing drugs are significant. A 1-year delay in the need for a $1 billion investment in a new antibiotic is worth roughly $60 million, even at a modest 6% discount rate (according to my calculations). We should therefore be willing to collectively spend at least that amount to shift the resistance curve back 1 year for a single antibiotic. It would cost hundreds of billions of dollars to replace our entire portfolio of antibiotics, so conservation would appear to be a viable strategy. Until recently, however, the United States has spent less than $5 million per year on conserving antibiotic effectiveness through public education, research, and surveillance, and even with recent increases in allocations to antibiotic resistance programs at the U.S. Centers for Disease Control and Prevention, the imbalance remains. As long as we inhabit a world of microbes, we must focus more resources and effort on the conservation of existing antibiotics by ensuring their appropriate—and less frequent—use, while finding ways to incentivize the development of new antibiotics, using mechanisms that promote appropriate use.

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