

***The next pandemic:***

***A pragmatic and ethical discussion about the looming threat of antibiotic resistance***

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ABSTRACT

Antibiotics are useful to stave off infection, though their misuse can be detrimental by creating drug-resistant infections. It is essential that we closely examine the leading causes of antibiotic resistance and consider the serious clinical and ethical ramifications around the issue. This paper will aim to achieve these goals, as well as to propose practical solutions directed towards combating this looming crisis.

INTRODUCTION

As drug companies race to develop vaccines and treatments in response to the COVID-19 pandemic, other impending public health threats may easily be forgotten and tucked away for another day. Experts are warning that “the same governmental inaction that helped foster the rapid, worldwide spread of the coronavirus may spur an even deadlier epidemic of drug-resistant infection...”<sup>1</sup> Dr. Jeffrey R. Strich, a researcher at the National Institutes of Health Clinical Center remarked, “If there’s anything that this COVID-19 pandemic has taught the world, it is that being prepared is more cost-effective in the long run.”<sup>2</sup>

Antibiotic resistant infections cause an estimated 700,000 annual deaths globally.<sup>3</sup> According to the Centers for Disease Control, in the United States alone, drug resistant infections sicken 2.8 million people annually and are responsible for at least 35,000 deaths each year.<sup>4</sup> The United Nations has suggested that, if the problem is not soon addressed, antibiotic resistant infections could kill up to 10 million people by 2050.<sup>5</sup>

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The genesis of antibiotic resistance is complex and multifaceted. Successfully combating antibiotic resistance will require a global response. This paper will closely examine the leading causes of antibiotic resistance. It will also devote discussion to the clinical and ethical ramifications of antibiotic use and misuse. Lastly, the paper will propose practical measures that countries, such as the US, should be taking now to help stem this ever-evolving public health emergency.

## I. Antibiotic misuse

Antibiotic resistance develops when bacteria are exposed to antibiotics, and propelled by the forces of evolutionary selection, mutate over time to adapt to the antibiotics.<sup>6</sup> This process is greatly accelerated when bacteria are overexposed to antibiotics.<sup>7</sup> Overexposure occurs in two primary ways – the first is through overuse/misuse of antibiotics in humans and the second is misuse/overuse in animals.

### A. In humans

According to studies, treatment decisions involving antibiotics, including whether to use an antibiotic, which antibiotic to use, and the appropriate duration of such use, are incorrect in 30 percent to 50 percent of cases.<sup>8</sup> Antibiotics may be overprescribed in cases where they are not truly needed, or the wrong type or dosage of antibiotic can be prescribed. These issues can contribute to the problem of antibiotic resistance.<sup>9</sup>

In many cases, faulty clinical determinations can be attributed to the lack of available microbial testing. Consequently, healthcare providers are unable to properly identify and classify bacteria, thus impairing their ability to make clinically sound treatment decisions. In one US study involving hospitalized patients suffering from community acquired pneumonia, for example, a pathogen was identified in only 7.6% of cases.<sup>10</sup> There is existing technology, specifically polymerase chain reaction (PCR) and semiquantitative PCR, that accurately identifies pathogens in approximately 89 percent of cases.<sup>11</sup> However, this technology is not widely used. When healthcare providers do use testing, they often rely upon culture testing, which is not rapid response and can delay proper treatment assessments.<sup>12</sup> As a result, providers may substitute inappropriate antibiotics in the interim.

Another type of antibiotic misuse among humans occurs when patients stop their antibiotic regimens prematurely, thereby allowing harmless bacteria, not fully eradicated due to the abbreviated treatment, to acquire resistance. This resistance is then genetically transferred to dangerous bacteria.<sup>13</sup> Antibiotic resistance is also an unfortunate, frequent occurrence in developing countries where antibiotics are often available without a prescription and can be accessed through unregulated supply chains.<sup>14</sup> Developing nations also frequently suffer from a dearth of standard antibiotic treatment guidelines, which further precipitates antibiotic overprescribing.<sup>15</sup>

B. In animals

Approximately half of the world's consumption of antibiotics is for agricultural purposes.<sup>16</sup> In the US, only 20 percent of antibiotic sales are intended for human use, while the remaining 80 percent is for use in livestock.<sup>17</sup> Despite this gross disparity, only 10 percent of publications discussing antibiotic resistance address the role that misuse of antibiotics in animals plays.<sup>18</sup>

Antibiotic misuse in animals contributes to antibiotic resistance. Farmers and agribusinesses widely distribute antibiotics, through feed or water, to healthy animal populations for non-therapeutic purposes -- including for growth promotion and disease prevention.<sup>19</sup> The need for antibiotic use for disease prevention arises when animals' living quarters are cramped and prone to disease.<sup>20</sup> Low concentrations of antibiotics have routinely been observed in the gastrointestinal tracts of livestock.<sup>21</sup> The presence of sub-therapeutic levels of these drugs fosters the growth of resistant bacteria and antibiotic resistance genes in the animals' guts.<sup>22</sup> When the animals that have developed these resistant bacteria and genes are used as sources of food, both the bacteria and genes are passed along to the food supply, contaminating milk, meat, and eggs.<sup>23</sup> Because the antibiotics used in animals are those that have critically important human applications, the resistant bacteria and genes that develop in response to these drugs can destroy the prospect of their use as effective treatment options in both animals and humans.<sup>24</sup>

According to the Environmental Working Group, supermarket meat and poultry contain extremely high levels of antibiotic resistant bacteria. Specifically, ground turkey was found to contain 79 percent resistant bacteria, pork 71 percent, ground beef 62 percent, and chicken 36 percent.<sup>25</sup> While antibiotic resistant bacteria may be killed with proper levels of heat (from cooking, for instance), antibiotic resistance DNA that accompanies the bacteria is not always eradicated. This resistance can then be transferred to the humans who consume it, conferring resistance upon otherwise benign bacteria in their digestive systems.<sup>26</sup> Resistant bacteria and genes contained in animal waste can also enter the environment as pollutants, settling in the ground, air, and water systems.<sup>27</sup> This further increases the transmissibility of antibiotic resistance from animals to humans and, ultimately, from human to human when a person acquires an antibiotic resistant infection from food and/or the environment and passes it along to others.<sup>28</sup>

Another unintended adverse consequence of antibiotic use in animals is that foods like meat, milk, and eggs often contain antibiotic residues.<sup>29</sup> Since up to 90 percent of antibiotics are excreted through an animal's waste, the drugs may also pollute the ground and groundwater.<sup>30</sup> Unnecessarily prolonged exposure to antibiotics increases the risk of acquiring bacterial resistance and/or an antibiotic resistant infection. The constant exposure to antibiotics can have other adverse health effects, ranging from drug hypersensitivity to carcinogenic effects.<sup>31</sup>

II. Ethical considerations and obligations of stakeholders

A. Tackling antibiotic resistance created through the healthcare sector

First, with respect to antibiotic misuse in humans, there needs to be vastly scaled-up pathogenic testing. This will help ensure that treatment decisions involving antibiotics are made with empirical data, rather than being an exercise in supposition. Increased testing would lead to a reduction in unnecessary antibiotic prescriptions and scripts for the wrong antibiotic. PCR technology should be made widely available, at least until more effective testing is developed. At the most basic level, physicians should seek out this testing to make it available in their practices and hospitals. Third-party payors should be poised to approve the costs associated with these tests, since they may expedite improvements in patients' health, thereby resulting in an overall cost savings.

The pharmaceutical industry should also develop accurate, rapid testing technology. Rapid testing could abbreviate patients' immediate illnesses, because knowledge provided by testing can help physicians quickly determine proper diagnoses. This will allow them to immediately prescribe the correct antibiotics.

Finally, on a global level, countries that lack regulations around antibiotic access and use must implement sufficient restrictions. Addressing antibiotic resistance on a global level is imperative. Like with COVID-19, from a pragmatic and ethical perspective, we must create global solutions to antibiotic resistance to prevent resistant bacteria from spreading.<sup>32</sup>

#### B. Ethical considerations around antibiotic prescriptions for human use

Some ethicists have argued that antibiotics are a public good, and their overuse can result in a sort of "tragedy of the commons."<sup>33</sup> In order to ensure the equitable distribution of antibiotics for all patients, society must create disincentives around antibiotic use. One such proposal involves taxing patients who use antibiotics for "minor and self-limiting" infections.<sup>34</sup> However, patients should not be punished for following their physicians' recommendations. Things like taxing schemes unjustifiably interfere with the doctor-patient relationship and can result in adverse clinical consequences for patients.

Others have asserted that physicians owe a duty of care to both present and future patients. Pursuant to this argument, physicians are ethically justified in increasing the risk of harm to present patients by a "small" amount by denying them antibiotics, if, in doing so, they are decreasing a significant risk of harm to future patients.<sup>35</sup> As per the Hippocratic Oath, physicians have an obligation first and foremost, to their current patients. This duty includes the obligation to act for the good of the patient (with beneficence) and to prevent harm from befalling the patient (non-maleficence). Nowhere in the Oath does it say that "a little" harm is acceptable. Failing to provide a patient with an antibiotic *when it is warranted* in order to "preserve" the drug for use by future patients is a violation of the physicians' bioethical obligations to the patient. There are cases where it may be in patients' best interests to avoid antibiotics, thus decreasing their own risk of antibiotic resistance from superfluous use. However, physicians must make these determinations

on a case-by-case basis, relying on clinical evidence, rather than an impermissible ethical imperative to future patients.

It is also a breach of the patient's right of autonomy if the patient believes the physician is acting strictly in his or her best interest and relies on the physician's treatment recommendations due to this belief. From a clinical perspective, a "small" amount of harm could easily become a "large" amount of harm, depending upon the patient and the infection at issue. A physician could also misjudge the level of risk involved in depriving a patient of an antibiotic, thereby creating an increased risk of morbidity or mortality for the patient. This is not to imply that the physician is never justified in proposing a reasonable waiting period before prescribing an antibiotic in order to determine if the illness is self-limiting and begins to improve on its own. However, again, this decision should be driven strictly by clinical criteria and the best interest of the present patient.

In addition, proposals that seek to disincentivize antibiotic use can be clinically and ethically dangerous. Although prudence around antibiotic use is necessary, physicians should not be dissuaded from prescribing them when, in the physicians' clinical judgements, they are necessary. Without antibiotics, seemingly benign infections can quickly turn deadly. Untreated bronchitis can rapidly progress to pneumonia. Untreated strep throat can lead to heart damage. A lingering urinary tract infection can induce sepsis.<sup>1</sup>

### III. Combating antibiotic resistance created by the agricultural sector

As one scholar aptly observed, "[t]he current debate on the ethics of [antimicrobial resistance] is heavily and disproportionately focused on the use of antibiotics in humans...this focus reflects the traditional discourse in medical ethics..."<sup>36</sup> It seems relevant to note the seeming irrationality of ethicists advocating for withholding antibiotics from people while failing to consider the widespread, indiscriminate, unregulated use of antibiotics in the agricultural sector. The bottom line is that the focus on antibiotic use in humans, while important, cannot overshadow the substantial role that antibiotic use in animals has played in the antibiotic resistance crisis. There are several key stakeholders that are under an ethical obligation to take immediate action.

The FDA should create a rule immediately banning the non-therapeutic use of antibiotics in healthy animals. The FDA took a small step in 2017 towards limiting antibiotic use in healthy animals when it finally restricted farms from using medically important drugs as growth promotion agents for animals.<sup>37</sup> This move, however, has been described as grossly insufficient. For one,

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<sup>1</sup> As an aside, taxation schemes on antibiotics may also discourage antibiotic development by the pharmaceutical industry or biotechnology startups. Already strapped for profits on antibiotics, as discussed further below, taxes will only worsen the situation.

antibiotics can still be used in healthy animals for purposes other than growth promotion, such as for “preventive health” purposes or in “times of stress,” which the FDA never clearly defines.<sup>38</sup>

Therefore, the newly imposed restriction is easy to circumvent. Farms simply can purchase antibiotics for use as a “preventive health” measure rather than for growth promotion purposes.<sup>39</sup> To complicate matters further, at least 30 percent of antibiotics intended for animals have labels that lack any parameters around duration of use, meaning they can be used indefinitely throughout animals’ lives.<sup>40</sup> Farms and pharmaceutical companies are still promoting “growth” as an ancillary benefit of antibiotics, encouraging their unbridled use.<sup>41</sup>

The next measure that the FDA must implement is the elimination of crowded, inhumane animal conditions in farms which create the need to administer “preventive” antibiotics. It is well established that “[a]ntibiotics are used at subtherapeutic levels to promote growth and to prevent disease in the extremely crowded conditions that food animals are raised in.”<sup>42</sup> The conditions present in many livestock farms has been compared to crowded hospitals “where everyone is given antibiotics, patients lie in unchanged beds, hygiene is nonexistent, infections and re-infections are rife, waste is thrown out the window, and visitors enter and leave at will.”<sup>43</sup> Eliminating crowded conditions will greatly reduce the need for preventive antibiotics.

Finally, the FDA must establish a surveillance and enforcement mechanism to ensure proper compliance with limiting antibiotic use in healthy animals and addressing crowded conditions. Surprisingly, and notwithstanding the documented link between antibiotic use in animals and adverse human health effects, the FDA lacks any means of monitoring farms’ use of antibiotics in animals. The only measure it uses to assess possible antibiotic use is the sale of antibiotics to farms.<sup>44</sup> The pharmaceutical and chemical companies that manufacture the antibiotics are required to provide this information to the FDA.<sup>45</sup> Although reports have indicated that around 80 percent of antibiotics are sold for agricultural purposes, the FDA contends that it cannot discern actual use from these numbers. At the same time, the FDA has failed to create any other rules that would establish an alternative means of monitoring use.<sup>46</sup> As a *New York Times* investigation revealed, public health investigators are often unable to access the most basic information regarding a farm’s practices.<sup>47</sup> The agricultural industry constructs roadblocks so that the government’s access to farms, and how they are using antibiotics in animals, is hindered.<sup>48</sup> Further complicating the matter are conflicts of interest where livestock industry executives hold high positions on advisory committees for government agencies, such as the US Department of Agriculture (USDA).<sup>49</sup>

The USDA does have a monitoring system that studies antibiotic use in the agricultural sector.<sup>50</sup> However, as an expert in a recent Washington Post article opined, “[t]he USDA’s oversight is laissez-faire. They test such a small fraction it can’t even be taken seriously...and they rotate the drugs they are testing for, because they can’t afford to test for all of them. They just don’t have the funds to do it. We raise 9 billion animals, and they test hundreds of cattle, not even thousands.”<sup>51</sup> The USDA’s antibiotic surveillance system also relies upon agricultural industry self-

reporting, using voluntary questionnaires,<sup>52</sup> which calls into question the completeness and veracity of the data.

In addition to the US government, the pharmaceutical industry must also help reign in imprudent antibiotic use in the agricultural sector. In 2007, legislation was introduced that would have required drug manufacturers to phase out use of antibiotics for healthy animals.<sup>53</sup> The meat and poultry industries, and several major pharmaceutical companies opposed the legislation.<sup>54</sup> It is ethically incumbent upon the pharmaceutical industry to support the fight against antibiotic resistance. The industry creates the products, doing a great deal of good, so some may argue they should not be tasked with overseeing poor uses of their products. But the pharmaceutical industry should encourage measures that ensure the responsible use of their products. It should also refrain from touting the “ancillary benefits” of antibiotics, such as “growth promotion,” which encourages their injudicious and illegal use.

Consumers pay the ethical price of all three industries’ actions. People eating animal products have no opportunity to consent to the use of antibiotics. Although they may choose antibiotic-free meat and dairy, or choose not to consume animal products, people do not have the opportunity to consent to the presence of antibiotic residues, antibiotic resistant bacteria, and resistance genes in their food supply, and they may not be aware of the risks. Consumers bear the burden while industries profit.

While there are animal food products designated “organic,” and their producers allege that no antibiotics were used in their production use, these foods tend to be significantly more expensive than food that is not organic. Therefore, those in lower socio-economic brackets are forced to buy foods that are detrimental to their health, while those in higher brackets can afford healthier food products. This is a violation of the ethical principle of distributive justice. Industry must work to find innovative ways to level the playing field and make all food safe for consumers, regardless of economic disposition. Simply put, no consumer should have to worry about antibiotics, antibiotic resistant bacteria, or resistance genes in their food supply.

#### IV. Creating incentives around antibiotic development

Addressing antibiotic resistance by chipping away at its causes is an important approach, though it is not sufficient to truly win the antibiotic resistance war. Since, even with mitigation of causal factors, resistance is inevitable on some level. Therefore, we must also address the crisis from the tail-end. This involves ensuring that, when resistance does occur, we are prepared for it. In order to do this, new classes of antibiotics that have the potential to treat resistant pathogens must be developed.

The current landscape for antibiotic research and development is a barren one. Pharmaceutical companies have largely bailed on this area and biotechnology startups are going bankrupt pursuing this venture. As a recent *New York Times* piece noted, “[i]n the 1980s, there were 18 major pharmaceutical companies developing new antibiotics; today there are three.”<sup>55</sup> Pharmaceutical companies prefer to focus on the development of drugs for chronic diseases,

which ensure long term, continuous profits.<sup>56</sup> Antibiotics, on the other hand, tend to be prescribed on a short-term basis for acute infections. This limits their inherent capacity to generate profits.<sup>57</sup> Finally, physicians tend to be reluctant to use new antibiotics, further limiting companies from recouping their investments.<sup>58</sup>

Bioethicist Dr. Ezekiel Emanuel has suggested using government-sponsored prize money for approved new classes of antibiotics, stating that “[t]he prestige, bragging rights and renewed sense of mission created by such a prize would alone make an investment in research worthwhile.”<sup>59</sup> Twenty pharmaceutical companies are pooling their capital and using it to fund smaller, biotechnology companies dedicated to developing antibiotics in collaboration with the World Health Organization. The companies recently announced that they are creating a \$1 billion fund for biotech start-ups. The pool, called the AMR Action Fund, will be short-term but intended to provide an investment “amid a collapsing antibiotics industry.” The money will go to approximately 24 companies already working on promising drugs.<sup>60</sup>

Although the foregoing approaches are laudable, they are not sustainable. Each new antibiotic can cost \$2.6 billion to develop.<sup>61</sup> The establishment of non-profit organizations dedicated to the research and development of new antibiotics may be a more promising approach. As an article published in the *New England Journal of Medicine* in 2019 explained, nonprofits “don’t face pressure to generate continuous revenue growth to drive up shareholder value – venture capitalist investors demand very high rates of return over short periods. There is also less pressure to increase drug prices.”<sup>62</sup> Some nonprofits, such as the TB Alliance and the Medicines for Malaria Venture, have proven to contribute to antibiotic development.<sup>63</sup> Ultimately, the challenge for non-profits will be to raise enough funds. Perhaps pharmaceutical funds, such as the AMR Action Fund, coupled with government funding, could be directed toward non-profits’ antibiotic development efforts.

## CONCLUSION

Antibiotic resistance is a growing concern for everyone around the globe and the problem demands our collective, focused attention. As the World Health Organization has observed, the antibiotic resistance crisis may seem slow-moving, and abstract compared to the COVID-19 pandemic.<sup>64</sup> Antibiotic resistance needs more attention and solutions. As one public health expert has warned, “...one day, all of us...will need an antibiotic. A world in which antibiotics no longer work is something that should terrify everyone.”<sup>65</sup>

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<sup>2</sup> Jacobs, A.

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- <sup>32</sup> Addressing antibiotic resistance from a global perspective will entail assisting developing nations in building infrastructure and developing rules and enforcement capabilities around antibiotic use in humans and animals. The vast nature of this topic, and its inherent challenges, warrants a separate discussion.
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- <sup>64</sup> Jacobs, A. "Drug Giants Create Fund to Bolster Struggling Antibiotic Start-Ups." *The New York Times*. (July 9, 2020)(citing Dr. Peter Beyer, Senior Adviser at the World Health Organization).
- <sup>65</sup> Jacobs, A. (Quoting Dr. Everly Macario, Public Health Expert at the University of Chicago Medicine).