HEALTH & MEDICINE

How Should Antibiotics Be Regulated?

Overuse of antibiotics is a public goods problem.

BY JONATHAN ANOMALY

We live in a microbial world. The average person hosts about 39 trillion bacteria. Many of these microbes do not threaten our health and some provide us with essential benefits by synthesizing vitamins, modulating our immune system, and helping us digest food. But others have the power to inflict enormous suffering.

Before the advent of antibiotics and vaccines, infectious diseases were probably the greatest source of human misery, premature death, and infant mortality. Not all infectious diseases are caused by bacteria, but many are. We catch tuberculosis from other infected people, cholera from tainted water, salmonella from undercooked food, and staph from crowded environments like locker rooms and hospitals. Even the ordinary bacteria that colonize our skin and digestive tract are dangerous if they enter our bloodstream; historically, many soldiers died from sepsis as their wounds became infected, rather than from the wounds themselves.

The mass production of antibiotics and vaccines changed everything. Many wounded soldiers are now saved, human lifespans have increased, and surgery has become so safe that we barely flinch at the thought that doctors routinely slice open their patients and stitch them back together. Without antibiotics, none of this would happen. However, the effectiveness of antibiotics began to decrease as soon as they came into widespread use. The more we use antibiotics, the less effective they become as bacteria develop resistance to the drugs. This is a necessary consequence of evolution by natural selection.

According to a recent estimate, antibiotic resistance kills about 700,000 people around the world every year. Alarming as this seems, this number can be misleading. First, antibiotics save far more people than antibiotic resistance kills. Second, antibiotic-resistant bacteria have existed for billions of years. This is because bacteria have been entangled in an evolutionary arms race with each other, and with plants and animals that defend themselves by producing chemicals that kill or disable bacteria.

We should never expect a world without antibiotic resistance. We can only do our best to minimize resistance, invent new antibiotics, and preserve existing supplies of antibiotics as the public goods they are.

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HOW RESISTANCE WORKS

Antibiotics are chemicals that plants or animals excrete to kill bacteria. Antibiotics work by destroying the walls that shield bacteria from the outside world or by preventing bacteria from replicating. Some bacteria have responded by building thick cell walls to block antibiotics, "efflux pumps" that eject antibiotics, and enzymes that degrade antibiotics into chemicals that don't harm them. These simple tools that bacteria use to resist antibiotics result from random genetic mutations and from exchanging stray strands of DNA with each other. (Bacteria don't reproduce sexually, but they do have ways of exchanging genes with each other.) When an antibiotic like penicillin kills most bacteria, but a few bacteria have genes that allow them to resist the antibiotic, the few survivors can replicate quickly and spread those genes to other bacteria. In some cases, our immune system will kill them anyway. But in other cases, there is no time to catch up. Without effective antibiotics, pathogenic bacteria multiply until they kill us.

There will never be a magic bullet to use against harmful bacteria. Even if we could isolate only those bacteria that threaten us, there are so many bacteria on earth, and they replicate so quickly, that we cannot permanently outrun them. We can only do our best to stay one step ahead of them.

GETTY IMAGES (6)

According to Brad Spellberg, past president of the Infectious Diseases Society of America:

> Microbes have most likely invented antibiotics against every biochemical target that can be attacked—and, of necessity, developed resistance mechanisms to protect all those biochemical targets. Indeed, widespread antibiotic resistance was recently discovered among bacteria found in underground caves that had been geologically isolated from the surface of the planet for four million years. Remarkably, resistance was found even to synthetic antibiotics that did not exist on earth until the 20th century.

One consequence of this observation is that even new, synthetically created antibiotics will lose their curative power quickly if they are used carelessly.

PUBLIC GOODS AND PRESERVATION

Antibiotics are a classic case of a public good. They provide benefits that accrue to third parties when they cure infected people and thereby prevent the spread of infectious disease. But the overuse of antibiotics is a classic case of a negative externality. The more we use antibiotics, the more likely we are to produce or spread resistant strains of bacteria to other people.

One response to the externalities of antibiotics is to socialize their production and distribution. If governments were run by benevolent bureaucrats who knew how to ration antibiotics efficiently and could figure out how to produce new ones, this socialist solution might be a good idea. But the world doesn't work that way. We need price signals even if governments intervene to adjust those signals or to set the basic rules of exchange. The general goal of these rules should be to try to ensure that when each of us pursues our own ends, we do so without imposing serious costs on others.

A minimally restrictive response to the problem of antibiotic resistance is to require prescriptions for use. Surprisingly, in many countries around the world, antibiotics are casually sold over the counter, even where recreational drugs are tightly regulated. These

policies should be reversed: we should worry about patterns of antibiotic use much more than recreational drug use. In fact, a strong argument can be made that antibiotics are the *only* drugs that should be regulated by requiring a physician's prescription. After all, antibiotics are the only drug for which health costs are borne by people other than the users themselves.

If I overdose on cocaine, my family may be sad, but I have not imposed health costs on anyone. If I overuse antibiotics and others do too, each of us contributes to a process in which all of us are more vulnerable to antibiotic-resistant infections. No one person's use matters much, but our collective use can matter quite a bit. In fact, if we flood our patients in hospitals and our animals on farms with antibiotics, we impose a cost on future people by spreading strains of bacteria that may be more expensive—or even impossible—to treat with antibiotics. Moreover, the genes that confer antibiotic resistance in bacteria can persist in the environment for many years after antibiotics are withdrawn.

A lot depends on the rate of innovation and the speed of evolution. When antibiotics were first discovered, they were found throughout nature, and some were synthesized in laboratories. For a few decades, the rate of innovation exceeded the rate at which antibiotic-resistant infections spread. But in the last few decades, the reverse has happened. Some infectious disease specialists have already started talking about a "post-antibiotic" era, though this rhetoric may be a bit overheated. More accurately, we are facing decreasing discoveries because we have picked the low-hanging fruit and because antibiotic use is growing.

The main problem is low-value use. Patients using antibiotics when they probably have a viral rather than a bacterial infection is one kind of wasteful use. Antibiotics can't kill viruses, but without a proper diagnosis some patients demand antibiotics anyway. This increases antibiotic resistance among the bacteria in our bodies without curing any infection. A much more dangerous kind of wasteful use occurs on factory farms, where antibiotics are routinely given to animals. This antibiotic use occurs because it can speed the rate of animal growth a bit and help prevent the spread of disease in crowded and cruel conditions. In fact, nearly half of all antibiotics in the world are given to farm animals for this purpose, and antibiotic-resistant bacteria often spread from farms to communities.

Some countries in Europe have banned the non-therapeutic use of antibiotics on farms and the United States is moving in that direction. Controlling the use of antibiotics on factory farms is a no-brainer: it costs very little, and without antibiotics readily available, factory farms would be nearly impossible. Farmers would have to give their animals a bit more space to roam and keep them in better conditions in order to avoid the quick transmission of microbes.

INCENTIVES AND INNOVATIONS

Apart from limiting the use of antibiotics in farm animals and requiring prescriptions for patients (and encouraging poor countries to do so), we might also invest more in basic science research. This could speed up the rate of innovations that can help us avoid some of the wasteful uses of antibiotics. These innovations might include precision diagnostics so that we can prescribe the right antibiotic for the right infection, and alternatives to antibiotics including vaccines that prevent infections and phage viruses that have been killing bacteria for at least a billion years.

Phage viruses have been studied for a century but they were not especially useful until we began to understand the biochemistry of how phage and bacteria interact. We are now on the cusp of being able to use a traditional source of disease (viruses) as a weapon against another source of disease (bacteria). The viruses that we might use as weapons are not the same as those that attack us; phage viruses are different than influenza or chicken pox. But it is a testament to human ingenuity that we can hijack viruses that parasitize bacteria and turn them into a weapon in our arsenal in the fight against infectious disease. Basic science research has made a lot of this possible.

The reason basic science research is needed to speed up the rate of innovation is that new approaches to infectious disease can take many years to produce, and the ideas that inform these approaches may be unpatentable and therefore unprofitable. Courts grant patents for new inventions, and this can incentivize innovation. But courts do not grant patents for discoveries about how microbes work or how viruses might be genetically altered to kill bacteria without endangering people. Pharmaceutical firms do not look as closely at cures that may come after decades of research, especially if the research itself cannot be patented and can be used by competitors.

Research on new alternatives and diagnostics is occurring, but it's mostly happening in universities and private labs that fund their research with grants issued by the National Institutes of Health or National Science Foundation. To be sure, some of this research might happen without government subsidies, via private donations from philanthropists. But it might not happen at a fast-enough rate to address the rise of resistant infections. Another innovation that subsidies for basic science research have made possible is the development of in vitro meat (sometimes called "clean meat"). This involves taking stem cells from cows or pigs and making them multiply until they create a beef steak or a hot dog. Again, while the private sector is best placed to mass-produce and market these innovations, there may be a role for government subsidies for basic science research that sheds light on how stem cells work.

Others have proposed that non-governmental organizations with a mission to reduce the global threat of infectious disease might create a fund that rewards pharmaceutical firms that create new antibiotics or new ways of accurately diagnosing infectious diseases. The reason for this is that some antibiotics are not especially profitable, but they create enormous social value. They do this if they target specific bacteria more precisely than general antibiotics like penicillin, or if they cure infectious diseases that

infect people who are too poor to afford medications to treat them. If infectious diseases are likely to spread around the world along with travel and trade, it can be important to target them at their point of origin. There may be reasons for each of us to support organizations whose aim is to create antibiotics that have high social value but are not especially profitable for a firm to create.

INFORMATION AND AUTONOMY

While I think some regulation of antibiotics is in order, there are reasons to think informed consumer choice will also reduce the socially harmful use of antibiotics without extensive regulation. As I emphasized above, antibiotic drugs are different than recreational drugs because of their potential to affect the health of third parties. I argued that there are good reasons to decriminalize recreational drugs and remove prohibitive policies that prevent us from accessing most medicines without a prescription. But I also argued that we have reasons to regulate antibiotics given their effects on third parties.

It may be worth comparing the kinds of collective harms created by the reckless use of antibiotics and the collective harms associated with burning coal in a way that creates air pollution. When I drive a car or heat my house and the energy comes from a coal-burning power plant, the amount of pollution I produce is trivial. The same goes for everyone else. Few people, if any, feel the consequences of the pollution they, themselves, create. But when people overuse antibiotics, they may incur substantial costs from their own behavior.

One cost is the chance of being colonized by a debilitating microbe called *clostridium difficile* (*c diff*). Patients who overuse antibiotics often kill friendly bacteria as well as pathogenic bacteria. Driving out friendly bacteria makes us much more likely to be colonized by *c diff*, which is a bacterium resistant to most antibiotics and which causes chronic inflammation and sometimes severe digestive difficulties.

Another cost each of us bears if we overuse antibiotics is an elevated risk of autoimmune disorders. There is now powerful evidence that continually treating our children with antibiotics when they are young makes them more likely to develop allergies and autoimmune diseases at a later age. These diseases include Crohn's and diabetes. Apparently, our immune system evolved to encounter a variety of microbes from an early age, and the absence of these microbes leads our immune system to target our own body's cells. According to this "hygiene hypothesis," which is now well-supported, allergies and autoimmune disorders are on the rise in part because we are dosing our children with unnecessary antibiotics and because we are not exposing them to the kinds of healthy microbes that stimulate their immune system.

Science is just beginning to reveal the full consequences of using antibiotics. As more is known, campaigns to inform patients of the harms from overusing antibiotics may lead them to change behavior. Economists since Friedrich Hayek have emphasized that people are rationally ignorant about how most things in a market society work. Hayek argued that there are real benefits to this. When each of us specializes in what we're good at and creates products that our customers want to buy, we're all better off. We don't need to know how everything around us works to be able to use it.

In the case of global pollution or overfishing in the oceans, consumers often remain ignorant of the problem because they have little power to change the outcome with their individual choices. But antibiotics are not quite like this. We each incur a substantial (but probabilistic) cost when we use antibiotics, along with the obvious benefits of curing bacterial infections. Physicians offering this information to patients may go a long way toward getting patients to change their behavior voluntarily. Public health organizations and even governments may have a role in making information about the personal and social costs of overusing antibiotics available to all.

I do not think informed consumer choice will fully solve the problem. Antibiotics, like vaccines, are some of the few drugs that have significant public health consequences, apart from their *private* effects on each of us. But that does not mean we should reject market-based solutions. It is by now a familiar refrain that market failure in a particular domain does not automatically imply a need for centralized solutions. We need to think about how governments might fund basic science research relevant to infectious diseases and alter rules to incentivize firms to translate basic science into innovative approaches to the problem of antibiotic resistance. There is no easy solution and there is no point denying the problem.

Information campaigns and basic science research can do a lot to curb the collective harms associated with widespread antibiotic use. Pressuring developing countries to control their skyrocketing use of antibiotics in agriculture will also be an important part of addressing a global problem without installing a global leviathan. *R*

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