The Phage Therapy Solution to Antibiotic Resistance: Regulatory Changes to Avert a Looming Crisis

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Abstract

Antibiotic resistance is a growing public health concern, although phage therapy is an effective alternative treatment that can mitigate this problem. The pharmaceutical regulatory regime in the United States keeps phage therapy from being economically viable. This paper evaluates the incentives created by this regulatory regime in light of their contributions to antibiotic resistance and stifling of phage therapy. From, it proposes a new regulatory regime that can make phage therapy viable and avert the crisis of widespread antimicrobial resistance. This proposed regulatory regime alters the approval process for phage therapy treatments, imposes requirements on reporting their use, and gives doctors and drug manufacturers broad freedom to refine and perfect treatments.

1 Introduction

In the United States in 2018, drug-resistant bacteria infected around three million Americans, killing about 50,000 of them. Worldwide, the death toll was approximately 700,000. By 2050, the global death toll is expected to reach 10 million and exceed total cancer deaths (Plackett 2020). Many of these infections are very treatable using bacteriophage therapy, (hereafter phage therapy) an alternative treatment used extensively in the Republic of Georgia that is barely practiced in the West. The use of phage therapy in the Republic of Georgia stretches back into the early Soviet period (Kutateladze 2015; Kutter et al. 2010). Bacteriophages, or phages, are naturally occurring viruses

that only target bacteria. Phage therapy uses specific phages to fight infection-causing bacteria.

Historically, many medical advances including antibiotics have originated in the United States and other Western countries. This can be attributed to institutions and infrastructure, but that begs the question of why so many people in the West are dying of things that were easily treated in the Soviet Union, which was hardly a model for quality health and human development. This paper hypothesizes that the reasons for this are that incentives in each place – the United States and the Soviet Union – led to the use of different treatments with different results. Institutional inertia in the West has kept it from learning from a Soviet success, even though that particular Soviet success had its earliest roots in the West.

Some literature considers antibiotic efficacy a common resource and antimicrobial resistance a tragedy of the commons stemming from overuse of antibiotics. If true, antibiotic resistance is a market failure. By analyzing the institutional structures governing drug development and use, this paper develops a different premise that antibiotic resistance is a combination of both market failure and government failure, with the latter being the dominant cause. Unless some reforms are made, both market failure and government failure could soon claim the lives of millions of people each year (Plackett 2020).

This paper first reviews relevant literature on antibiotic resistance and phage therapy. From there, it discusses the causes of antibiotic resistance in section 3. The proximate cause differs from the ultimate causes, which are institutional in nature. Section 3 also discusses these institutional causes and explains why eliminating the role of the state is a practical impossibility, despite government failure. Eliminating the role of the state could potentially replace the government failure with a market failure that is just as bad. Section 4 follows with a historical and technical overview of phage therapy, which is an integral component of this paper's proposal to solve the increasing problem of antimicrobial resistance. Because antimicrobial resistance is an institutional, not scientific, failure, section 5 proposes an institutional structure that will facilitate the use of phage therapy as an alternative approach to bacterial infection.

2 Literature Review

Antibiotic resistance is a well-known problem among researchers in medical sciences. Among economists, however, it has received little attention. A search on July 12, 2021 in EconLit for "phage therapy" found no results among peer-reviewed articles, collected volumes, working papers, books, or dissertations. A search for "bacteriophage" returned two articles, neither of which was relevant to phage therapy. On related topics, "antibiotics or antibiotic" returned 295 peer reviewed articles, not all of which were about antibiotic resistance, a search for which only showed 84 results. Other health economics topics have been far more popular; a search for "cancer" turned up 1,996 articles, "pharmaceutical" returned 4,532, and "health" found 122,368. The institutional structures governing the development and use of pharmaceuticals center intellectual property and government regulation, both of which interact closely in the drug development process. The relationship between these institutions and antibiotic resistance has received even less attention.

Intellectual property (IP) can be a philosophically contentious issue. Although it is now a bedrock of pharmaceutical research incentives, the medical profession has not always looked fondly on pharmaceutical IP, and once viewed it as contrary to medical ethics (Gabriel 2014). The case for IP is straightforward, namely that market exclusivity provides an incentive for medical research that would not otherwise take place. "Market exclusivity" encompasses far more than the length of the patent term, which often is nearly exhausted by the time patients take a drug; rules about research data exclusivity, timing of generic approval for bioequivalence, etc. grant drug manufacturers a period of exclusivity that is intertwined with pharmaceutical regulation (Feldman 2016). Intuitive as the justification may be for IP, it is criticized both on philosophical and utilitarian grounds.

Regulation is almost inseparable from IP in American pharmaceutical research and production and, like IP, it too attracts its critics. Friedman and Friedman (1980) famously argued that the costs of obtaining FDA approval needlessly stifle many good drugs from reaching the market. This point has also been made by Geiringer and Peltzman (1973). When examining this argument, it is worth remembering that unsafe drugs were rampant and exposed by muckrakers before pharmaceuticals were regulated

during the Progressive Era (Gabriel 2010; Valuck et al. 1992). Wiebe (1967) viewed Progressive Era regulations as an attempt to stabilize society and mitigate change in the face of rapid development. Pharmaceutical regulation during this time often did not adequately address the real public health problems in the pharmaceutical industry (Cassedy 1964; Friedman and Friedman 1980). Viewing the paradigm of pharmaceutical regulation in this light helps explain why it has proven ill-equipped to combat antibiotic resistance, as section 3 shows.

Although pharmaceuticals have become safer since regulation, many new costs have been introduced into drug development process, possibly preventing many beneficial drugs from reaching the market. Many of these costs are regulatory and nature and have little relationship to safety and efficacy and may exceed one billion dollars (DiMasi et al. 2003, 2020). In this paper, I take the view that IP and regulation do not encourage or discourage pharmaceutical innovation per se, but they do alter incentives for specific areas of pharmaceutical innovation. High upfront costs skew the incentives for drug development toward drugs with a lucrative market, such as chronic conditions like heart disease and cancer. This point has been noted by Conly and Johnston (2005) Gallini (2017), and Plackett (2020), who point out that incentives created by the regulatory system and IP regime deter investment in antibiotics. Lack of investment in antibiotic research contributes to antibiotic resistance, prompting some to call for changes to pharmaceutical regulation system (Eswaran and Gallini 2019).

Antibiotic resistance was always a theoretical possibility, but it is increasingly apparent that it is becoming a reality. The increasing numbers of fatalities from bacterial infections has rekindled interest in phage therapy in the West (Reardon 2014). Phage therapy is discussed in section 4, and is fundamental to this paper's proposal for a new regulatory regime to mitigate antimicrobial resistance. Phage therapy has received little attention from economists. Models of antibiotic-induced antimicrobial resistance are less applicable to phage therapy, the entire approach of which is fundamentally different than that of broad-spectrum antibiotics.

Antibiotic efficacy has been viewed as a common resource and antibiotic resistance as a tragedy of the commons (Roope et al. 2019). This has prompted some to call financial mechanisms to encourage new antibiotic development and more prudential use (Antoñanzas and Goossens 2019; Luepka et al. 2017; Rudholm 2002). This has

been the thrust of most recent economic research on antibiotic resistance, which has largely ignored institutional incentives and alternative therapies. In discussing the future of phage therapy, Anomaly (2020) notes that the value of phages may be a public good that the market underprovides, just like antibiotics. This is an artifact of the regulatory regime governing this market for pharmaceuticals, so it is to some degree a government failure as well as a market failure. There is little potential for a private solution of the sort articulated by Ostrom (1990) when government failure is the problem.

3 Causes of Antibiotic Resistance

Bacteria are living organisms that evolve through natural selection in response to their environment. Antibiotics, in contrast, are chemical substances that do not evolve. As bacteria mutate and acquire resistance, it is only natural that resistant strains become more prevalent. In modeling the optimal use of antibiotics to minimize resistance, Laxminarayan and Brown (2001) consider antimicrobial effectiveness to be a nonrenewable resource which can ultimately be exhausted. This paper contends that this resource is indeed renewable and that the nonrenewability is only an illusion that stems from a poorly designed regulatory system. This claim rests on the use of phage therapy, not just antibiotics.

3.1 Proximate Cause

Antibiotics are a product of pharmaceutical innovation and production. Widespread antibiotic resistance is a product of institutions governing pharmaceutical innovation and production. Proximately, antibiotic resistance results when mutated bacteria survive the use (or overuse) of antibiotics and multiply, propagating resistant genes. Institutional structures centered on both IP and pharmaceutical regulation deter development of both new antibiotics and alternative approaches like phage therapy. Fixing these institutional shortcomings will solve the government failure and market failure.

Prophylactic use of antibiotics in agriculture has been highlighted as a potential cause of antibiotic resistance. China, which consumes around half of the world's antibiotics, slightly more than half of which are used in Chinese agriculture, has had

problems with resistant infections, including tuberculosis, prompting successful efforts to reduce their use (Schoenmakers 2020). Focusing on the United States, Adda (2020) casts doubt on whether agricultural use is a problem, showing that use of antibiotic use in humans is more closely linked to resistant bacterial infections in humans. Alarmingly, he also showed that resistant infections are most sensitive to the newest antibiotic drugs, which are often variations on existing drugs. Regardless of who is right, resistant strains of bacteria are on the rise and antibiotic use more generally is a major contributing factor.

The proximate cause of antimicrobial resistance is antibiotic overuse, but the ultimate cause is the institutional structure governing the pharmaceutical industry. In very broad terms, the critical problem with existing pharmaceutical regulation and the IP regime is that they do not encourage the use or development of antimicrobial therapies that take into account organic evolution. They encourage the use of inorganic antibiotics, the efficacy of which is a nonrenewable resource. Worsening the problem, they have not encouraged development of new antibiotics and discouraged the use of antimicrobial therapies that take organic evolution into account. Wiebe's 1967 view of Progressive Era regulation as a stabilizing, though not necessarily efficiency-enhancing, force is relevant here.

3.2 Pharmaceutical Regulation

Inefficiencies of the drug approval process, and of the FDA in general, have been well documented, so this section provides only a brief overview with relevance for phage therapy. Obtaining FDA approval to market a new drug is a time-consuming and expensive process. Costs are easily in the millions of dollars and can exceed one billion. Early-stage research is costly in its own right before regulatory costs begin to mount. Many drugs never reach clinical trials and, of those that do, only about 12% reach the market (DiMasi et al. 2020). Pharmaceutical manufacturers must pay the costs of their unsuccessful efforts out of revenues from marketed drugs. The role of regulation centers on demonstrating safety and efficacy and ultimately involves multiple stages of human clinical trials.

Phage therapy is not economically viable under this regulatory system. As the

rules currently stand, each individual phage would have to be approved as a new drug. Specifications of inert compounding ingredients and purity would have to be established each time. FDA market exclusivity rules would mean that any prospective competitor would have to prove bioequivalence. The cost burden is simply too high to produce a medicine from a naturally occurring phage and continually update the formulation.

3.3 Intellectual Property

IP can be a contentious issue. To allay some readers concerns about IP in general, I start this section with three premises that should be noncontroversial.

1. IP creates and/or alters incentives for some economic activity.
2. IP causes different things to be developed than would be produced without IP.
3. IP *may* cause more beneficial drugs to be developed.

None of these three claims makes a normative judgment on the social welfare effects of IP. For the first claim, by securing an exclusive profit stream for new inventions, IP creates an incentive to invent that did not exist before. The second claim follows, but "different" does not necessarily mean "better." The third claim is not a given; it is qualified as a possibility. There is no a priori reason why IP must result in "better" things, the judgment of which is subjective. These premises merely reflect the fact that IP is inextricably linked to economic incentives. These economic incentives may be viewed favorably by those seeking certain outcomes, but there is considerably more at stake in reaching most outcomes than the existence of IP. In the United States and other Western countries, IP interacts closely with pharmaceutical regulation to produce observed outcomes.

3.4 Interaction of Regulation and IP

IP is fundamental to the modern pharmaceutical industry. Most drug development likely would not occur without it, but to a some degree this is because regulatory costs require a substantial profit stream, meaning that market exclusivity is a necessity, although costs could still be high even without FDA regulation. IP is thus a necessity in part because of high regulatory costs. However, the time from a patentable idea to

final marketing approval from the FDA exhausts most of the patent term. A set of FDA regulations grants market exclusivity to the developing term beyond the patent length (Feldman 2016). The function of a patent is mostly to preserve exclusivity during the development phase, after which FDA exclusivity regulations are what matter.

High costs of development and regulatory approval make IPRs and FDA exclusivity regulations necessary for drug development. However, the size of the profit stream is highly dependent on the type of drug produced. Chronic conditions like cancer and heart disease that require ongoing treatments have received much attention. Vaccines and antibiotics have received far less. This could be due to the threat of compulsory licensing in foreign countries that lack strong IPRs. Alternatively, it could simply result from the high costs of drug development that discourage production of something that only needs to be taken once or occasionally. The most recent high profile vaccines, those that prevent COVID-19 infection, are protected by IPRs as of the time this paper was written, but they were developed with large government subsidies and purchase commitments. Many countries pleaded for IPRs to be waived.

3.5 Why Can't We Easily End State Involvement?

Governments in developed countries are involved in the production, regulation, and marketing of new drugs. The desirability of this may be questioned, however ending it is a political non-starter. Setting aside arguments about the history of unsafe medicines before government regulation, which may or may not be well-founded, existing institutional structures will impede the development of new, safe, and effective drugs. This section discusses these issues, reaching the conclusion that state involvement in drug regulation cannot easily be ended.

3.5.1 Perfect Information

Elementary models of efficient free markets assume that buyers and sellers both have perfect information. Lack of perfect information is a source of market failure. In the absence of drug patents and FDA regulation, both of which require disclosure of information, consumers will not have perfect information. If there were no IP or FDA disclosures, the only logical way to maintain profitability is through trade secrets.

Trade secrets are widely used in other sectors, but their use in pharmaceuticals is mostly limited to production processes, not the nature of active ingredients.

Trade secrets were widely used in the pharmaceutical industry before regulation, and many dangerous substances were marketed during this time. This was a major impetus for regulation and for the medical community to embrace drug patents, which it had previously derided as contrary to medical ethics (Gabriel 2014). A return to trade secrets instead of patents and regulation could mean a return to these days. It is already unreasonable to expect ordinary consumers to know enough biological science to judge whether a substance should be taken. Doctors are expected to know these things but if they do not know what a medicine contains, they cannot make these judgments.

3.5.2 The Role of Tort Law

Friedman's argument that the FDA is unnecessary because drug makers know it is not profitable to poison consumers is intuitive, yet countered by historical examples of unsafe drugs (Gabriel 2014). His argument that it stifles the development of new drugs had considerable merit. However, it need not follow that abolishing the FDA would necessarily stimulate rapid new drug development or lead to the rapid adoption of phage therapy. Other incentives can prevent the development and marketing of potentially useful drugs.

Tort law is a major part of the incentive not to do harmful things – not only will a business lose customers, it could face substantial penalties for negligence or overtly harmful products. Tort claims in medicine, along with malpractice insurance premiums, can be exorbitant (Viscusi and Born 2005). Without FDA approval, and especially without full disclosure of substances, malpractice claims and insurance premiums would likely increase markedly. There is a real possibility that the threat of judgment could deter investment in drugs in the absence of FDA regulation. Moreover, FDA approval does not always grant a drug manufacturer immunity from tort claims (Field 2009). If private organizations took over the role of vetting drugs, the threat of tort liability still exists and, if anything, is magnified. The FDA has sovereign immunity from judgment, which these private organizations will lack. Drug certification organizations will join drug makers and doctors as yet another entity subject to judgment,

further increasing the deterrent effect of tort liability.

Nothing in this section should be taken as a rejection of arguments against the FDA and pharmaceutical IP; both have contributed to the crisis of antibiotic resistance. I present tort law and information issues simply to show that abolishing the FDA and drug patents may not lead to the desired circumstances that both the FDA and drug patents proximately prevent.

4 Bacteriophage Therapy

Phages are viruses that infect and kill bacteria, but not other organisms. There are estimated to be 10^{31} phages on earth, making them more abundant than any other type of organism, including bacteria (Comeau et al. 2008). Phages are highly specific, meaning that each phage kills only a very small range of bacteria, although any type of bacteria may be susceptible to a vast number of phages. Antibiotics, in contrast, are broad-spectrum and affect all bacteria that are not resistant, including beneficial bacteria in the human gut microbiome. Phages exist that target infectious but not beneficial bacteria (Loc-Carrillo and Abedon 2011; Principi et al. 2019). Antibiotics can be thought of as a macroeconomic policy like altering interest rates, and phages in contrast being analogous to finely targeted micro interventions.

Phages were discovered by English researcher Frederick Twort in 1915 and French microbiologist Félix d'Hérelle in 1917. D'Hérelle experimented with phages for treating infections. Like many new treatments, phage therapy was controversial, although it was used in France and d'Hérelle came to the United States for more research. Antibiotics were developed shortly thereafter and, because they were broad spectrum, they attracted far more attention than highly specific phages. In 1934, d'Hérelle co-founded the Eliava Institute in Tbilisi with Georgian colleage George Eliava. This was in part due to the lack of enthusiasm in the West for phage therapy and the need for infections to be treated in the Soviet Union, which had limited access to Western pharmaceuticals. After the Second World War, the tensions of the Cold War dampened any interest in phage therapy in the West (Summers 2012).

As living organisms, phages evolve alongside bacteria, unlike antibiotics. Phages found in nature can be isolated, cultured, and administered to a patient to cure bac-

terial infections. This is the practice of phage therapy (Lin et al. 2017). Bacteria can evolve resistance to phages, but the vast availability of evolving phages means that untreatable infections are unlikely to develop. Continual reformulation of treatments, however, is necessary to provide the most up-to-date treatments. Producing phage therapeutic treatments is straightforward and low-cost. Importantly, because resistance mechanisms differ, resistance to phages or antibiotics never implies resistance to the other (Loc-Carrillo and Abedon 2011).

Phage therapy requires ongoing research. Some phages can have muted effects or possibly reprogram bacteria to have antibiotic resistance, thus being counterproductive. These phages have a lysogenic cycle. In contrast, phages with a lytic life cycle rapidly kill target bacteria, but there is still a risk of horizontal gene transfer that could lead to antibiotic resistance (Anomaly 2020).

5 Model

This section describes a regulatory model that will support phage therapy. It first describe the needed attributes of a system, and then presents specific details about intellectual property, reporting and practices, and pharmaceutical regulation.

5.1 Needed Attributes

To promote the use of phage therapy, a regulatory system must be flexible enough to permit the updating of therapeutics as phages and bacteria evolve. Related to this, it must encourage optimal use, which the current antibiotic-based approach does not. Lastly, the interaction between regulation and IP must not prevent the use of phages.

5.1.1 Evolutionary Stability

Phages are not a silver bullet to instantly and permanently cure bacterial infections. Bacteria can develop resistance to phages as well as antibiotics. Developing resistance to phages can have fitness costs to the bacteria, possibly benefiting the host by making antibiotics more effective (Oechslin 2018). Discovery efforts to find new phages must be ongoing, but this should be possible because phages mutate and evolve. Only

with continual development that respects the evolutionary tendencies of bacteria and phages can phage therapy become a viable part of the medicinal arsenal against harmful bacteria.

Approval of each individual phage of the sort that the FDA mandates for new drugs is time consuming and expensive to the point that it discourages phage therapy research (Pelfrene et al. 2016). However, the current American standards for updating the seasonal influenza vaccine hint at a regulatory approach for updating phage cocktails. Influenza vaccines are produced using an FDA-approved process, but they are targeted toward new strains of constantly evolving influenza viruses. The FDA does select strains used for each vaccine and verifies the safety and potency of the vaccine (Food and Administration 2020). The focus is on manufacturing standards with some attention to the specific strains of the virus used.

5.1.2 Optimal Use

Regulating phage therapy in a way that respects organic evolution should rely on updates to therapeutics produced using known processes, just like the influenza vaccine which does not require de novo regulatory approval each year. Beyond this, however, the regulatory regime must offer incentives for optimal use of specific phages, meaning that it discourages overuse and encourages continual updating of the combinations.

5.2 Intellectual Property

Intellectual property will have far less importance under a well-designed phage therapy regulatory system than it has under the current American regime for developing new pharmaceuticals. Phages are naturally occurring and thus theoretically unpatentable, although questions of patentability will ultimately be decided by courts. This unpatentability prevents an exclusive profit stream from being secured, which is needed to cover the costs of FDA approval. A lack of patent protection need not discourage phage therapy if the regulatory system is altered in ways that reduce approval costs, described below in section 5.3. New methods used for isolating phages, producing purified treatments, and evaluating efficacy are patentable, and this could provide an incentive for efficiency-improving innovations, although existing methods are and will

remain in the public domain.

Although phages are naturally occurring, there are costs to discovering, isolating, and testing them. For phage therapy to be viable, cataloguing of newly discovered phages must be economically viable. Patent protection cannot be granted, but a type of market exclusivity analogous to the plant variety protection granted by the United States Department of Agriculture could serve this purpose. This protection applies to plants that are new, distinct, uniform, and stable. An analogous approach for phages would allow manufacturing firm exclusive rights to a phage never before in commercial use if it can successfully and continually be produced into a purified treatment. This exclusivity would be time limited (e.g. 20 years) and prohibit competitors from mixing it with other phages in their own cocktails, however no cocktail of multiple known phages would qualify for protection in its own right. A great many phages are yet to be discovered, so this approach would create an incentive to discover and catalogue them (Grose and Casjens 2014).

Section 5.3.1 describes an information repository as an essential element of the rules governing phage therapy. Repositories could be maintained by government or the private sector, but if the private sector does it, copyright protection for the database are imperative to secure a needed revenue stream to maintain it. Whether in enforcing intellectual property rights or maintaining the repository directly, there is no realistic way to fully eliminate government's role. This is the author's judgment of political reality, not an expression of ideological preference.

5.3 Phage Therapy Regulatory Regime

Although found in nature, phages are not used in their unrefined, naturally occurring form. They must be collected, concentrated, and purified to form a phage cocktail containing one or more phages. Phages are found alongside bacteria which are often harmful, so the therapeutic cocktail must meet a threshold of purity. This purity threshold means an upper limit on unknown phages and bacterial debris. Without purification, the phage cocktail could be harmful. Whether mandated by government or some other organization or voluntarily followed, there must be a high manufacturing standard for phage cocktails. Manufacturing standards should govern techniques of

preparation, but not individual phages. The need for an evolutionarily stable system means that the catalog of phages in use needs regular updates. This is discussed at greater length in section 5.3.2 below.

The need for an evolutionarily stable system means that regulatory standards should not go beyond basic standards of safety because phage combinations must be updated. A similar approach is already in use for influenza vaccines, which do not require *de novo* regulatory approval with each update (Chan et al. 2013; Furfaro et al. 2018). Any regulatory regime should take account of the need for antimicrobial therapy in agriculture and aquaculture, where phage therapy shows promise (Kowalska et al. 2020).

5.3.1 Information Repository

With evolving bacteria and vast numbers of patients being treated concurrently, there is a great need for physicians and regulators to know the attributes of phages in use. A repository of information about known phages and their attributes needs to be maintained and accessible. This does not automatically mean that maintaining this repository is a government responsibility. In the former Soviet Union, and now the Republic of Georgia, the Eliava Institute maintained much of this information.

Besides knowing the attributes of phages, this repository should have information about use frequency so that plans can be made about increasing or decreasing the use of individual phages to prevent resistance. Doctors administering phage therapy should report all details of the treatment, including the specific phage(s) used, the target bacteria, whether antibiotics were also used, and the treatment outcome, as well as relevant patient data. Reporting must be mandatory.

For avoiding undue government influence and bureaucratic red tape, private organizations could maintain these repositories. If this approach is used, three rules are necessary to prevent these organizations from becoming ineffective or counterproductive. First, they should not be immune to antitrust rules; healthy competition is essential. Antitrust ideally should mandate some competition (European approach) as well as adherence to the consumer welfare standard followed in the United States to keep prices low. The exorbitant fees charged by the American Medical Association for access to its proprietary codes for procedures, and its byzantine rules for updating

them, are things to be avoided. Structuring repositories as cooperatives or nonprofits could contain costs if there is sufficient competition. Second, they should be required to publish their data to the public, although reasonable subscription fees should be expected, which require copyright protection. This serves to allow third-party analysis of efficacy. Third, any organization serving as a repository should be prohibited from doing anything other than maintaining the repository to avoid mission creep and the establishment of irrelevant standards. It is vital that repositories not be directly involved in phage cocktail manufacturing. One possible exception would be warning of overuse or misuse of specific phages, but this should not extend to the authority to "certify" doctors who comply with its warnings.

5.3.2 Safety Standards and Safe Harbor

Verberken et al. (2014) describe a system of regulation to ensure safety and efficacy, but their work focuses on biological attributes of phages and specifics of what should and should not be permitted. This section takes a different approach by focusing on the structure of the regulatory system with a view toward incentivizing optimal use and ongoing development. The institutional structures described in this section may embrace or disregard the suggestions of Verberken et al. (2014).

Regulating standards of acceptable use of phages and the preparation of treatment cocktails are two areas where some role of government will almost certainly remain. As inefficient as the government may be, tort liability may dissuade private organizations or individual doctors from administering these treatments, even if it were legal. Limiting tort liability removes a powerful incentive for safety.

The role of government in setting standards for phage therapy should be limited to requiring nontoxicity but not efficacy. It ought not to be the function of the government to approve or reject specific phages. If information repositories are well-maintained, judgments of efficacy can be outsourced to doctors and independent researchers. Minimum safety standards should be established and, if the treatment cocktail meets the standard, there should be safe harbor from liability. Nontoxicity standards must encompass both nontoxicity of the phage itself as well as nontoxicity of other ingredients in the cocktail, necessitates a certain level of purity.

A minimum standard for safety inevitably encompasses a threshold for demonstrat-

ing safety, especially because cocktails must be regularly updated and reformulated. One example of how such a standard could work is a requirement for in vitro tests of new cocktails, which could then permit limited in vivo trials (with patient informed consent), after which safe harbor for general use would be established. Rules for establishing safe harbor should focus on safety, not efficacy because new strains of bacteria could be discovered and a seemingly useless but safe phage could eventually find use. To establish safe harbor, physicians and cocktail manufacturing firms have a strong incentive to record all relevant data and report it to a repository. To promote competition among repository organizations, a rule requiring doctors to report to at least two or three independent repositories could be beneficial.

5.4 Antibiotic Regulation

Insofar as excessive use of antibiotics is a proximate cause of antimicrobial resistance, this overuse must be curtailed to prevent potentially deadly consequences. As promising as phage therapy is, one cannot rule out the possibility of a biological disaster that could necessitate the use of broad spectrum antibiotics. Curtailing overuse of antibiotics means limiting their use in humans and sharply curtailing prophylactic use in agriculture and aquaculture.

For humans, phage therapy should be treated as a first-use option, not a last resort. One approach would be to prohibit the use of antibiotics if cocktails of known phages prove ineffective. Doctors would ultimately have discretion, but their use of phage therapy and antibiotics would be reported to information repositories.

Prophylactic use of antibiotics maintains the health of livestock. Not using cheap antibiotics will raise the cost of meat, milk, and eggs because livestock conditions will have to be improved so bacteria will breed less. The cost of maintaining the health of livestock will fall on the consumer in monetary terms. Continuing the prophylactic use of antibiotics also imposes a cost. This cost is to more people than just the consumer, and it is borne in the form of antimicrobial resistance which can threaten populations of humans and animals with disease. Whether prophylactic use of antibiotics is permitted or proscribed, a cost is imposed. To the extent that antimicrobial resistance is viewed as a serious threat, this prophylactic use should be prohibited or sharply curtailed.

Because phage therapy, when properly administered, is an evolutionarily stable remedy, prophylactic use of phages may be reasonable, but as with human use, agricultural use should be reported to information repositories.

6 Conclusion

Antimicrobial resistance is a growing threat to public health. Bacteria can evolve to become resistant to antibiotics, so antibiotic overuse is a proximate cause. Antibiotics, in contrast, are chemical substances that do not evolve. The root cause, however, is institutional structures governing pharmaceutical research and practice that deter investment in treatments that can be effective in the face of bacterial evolution. Institutional structures center on pharmaceutical regulation and intellectual property.

To reach the market, a new drug must complete an expensive and time-consuming regulatory process. In order to recoup the costs, a drug must have a large market and its manufacturer must have exclusivity to prevent competitors from copying it without incurring development costs. This makes intellectual property a commercial necessity for drug development.

Phage therapy is an alternative therapy relying on phages, or viruses that target specific bacteria. It has been used extensively in the former Soviet Union with considerable success. However, the current regulatory system does not facilitate the use of phage therapy. Phages are naturally occurring, and thus ineligible for patent protection. Moreover, they evolve and combinations of phages used to treat specific infections must regularly be updated to prevent bacteria from developing resistance to treatments. This means that regulatory approval is an ongoing process, which is far more expensive than a one-time process. The high costs and lack of market exclusivity make phage therapy a practical impossibility in the United States, leading to antibiotic overuse and antimicrobial resistance.

This paper proposes a new regulatory structure to encourage the use of phage therapy. This regulatory structure centers on development and manufacturing processes, rather than on testing and approval of specific phages. Treatments produced in accordance with these processes would be acceptable, and manufacturers and doctors would not face liability. In the face of organic evolution, efficacy is a moving target, so it

ought to be beyond the scope of regulation, which should focus solely on safety.

Information repositories, whether run by government or the private sector, are a critical component of this system. Any production and use of phage treatments should be recorded, along with outcomes. This is a necessary complement to the lack of efficacy regulation. Doctors must be able to make judgments about which phages will be effective, and this means knowing what is currently used or overused.

As threatening as pervasive antimicrobial resistance is, relying on phage therapy in addition to or instead of broad spectrum antibiotics is a simple solution. The regulatory environment has prevented its use and thus is a major cause of antimicrobial resistance. The regulatory changes outlined in this paper will make its use more feasible and help alleviate this looming public health crisis.

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