Ethics, Antibiotics, and Public Policy

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Abstract

The widespread use of antibiotics in medicine and agriculture is encouraging the proliferation of antibiotic-resistant infections around the world. Our use of antibiotics is a global, inter-generational collective action problem. Public policies intended to solve the problem involve difficult moral tradeoffs.

Table of Contents

Introduction 999

I. Biological War and Human Health 1000

A. The Anatomy of Resistance 1000

B. The Cost of Resistance 1003

C. When Treatments Cause Disease 1005

II. Moral Problems 1006

III. Policy Prescriptions 1008

A. Supply 1008

B. Demand 1011

C. Alternatives 1014

Conclusion 1015

Introduction

Antibiotics make modern medicine possible, but the more we use them the less effective they become. When appropriately prescribed, antibiotics confer visible benefits: they cure bacterial infections that our immune systems struggle with, and they enable us to undergo complex surgeries that would otherwise kill us by exposing our internal organs to a bacterial world for which they are unprepared. Yet the unseen effects on our microbial environment make our choice to use antibiotics a morally weighty one. The more we use antibiotics, the more likely we are to turn ourselves into vectors for antibiotic-resistant bacteria that are difficult or impossible to treat.

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Apart from antibiotic resistance, increasing evidence suggests that by routinely giving antibiotics to children and altering their microbiome, we elevate their risk of acquiring autoimmune disorders ranging from allergies and asthma to Crohn's disease and Type 1 diabetes. Sometimes the *absence* of particular microbes at critical developmental stages leads the immune system to target the body's own cells in an effort to find and destroy the kinds of microbes it evolved to anticipate. I review the evidence for these claims, discuss the moral issues they raise, and then turn to policy proposals aimed at mitigating the problem.

Just as using antibiotics affects our microbial environment in ways that are not immediately obvious, policies to control antibiotic resistance and fight infectious diseases can produce welfare consequences that are surprising to scientists, invisible to the general public, and hard for policymakers to predict with much precision. Thoughtful approaches to problems raised by the widespread use of antibiotics should recognize both the importance and limitations of policy solutions. To paraphrase the French economist Frederic Bastiat, the myopic policymaker confines himself to thinking about the visible and immediate consequences of public policies, but the prescient policymaker keeps an eye on their unseen and distant effects.[1]

I. BIOLOGICAL WAR AND HUMAN HEALTH

A. The Anatomy of Resistance

We live in a bacterial world. It is estimated that the average person hosts about thirty-nine trillion bacteria, many of them in our gut.[2] Most of these bacteria have forged a symbiotic, or co-dependent, relationship with us. Some bacteria that we house in our gut and on our skin are along for a free ride: they use us for shelter and feed off the scraps of food we consume. These *commensal* bacteria usually do us no harm, and occasionally do us a favor by crowding out pathogenic bacteria. Other bacteria have a *mutualistic* relationship with us: they extract benefits but also give back by synthesizing vitamins, modulating our immune system, and even affecting hormones and neurotransmitters that control our appetite. Very few of the bacteria around us are *parasites* that make us sick when they find a way into our body. Even parasitic bacteria are typically benign in the presence of other bacteria, unless they invade certain parts of our body and multiply too fast for our immune system to destroy.

Most parasitic bacteria do not kill their host since this can be an evolutionary death sentence: biting the hand that feeds you is a risky strategy for increasing

1. FRÉDÉRIC BASTIAT, *What is Seen and What is Not Seen* (1848), *reprinted in* SELECTED ESSAYS ON POLITICAL ECONOMY (Seymour Cain trans., 1995), http://www.econlib.org/library/Bastiat/basEss1.html [https://perma.cc/UQ62-SZNS].

2. Ron Sender et al., *Revised Estimates for the Number of Human and Bacterial Cells in the Body*, PLOS BIOLOGY (2016), http://dx.doi.org/10.1101/036103 [https://perma.cc/2DBT-PB5A].

your long-run food supply.[3] But many bacteria make us seriously ill, or increase our morbidity when we have other diseases or when our immune system is weak. It is against these bacteria—the ones that kill us or make us sick—that antibiotics act as a crucial weapon that can save and extend life, or make life more comfortable by shortening the duration of an infection.

Antibiotic resistance occurs when a bacterium acquires the ability to resist the deleterious effects of antibiotics. Resistance can originate from the *mutation* of a gene on a bacterial chromosome or from the *lateral transfer* of genes from one bacterium to another. Mutations typically arise from random copying errors during cell division or from exposure to radiation, whereas lateral gene transfer occurs when bacteria swap genes with other bacteria or with viruses that parasitize them. Lateral gene transfer is a clever way for bacteria to acquire new genes without sexual reproduction. Sex may be fun, but the vertical transfer of genes from parents to children is costly: eukaryotes who reproduce sexually only transfer half of our genes to our offspring, and can only draw from the genetic novelty of a few partners in any given generation.[4]

By contrast, bacteria can acquire genes from other bacteria (by "conjugation") and viruses (by "transduction") in their environment. Since viruses, bacteria, and free-floating strands of DNA around bacteria are all potential sources of genetic change, some refer to this environment as a *metagenome* from which bacteria can manufacture new tools to resist antibiotics.[5]

Antibiotics typically work by disabling a bacterium's ability to repair or replicate itself. While most of the random mutations or plasmids bacteria pick up from their environment are either harmful or neutral, some genetic novelties allow bacteria to defend themselves from antibiotics. The main defense mechanisms include extra thick cell walls, enzymes that transform antibiotics into harmless chemicals, and efflux pumps that flush antibiotics out of the cell.[6]

Bacteria have waged a three-and-a-half billion-year war against one another, so antibiotics have been around for a long time. More recently, plants, animals, and fungi evolved their own endogenous antibiotics, but only in the last century have people discovered how to turn these naturally occurring compounds into medicine. The ancient origin and ubiquity of antibiotics and antibiotic resistance strongly suggests that new, synthetically created antibiotics will not be much

3. This is true of both viruses and bacteria: the virulence of a parasite tends to decline as it co-evolves with its host over many generations. *See generally* DOROTHY CRAWFORD, THE INVISIBLE ENEMY (2000). A counterexample to this general rule is cholera, which uses its host to spread billions of copies of itself by inducing it to involuntarily empty its fluids near local water supplies, allowing it to be consumed by others who drink the water.

4. The best general account of the origin and evolutionary benefits of sexual reproduction is MATT RIDLEY, THE RED QUEEN: SEX AND THE EVOLUTION OF HUMAN NATURE (2003). *See also* NICK LANE, POWER, SEX, SUICIDE: MITOCHONDRIA AND THE MEANING OF LIFE (2005).

5. NICK LANE, THE VITAL QUESTION: ENERGY, EVOLUTION, AND THE ORIGIN OF COMPLEX LIFE 180–81 (2015).

6. For an overview of common resistance mechanisms, see STUART LEVY, THE ANTIBIOTIC PARADOX: HOW THE MISUSE OF ANTIBIOTICS DESTROYS THEIR CURATIVE POWER 71–114 (2002).

better or longer lasting than those antibiotics that already exist. According to Brad Spellberg, former 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."[7]

As I will argue in the next two sections, this fact has significant implications for how to conceptualize antibiotic resistance (as a permanent arms race), and how to think about the most effective ways of addressing the problem (for example, if the efficacy of traditional antibiotics necessarily declines with increased use, we should shift resources and attention to preventing infections with vaccines, and to developing novel treatments like phage therapy).

Understanding antibiotic resistance as an evolutionary arms race helps explain why it is found virtually everywhere, but it does not explain how difficult it is to eliminate resistance once it arises. A number of remarkable studies from the late 20th century show that natural selection often takes a long time to eliminate bacteria with resistance genes, even after removing antibiotics from the environment.[8] This result is especially surprising since the energetic cost to bacteria of expressing a gene is up to 200,000 times that of their more complex eukaryotic cousins.[9] If it is energetically burdensome to express a gene, bacteria should be under constant pressure to streamline their genome by shedding genes that impose fitness costs, such that any genes for antibiotic resistance should be punished in an antibiotic-free environment.

Two factors mitigate the cost of retaining resistance genes. First, some genes are only conditionally expressed in the presence of chemical cues like antibiotics. In these cases, retaining a gene for antibiotic resistance that becomes (temporarily) useless when antibiotics are removed carries almost no cost at all since the gene does not squander energy by creating pointless proteins. But if the bacterium is exposed again to antibiotics, these genes can re-activate resistance and confer enormous reproductive benefits at minimal cost.

Second, genes that confer resistance to one kind of antibiotic are often genetically linked to other resistance genes, and sometimes to genes unrelated

7. Brad Spellberg, *The Future of Antibiotic Resistance*, 368 NEW ENG. J. MED. 299, 299–302 (2013).

8. Dan Andersson, *The Biological Cost of Mutational Antibiotic Resistance*, 9 CURRENT OPINION MICROBIOLOGY 461 (2006); Richard Lenski. *Bacterial Evolution and the Cost of Antibiotic Resistance*, 1 INT'L MICROBIOLOGY 265 (1998); Abigail Salyers et al., *Why are Antibiotic Resistance Genes So Resistant to Elimination?*, 41 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 2321 (1997).

9. The reason is that bacteria lack mitochondria, which are organelles that make complex life possible by providing an extremely efficient source of energy. *See* Lane, *supra* note 5, at 173.

to resistance.[10] One of the more disturbing things about resistance is that the longer bacteria are exposed to antibiotics, the cheaper it gets for them to carry resistance genes.[11] This is a consequence of evolution by natural selection: over time, bacteria find novel ways—through mutation or lateral gene transfer—to economize the energy required to stave off threats posed by antibiotics. Still, according to a recent meta-analysis, most resistance genes impose *some* costs on bacteria, so withdrawing antibiotics from an environment is likely to eventually minimize and perhaps eliminate most resistance genes.[12]

An important consequence of the long persistence of resistance genes in a bacterial population is that antibiotic resistance is not a typical pollution problem like mercury in the atmosphere or arsenic in ground water: it does not go away quickly after the source of pollution is addressed. Antibiotic resistance is more like anthropogenic global warming or ozone depletion: In these cases, the effects of the chemicals that cause the relevant problem take quite a while to cease having an effect. Moreover, unlike some kinds of pollution, antibiotic resistance cannot be stopped—even if we took the counterproductive step of eliminating the use of all antibiotics. Antibiotic resistance can only be minimized and mitigated through responsible use.

B. The Cost of Resistance

Antibiotic resistance is a moral problem because using antibiotics imposes a probabilistic benefit or harm on other people. Each of us has a trivial effect on the microbial environment around us, but our collective use of antibiotics has morally significant consequences. Our choice to use antibiotics is a lot like our choice of whether to vote for a particular candidate in a large election, or to reduce the amount of pollution we release into the atmosphere: none of us has an appreciable impact, but the aggregate effect of our choices has important consequences for human welfare.

Resistant infections can be difficult or expensive to treat, and in some cases cause the premature death of patients—either because second-line treatments are too expensive or because they don't exist. According to a recent estimate by the British Review on Antimicrobial Resistance, at least 700,000 people die every year from resistant infections, and that number is expected to rise considerably in the coming decades.[13] Antibiotics are *saving* many more lives than antibiotic resistance is ending, so this number is not by itself informative. But since resistance is partly under our control, the number can be changed based on our personal choices and public policies.

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10. Dan Andersson et al., *Antibiotic Resistance and its Cost: Is it Possible to Reverse Resistance*?, 8 NATURE REVS. 260 (2010).

11. *Id.*

12. Anita Melnyk et al., *The Fitness Costs of Antibiotic Resistance Mutations*, 8 EVOLUTIONARY APPLICATIONS 273 (2014).

13. Jim O'Neill et al., *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, REVIEW ON ANTIMICROBIAL RESISTANCE (2016), http://amr-review.org/ [https://perma.cc/FJM4-6QBS].

In addition to the problem of premature deaths, the economic cost of resistance is staggering: it is already in the trillions worldwide, and is expected to grow to an estimated 100 trillion dollars by 2050 if trends continue.[14] Costs include the money spent on additional treatments of resistant infections by health care systems, insurance companies, and individuals, and also include lost productivity due to illness or death caused by resistant infections. Again, this means projected costs can be altered by altering consumption patterns, by public policies that determine who pays for health care and how benefits are allocated, and by policies that aim to control resistance by restricting access or developing new treatments.

Regardless of the specific estimates, there is widespread consensus among infectious disease experts that the problem is getting worse, and at an accelerating rate.[15] This is partly because demand for antibiotics is rising around the world along with rising incomes, and additionally because this increasing wealth is creating higher demand for meat, which increasingly comes from animals raised on factory farms.

About half of all antibiotics worldwide go directly into animal feed, and this number is growing fast.[16] While gains to farmers from adding antibiotics to animal feed to speed growth are small, even these limited gains create a prisoner's dilemma in which the rational, profit-maximizing strategy makes everyone worse off than they would be with restrictions on antibiotic use. Antibiotics are also likely required to prevent illness and death on factory farms where animals are densely packed into spaces that are ideal environments for the spread of infectious diseases.[17] Since we share many microbes with other animals, and resistance to different kinds of antibiotics is either genetically linked or easily spreads between different species of bacteria through lateral gene transfer, the problem of antibiotics in agriculture threatens not just the health and welfare of animals, but also people. People who work in agriculture can be vectors for spreading resistant infections, but so too can the meat we consume, the produce that is fertilized with waste from animals on factory farms, and the water and sewage that runs from factory farms into the surrounding environment.

As we will see in the policy section, antibiotics in many developing countries—especially China, India, and Pakistan—are available to consumers without prescription.[18] Because of easy availability and low cost, antibiotic use in

14. *Id*. at 4.

15. Nearly every paper cited in this essay contains evidence for this claim. Perhaps the best general overview of expert opinion is HELEN GELBAND ET AL., THE STATE OF THE WORLD'S ANTIBIOTICS, https://cddep.org/sites/default/files/swa_2015_final.pdf [https://perma.cc/6JS9-H5WB].

16. T.P. van Boeckel et al., *Global Trends in Antimicrobial Use in Food Animals* 112 PROC. NAT'L ACAD. SCI. 5649 (2015).

17. Jonathan Anomaly, *What's Wrong with Factory Farming*, 8 PUB. HEALTH ETHICS 246 (2015).

18. Even when laws require prescription, poor institutions and corruption can lead to virtual over-the-counter availability. *See* Peter Collignon et al., *Antimicrobial Resistance: The Major Contribu-*

agriculture is accelerating in developing countries faster than it is shrinking in Europe and the US.[19] It is finally beginning to decline in the US due to increasing consumer demand for antibiotic-free meat, and threats of regulation from agencies like the US Food and Drug Administration.[20] Since developing countries also have the greatest population growth, and can least afford more advanced second line therapies, it is likely that both the source and the burden of antibiotic resistance will shift toward poorer countries in the coming decades.

C. When Treatments Cause Disease

This paper will principally focus on the tradeoffs of different policy solutions to growing antibiotic resistance. But there is one more important respect in which antibiotics affect human health apart from curing bacterial infections or spurring antibiotic resistance. According to the "hygiene hypothesis" proposed in the late twentieth century, the global surge in autoimmune diseases can be traced partly to the fact that children in industrialized countries grow up in relatively sterile environments. An increasing number of studies corroborate this hypothesis.

The correlation between Caesarian sections in women and autoimmune disorders in their children is among the most intriguing sources of evidence. According to a recent meta-analysis, C-sections seem to increase the risk of allergies and autoimmune disorders like Type 1 diabetes.[21] Microbiologist Martin Blaser argues:

> [T]hroughout the animal kingdom, mothers transfer microbes to their young while giving birth . . . . This microbial handoff is also a critical aspect of infant health in humans. Today it is in peril . . . . The high rate of Caesarian sections and the overuse of antibiotics in mothers and newborns are altering the types of microbial species that mothers have always passed on to their newborns.[22]

For example, some beneficial bacteria—such as *lactobacilli*, which newborns pick up when passing from the sterile womb through the bacteria-rich birth canal—provide protection from pathogenic microbes.

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tion of Poor Governance and Corruption to this Growing Problem, PLOS ONE (2015), http://dx.doi.org/10.1371/journal.pone.0116746 [https://perma.cc/9G3L-KWUM].

19. GELBAND et al., *supra* note 15, at 38–49.

20. *Id.*

21. *See* J. Neu et al., *Caesarian Versus Vaginal Delivery: long-term infant outcomes and the hygiene hypothesis*, 38 CLINICAL PERINATOLOGY 321 (2011).

22. MARTIN BLASER, MISSING MICROBES: HOW THE OVERUSE OF ANTIBIOTICS IS FUELING OUR MODERN PLAGUES 90 (2015).

More importantly, some bacteria (as well as some viruses, worms, and other microbes) prime the immune system to deal with future threats.[23] Removing these can trigger a developing child's immune system to target its own cells rather than the parasitic microbes it evolved to encounter. According to Martin Blaser, our *innate* immunity, which is more strictly controlled by genetics, should be distinguished from our *adaptive* immunity, which enables our immune system to learn to distinguish self from non-self and friend from foe. Continual antibiotic use from an early age raises the probability that a child will eventually develop diseases like Celiac, Type 1 diabetes, Crohn's, and a variety of allergies.[24] Yet Americans born in the 1990s will have had, on average, seventeen courses of antibiotics by age twenty, and thirty by age forty.[25]

One way to think about the hygiene hypothesis is that the *absence* rather than *presence* of some bacteria can cause disease: what begin as parasites evolve into mutualists to which our bodies outsource part of our immunity. A vivid analogy can be made between the loss of endogenous vitamin-c production and the loss of certain kinds of innate immunity:

> At some point in our evolutionary past . . . as we gorged on a vitamin-c rich diet, our own vitamin-c manufacturing genes became non-functional . . . the primate lineage outsourced vitamin-c production to plants. Now transpose the model to immune functioning. Contact with another organism . . . develops your immune regulatory circuits. Over evolutionary time, the ability to regulate immune function yourself dulls or disappears. Losing this capacity incurs no immediate cost . . . you've just outsourced your immunoregulation to microbes. Now you're dependent on them.[26]

Widespread use of antibiotics can both cure and create diseases in ourselves and in other people. This raises a difficult moral problem to conceptualize and address.

II. MORAL PROBLEMS

The availability of antibiotics in modern medicine and animal agriculture creates a global, intergenerational collective action problem. Each choice to prescribe or consume antibiotics has a trivial impact on ourselves and our microbial environment, but all of our choices, taken together, affect the welfare of current and future people. The collective action problems associated with preserving the efficacy of existing antibiotics and incentivizing the production of new treatments are a permanent part of our evolutionary arms race with pathogenic microbes, so the problem can only be *mitigated* rather than *solved*.

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23. MOISES VELASQUEZ-MANOFF, AN EPIDEMIC OF ABSENCE: A NEW WAY OF UNDERSTANDING ALLERGIES AND AUTOIMMUNE DISEASES (2013).

24. BLASER, *supra* note 22.

25. *Id*. at 71.

26. VELASQUEZ-MANOFF, *supra* note 23, at 113.

Because the benefits of using antibiotics are mostly internalized (when they cure a bacterial infection) but the costs are socialized (in the form of resistance), patients and farmers overuse antibiotics, and physicians and veterinarians over-prescribe them. One problem with thinking through the moral dimensions of antibiotic resistance is that our actions usually only produce a small probability of harm (apart from their immediate potential benefits). Another problem is that, given current technology, it is virtually impossible to trace the emergence or spread of a resistance gene to a particular actor. In other words, the harms are probabilistic and invisible, and it is unclear who (if anyone) bears responsibility for spreading any particular strain of resistance.[27]

Actions that tend to increase antibiotic resistance should be thought of as contributing to a process in which genetic pollution accumulates in the environment. When we consume antibiotics—whether or not they are appropriately taken—the environment is mostly our own body, but we also share bacteria with those around us. When veterinarians or physicians prescribe large amounts of antibiotics, the environment is other people's bodies, and through their bodies the broader microbial environment. In all of these cases, even when antibiotics are used appropriately and cure an infection—thus benefitting both the infected person and those around him—their aggregate use tends to create long-run social costs by increasing resistance. The fact that the costs are invisible and probabilistic rather than visible and discrete may help explain why so many people are ignorant of the problem. A deeper explanation owes to our implicit understanding that, for large scale collective action problems, our individual actions have very little impact on the outcome.

As economists since Anthony Downs have argued, people tend to have poorly formed beliefs about subjects that require significant investments of time or energy when their effort is unlikely to make a difference to solving the problem.[28] When I buy a can of soup or a pint of beer, I have good reason to make sure it doesn't contain toxic pollutants since I would bear that cost directly. But people who consume meat from animals fed antibiotics have little incentive to understand how this choice elevates the risk of disease and death. Consumers are, in many cases, *rationally* ignorant of these problems.[29] The incentives surrounding public goods problems like preserving the efficacy of antibiotics do not *excuse* consumer ignorance, but they do help *explain* it.

When responsibility for a problem is diffuse and difficult to detect, and when our individual actions are neither necessary nor sufficient to bring about an

27. Jasper Littmann et al., *The Ethical Significance of Antimicrobial Resistance*, 8 PUB. HEALTH ETHICS 209, 211 (2015). Notice that we cannot directly *create* resistant strains of bacteria (except perhaps through genetic engineering), but we can create conditions that make the emergence and spread of resistance more likely—e.g., on factory farms or in hospitals.

28. Anthony Downs, *An Economic Theory of Political Action in a Democracy*, 65 J. POL. ECON. 135 (1957).

29. Most people do not know the difference between a virus and a bacterium, and among those who do, many falsely believe that their *immune system* rather than *bacteria* become resistant to antibiotics.

undesirable outcome, our obligations seem to change. As Walter Sinnott-Armstrong argues in the case of burning fossil fuels that contribute to global warming, each of us has a negligible effect on the problem and so does not *cause* it (even if we contribute to it).[30] If I disappeared, the globe would still warm or cool at about the same rate.

Changing our individual consumption of antibiotics may be prudent, and socially beneficial, but is not likely to alter the global microbial environment much or cause other people to change their behavior. Discussing the problem with others is arguably more important than changing our own behavior—at least if our beliefs are justified and we are reasonably good at persuasion. Perhaps the ultimate moral obligation for those who understand the problem is to figure out how to explain the structure of the problem to other people, and to try to influence social norms and public policies to move in a direction that increases the extent to which individually rational behavior is socially beneficial, or at least not socially harmful.

III. POLICY PRESCRIPTIONS

Antibiotic resistance is one of the most urgent problems humanity faces, and lawmakers are finally starting to take notice. The White House commissioned a task force in 2014 and issued a report on the problem in 2015.[31] Prime Minister of the United Kingdom David Cameron also created a commission in 2014, which published the comprehensive Review on Antimicrobial Resistance in 2016.[32] Just before the British publication, a bacterial plasmid resistant to nearly all known antibiotics was found in factory farmed pigs and people in China[33] and a few months later in the United States.[34]

A. Supply

Many scholars have weighed-in on how to best address resistance. To those unfamiliar with the issue, it might seem puzzling that antibiotic development has not kept pace with the rise in resistance. After all, pharmaceutical firms can apparently profit from developing new drugs to treat infections that resist old drugs. Of course, these firms *have* developed new drugs, but most experts agree

30. WALTER SINNOTT-ARMSTRONG, *It's Not My Fault: Global Warming and Individual Moral Obligations*, *in* 5 ADVANCES IN THE ECONOMICS OF ENVIRONMENTAL RESOURCES: PERSPECTIVES ON CLIMATE CHANGE: SCIENCE, ECONOMICS, ETHICS 293–315 (2005).

31. THE WHITE HOUSE, NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA (2015), https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf [https://perma.cc/F2YF-WHB5].

32. O'Neill et al., *supra* note 13.

33. Yi-Yun Liu et al., *Emergence of Plasmid-Mediated Colistin Resistance Mechanism MCR-1 in Animals and Human Beings in China*, 16 LANCET INFECTIOUS DISEASES 161 (2016).

34. According to the US Centers for Disease Control, the MCR-1 gene was recently found for the first time in an American patient with a common *e. coli* urinary tract infection. U.S. Dep't Health Hum. Servs, *Discovery of First MCR-1 Gene in E. Coli Bacteria Found in a Human in United States*, http://www.cdc.gov/media/releases/2016/s0531-mcr-1.html [https://perma.cc/ZT99-6WHJ].

that resistance has outpaced the development of new drugs. Several explanations have been offered.

One explanation is that many early drugs—including most versions of penicillin—were extracted from common plants and fungi and so were easier to discover and cheaper to produce than synthetically created drugs, which require costly research and development. There is consequently a longer delay between when a particular kind of resistance emerges and when a new synthetic drug is created to address it.[35] A related explanation is that off-patent antibiotics still work for some infections, since antibiotic resistance typically comes in degrees rather than being an all-or-nothing fact about bacteria. This means that patented drugs compete with much cheaper generic drugs, so the market for more expensive patented antibiotics is considerably smaller than the generic market. In fact, pharmacies often give away generic drugs for free to get people in the door, and farmers buy these drugs in bulk at very low prices to add them to animal feed.[36]

Another common explanation for why resistance outpaces new antibiotic development is that companies must clear burdensome regulatory hurdles in order to get new drugs approved. But while approval is expensive, safety and efficacy testing is required for lots of drugs, not just antibiotics, so this explanation is unconvincing.[37]

The most plausible explanation is that new synthetic drugs and novel approaches to antibiotic resistance require basic science research that cannot be patented. Even when it can be patented, insights derived from basic science research often take years to discover. Pharmaceutical firms can last for a long time, but they are run by people with much shorter time horizons, so it may not be desirable to executives or shareholders for the firm to invest in the prospect of a payoff that comes much later.

This suggests a potential market failure, and a public goods rationale for government intervention.[38] If the social value of new antibiotic drugs or novel approaches to the problem of resistance is not reflected in drug prices or the amount firms spend on research, perhaps governments can improve outcomes by allocating more money to basic science research.[39] Governments are in a unique position to finance research carried out by universities and laboratories that compete for grants. But private firms are in a much better position, and have better incentives, to translate basic science research into new drugs and treatments.

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35. Kim Lewis, *Platforms for Antibiotic Discovery*, 12 NATURE REV. 375 (2013).

36. Kevin Outterson et al., *Repairing the Broken Market for Antibiotic Innovation*, 34 HEALTH AFFAIRS 278 (2015). In 2015, a popular pharmacy chain in the United States (CVS Drugs) had a campaign advertising "Free antibiotics—14 day supply!" at many of their stores.

37. GELBAND et al., *supra* note 15, are also unconvinced for this reason.

38. But how much intervention, if any, raises moral questions about the proper role of government. *See* Jonathan Anomaly, *Public Goods and Government Action*, 14 POL. PHIL. & ECON. 109 (2015).

39. Brad Spellberg et al., *Combating Antimicrobial Resistance: Policy Recommendations to Save Lives*, 52(5) INFECTIOUS DISEASE SOC'Y OF AM. PUB. IDSA POL., 416 (2011).

Other proposals for stimulating new drug development include offering prizes for specific drug types, and wildcard patent term extensions. The idea of prizes is simple. Policymakers (or scientists working for a government task force) would identify the need for an urgent treatment and create a prize that reflects an amount somewhere between the private costs and social benefits associated with the new treatment. The government would award the prize to the first company to develop the treatment.

Wildcard patent term extensions (or "transferable vouchers")[40] work by offering firms the opportunity to extend the patent term on a drug they already manufacture by a few years in exchange for developing new antibiotics. While some drugs are extremely profitable for pharmaceutical firms to produce and others are not, profitability does not always accurately measure social value. We can allow firms to make large profits on some drugs in exchange for producing other drugs deemed more socially valuable by policymakers. Brad Spellberg thinks we should experiment with this idea.[41] A problem with wildcard patent term extensions is that, even if they stimulate new drug development, they may be a relatively unfair and inefficient tool.

Wildcards operate as a kind of implicit tax on the consumption of whatever patented drug a pharmaceutical firm profits most from, since it extends the length of time over which that firm can reap monopoly profits. The patented drug may be an important blood pressure medication or a treatment for an autoimmune disease, and a patent term extension for those drugs creates a real welfare loss for patients who depend on them. Extending patent terms for antibiotics themselves, rather than offering transferable patent term extensions, also has costs, since it may encourage firms to sell the drug at high prices in the first few years after invention and then sell it at extremely low prices in the last few years as resistance to the drug rises, and other drugs that compete with it emerge.[42] The net effect of this is hard to calculate, and almost certainly varies between drugs, and depends on contingencies that policy makers are unlikely to understand in any detail.

A potential social cost associated with prizes and transferable patent term extensions is what economists call rent-seeking, which occurs when private actors lobby government agents to decrease competition, increase regulations faced by competitors, or simply ask for handouts. Firms typically couch their pleas for government favors in the language of social welfare, so it will always be difficult to figure out whether a patent prize is the right size, or appropriately awarded. The more discretion we give policymakers to make these determinations, the more we encourage rent-seeking. This suggests a rule of thumb for

40. This is the name given to the idea in the recent British Review on Antimicrobial Resistance. O'Neill et al., *supra* note 13.

41. Brad Spellberg, RISING PLAGUE: THE GLOBAL THREAT FROM DEADLY BACTERIA AND OUR DWINDLING ARSENAL TO FIGHT THEM (2009).

42. Kevin Outterson et al., *Will Longer Antimicrobial Patents Improve Global Public Health?* 7 THE LANCET 559, 562 (2007).

public policy akin to Occam's Razor in the natural sciences: if there is a simpler way to achieve the same result, it is generally preferable. Not because simplicity is inherently good, but because complex rules and decision procedures offer more opportunities for bureaucrats and politicians to exploit the (rational) ignorance of citizens in order to use policy to enrich themselves rather than benefit citizens and consumers.

B. Demand

There appears to be little downside to providing public funding for basic scientific research other than the opportunity cost of using the money in alternative ways.[43] This makes it different than other policies like subsidizing particular kinds of drugs, which can encourage rent-seeking. But unless it is paired with efforts to limit consumption, investing more to stimulate the supply of new drugs may just accelerate the arms race between bacteria and antibiotics.

In fact, according to a recent report, supply is less problematic than demand: "contrary to a view that predominates in policy discussions, the antibiotic pipeline is healthy and continually producing antibiotics. Insufficient attention has been paid to developing incentives to conserve the existing universe of antibiotics."[44] Promoting conservation does not just mean exercising more care when consuming existing antibiotics; it also involves encouraging the development of alternative ways of preventing, diagnosing, and treating infections so that antibiotics are needed less.

The most obvious way to limit demand for antibiotics is to restrict access. By far the easiest, most important, and least controversial thing governments can do is to make antibiotics accessible only by prescription. As I have argued elsewhere, antibiotics may be the *only* drug that should require a prescription, since they are arguably the only kind of drug that substantially impacts the welfare of others.[45] Many relatively poor countries around the world mete out severe penalties for using or selling recreational drugs, yet allow citizens to buy antibiotics over the counter. Nothing could be further from a liberal policy, which grants adults the right to use their own bodies as they see fit, but not the right to use their bodies as biological weapons. Under pressure from Western governments, developing countries like India have started becoming serious about imposing restrictions on antibiotic use.[46] One problem with these policies is that government corruption and limited budgets may make them difficult to enforce. Internet pharmacies exacerbate the problem of black markets for

43. Even if we think governments should be much smaller than they are, and perform far fewer functions, funding for basic science research will—up to a point—be among the most effective and mutually beneficial things governments can do.

44. GELBAND et al., *supra* note 15, at 60.

45. Jonathan Anomaly, *Collective Action and Individual Choice: Rethinking How We Regulate Narcotics and Antibiotics*, 39 J. MED. ETHICS 752 (2013).

46. A. Ghafur et al., *The Chennai Declaration: A Roadmap to Tackle the Challenge of Antimicrobial Resistance*, 50 INDIAN J. CANCER 71 (2013).

antibiotics, since they operate globally and ship their (often illegal) products around the world.

Along with requiring physician prescriptions for antibiotics, many agree that we should ban the use of antibiotics as growth promoters in agriculture and require a physician prescription when farmers want to use antibiotics to treat disease. While this may seem like an obvious way of solving the prisoner's dilemma created by unrestricted access to antibiotics as growth promoters, it also creates a new one: the reclassification by farmers of antibiotics as treatments rather than enhancements. Evidence from Denmark, the first country to ban antibiotics as growth promoters, suggests that although total use has declined, prophylactic use has increased.[47] This problem would likely be far worse in other parts of the world, like China and the United States, where animal welfare standards are lower.[48] The reason this is a problem is that conditions on factory farms are often so bad that antibiotics might actually be needed as a prophylactic treatment even if their use as growth promoters is forbidden. In other words, unless governments require farmers to treat animals as more than mere meat machines to pack together in cruel and often unhygienic conditions, imposing mandatory prescriptions for antibiotics may do little if anything to prevent widespread antibiotic use on farms.

Another policy is to tax *all* antibiotics used in agriculture, in addition to banning their use as growth promoters. Pigovian taxes attempt to tax socially costly activities so that those who create the costs internalize them. The idea motivating this strategy is that we can thereby minimize socially inefficient externalities and use money generated by the tax to compensate victims or fund programs aimed at mitigating the harm.[49] A perennial problem with Pigovian taxes is that the information needed to calibrate them is often complex or unavailable—and in this case the information would change over time as new resistance patterns emerge and new treatments become available. A simpler alternative is to impose user fees on antibiotics.[50] The justification is similar, but rather than requiring scientists or policymakers to calculate the precise social costs (and benefits) of using any particular antibiotic, we can impose a flat fee, which might vary for different classes of antibiotics. The goal is to make the fee high enough that it deters relatively inefficient uses, but not so high that animals with serious infections—especially infections that arise through no fault of a farmer—cannot be treated.

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47. Denmark keeps meticulous data on the agricultural use of antibiotics and posts it on DANMAP, http://www.danmap.org/downloads/reports.aspx [https://perma.cc/PQ5U-ZL8M] (last visited June 23, 2017).

48. I discuss this point and its implications in detail in Anomaly, *supra* note 17.

49. Evidence suggests Pigovian taxes are much more popular than general taxes, provided the revenue really does go to addressing the source of the problem. *See* Steffen Kallbekken et al., *Do You Not Like Pigou, or Do You Not Understand Him?: Tax Aversion and Revenue Recycling in the Lab*, 62 J. ENVTL. ECON. & MGMT. 53 (2011).

50. Aidan Hollis & Ziana Ahmed, *Preserving Antibiotics, Rationally*, 369 NEW ENG. J. MED. 2474 (2013).

User fees are also a good idea for the human use of antibiotics for the same reasons: if people (or insurance companies) have to pay a higher price for a drug, they will likely think twice before buying it. The fees can then be used to fund basic science research associated with antibiotic resistance, infection diagnosis, vaccines, and so on. But no policy is perfect. A user fee will have less effect on limiting demand in health care systems that rely on third-party payers, like insurance companies and governments, than it would if individuals paid their own costs. The effect may still be positive if government-run health systems impose the fees on users, and if insurance companies pass (at least part of) the fee onto consumers. One worry about user fees is that although they might discourage low-value use of antibiotics for ordinary people, they might price poor people who actually need antibiotics out of the market, while wealthy consumers remain insensitive to price increases.[51] These unintended consequences are worth bearing in mind, but also apply to all pollution taxes. They are not an argument against user fees, but a reason to avoid making such fees too large.

We have already seen why most people are rationally ignorant about the problem of antibiotic resistance. One of the cheapest ways to mitigate resistance is to fund information campaigns for both physicians and patients. The most effective information to convey to patients through mass media and in health care facilities concerns the cost to individuals and their children of overusing antibiotics. If people understood that by overusing antibiotics they become reservoirs of antibiotic-resistant bacteria that might come back to harm them later, they might be more reluctant to use antibiotics every time they have a cold and might think twice before getting trivial surgeries (such as cosmetic surgeries). Many people are beginning to understand that hospitals can be dangerous places to visit because they typically have very high rates of MRSA (methicillin-resistant *staph aureus*) and other resistant bacteria. Even outside hospitals, people are more likely to acquire a *c. difficile* infection the longer or more often they take antibiotics. All of these exposures can cause serious health problems, including death, but most people do not factor them into their decisions to use antibiotics. Some patients will also be motivated to reduce unnecessary use if they know they are contributing to a process that harms others. Information campaigns aimed at consumers already seem to have had a significant effect in many Western countries,[52] including the United States, and such campaigns are far easier to justify than paternalistic campaigns aimed at decreasing cigarette and recreational drug use.

Common physicians and surgeons cannot keep up with every medical advance and have little ability to understand the details of changing patterns of resistance. They too are rationally ignorant about most facets of modern medicine, though they certainly have stronger incentives to pay attention to epidemio-

51. O'Neill et al., *supra* note 13, at 67.
52. GELBAND et al., *supra* note 15, at 35–37.

logical trends than their patients do. So there may be reasons for hospitals and organizations like the American Medical Association to adjust medical curricula to ensure that physicians understand the problem, and for governments to provide feedback to high-volume prescribers. At the very least, government agencies like the U.S. Centers for Disease Control are in a good position to fund surveillance programs so that physicians, hospitals, and clinics have a sense of the broader patterns of resistance outside of their own private practices.

C. Alternatives

Prescription requirements, user fees, and information campaigns can help decrease demand for low-value uses of antibiotics. But the main thing policymakers should focus on is basic science research—funded at least in part by antibiotic user fees—that is likely to lead to breakthrough treatments and diagnostics.

One of the main reasons for inefficient prescription is that very few bacterial infections can be detected quickly and precisely. Patients in hospitals or community clinics show up with a set of symptoms, and physicians often prescribe broad-spectrum antibiotics hoping to kill off whatever infection the patient has. This is extremely wasteful since it means many different species of bacteria are targeted at once, most of them non-pathogenic. This elevates the risk that some strains will develop and spread resistance, and also minimizes the chances of targeting the right bacteria (assuming the patient has a bacterial infection, which is often not the case). There is a strong public goods rationale, then, for funding basic science research that might eventually translate to faster, more accurate diagnostic tools. The benefits go to all potential antibiotic users and all potential victims of bacterial infections—which is to say, everyone.

Another way to reduce demand for antibiotics is to stimulate the development of vaccines for bacterial infections like tuberculosis and gonorrhea, some strains of which are now resistant to all antibiotics. A related possibility is immuno-enhancements through genetic engineering, which new technologies like CRISPR could enable in coming decades. Prevention is the cheapest medicine, but in the case of vaccines and genetic engineering prevention requires quite a bit of scientific knowledge that private firms are not always in the best position to produce.

Finally, new strategies for treating bacterial infections are being explored—ranging from phage therapy (which uses viruses to attack pathogenic bacteria) to technology that disrupts bacterial communication or otherwise inhibits virulence.[53] Once again, these advances are facilitated by publicly-financed basic science research, much of which occurs at university labs.

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53. Joseph Gerdt & Helen Blackwell, *Competition Studies Confirm Two Major Barriers That Can Preclude the Spread of Resistance to Quorum-Sensing Inhibitors in Bacteria*, 9 ACS CHEMICAL BIOLOGY 2291 (2014).

CONCLUSION

Because resistance is a global problem, people in each state have a strong interest in how people in other states use antibiotics. This suggests that a global treaty may be required to adequately address the problem.[54] In the case of climate change, unilateral action to reduce greenhouse gasses can sometimes be counterproductive. For example, as the United States uses more environmentally-friendly natural gas (made possible by hydraulic fracturing technology), American (and Australian) companies now export more coal to China, which tends to burn it in a way that causes more pollution, given its lower environmental standards. This means that global emissions of carbon dioxide could rise rather than fall. At the very least it shows that unilateral action can produce unintended negative consequences (though it is important to emphasize that collective action that slows economic growth also produces unintended negative consequences—a point often overlooked by those who endorse sweeping restrictions on fossil fuel use).

The same is true of antibiotic resistance, though to a lesser extent. The greenhouse gasses that affect global temperature mix evenly in the atmosphere, but antibiotic resistance can, to some extent, be concentrated in local areas. Over time, bacteria move across borders due to trade and travel. But at any given time, people living in a particular country disproportionately bear the cost of the misuse of antibiotics in people and agriculture. This suggests that each country incurs enough of the cost of resistance to justify *some* unilateral efforts at antibiotic conservation, even if we would all be better off if all countries made an effort to coordinate with a global treaty.

As we learn more about the microbiome, people will have stronger prudential reasons to figure out which bacteria they are colonized by (and should be colonized by) and stronger moral reasons to make sure their children's microbiomes are healthy. Some people will presumably choose to ignore this information, just as many people today use antibiotics without understanding how they work or what effects they have. Since we do not have a right to act in ways that significantly elevate the risk of collective harms, we cannot use ignorance as an excuse for making choices that put others at risk (even if our ignorance is, in the economic sense, rational). Antibiotics should be regulated to minimize the problem of resistance. But doing so is a difficult problem that will require us to look to the distant and unintended consequences of using antibiotics, and of policies aimed at controlling antibiotic resistance.

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54. See Richard Smith & Joanna Coast, *Antimicrobial Resistance: a global response*, 80 BULL. WORLD HEALTH ORG. 126 (2002); Jonny Anomaly, *Combating Resistance: The Case for a Global Antibiotics Treaty*, 3 PUB. HEALTH ETHICS 13 (2010); Kevin Outterson et al., *Repairing the Broken Market for Antibiotic Innovation*, 34 HEALTH AFF. 277 (2015). While I still endorse a treaty, the pricing and patent mechanisms I advocated earlier strike me as overly simplistic. I now think the main priorities should be pressuring developing countries to conserve existing antibiotics by requiring prescriptions and minimizing their agricultural use, and encouraging all countries to fund basic science by awarding grants to researchers on a competitive basis.