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Perilous Passivity: The Insufficient Response to Antimicrobial Resistance

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INTRODUCTION

Antimicrobial resistance is a growing problem with a global scope. If left unaddressed, it threatens to diminish the effectiveness of antibiotic, antiviral, and antifungal medications. These medications, in tandem with vaccination, are largely responsible for the dramatic decline in the spread and mortality of infectious diseases worldwide since penicillin was first mass produced in 1941. Thus, they are major contributing factors to one of the great achievements of modern humanity: the reduction of global childhood mortality in from between 30% and 50% in the 19th century to less than 0.5% today in industrialized nations.[1]

Repeated use of antimicrobial products causes antimicrobial resistance to develop. As antimicrobial-resistant traits emerge and spread to pathogens, they threaten the security from infectious diseases that antimicrobial medicines grant to society. Therefore, to preserve the life-saving power of these medicines, antimicrobial products must be used judiciously. However, in practice, they are used wantonly and without regard to the gradual, building effects of their overuse throughout the world. This is especially prevalent in commercial settings, as over 80%

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[1] Child Mortality, OUR WORLD IN DATA, https://ourworldindata.org/child-mortality (last visited Dec 14, 2018).

of antimicrobial products are used for agriculture.[2] Nevertheless, it is similarly imperative to control their medical uses, as up to 50% of antibiotic prescriptions in the United States alone are either sub-optimal or entirely unnecessary.[3]

The tension between the long-term need to preserve the effectiveness of antimicrobial products and the immediate benefits of their use lies at the heart of the crisis surrounding resistance. To that end, the object of an effective regulatory scheme should be to deter the use of antimicrobials solely for profit or convenience, and to confine them to settings where their use is medically appropriate.

Alongside regulation, research and development of novel drugs with antimicrobial effects that are not currently countered by resistance traits can be an effective tool in solving this crisis. However, no drug is immune to the process by which resistance develops; even novel drugs will in time become subject to the same limitations that current drugs face.[4] Research and development alone, without simultaneous regulation of the use of currently effective drugs, cannot completely ameliorate the problem.

Thus, governments throughout the world have a responsibility to regulate the use of antimicrobials in industry. Because the problem is of a global scale, there are global efforts to coordinate a response. Correspondingly, the United States government has taken steps to combat the problem within its own borders. Although totality of these efforts, both national and

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[2] The Overuse of Antibiotics in Food Animals Threatens Public Health, CONSUMERS UNION(2013), https://consumersunion.org/news/the-overuse-of-antibiotics-in-food-animals-threatens-public-health-2/ (last visited Dec 14, 2018).
[3] TOM FRIEDEN, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2013(2013).
[4] Julian Davies & Dorothy Davies, *Origins and Evolution of Antibiotic Resistance*, 3 MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS417–433 (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2937522/ (last visited Dec 14, 2018).

international, offer promising courses of action and demonstrate situational awareness, they are nevertheless insufficient to impede the rampant progression of antimicrobial resistance. In many areas, more stringent regulation is required to stop this threat to global public health. Without disrupting the monetary incentives that exist to use antimicrobial products in situations that are not medically necessary, the problem will not lessen.

SCOPE AND MECHANICS

In order to accurately assess the appropriateness of measures taken to combat antimicrobial resistance, or suggest new ones, it is necessary to understand both the scope of the problem, and certain key scientific concepts that would affect the efficaciousness of any candidate policy.

A. Scope of the Problem

Antimicrobial resistance affects every nation on Earth, but it affects developing nations especially grievously. In Europe, antimicrobial-resistant pathogens are responsible for over 25,000 fatalities and 2.0 million extra hospital days per year.[5] In Thailand, they are responsible for 25,000 fatalities and 3.2 million extra hospital days per year.[6] This is substantially larger relative to its population than the number of fatalities in Europe. Furthermore, that burden is felt substantially by the child and infant population. In India, antimicrobial-resistant pathogens are responsible for 58,000 infant deaths per year.[7] This number exceeds the combined total fatalities in the examples of Europe and Thailand. Even relative to India's larger population, the number

[5] Antibiotic / Antimicrobial Resistance (AR / AMR), CENTERS FOR DISEASE CONTROL AND PREVENTION(2018), https://www.cdc.gov/drugresistance/about.html (last visited Dec 14, 2018).
[6] *Id.*
[7] *Id.*

of infants affected is disproportional. Furthermore, these numbers are growing as superfluous use of antimicrobials continues.[8]

In the United States, antimicrobial-resistant pathogens are responsible for 23,000 fatalities and over 2.0 million extra hospital days.[9] This puts additional logistical and financial strain on an already overburdened healthcare system that is dealing with a physician shortage, an uninsured population of 28.9 million,[10] and an underinsured population of 41 million.[11] In addition to these deaths and illnesses, the United States deals with 15,000 deaths and nearly 500,000 cases of *Clostridium difficile* per year.[12] Because people taking antibiotics are 7 to 10 times more likely to contract *C. difficile,*[13] this is yet another compounding effect of the overuse of antibiotics by medical professionals. Similar to the worldwide trend, these numbers form an increasing trend of complications that arise from antimicrobial resistance.[14]

B. Causes of and Contributors to the Problem

There are two main forces that contribute to the development of antimicrobial resistance: medicine and agriculture. Each of these two causes carries its own set of challenges that must be overcome to effectively combat the problem. Despite this distinction, however, the two share common ground. Both have entrenched systems that monetarily incentivize the use of antibiotics

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8 *Id.*
9 *Id.*
10 National Center for Health Statistics, CENTERS FOR DISEASE CONTROL AND PREVENTION(2017), https://www.cdc.gov/nchs/fastats/health-insurance.htm (last visited Dec 14, 2018).
11 Sara R. Collins, Munira Z. Gunja & Michelle M. Doty, HOW WELL DOES INSURANCE COVERAGE PROTECT CONSUMERS FROM HEALTH CARE COSTSCOMMONWEALTH FUND, https://www.commonwealthfund.org/sites/default/files/documents/___media_files_publications_issue_brief_2017_oct_collins_underinsured_biennial_ib.pdf (last visited Dec 14, 2018).
12 CDC. Antibiotic Use in the United States, 2017: Progress and Opportunities. Atlanta, GA: US Department of Health and Human Services, CDC; 2017.
13 *Id.*
14 *Id.*

when not medically necessary. Both are in fact parts of a larger, interconnected network of associations that spreads reserves of resistant traits throughout the microbial populations of the country:

Figure 1[15]:

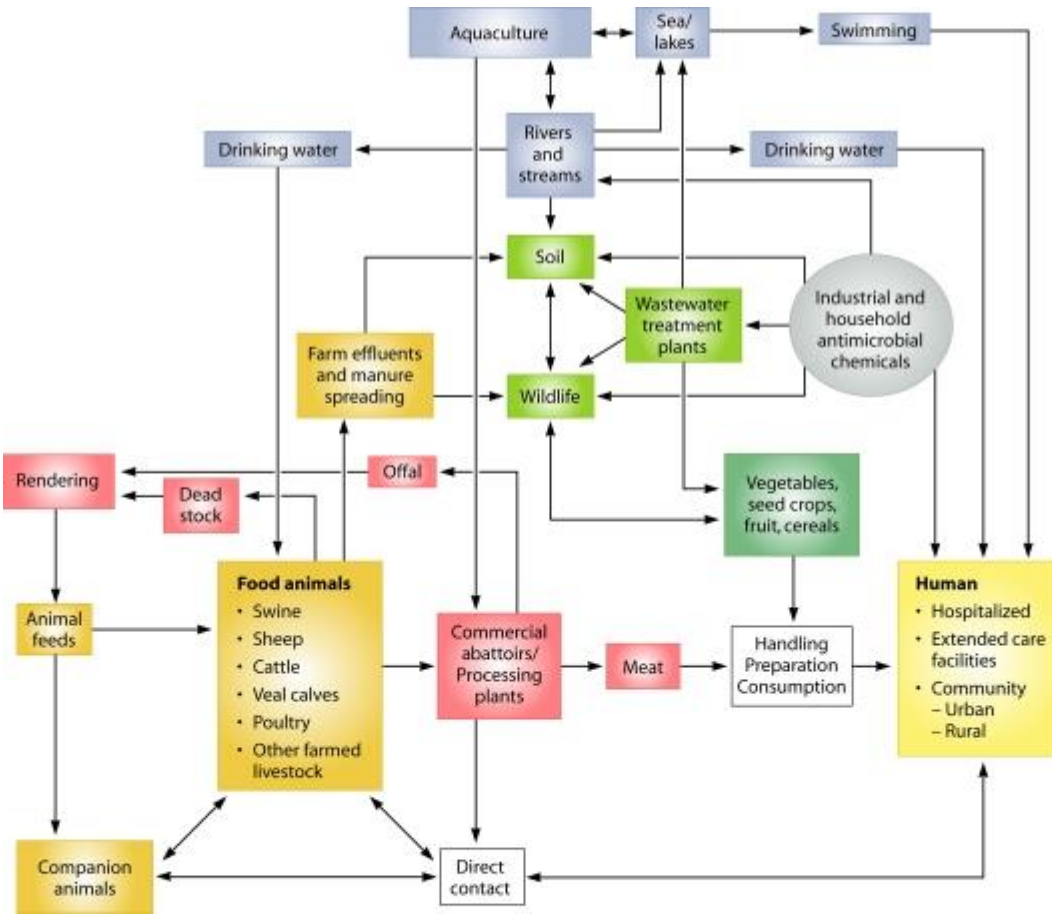

Figure 1 demonstrates that superfluous use of antimicrobial products anywhere contributes to the problem of antimicrobial resistance everywhere. It is impossible to solve this crisis by focusing solely on one area where a reserve of antimicrobial resistance exists. Because of the communicability of resistance traits between separate populations of microbes, stopping,

15 Davies & Davies, *supra* note 4.

for example, only the medical overuse of antibiotics without even considering the other reserves of resistance would not impede the exacerbation of the problem overall.

C. Some Essential Scientific Concepts

It is difficult to understand the effects of policy regarding antimicrobial resistance without understanding certain conceptual elements of the mechanics of its development and spread.

Chief among these concepts is selective pressure, a term in evolutionary biology that refers to one of the driving forces of evolution by natural selection, or the idea that organisms gradually change over time based on which organisms have traits that make them more likely to survive and reproduce.[16] When a factor causes some members of a population to be more likely to survive and reproduce than other members of the same population, evolutionary biologists call that factor a selective pressure.[17] For example, limited access to water is a selective pressure that shaped the evolution of flora and fauna in deserts around the world. Cacti exist in deserts in large part because plants that are best at storing and economizing water are more likely to survive and reproduce in deserts than plants that are not.

In the case of antimicrobial resistance, every time an antimicrobial product is used, it applies an extremely heavy selective pressure to the population of microbes it comes into contact with.[18] It kills the vast majority of them, and the few survivors are far more likely to have traits that resist the antimicrobial effects. These survivors repopulate, creating an entirely new generation of bacteria, all of which share the increased resistance of the generation before it.[19] A single application of selective pressure has a negligible effect, but the timeframe for a generation

[16] Glossary, ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, http://emerald.tufts.edu/med/apua/about_issue/glossary.shtml (last visited Dec 14, 2018).
[17] *Id.*
[18] *Id.*
[19] *Id.*

of bacteria can be a matter of minutes. The repeated application of this heavy selective pressure causes the buildup of resistant traits over time and can render some populations of bacteria resistant to many types of antibiotics. For example, S. Aureus exhibited resistance to methicillin as early as 1962, a mere 3 years after it was first exposed to the drug.[20] In the context of evolutionary timescales, antimicrobial resistance develops blindingly fast.

The final concept that must be understood in order to contextualize policy is horizontal gene transfer. Many organisms, such as humans and animals, can only pass genetic information from parent to offspring, and only within the same species. This is vertical gene transfer. Bacteria, however, have an array of methods to pass genetic information from one member of a contemporary generation to another, and between species. This concept is paramount because it means that antibiotic resistant traits are dangerous in all species of bacteria, not just the ones that cause disease.[21] When a patients or livestock take antibiotics, it subjects all susceptible bacteria within them to the same selective pressure. Over time, the resultant traits spread throughout the chain of commerce and can extend even to the farthest reaches of the world.

GLOBAL RESPONSE

Because antimicrobial resistance is a global problem, there necessarily exists international cooperation in combatting it. Due to the phenomenon of globalization, national action plans are not sufficient to combat the problem by themselves.[22] Microbes move freely about the world, unhindered by borders, and cross oceans in the process of global trade. The

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[20] *Id.*
[21] *See supra* note 16.
[22] David P. Fidler, LEGAL ISSUES ASSOCIATED WITH ANTIMICROBIAL DRUG RESISTANCE - VOLUME 4, NUMBER 2-JUNE 1998 - EMERGING INFECTIOUS DISEASES JOURNAL – CDC CENTERS FOR DISEASE CONTROL AND PREVENTION(2010), https://wwwnc.cdc.gov/eid/article/4/2/98-0204_article (last visited Dec 14, 2018).

central coordinator of international efforts to combat antimicrobial resistance is the United Nations (UN). Most initiatives and policies occur through the World Health Organization (WHO), but some activity also that takes place through the Food and Agriculture Organization (FAO), the Organization for Animal Health (OIE), the office of the Secretary General and the General Assembly.

A. UN General Assembly

In 2015, the UN General Assembly passed Resolution 70/183, which, among other things, called upon heads of state to hold a meeting to address the growing problem of antimicrobial resistance.[23] Included in this resolution is the globally unified recognition that "antimicrobial resistance threatens the sustainability of the public health response to many communicable diseases, including tuberculosis, malaria and HIV/AIDS."[24] Particularly notable here is the mention of malaria. Although its localized eradication has eliminated it as a threat in the United States, it is nevertheless one of the deadliest infectious diseases in the world, claiming an annual toll of 212 million infections and 429,000 fatalities.[25] The fact that the protozoan parasite that causes the disease is developing antimicrobial resistance has a particularly devastating impact on developing nations.[26]

As a result of the 2016 meeting of the heads of state called for by Resolution 70/183, member nations passed Draft Declaration 16-16108. This draft declaration contained another

[23] General Assembly Resolution 70/183, *Global health and foreign policy: strengthening the management of international health crises*, A/RES/70/183 (17 December 2015), available from https://undocs.org/A/RES/70/183.
[24] *Id.*
[25] Malaria Drug Resistance, IVERMECTIN EXPOSURE IN SMALL CHILDREN STUDY GROUP | WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK(2014), http://www.wwarn.org/about-us/malaria-drug-resistance (last visited Dec 14, 2018).
[26] *Id.*

affirmation of global consensus regarding the critical nature of the crisis of antimicrobial resistance, this time from a gathering of many of the world's heads of state. It also contained the resolution of the member heads of state to each form their own national action plans for the purpose of combatting the crisis.[27] Other notable language from the declaration includes the recognition that "achievements of the twentieth century are being gravely challenged, in particular: the reduction in illness and death from infectious diseases achieved through social and economic development; access to health services and to quality, safe, efficacious and affordable medicines…"[28] This language accurately captures the severity of the problem.

The totality of the actions of the UN General Assembly consistently display situational awareness and an appropriate tone. They rightly account for the scientific consensus regarding the gravity of the problem and demonstrate a global commitment to solving it. However, they contain no mechanism to enforce consequences for any nation that fails to follow the resolution and draft declaration. If a member nation were to undergo a sudden, drastic change in governmental leadership as, for example, the United States did shortly after the passage of the draft declaration on September 21, 2016, nothing could compel it to uphold the promises of its former head of state. Furthermore, if a member nation were to fail to effectively combat the problem due to persistent monetary incentives to use antimicrobial products in situations that are not medically necessary, then the international community is similarly left without recourse.

B. Office of the UN Secretary General

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[27] United Nations, Draft Declaratoin 16-16108, *Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance* (21 Sepbember 2016), available from un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf.
[28] *Id.*

Another action taken by the UN to facilitate the worldwide fight against antimicrobial resistance is the formation of the Interagency Coordination Group (IACG) by the Secretary General. The purpose of the IACG is to effectuate communication and collaboration between the several UN organizations that have separate interests and responsibilities in controlling the antimicrobial resistance crisis.[29] These organizations include the WHO, the FAO, and the OIE.[30]

Although there are no affirmative plans put forward by the IACG, it is worthy of mention because it accounts for the interconnectivity of reserves of antimicrobial-resistant traits discussed earlier. Only by ensuring that all sectors of the global economy that contribute to the problem are fighting it effectively can the problem be sufficiently mitigated.

An example of cross-organizational cooperation can be found in the World Antibiotics Awareness Week, which takes place every November. All three organizations have observance programs which include public events across the globe and ways for individuals and organizations to get involved.[31] Lack of general public awareness is one of the most difficult challenges that the effort to combat antimicrobial resistance faces. Much like with global climate change before it was popularized, the low general awareness makes it difficult to galvanize action. The fact that there is a synchronized effort to spread the word across the world is critical to response efforts across the globe.

C. WHO

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[29] UN Interagency Coordination Group on Antimicrobial Resistance, WORLD HEALTH ORGANIZATION(2018), https://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/ (last visited Dec 14, 2018).
[30] *Id.*
[31] WORLD HEALTH ORGANIZATION, http://www.who.int/who-campaigns/world-antibiotic-awareness-week (last visited Dec 14, 2018).

The WHO is one of the three UN organizations with a primary role in the response to antimicrobial resistance. It has a main program that is a part of the effort to combat the crisis.

The WHO's Global Action Plan (GAP) is a five-pronged strategy for how to proceed in the global response to antimicrobial resistance. The five objectives of the plan are to: (1) improve awareness and understanding of antimicrobial resistance through effective communication, education, and training; (2) strengthen the knowledge and evidence base through surveillance and research; (3) reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures; (4) optimize the use of antimicrobial medicines in human and animal health; and (5) develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.[32]

All of the WHO's actions in response to antimicrobial resistance are guided by the prongs of the GAP. World Antibiotic Awareness Week is an example of the first prong. In accordance with the second prong, the WHO has proposed that there be a recognized international standard for the collection of data and antimicrobial resistance in human health, and a global form for the rapid sharing of information about the crisis, both of which currently do not exist.[33] In accordance with the third prong, the WHO has advocated for the widespread use of immunizations and vaccinations to prevent incidence of infection.[34] In accordance with the fourth prong, the WHO has resolved that the scientific consensus supports the conclusion that the

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[32] Global Action Plan on Antibiotic Resistance (2015), available from http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf (last visited Dec 14, 2018).
[33] *Id*. at 9.
[34] *Id*.

massive volume of antimicrobials being used worldwide is driving the problem of resistance.[35] In accordance with the fifth prong, the WHO has suggested that novel drugs and screening technology be made available and affordable, so as to satisfy the needs of all member nations.[36] The GAP concludes by setting a framework for its implementation in which it urges member nations to develop similar plans and apply them nationally.

Overall, the GAP, like many of the other international efforts to coordinate a response to antimicrobial resistance, shows apt cognizance of the issues and suggests reasonable and effective measures to combat the problem. However, also like its counterpart international efforts, it fails to recognize the immense difficulty that member nations will face in implementing these plans despite the entrenched monetary incentives to use antimicrobial products when not medically necessary.

D. FAO and OIE

The FAO and OIE have each promulgated similar four-pronged strategies for how their respective domains will proceed in the global response. The FAO's plan is to: (1) improve awareness on AMR and related threats; (2) develop capacity for surveillance and monitoring of AMR and AMU (antimicrobial use) in food and agriculture; (3) strengthen governance related to AMU and AMR in food and agriculture; and (4) promote good practices in food and agricultural systems and the prudent use of antimicrobials.[37]

Again, the familiar themes of awareness and monitoring, both fundamental elements that need improvement, are mentioned first. The third prong, however, deviates from the other plans

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[35] *Id*. at 10.
[36] *Id*. at 11.
[37] FAO's role | www.fao.org, INTERNATIONAL RICE COMMISSION NEWSLETTER VOL. 48, http://www.fao.org/antimicrobial-resistance/background/fao-role/en/ (last visited Dec 14, 2018).

in a way that is encouraging. When the plan says to, "strengthen governance," it advocates for member governments to compel their food and agriculture industries to use antimicrobials more judiciously. Despite its lack of binding authority, this plan recognizes that a large obstacle in its implementation is the ability and willingness of member governments to compel industry to make monetary sacrifices to solve a long-term public health problem.

The OIE's plan is identical on the first three prongs, but the fourth is to implement international standards. This is a sensible inclusion because the existence of international standards for the prudent use of antimicrobials will streamline the process of global advocacy to curtail their rampant overuse.

When viewed as a whole, the coordinated international response to antimicrobial resistance, though unequivocally moving in the right direction, is insufficient on its own to remove the problem as a threat. Although programs like WHO's Global Antimicrobial Surveillance System (GLASS), a means to achieve the second prong of the GAP by establishing an internationally accessible and comprehensive surveillance system for the detection of new antimicrobial resistant traits,[38] create real positive change, that change is not enough without member nations curbing the overuse of antimicrobial products.

<u>DOMESTIC RESPONSE</u>

The United States government has its own set of plans and has taken its own set of actions to deal with the antimicrobial resistance crisis within its borders. These include both regulations with binding authority and industrial suggestions without any means of enforcement. The plans and actions are promulgated both by government agencies and by industry leaders.

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[38] Call for participation: Global Antimicrobial Resistance Surveillance System (GLASS), WORLD HEALTH ORGANIZATION(2016), http://www.who.int/drugresistance/surveillance/glass-enrolment/en/ (last visited Dec 14, 2018).

A. CDC

The Center for Disease Control (CDC) has both implemented programs and promulgated plans for dealing with antimicrobial resistance domestically. Much of what it does nationally is analogous to what the WHO does internationally.

i. Surveillance

The CDC participates in partnership with the FDA in the National Antimicrobial Resistance Monitoring System (NARMS).[39] In many ways, NARMS is the domestic equivalent of GLASS. It monitors and records emergent antimicrobial traits and their presence in pathogens. This, like all surveillance, is an effective tool in the fight to mitigate the effects of antimicrobial resistance, but it cannot remove the presence of selective pressure. As long as antimicrobial products are still overused, the problem will continue to grow.

Additionally, the CDC has promulgated a list of response tiers to prioritize the threats posed by the many antimicrobial-resistant pathogens that are on record. The tiers are: (1) organisms whose mechanisms of resistance are novel to the United States, or that are pan-resistant (e.g. Vanomycin-resistant S. Aureus [VRSA])[40]; (2) multi-drug resistant organisms (MDROs) that are typically found in healthcare settings, but not generally in the surrounding region;[41] and (3) MDROs that have already been identified and established in the United States.[42]

ii. Five-point plan

[39] National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS), CENTERS FOR DISEASE CONTROL AND PREVENTION(2018), https://www.cdc.gov/narms/about/index.html (last visited Dec 14, 2018).
[40] Healthcare-associated Infections, CENTERS FOR DISEASE CONTROL AND PREVENTION(2018), https://www.cdc.gov/hai/containment/guidelines.html (last visited Dec 14, 2018).
[41] *Id*.
[42] *Id*.

The CDC, in compliance with the WHO's GAP, has promulgated its own five-point plan to combat antimicrobial resistance. The prongs are: (1) awareness and education; (2) surveillance; (3) infection prevention and control; (4) optimization of use; and (5) R&D and investment.

These tiers and plans are effective to facilitate the containment of already-existing MDROs, but like the surveillance programs, do not effectively deal with the problem of selective pressure, and are not enough on their own. Point 4, optimization of use, would account for the necessity for judicious use of antimicrobial products, but without a means to compel industry to comply, it is ineffective.

The CDC has the power to promulgate regulations, but it is not the ideal government agency to pass regulations banning the overuse of antimicrobial products. Although it has the power the power to enact regulations to control the spread of infectious diseases,[43] this power is, with one exception, limited to the function of quarantine powers in times of emergency and war. That exception is that the Surgeon General may, with the approval of the secretary, make and enforce regulations that are, "necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession."[44]

resistance, which is rather the development of resistant traits in already extant diseases.

B. FDA

[43] *See* 42 U.S.C. §264.
[44] 42 U.S.C. §264(a).

The Food and Drug Administration (FDA) unquestionably has the authority to regulate, ban, or otherwise limit the use of antimicrobial chemicals because they are drugs. In their hands is the power to compel industry to act.

i. Antibacterial Soap

One decisive action that the FDA has taken to secure the judicious use of antimicrobial products and combat antimicrobial resistance was ban the sale soaps that use certain antibacterial compounds, most prominently triclosan.[45] These products, advertised as killing bacteria, are not more effective at cleaning than non-bactericidal soaps. This is because soap cleans by emulsifying the germs on surfaces and making them water soluble, allowing water to physically remove them from a surface. The needless addition of a bactericidal effect does nothing salutary, and in fact applies selective pressure to bacteria that are exposed to it, contributing to antimicrobial resistance.

However, the final rule that banned these antibacterial soaps is imperfect. It only banned a limited list of antibacterial chemicals, not bactericidal effects in general.[46] Thus, antibacterial soaps using chemicals that are not on the list may still be sold, and industrial chemists are free to develop more chemicals for use in soaps that would kill bacteria. In this way, antibacterial soap maintains a limited presence in the market, and the label "kills 99.9% of germs and bacteria" may still appeal to the general consumer.

ii. Agricultural Industry

Antibiotic use in the agricultural industry, comprising over 80% of the world's antibiotic use, is different from ordinary medical use. Antibiotics are used in limited capacity on livestock

[45] 81 FR 61106
[46] *Id*.

to preemptively prevent or reactively treat diseases, but their main use is that when they are added to livestock's feed, they improve the feed conversion ratio of the livestock.[47] The feed conversion ratio is the ratio to the cost to feed an animal to the revenue yielded by selling its products. In other words, antibiotics make livestock grow larger for less money. In fact, they increase the feed conversion ratio between 3% and 9%, and the total size of livestock between 2% and 10%.[48] Considering the amount of meat that is produced in the United States annually, antibiotics account for a significant profit.

To combat the crisis of antibiotic resistance, the FDA has promulgated Guidelines for Industry (GFI), to communicate the best practices and the agency's current thinking on topics of interest. The two GFIs that address antibiotic use in agriculture are GFI #209[49] and GFI #213.[50]

GFI #209 addresses the problem that superfluous use of antibiotics in animal feed is wildly exacerbating the problem of antimicrobial resistance. This occurs because of horizontal gene transfer; the danger does not particularly lie in the pathogenic bacteria that get refined by the rampant use of antibiotics, but the development of resistance traits in non-pathogenic bacteria that are then transferred to pathogenic bacteria as the meat from the livestock travels down the stream of commerce. This GFI articulates a progressive and solution-oriented position by the

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[47] Overview of Growth Promotants and Production Enhancers - Pharmacology, MERCK VETERINARY MANUAL, https://www.merckvetmanual.com/pharmacology/growth-promotants-and-production-enhancers/overview-of-growth-promotants-and-production-enhancers (last visited Dec 14, 2018).
[48] *Id*.
[49] Guidance for Industry #209, the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals
[50] Guidance for Industry #213, New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209.

FDA, stating, "[the] FDA is providing a framework for the voluntary adoption of practices to ensure the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals."[51] Furthermore, to achieve this end, the FDA prescribes two main modes of action, which are: "(1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and (2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation."[52]

Although the distinction of "medically important" drugs, defined in a footnote as drugs "important for therapeutic use in humans,"[53] allows compliant companies to curtail their use of antibiotics while ignoring the underlying problem posed by horizontal gene transfer, any decrease in the use of antibiotics in farming is a massive victory toward impeding antimicrobial resistance.

GFI #213 expands on some of the restrictions set forth in GFI #209 while loosening. It states that its purpose is to help phase out the use of "medically important" drugs in livestock for non-medical purposes entirely.[54] It expands a level of oversight for certain drugs whereby compliant companies would need to obtain a Veterinary Feed Directive (VFD) in order to infuse animal feed with antibiotics, certifying that it is medically necessary.[55] A VFD is less stringent of a barrier to obtaining antibiotics than a prescription is.[56] It moves many drugs that were once prescription-only into the category of VFD, thus expanding access to those drugs. However, it

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[51] *Supra* note 44 at 3.
[52] *Id.*
[53] *Id.*
[54] *Supra* note 45 at 4.
[55] *Id.*
[56] *Id.*

also moves many drugs that were once available over the counter to VFD, thus limiting access to those drugs.[57]

Overall, the liberality with which a veterinarian may issue a VFD is concerning, especially considering the tendency of companies form working relationships with veterinarians. Additionally, the retention of the label “medically important” to the drugs being phased out leaves the same problems that were present in GFI #209 unresolved.

Accompanying the continued permissiveness of antibiotic use in compliant companies, the GFI’s have one additional fatal flaw. In both GFI #209 and GFI #213, there is a block of text just before the introduction that states that the entire document is nonbinding.[58]

This means that compliance with FDA GFI’s is entirely voluntary. Should a company wish to simply use antibiotics at its own will to maximize profits, it is free to do so. Thus, using antibiotics in animal feed is still a common practice to this day. Some industry leaders, such as Tyson, offer antibiotic-free options for beef and pork at a markup alongside their antibiotic-fed options.[59] Although the argument can be made that allowing consumers to vote with their wallets leaves an avenue to affect change at the supermarket, most people just want an affordable cut of meat, which limits the effect that a conscientious bloc of consumers can have. Rather, the antibiotic-free label is a token offering, an excuse to charge some conscientious consumers or misguided health-conscious consumers a markup, standing brazenly in defiance of the global imperative to halt the superfluous use of antimicrobial drugs.

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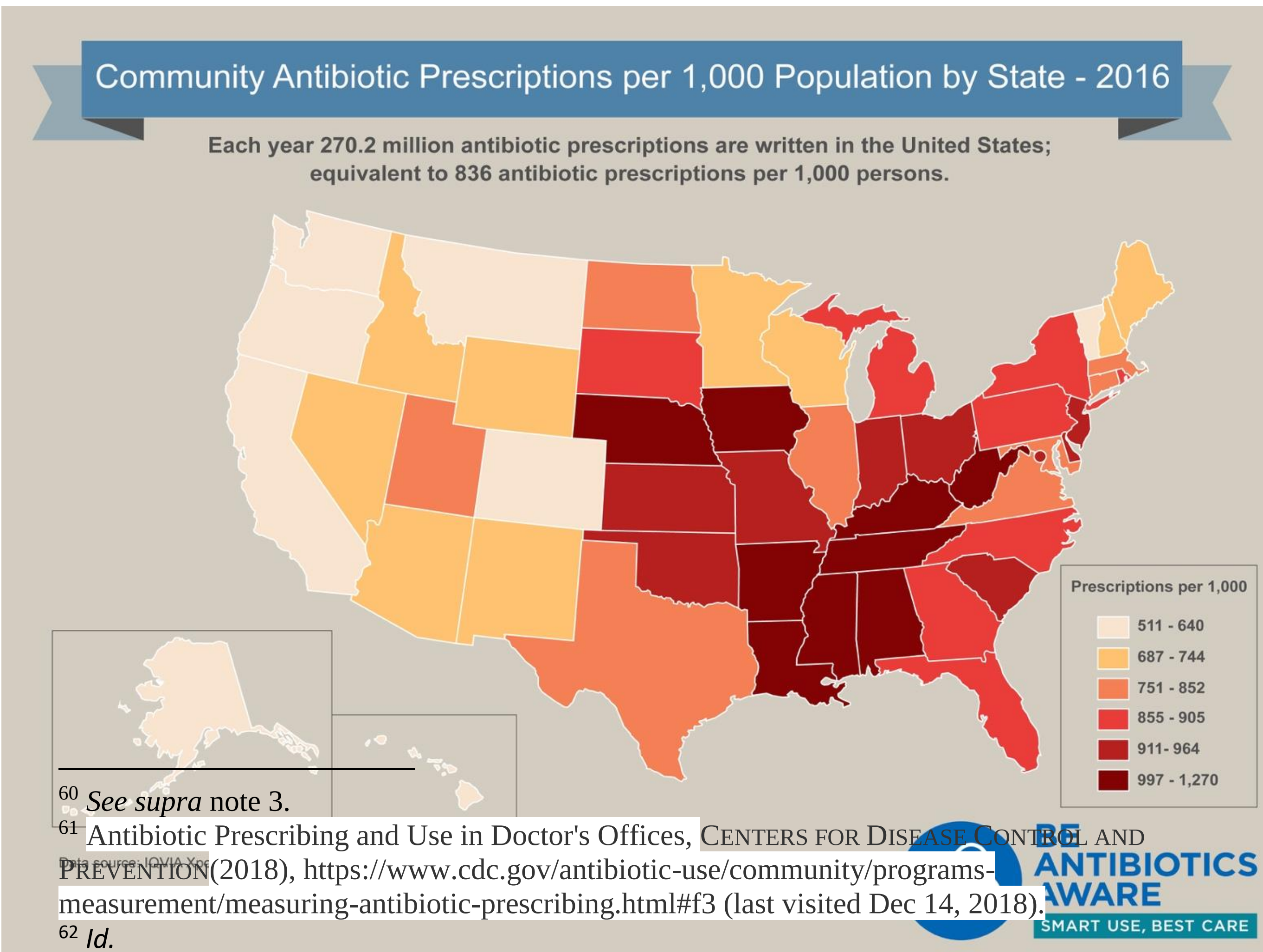
[57] *Id.*
[58] *See supra* note 44 and *supra* note 45.
[59] Open Prairie® Natural* Meats, WHO WE ARE | TYSON FRESH MEATS, https://www.tysonfreshmeats.com/our-brands/open-prairie-natural-meats?gclid=CjwKCAiA_ZTfBRBjEiwAN6YG4Zn7K1htLbck9_xf2a8asqDIzv0jPj6m15o0OlT5ufK04xsC6gYX1hoCnoMQAvD_BwE (last visited Dec 14, 2018).

C. Medical Industry

The remainder of global antimicrobial use is for medical purposes. Unfortunately, the over-prescription of antibiotics is a rampant problem, especially in the developed world. There are many causes for this worldwide overuse, ranging from misperceptions about the role of physicians to perverse incentive structures for the physicians themselves.

In the United States, approximately 1 in every 3 prescriptions for a course of antibiotics is unnecessary.[60] The total amount of inappropriate use of antibiotics, including inappropriate selection, dosing, and duration, approaches 1 in every 2 uses.[61]

Figure 2[62]



[60] *See supra* note 3.

[61] Antibiotic Prescribing and Use in Doctor's Offices, CENTERS FOR DISEASE CONTROL AND PREVENTION(2018), https://www.cdc.gov/antibiotic-use/community/programs-measurement/measuring-antibiotic-prescribing.html#f3 (last visited Dec 14, 2018).

[62] *Id.*

The volume of outpatient prescriptions in an area can affect local resistance patterns.[63] Figure 2 demonstrates that there is a high variance of prescription volume among the states. However, every state still grievously over-prescribes.[64]

Furthermore, the bulk of the over-prescription problem occurs in outpatient settings. Over 60% of all antibiotic prescriptions in the United States occur in outpatient facilities.[65] Between 80% and 90% of the total volume of antibiotics consumed by humans in the United states occur as a result of prescriptions in an outpatient setting.[66]

Respiratory infections are the most common causes of antibiotic prescriptions.[67] However, the majority of respiratory infections are not caused by bacteria.[68] This disparity is a microcosm of the larger problem of antibiotic over-prescription.

Among physicians, there have been numerous initiatives to promote antibiotic stewardship. For example, the American Medical Association (AMA) has spearheaded several plans to reduce antibiotic prescription rates. For example, in several clinics, AMA doctors displayed an open letter, written in large font and in eighth grade-level English, about the

[63] *Id.*
[64] *Id.*
[65] *Id.*
[66] *Id.*
[67] Carl Llor & Lars Bjerrum, *Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem*, 5 THERAPEUTIC ADVANCES IN DRUG SAFETY229–241 (2014).
[68] *Id.*

importance of antibiotic stewardship. Clinics that displayed this letter saw average drops of around 9% in antibiotic prescription rates for respiratory infections.[69]

The AMA is also experimenting with more overt methods to reduce prescription rates. At some clinics, physicians that enter a diagnosis of a respiratory infection into a patient's electronic health record (EHR), accompanied by a prescription for antibiotics, must fill in an additional line of text stating the justification for the prescription. If no justification is entered, the EHR displays "NO JUSTIFICATION FOR PRESCRIBING ANTIBIOTIC."[70] Additionally physicians at clinics are ranked by their antibiotic prescription rates, giving a sense of peer accountability.[71] Clinics that implement these experimental methods have seen a drop of 16%-18% in prescription rates.[72] These simple methods of holding physicians to some rudimentary form of accountability make tangible progress in curbing antibiotic prescription rates. However, none of them have yet seen widespread adaptation.[73]

Furthermore, the CDC makes efforts to communicate with physicians about the importance of antibiotic stewardship. For example, it has promulgated a table of recommendations about how to determine whether it is appropriate to prescribe antibiotics with certain common conditions, as well listing the proper course of treatment in situations when

[69] Simple ways to deter improper antibiotic prescribing, SELECTING & USING A HEALTH INFORMATION EXCHANGE | AMA, https://www.ama-assn.org/delivering-care/public-health/simple-ways-deter-improper-antibiotic-prescribing (last visited Dec 14, 2018).
[70] *Id.*
[71] *Id.*
[72] *Id.*
[73] *Id.*

antibiotics are not appropriate.[74] Additionally, it offers a course on antibiotic stewardship for continuing education credits.[75]

Although these efforts to stop the over-prescription problem in the United States are admirable, they are insufficient. What is missing from the larger picture of reducing prescription rates is any binding provision. As it stands, there is no enforced negative consequence for physicians who unnecessarily prescribe antibiotics for illnesses that do not in fact require them.

Rather, there are perverse incentives for physicians to continue to prescribe antibiotics at current rates. First, physicians are pressured by patients who have expectations about how their treatment will go.[76] Specifically, patients who present with an illness expect to be given a medication that fixes their illness.[77] However, there are many illnesses with no simple pharmaceutical cures. Thus, physicians often motivated by the demand to meet consumer expectations when they prescribe antibiotics when medically unnecessary, and when the correct treatment is to wait for the illness to expire while treating ancillary symptoms.[78]

Additionally, in outpatient settings, physicians often have a limited time to meet with patients. Often, that time is not enough to diagnose an illness and formulate a treatment plan. Thus, physicians can rely upon prescribing antibiotics as a heuristic method of dealing with problems.[79] This problem is confounded even more by the fact that viral and bacterial infections

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[74] Antibiotic Prescribing and Use in Doctor's Offices, CENTERS FOR DISEASE CONTROL AND PREVENTION(2017), https://www.cdc.gov/antibiotic-use/community/for-hcp/outpatient-hcp/adult-treatment-rec.html (last visited Dec 14, 2018).
[75] *Id.*
[76] Why Doctors Prescribe Antibiotics-Even When They Shouldn't, THE PEW CHARITABLE TRUSTS, https://www.pewtrusts.org/en/research-and-analysis/articles/2017/06/30/why-doctors-prescribe-antibiotics-even-when-they-shouldnt (last visited Dec 14, 2018).
[77] *Id.*
[78] *Id.*
[79] *Id*.

often present similar symptoms. In these cases, prescribing antibiotics is preferable to the risk physicians incur by not prescribing them.[80] Often, it is more time-efficient for physicians just to prescribe antibiotics rather than to lengthily explain why antibiotics are not required.[81] These efficiencies add up to significant amounts over time. Finally, pharmaceutical companies are permitted to advertise to physicians through representatives. The interactions between the representatives and the physicians, often involving gifts, influences physicians' prescribing habits.[82]

D. Research Efforts

There have been significant efforts to combat the problem of antimicrobial resistance through researching innovative solutions. One method that researchers use to combat the problem is to develop new antimicrobials that are not yet resisted.[83] These can be effective means of slowing the problem. However, creating new antimicrobial drugs cannot stop the process of selective pressure, or remove the bacterial trait of horizontal gene transfer.[84] New drugs cannot be a permanent solution to antimicrobial resistance, but they can slow it significantly.[85]

Phage therapy is a second avenue of research that, though underdeveloped relative to antimicrobials, may provide promising results in the future.[86] It functions by combatting bacterial

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[80] *Id.*
[81] *Id.*
[82] *Id.*
[83] Derek M Lin, Britt Koskella & Henry C Lin, *Phage therapy: An alternative to antibiotics in the age of multi-drug resistance*, 8 WORLD JOURNAL OF GASTROINTESTINAL PHARMACOLOGY AND THERAPEUTICS162 (2017).
[84] *Id.*
[85] *Id.*
[86] *Id.*

infections using bacteriophages, or viruses that infect bacteria.[87] These phages are harmless to humans and highly specific infectors of their bacterial targets.[88] Through controlled introduction to an infected patient, phage therapy may one day be able to defeat bacterial infection as effectively as antibiotics would.[89] The bacteria would not stop evolving, and would develop resistances to bacteriophage infection the same way they develop resistances to antibiotics.[90] However, there is evidence that suggests that when bacteria develop resistance to bacteriophages, they sacrifice resistances to antibiotics, and when they develop resistances to antibiotics, they sacrifice resistances to bacteriophages.[91] Thus, phage therapy, once developed, remains a promising hope to bringing a permanent end to the threat of antimicrobial resistance in the future.

CONCLUSION

Antimicrobial resistance is a long-term danger with potentially disastrous results. If current levels of antimicrobial product use do not drop, the phenomenon threatens to undo some of the landmark achievements of human development, such as the lowered deaths from infectious diseases and the reduction in infant and child mortality.

Global efforts to impede its progression focus primarily on surveillance, monitoring, the development of new drugs, and the spreading of awareness. These are effective tools, and the world is objectively better off as a result of these efforts. However, they paint an incomplete picture of the solution to antimicrobial resistance.

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[87] *Id.*
[88] *Id.*
[89] *Id.*
[90] *Id.*
[91] *Id.*

Selective pressure is a natural law that acts constantly on every organism alive. It, compounded with the bacterial phenomenon of horizontal gene transfer, indicate that there can be no sufficient solution to antimicrobial resistance without limiting the use of antimicrobial products to situations where they are medically necessary.

The rampant over-prescription of antimicrobial drugs, combined with the commonplace use of antibiotics in animal feed, accelerate the problem of antimicrobial resistance more than the current combined totality domestic and global efforts are able to slow it down. Therefore, the response to the problem is insufficient. Only by compelling physicians and agricultural companies to cease the superfluous use of antimicrobial products can a response to the crisis be effective enough to mitigate the damage caused by the rapid global development of antimicrobial resistance.

However, there remains hope that through continued research, humanity may develop a permanent solution to the problem. The continued development of new drugs, and promising research into the relatively novel field of phage therapy, shine as beacons of hope that in the long term, antimicrobial resistance is solvable.