

The Politics of Antibiotics

An interview with Ramanan Laxminarayan

By Adrien Allorant and Jules Naudet

The growing resistance to antibiotics potentially threatens the future of mankind. Ramanan Laxminarayan suggests that this major political challenge requires as much international cooperation as the fight against global warming does.



Ramanan Laxminarayan is founder and director of the Center for Disease Dynamics, Economics & Policy (CDDEP) in Washington, D.C., and a senior research scholar at Princeton University. He is an affiliate professor at the University of Washington and a visiting professor at the University of Strathclyde in Scotland and at the University of Kwazulu Natal in South Africa. Laxminarayan chairs the board of GARDP, a global product development partnership, that aims to develop and deliver new treatments for bacterial infections. He is also board chair at HealthCubed, which works to improve access to healthcare and diagnostics worldwide.

Since 1995, Laxminarayan has worked to improve the understanding of antibiotic resistance as a problem of managing a shared global resource. Laxminarayan has served on the U.S. President's Council of Advisors on Science and Technology's antimicrobial resistance working group and is currently a voting member of the U.S. Presidential Advisory Council on Combating Antimicrobial Resistance. He is a series editor of the Disease Control Priorities for Developing Countries, 3rd edition. In 2003-04, he served on the National Academy of Science/Institute of Medicine Committee on the Economics of Antimalarial Drugs and

subsequently helped create the Affordable Medicines Facility for malaria, a novel financing mechanism for antimalarials.

Laxminarayan's work has been covered in major media outlets including Associated Press, BBC, CNN, the Economist, LA Times, NBC, NPR, Reuters, Science, Wall Street Journal, and National Journal.

Books & Ideas: How did the invention of antibiotics change the face of the world?

Ramanan Laxminarayan: Antibiotics are truly wonder drugs. Prior to the arrival of antibiotics, even simple cuts could result in deadly infections. The arrival of sulfa drugs was an improvement, but these were highly toxic and with difficult side-effects for patients. When penicillin was discovered in 1928, it was not clear that it would indeed be a miracle drug. After all, it was important for an antibiotic to not just kill bacteria but also to be ingested by a patient, make its way to the site of infection and selectively kill bacteria without harming human cells. If one had to find a substance that killed bacteria, then alcohol worked perfectly well! But consuming alcohol did not result in bacterial infections being treated.

When penicillin was introduced into medicine in 1942, its effect was nothing sort of revolutionary. It both allowed for the treatment of common bacterial illnesses like scarlet fever, pneumococcal pneumonia. Prior to the introduction of antibiotics, 80% of patients with bacterial pneumonias died. Penicillin lowered that proportion to just 18%. More importantly, antibiotics made possible much of what constitutes modern medicine today. The ability to perform organ transplants and complex surgeries requires that we be able to keep the human body free of infection. Antibiotic prophylaxis makes this possible. Even the most stringent infection control could not prevent bacteria from entering through a surgical opening simply because bacteria are everywhere.

Antibiotics also made possible the massive scale up in the production of animals that was possible after the second World War. In the late 1940s, it was discovered that providing poultry and pigs with sub-therapeutic concentrations of antibiotics on a daily basis helped them gain weight faster. Particularly when animals were grown in conditions of poor sanitation and nutrition, the antibiotics appeared to help lower their mortality and increased production, thereby lowering the price of meat. The effect on human diets, particularly in the currently high-income world was profound. Chicken went from being a once-a-week, Sunday dinner treat to being on lunch and dinner menus throughout the week. Consumption of animal protein skyrocketed. The currently-middle income world was not far behind. In China, consumption of pork went up six-fold between 1975 and 2005.

Books & Ideas: Is there any risk that we lose the benefits of this progress?

R.L.: Using antibiotics comes with a penalty. Exposure to antibiotics exerts selection pressure on bacteria, encouraging the survival of organisms with genetic mutations that allow them to withstand the drug treatment. Every use of antibiotics contributes to the development of “antibiotic resistance,” and the number of antibiotic resistant organisms increases with antibiotic use. Antibiotic resistant infections are dangerous and can be deadly—the most widely reported resistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), now accounts for more deaths in the United States than AIDS, tuberculosis, and Hepatitis B combined.

The declining effectiveness of antibiotics in treating bacterial infections is now a global phenomenon. The lack of sufficient access to basic public health and sanitation is a serious problem, particularly in countries where diarrheal disease is common and a major driver of antibiotic use. In high-income countries, the burden of infections has been reduced largely through improved nutrition, chlorination of water, sanitation, and the establishment of public health departments, but in low-income and many lower-middle income countries, antibiotics are being used as a substitute for these measures. For example, infectious disease mortality had already declined to 200 per 100,000 people when antibiotics were introduced in the United States in 1942; but they are being used in countries with higher rates of infectious disease even today.

In high-income countries, where the burden of infectious diseases is relatively modest, the decreasing effectiveness of first-line antibiotics is overcome by more expensive second- and third-line antibiotics, driving up healthcare costs. In low and middle income countries, patients with resistant pathogens are frequently unable to obtain or afford expensive second-line treatments, and this contributes to greater morbidity and mortality.¹⁰

An estimated 25 000 people die every year in Europe from antibiotic-resistant bacteria. In the USA in 2005, an estimated 94 000 invasive MRSA infections required hospitalisation and were associated with 19 000 deaths. The US Centers for Disease Control and Prevention conservatively estimates that at least 2 million illnesses and 23 000 deaths a year in the USA were caused by antibiotic resistance. Globally, an estimated 214,000 newborns die because of sepsis caused by pathogens resistant to first line antibiotics (see figure 1).

Books & Ideas: What are the causes of the increase of antibiotics resistance?

R.L.: Antibiotic resistance is driven by ever-higher rates of antibiotic use, poor water, sanitation and public health measures to tackle infections, demographic changes with more elderly people, and increased utilization of medical procedures, hospitalizations, and tertiary care.

Every time antibiotics are used, whether they save a life or are used to no effect (e.g., to treat viral rather than bacterial infections), the effective lifespan of that antibiotic and perhaps related drugs is shortened. The tension between individual good and collective good is central to the issue. The average patient suffering from a cold or an ear infection wants immediate relief and sees a prescription for antibiotics as the ticket to recovery, and the physician may be only too happy to oblige if writing it benefits her practice. Neither may consider that antibiotic use by one patient eventually reduces the drug's effectiveness for everyone.

Hospitals, too, ignore the larger context of their response to infection, particularly hospital-acquired infection, by preferring treatment over prevention. Antibiotics are often less expensive than other forms of infection control, and hospitals can even pass off the costs of antibiotic treatment to managed-care providers. Compounding the problem, hospitals have no incentive to ensure that the patients they discharge are not carrying a resistant pathogen from their facilities to other health care institutions.

And antibiotics are not only used in treating humans, but they also are used in livestock to help them gain weight faster (subtherapeutic use) and to avoid and treat disease (prophylactic and therapeutic use). It is estimated that more than half the antibiotics produced in the United States are used in the animal health industry, and the bulk of this is for growth promotion. Because these uses promote the development of drug-resistant bacteria in animals, and routes exist for the movement of these resistant bacteria to humans, drug resistance in bacteria associated with food animals can influence the level of resistance in bacteria that cause human diseases. Several compelling studies have documented the impact of subtherapeutic use of antibiotics on resistance in humans, and the evidence is mounting. Population biology predicts that the strong selection pressure imposed by the use of antibiotics in animal feed will lead to the evolution of resistant microorganisms. Although more studies will help improve our understanding of the links between antibiotic use in animals and resistant infections in humans, our wait for even more conclusive evidence will come at the cost of losing valuable drugs that will be very expensive to replace. Many developed countries use antibiotics for veterinary uses both for improving feed efficiency and rate of weight gain (subtherapeutic use) and for disease prevention and treatment (therapeutic use). Although the extent of antibiotic use in animals in developing countries is unknown, one study from Kenya reported that tetracyclines, sulfonamides and aminoglycosides were the most commonly used antimicrobials used for veterinary use. Over ninety percent of the antibiotics used were for therapeutic purposes and there was no evidence of use for growth promotion.

Although pharmaceutical companies, the makers of antibiotics, have a profit motive to consider the effect of resistance on the antibiotics they own, other firms may have drugs that work in similar ways. Just as many farmers drawing water from the same aquifer have no incentive to care about how fast the aquifer is being depleted, no one firm needs to care about resistance because the burden of resistance as it relates to the lifespan of salable antibiotics is borne by all firms.

Those barriers to addressing the problem of antibiotic resistance all involve conflict between the interest of individual decisionmakers and the interest of society as a whole, now and in the future. Incentive-based policy solutions can help patients, physicians, hospitals, and pharmaceutical companies consider the impact of their decisions on others and give them the opportunity to help the solution evolve.

Books & Ideas: Are these dynamics homogeneous worldwide or are there parts of the world where these trends are more worrying?

R.L.: The problem of resistance is particularly severe in developing countries, where the burden of infectious diseases is relatively greater and patients with a resistant infection are less likely to be able to access or afford expensive second-line treatment that typically have more complex treatment regimens than first-line drugs. Furthermore, the presence of exacerbating factors, such as poor hygiene, unreliable water supplies, civil conflicts and an increase in the number of immuno-compromised patients attributable to the ongoing HIV epidemic, can further increase the burden of antimicrobial resistance by facilitating the spread of resistant pathogens.

Rising prosperity and its domestic pharmaceutical production in a country like India has allowed its people to consume dramatically more antibiotics than ever before. It is not alone in this, particularly among emerging economies. Antibiotic consumption in Brazil, Russia, India, China and South Africa (“BRICS” countries) is expected to double between 2010 and 2030, alongside large per capita increases. This increasing consumption is key to the rise in antimicrobial resistance that has been detected over the last decade. A major problem is that policies to limit antibiotics to appropriate uses have not kept up with the increase in income and antibiotic availability. This is true for both human and animal use.

A host of factors is driving antibiotic overuse and resistance: inappropriate prescribing by doctors, over-the-counter sales of antibiotics without prescriptions, substandard antibiotics being sold, low vaccination levels to prevent disease, poor infection control in hospitals, poor sanitation (clean water and sewerage), lack of environmental controls for antibiotic manufacturing, and a growing appetite for meat, especially poultry. Environmental antibiotic pollution is a growing problem. It encourages the transfer of resistance genes to human commensal and pathogenic

bacteria. In particular, waste water treatment plants serving antibiotic manufacturing facilities have been implicated in the transfer of resistance genes into human microbiota and pose a serious threat to antibiotic effectiveness given the size of India's pharmaceutical sector. In many countries, including India and China, there are no regulations governing the discharge of antimicrobial waste into the environment and these are needed.

Books & Ideas: What could be done to avoid the darkest scenarios? Should we be worried by the fact that nationalism is more and more rampant and that the willingness for international cooperation is declining?

R.L.: A dangerous future can be averted by both conserving the effectiveness of antibiotics that we have and investing in new methods of dealing with infections, including new antibiotics. Much can be done to reduce antibiotic consumption not just by people but also by reducing their use in animal production. Priorities for action has to be country specific. For instance, China would do well to focus on hospitals' incentives to sell antibiotics as a way of generating revenue. In India, the unregulated sale of irrational fixed dose combinations is the greatest threat. And in the United States, the significant level of community use of antibiotics because of doctors' overprescribing of drugs should be the primary focus for action. A lot of this is possible without international cooperation but ultimately the actions of a single country in not controlling resistance can have global consequences in much the same way that carbon emissions in any single country have consequences for everyone. My worry is not so much about declining international cooperation now but by the fact that we have not educated the next generation on the urgency of these problems and that these can be solved only by their taking the responsibility as a citizen of the world seriously.

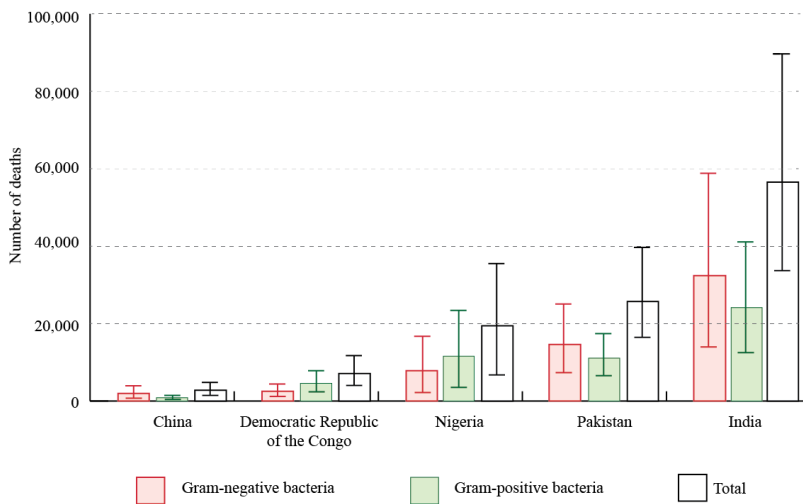


Figure 1: Estimated neonatal sepsis deaths attributable to resistance to first-line antibiotics in five high-burden countries.