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Antimicrobial Resistance

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FROM THE EDITOR

What Is Ethically Important About Antimicrobial Resistance?

Olivia S. Kates, MD, MA

There were approximately 2 billion people living on our planet when Alexander Fleming discovered penicillin in the late 1920s.[1] Nearly a century later, there are over 4 times that number.[1] But as humans shape their environment through forces like agriculture, industrialization, globalization, and technology, that environment pushes back. Smoke from raging wildfires is visible from the International Space Station[2]; little spotted lanternflies bedeck and blight mid-Atlantic hardwoods[3]; and, far smaller still, microorganisms evolve and evade our arsenal of infection-fighting medicines. Antimicrobial resistance (AMR) is the phenomenon of adaptive change in bacteria, fungi, viruses, and parasites that renders these potential agents of disease and ecological change less susceptible to treatments designed to control them. In 2019, the World Health Organization (WHO) in 2019 named AMR one of the top 10 threats to global health, alongside viral pandemics and climate change.[4] These topics, and others on the WHO's list, have been explored in past theme issues of the *AMA Journal of Ethics*,[5,6,7,8] but this will be the first in-depth issue to explore the threat of AMR.

AMR is not only a technological or medical challenge but also an ethical challenge affecting individuals, communities, societies, and even ecosystems. In the most straightforward example, a patient with an infection may face longer, more invasive, and more costly treatment; diminished quality of life; or even death as a consequence of AMR. But the same patient might also face stigma, isolation, and uncertainty. Isolated patients are visited less frequently by health professionals wearing added layers of personal protective equipment and are alerted to the dangers of spreading resistant microbes to other patients by signage and special handling but offered little or no advice for protecting their loved ones when they go home.[9,10] Even in the absence of illness, patients who carry antimicrobial-resistant microbes may be treated differently during elective surgery or cancer treatment or denied a life-saving organ transplant because of the microbes they carry within them.[11]

The human body provides an environment for trillions of microorganisms. While human cells are *not* outnumbered 10:1 (the true ratio is roughly 1:1), we carry with us a large and diverse microbiome whose members play a surprising role in health and disease.[12] As vital as the microbiome is to the healthy functioning of the human body, many human infections arise from overgrowth, invasion, or translocation by members of this community: urinary tract infections are often caused by bacteria from the

gastrointestinal tract; pneumonias are often caused by bacteria from the mouth and throat; boils and abscesses are often caused by bacteria that live, usually unnoticed, on the skin. A person's microbiome might include antimicrobial-resistant organisms, which often prove tenacious members of the ever-changing microbial community.[13] When a person and their microbiome are seen separately, AMR is simply a coincidental feature of microorganisms in the individual. But when a person and their inseparable microbiome are seen as an entire unit, AMR becomes a contingent feature of the individual.

Who experiences this coincidence or carries this "trait" of AMR? The most commonly cited driver of AMR is antimicrobial use, often called out as "overuse." (*Use* is a descriptive claim, *overuse* a normative one that requires framing.) However, the burdens of AMR are not borne primarily by the most privileged patients. People with limited access to health care, in developing countries, living in poverty; members of marginalized communities like Black Americans or men who have sex with men; and young children are disproportionately affected by AMR.[14] Individual antimicrobial use as well as community antimicrobial use, agricultural and environmental use, wastewater management and sanitation, crowding, and other structural forces that affect human health and susceptibility to disease all shape who carries and suffers from antimicrobial-resistant organisms.[15]

Although microbes play crucial roles in ecosystems, including in soil health, nutrient cycling, and water purification, the spread of AMR threatens these delicate balances, with cascading implications for ecological sustainability.[16] Like other sustainability challenges, the threat of AMR reaches across time. Today's patterns of AMR reflect past antimicrobial use; today's antimicrobial use further shapes the patterns of AMR that will test future generations. But unlike weather patterns or deforestation, AMR isn't simply a consequence of human actions manifest in the environment; it is a consequence of human actions manifest in ourselves. Even if climate change drives colder temperatures in some places, rising sea levels drive us to higher ground, or giant leaps for mankind carry us beyond Earth itself, wherever we go, AMR is something that we will carry with us and within us.

In this issue of the *AMA Journal of Ethics*, contributors explore the topic of AMR as a multimodal phenomenon—as both a trait and an experience, a cause and a consequence, an individual burden and an ecological challenge. Their work sets the stage for the next issue of the journal, "Antimicrobial Stewardship," the interventional tool kit that health professionals and organizations use to promote an array of aims, chief among them changing the future of AMR.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Antimicrobial Resistance Limit Access to an Organ Transplant?

Andrew Courtwright, MD, PhD

Abstract

Burkholderia cenocepacia (*B cenocepacia*) is a gram-negative bacteria associated with significant morbidity and mortality following lung transplantation. Most US transplant programs consider *B cenocepacia* colonization to be an absolute contraindication to transplantation. This article argues that, if clinicians have good clinical reasons to expect poor outcomes for patients with *B cenocepacia*, then offering transplantation anyway is an abrogation of clinicians' fiduciary duties. This article also discusses other fiduciary obligations transplant programs might have to patients with *B cenocepacia,* such as referring to another transplant center, considering novel treatment options, and investigating how the infection's virulence factors stratify that patient's risk for poor transplant outcomes.

Case

J is a 26-year-old person with advanced lung disease due to cystic fibrosis (CF) being evaluated for lung transplantation. Throughout their life, J has had recurrent exacerbations of respiratory symptoms that have been treated with a wide range of antibiotics. As part of the pretransplant evaluation, lung transplant and infectious diseases specialists review J's past respiratory cultures. A multidrug-resistant *Burkholderia cenocepacia* (*B cenocepacia*) is growing in multiple recent samples. The bacterium is resistant to most commonly used antibiotics. The few antibiotics to which it remains susceptible have a high rate of toxicities, including kidney injury or kidney failure. Some strains of *B cenocepacia* are also readily transmissible between patients with CF. It does not seem like *B cenocepacia* has ever made J sick, but it has clearly persisted in J's lungs over many months.

J is asked to isolate from other CF patients to avoid spreading *B cenocepacia* to others. This means J cannot easily participate in in-person educational and social events related to CF or lung transplantation. The lung transplant and infectious diseases specialists reviewing J's case are worried that the presence of *B cenocepacia* increases the risk that J will have serious complications after a lung transplant. Transplant recipients must take lifelong immunosuppression to prevent their bodies from rejecting the donor organs. In an immunosuppressed patient, bacteria like *B cenocepacia* could grow in the lungs or spread throughout the body, leading to serious infection. If there are few antibiotics available to safely treat the infection, it could be fatal. The transplant

program has many patients waiting for lung transplants, many of whom die each year before they are able to get a transplant. They meet to discuss whether J should be added to their waiting list or not.

Commentary

In 2021, the International Society for Heart and Lung Transplantation published consensus guidelines for lung transplant candidate selection.[1] Among the conditions labeled "factors with high or substantially increased risk" were infectious diseases—such as *Burkholderia gladioli* and *B cenocepacia* infections—that are extremely difficult to treat following immunosuppression or whose treatment carries significant toxicity. *B cenocepacia*, in particular, has a complex history with CF and lung transplantation.

B cenocepacia is a member of a group of environmentally widespread gram-negative bacteria. *B cenocepacia* is naturally resistant to several antibiotic classes and can undergo transcriptional reprogramming to adapt to host immune responses and antimicrobial therapy. Patients with CF and other forms of bronchiectasis are particularly susceptible to *B cenocepacia* infection.[2] While some patients with CF maintain stable lung function following *B cenocepacia* infection, others have a rapid pulmonary decline.[2] In severe cases, they can develop a clinical entity referred to as cepacia syndrome, which carries high mortality.[3] Unfortunately, lung transplantation does not guarantee *B cenocepacia* eradication because of sinus reservoirs, intraoperative spillage with infection of the chest cavity, or reinfection of the allograft from upper airway colonization.

B cenocepacia is associated with life-threatening posttransplant complications, including bronchial anastomotic dehiscence, empyema, sepsis, and persistent bacteremia.[4] Treatment includes antimicrobial regimens with significant renal, hepatic, and bone marrow toxicities. It also requires net reduction in immunosuppression, which can increase the likelihood of acute and chronic rejection. In 2 centers, the rate of 1-year survival for patients with *B cenocepacia* infection was 25% and 60%.[5,6] There are, however, case reports and case series of successful transplantation of patients with *B cenocepacia* infection or colonization.[7,8] These are generally from programs that employ highly protocolized care pathways, such as the University of Pittsburgh Medical Center.[5] Successful approaches include irrigation of the chest and bronchi with 0.5% povidone-iodine solution or taurolide, continuous antibiotic infusions, or uncommonly employed antibiotic combinations.[5,7] Most centers, however, are reluctant to offer transplantation for patients with *B cenocepacia* because of concern for poor posttransplant outcomes. Is this ethically justified?

Transplant Centers' Fiduciary Duties

Rather than applying the traditional organ allocation principles of utility, respect for persons, justice, and so on, I will approach the question of whether a transplant program should list a patient with *B cenocepacia* from the perspective of the fiduciary duties between transplant centers and their patients. While fiduciary duties have legal dimensions, my focus here will be on fiduciary duties as developed within normative ethics.[9]

Fiduciary duties derive from a relationship in which one party is entrusted with the welfare of another party who has a particular vulnerability. These relationships have 3 characteristics: (1) the beneficiary's vulnerability makes them dependent on the fiduciary; (2) the fiduciary has superior knowledge and skills related to the beneficiary's

vulnerability; and (3) the beneficiary trusts the fiduciary to use their knowledge and skills to promote the best interests of the beneficiary.[10] The patient-physician relationship is a paradigmatic fiduciary relationship. Transplant committees—which are composed of individual health care professionals who stand in a fiduciary relation to their patients—also have a fiduciary relationship with transplant candidates. Patients with advanced lung disease are dependent on the committee; the committee has superior knowledge and skills related to their advanced lung disease; and patients trust that the committee will use its experience and skills to act in their best interests.

Fiduciary duties—like all duties—create specific obligations, organized around the idea that the fiduciary must act to protect and promote the best interests of the beneficiary with respect to their vulnerability. In the transplant setting, these include a mix of positive and negative duties: to obtain informed consent for transplant evaluation and listing, to avoid conflicts of interest in the decision-making process, not to abandon a patient before or after transplant, and not to recommend or pursue treatments that will not benefit or are significantly more likely to harm than benefit the patient. This last obligation is central to the decision of whether to offer transplantation to *B cenocepacia* patients.

Decisions about transplant candidacy are often framed as being about patients' contraindication to transplantation instead of the centers' ability to offer them a high enough probability of the outcome they desire. The way that rejections are expressed—"you are not a candidate for lung transplantation"—might subtly shift responsibility or blame to the patient. There is a counterfactual implicit in this framing—namely, that if the patient had not acquired *B cenocepacia*, had worked harder to lose weight, or had not developed cardiac disease, and so on, they would otherwise have been an acceptable candidate. If we take the idea of fiduciary duties seriously, however, the limitation is not on the patient's side but on the program's. If the center has not had successful outcomes—or, in reviewing others' experiences, does not believe it would have successful outcomes—with patients with a certain condition, it is an abrogation of the center's fiduciary duties to offer transplantation anyway. Part of standing in a fiduciary relationship with a patient is not to offer treatments that are significantly more likely to cause harm than benefit.

But what if the alternative is death or what if the patient is willing to take the risk, no matter how unlikely a good outcome? The traditional response is to shift to the stewardship role of transplant committees and to point out that programs are responsible to donors, their families, and society not to "waste" organs. Taking fiduciary duties seriously, however, means that, even if the program has available organs, not everyone will be a candidate. This is true even if the alternative is death or patients are willing to take any risk. The fact that a patient's vulnerability increases their willingness to assume the risks is a sign that more—not fewer—protections are needed. Just as surgeons do not offer certain interventions—total bowel resection in a patient with widely metastatic cancer or extracorporeal membrane oxygenation in refractory septic shock—that are significantly more likely to cause harm, so transplant committees must acknowledge similar limitations. A clinician who performs an intervention that causes suffering and then death for a patient who was going to die regardless of the intervention abrogates their fiduciary duties to the patient.

Regulations and Fiduciary Duties

The current US regulatory environment adds an additional layer of complexity for a program assessing its fiduciary responsibilities to patients with *B cenocepacia*. Private insurance and government agencies, such as the Centers for Medicare and Medicaid Services, have thresholds for poor posttransplant outcomes, including survival, that trigger program flags.[11] In extreme cases, flagging can result in loss of insurance contracts, referral relationships, and regulatory authorization to continue to offer transplantation. While regulatory flags can have serious institutional financial implications, the reason to avoid regulatory flags is not because transplant committees have specific obligations in this regard to their hospitals. Rather, failure to meet regulatory standards has a direct impact on their patients, including those who are listed and those who are undergoing evaluation. For example, flagged programs display a set of compensatory behaviors, including decreasing transplant volume, increasing selectivity of donor offers, and declining to list perceived high-risk patients.[12] Perceived high-risk patients include currently listed candidates and patients known to the program who would have accepted before being flagged. When deciding to list a patient—or patients—with *B cenocepacia*, centers must consider not just their ability to provide an acceptable outcome. The impact of an unanticipated mortality on the program's ability to transplant other candidates also matters (including to other patients with *B cenocepacia*).

As an example of one approach to considering conflicting fiduciary duties, the program with which I am affiliated is willing to list patients with a history of *B cenocepacia* in a limited set of circumstances. First, they cannot have recent sputum cultures with *B cenocepacia* growth, even if it is felt to be colonization rather than active infection. Second, at the time of their transplant evaluation, repeat sputum, bronchioalveolar lavage (when safe), and endoscopic sinus cultures are collected to confirm the absence of *B cenocepacia*. If these are negative and the patient is otherwise an appropriate candidate, the committee will authorize listing. Surveillance sputum cultures are obtained while the patient is awaiting an organ offer. Short- and long-term outcomes utilizing the program's protocol have been favorable, allowing the committee to fulfill its fiduciary obligations to this group of patients.

Alternatives

A program's decision that it cannot offer transplantation does not exhaust its obligations to patients with *B cenocepacia*. First, it should provide referral to another program that has had better outcomes for *B cenocepacia*. If treatment at another facility would entail extensive travel or relocation, the original program should partner with the referral group to coordinate evaluation testing and pretransplant care. Following transplantation, the original program should offer to collaborate on or fully transition the patient's care after a defined period. Second, because the treatment of *B cenocepacia* patients has evolved significantly, transplant programs should stay abreast of advances in the management of *B cenocepacia* infections by learning from peer programs that offer *B cenocepacia* patients transplantation, evaluating virulence determinants for specific *B cenocepacia* strains, exploring novel therapeutics such as bacteriophage therapy, and understanding the role of new antimicrobial drugs with a lower toxicity profile in treating *B cenocepacia*.[13,14] Some of these avenues—such as bacteriophage treatment—are superogatory in the sense that they are morally praiseworthy rather than obligatory.

Does the etiology of the *B cenocepacia* infection have moral relevance for the committee decision? Molecular typing has made it possible to identify *B cenocepacia*

clusters, often within a CF program or clinic site.[15] However, the extent to which transmission is a function of lax infection control policies, incomplete health care provider or patient adherence to these protocols, or exposure through patient-to-patient interactions outside the clinic remains difficult to assess. Even a case of negligent infection control policies does not change the balance of considerations for the transplant program regarding candidate risk and benefit. It does, however, have significant moral implications for the bronchiectasis program, which is charged with protecting patients within the health care environment. Relatedly, the CF team's failure to respond appropriately to a *B cenocepacia* outbreak with a review of its infection control policies or consideration of postexposure prophylaxis has moral implications for its program.[16] However, as with the source of infection, failing to control the infection should not change the overall balance of considerations for the transplant team—specifically, the imperative to focus on balancing risks and benefits in the care of a patient.

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The case to which this commentary is a response was developed by the editorial staff.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

How Should We Manage Antimicrobial Resistance in Resource-Limited Settings?

Elizabeth A. Gulleen, MD and Margaret Lubwama, MBChB, MMed

Abstract

Patients living in low- and middle-income countries (LMICs) shoulder the greatest burden of infections caused by antimicrobial-resistant pathogens. Speedy access to appropriate broad-spectrum antimicrobials significantly improves health outcomes and reduces transmission of antimicrobial-resistant pathogens, but persons living in LMICs have compromised access to these antimicrobials. This article considers how inequities in microbiology diagnostics, antimicrobial access, and antimicrobial affordability influence outcomes for patients infected with antimicrobial-resistant pathogens who live in resource-limited settings.

Case

"What are your final antibiotic recommendations?" asked the medical officer.

The three of us considered the question as we stood in an inpatient oncology ward in Kampala, Uganda. Our 20-year-old patient was critically ill: hypotensive, febrile, and obtunded. Three weeks ago, she had received her first dose of chemotherapy to treat her newly diagnosed acute myelogenous leukemia. She was now experiencing a common chemotherapy-related side effect, neutropenic fever. This oncologic emergency required rapid initiation of appropriate antibiotics. Each hour of delay increased her risk of death.

Our discussion continued down an all-too-familiar path. "Which intravenous antibiotics does the hospital pharmacy currently stock?" we asked.

"Ceftriaxone and levofloxacin," the medical officer responded. "But she's been receiving ceftriaxone for the past 3 days without improvement and was taking levofloxacin prophylaxis when her fever started."

"Have you been able to obtain blood cultures?" we queried.

"No," replied the medical officer. "She couldn't afford them. Her family is trying to gather the money, but they haven't been able to yet. Do you know if there are any active research studies that supply blood cultures?"

"Yes," we replied. "There is one research study that supplies blood cultures and is enrolling participants. We can contact the study coordinator to see if our patient qualifies."

Even without culture results to guide us, our patient's clinical picture was consistent with a bacterial bloodstream infection. At our hospital, there was a 75% chance that this infection was caused by multidrug resistant gram-negative bacteria. According to the medical officer, the 2 first-line antibiotics for treating neutropenic fever—meropenem and chloramphenicol—were out of stock at the free on-site pharmacy. Our patient's family would need to secure funding, travel to an off-site pharmacy, and buy antibiotics. Without the appropriate antibiotics, her chance of dying was over 80%.[1]

"Ideally, we would start her on meropenem since it won't worsen her ongoing bone marrow suppression," we reminded the medical officer. "Can her family afford this?"

The medical officer glanced at our patient's family members, now clustered around us. "The family has few resources. If they can't afford blood cultures, they won't be able to afford meropenem. They can afford 3 days of chloramphenicol. Since she will need at least 7 days of antibiotic therapy, this should give enough time for the meropenem to be restocked in our pharmacy."

The medical officer handed the chloramphenicol prescription to the patient's family member, instructed them to travel as quickly as possible to the nearest private pharmacy, and return to the ward so it could be administered to our patient.

Commentary

As an infectious diseases physician and a medical microbiologist who provide care at a cancer institute in Uganda, we recognize this case as representative of one of our typical patient consults. It highlights many of the challenges faced by patients, families, and health care professionals who manage infections in settings where there are high rates of antimicrobial resistance (AMR) but limited resources and little access to broad-spectrum antimicrobials. AMR occurs when an infectious microorganism (eg, bacteria, fungus, virus) develops resistance to an antimicrobial agent, rendering that antimicrobial useless. As a result, if a patient develops an infection from a resistant organism, the number of antimicrobials that can successfully treat that pathogen decreases. In 2021, the World Health Organization listed combatting AMR as 1 of the top 10 public health issues.[2] Recent headlines tell us that "Antimicrobial resistance will be worse than COVID"[3] and that the "superbugs" are here to stay.[4] But what does this mean for 85% of the global population who live in low- and middle-income countries (LMICs), bear the majority of the burden of AMR, and lack the resources to appropriately treat these infections?

Recent studies show that approximately 20% of global deaths are related to sepsis, a dysregulated inflammatory response in the setting of an infection. Sepsis-related mortality rates are highest in LMICs[5]; the rates of death attributable to AMR are also highest in some LMICs.[6] For patients with infections, survival depends upon the ability of clinicians to rapidly select, procure, and administer the appropriate antimicrobials and patients' own ability to complete the full course of treatment. Inability to complete these steps increases patient mortality and contributes to AMR. For those living in resource-limited settings, the disproportionate number of AMR-related deaths are deeply rooted

in inequities: inequities in microbiologic diagnostic access, inequities in antimicrobial access, and inequities in antimicrobial affordability.

Diagnostic Inequity

In resource-limited settings, access to microbiology laboratories is often limited. Microbiology laboratories are costly—they require skilled personnel and consistent access to laboratory supplies.[7] For this reason, they are often located in large urban centers. However, as our story illustrates, even patients with access to a microbiology laboratory may not be able to afford diagnostic testing. In Uganda, where the poverty rate is high,[8] a blood culture costs 60 000 to 75 000 Uganda shillings (15 to 20 USD), or 6 to 8 days' wages. Given patients' lack of access to diagnostic testing, clinicians rely heavily on clinical practice guidelines to direct empiric antimicrobial therapy. However, most infection management guidelines were developed in the United States and Europe, where there is widespread access to microbiology diagnostics and infection surveillance networks. Since AMR is less prevalent in these settings and the microbiology of infections differs regionally,[6] international guidelines do not adequately account for the patterns of resistance and the specific pathogens that occur in many LMICs. For example, we and our colleagues found that more than 50% of the bacteria isolated from Ugandan patients with neutropenic fever were resistant to the first-line antibiotics recommended in the US-based neutropenic fever guidelines.[9,10] As a result, the 30-day mortality rate for patients with neutropenic fever was 46% to 54%,[10,11] which contrasts starkly with the 2.6% to 21.4% mortality rate—depending on the number of comorbidities—for patients being treated in the United States.[12]

As highlighted by our case, research studies may be one of the few avenues through which patients have access to affordable laboratory diagnostics. Only after we began research studies of AMR among Ugandan patients with cancer were we able to update the US-based neutropenic fever guidelines to reflect local patterns of resistance and feel confident about which antibiotics to give patients. Development of local guidelines is predicated upon increased access to microbiology laboratories. Clinicians and researchers play a critical role in advocating for increased global and local investment in laboratory infrastructure.[13] Without supporting and strengthening local microbiology laboratories, the burden of deaths due to AMR will continue to increase for those living in LMICs.

Antimicrobial Access Inequity

Of course, selecting the appropriate antimicrobial is only one piece of the puzzle. Patients must also be able to procure the antimicrobial. In some ways, our patient was fortunate. Since she was receiving care in the capital city of Kampala, there were 3 private pharmacies within walking distance that routinely stock meropenem. Patients in rural Uganda may travel many kilometers to procure meropenem. This barrier results in further antibiotic treatment delay, thus increasing patient mortality.

Countrywide antibiotic access is also a concern. In our studies with colleagues, 10% to 25% of identified bacteria were resistant to all the locally available antibiotics (M. Lubwama, et al, unpublished data, 2017-2021). Recently developed antibiotics that most effectively combat resistant gram-negative bacteria (eg, ceftazidime-avibactam, ceftolozane-tazobactam) are not available for purchase in Uganda. Antimicrobials are typically developed in high-income countries (HICs) and, given the high cost of drug development, new antimicrobials are often first marketed and sold in HICs.[14] For a patient living in a place like Uganda, it may take 10 years before a newly developed

antimicrobial is available.[15] Thus, countries with the highest rates of AMR have the least access to antimicrobials most likely to treat these infections. These structural injustices perpetuate and worsen inequities in patient outcomes. Recent efforts have been made to improve the development and rapid dissemination of new antimicrobial agents in LMICs, including government investment in developing new antimicrobials; industry-sponsored funding of the AMR Action Fund; technology transfer to manufacturing sites in South America, Africa, and the Middle East; routine use of best-practice plans to address global access issues for newly developed antimicrobials; and implementation of standardized forecasting processes to ensure uninterrupted antibiotic supplies in LMICs.[14] These mechanisms must be strengthened to ensure access to antimicrobials for those who need them most.

Antibiotic Affordability

Our case poignantly illustrates the ways in which a patient's finances affect their treatment in resource-limited settings. Our patient was unable to afford meropenem, the best available antibiotic to treat her infection. While she could afford chloramphenicol, she could only purchase half of the recommended treatment regimen. For many of our patients, the process of obtaining funds leads to significant antibiotic treatment delays.

Recently, we and our colleagues conducted a survey[16] and focus groups of health care workers to assess barriers to antibiotic delivery at our institute. The health care workers described more than 20 ways in which patients obtain funds (ie, "mobilize money") to purchase antibiotics. These included asking friends and family, selling animals or land, being sponsored by religious institutions, and asking for money on the street (E. A. Gulleen, et al, unpublished data, 2022). They pointed out that mobilizing money can take hours or even days. For those with severe infections, a 1-hour delay in antibiotic initiation is associated with increased mortality.[17] Thus, the speed at which a family can mobilize money can be the difference between life and death.

As we reviewed the ways patients mobilize money, one physician commented, "Of course some people try to mobilize money, but just can't."

"What do you do when a patient can't mobilize money?" we asked.

The doctor held up her hands in a gesture of defeat. "You just use an antibiotic that is available at the free on-site pharmacy, since there's a small chance that it still might work."

This conversation highlights the moral dilemmas faced by clinicians who manage infections in settings where there are high rates of AMR and access to antimicrobials is a challenge. The clinician has a moral obligation to provide the best possible care for the patient within the allotted resources. In our focus groups, the clinicians told us of many ways they personally help patients mobilize money. These included paying for medications for the patients, contacting local donors, calling friends at private pharmacies, and working with local leadership to increase funding for antimicrobials at the on-site pharmacy (E. A. Gulleen, et al, unpublished data, 2022). The clinicians emphasized that these actions helped them cope with the moral injury that comes with providing care in a broken system in which the tools are often inadequate.

Implications for the Future

With the growing burden of AMR falling squarely on the shoulders of those living in LMICs, what is the solution? We have highlighted how inequities in microbiology diagnostic access, antimicrobial access, and antimicrobial affordability contribute to worse outcomes for patients in LMICs who develop infections with antibiotic-resistant organisms. The COVID-19 pandemic revealed how infections can rapidly traverse the globe. Likewise, antibiotic-resistant pathogens can rapidly disseminate. Thus, there is an urgent need to combat AMR on a global scale. However, we cannot combat AMR unless we address the inequities that drive differences in infection-related outcomes for those living in LMICs.

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Editor's Note

The case to which this commentary is a response was developed by the editorial staff. The 2 studies whose findings from unpublished data are summarized in this article were reviewed by Fred Hutchinson Cancer Center Institutional Review Board (FHIRB0008433, 2017; FHIRB0010736, 2022) and the Ugandan Cancer Institute Research and Ethics Committee (SBS 390, 2018; 15-2020, 2022).

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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AMA CODE SAYS

AMA *Code of Medical Ethics*' Opinions Related to Antimicrobial Resistance

Maura McGinnity

Abstract
The AMA *Code of Medical Ethics* does not directly address the issue of antimicrobial resistance, but parts of the AMA *Code* contain relevant guidance. This article summarizes how the AMA *Code* may be applicable to antimicrobial resistance.

The World Health Organization and Antimicrobial Resistance

The World Health Organization (WHO) declared antimicrobial resistance 1 of the top 10 global public health threats in 2023.[1] Antimicrobial resistance happens when bacteria, fungi, viruses, and parasites adapt over time and no longer respond to medicines, making it more difficult to treat disease and prevent its spread.[1] For common bacterial infections, high rates of antibiotic resistance have been observed around the world.[1] For example, the rate of resistance for ciprofloxacin, an antibiotic used to treat urinary tract infections, varied from 8.4% to a staggering 92.9% across 33 countries.[2]

To combat this ongoing threat, a transdisciplinary approach is necessary that includes physicians. While there may not be a specific opinion in the American Medical Association (AMA) *Code of Medical Ethics* to guide physicians, there are principles and opinions that may be applied to the issue of antimicrobial resistance. Principle V[3]; Opinion 2.2.1, "Informed Consent"[4]; and Opinion 8.5, "Disparities in Health Care"[5] offer guidance to physicians on ethical issues that may arise in conjunction with this important issue.

Principle V

Principle V states: "A physician shall continue to study, apply, and advance scientific knowledge, maintain a commitment to medical education, make relevant information available to patients, colleagues, and the public, obtain consultation, and use the talents of other health care professionals when indicated."[3] Because bacteria, fungi, viruses, and parasites all can become resistant to drugs over time and it is difficult to predict when and how this will happen, physicians must continue studying antimicrobial resistance and sharing knowledge with colleagues and the public. For example, in 2015, the WHO launched the Global Antimicrobial Resistance and Use Surveillance System to work towards filling knowledge gaps and getting information out to all levels working on the issue.[1]

Informed Consent

Informed consent to treatment is an essential part of medical ethics. Physicians must inform their patients of any risks, benefits, or other important elements of their treatment so that patients can make an informed decision. Opinion 2.2.1 states that, to gain a patient's informed consent, a physician should:

(a) Assess the patient's ability to understand relevant medical information and the implications of treatment alternatives and to make an independent, voluntary decision.
(b) Present relevant information accurately and sensitively, in keeping with the patient's preferences for receiving medical information. The physician should include information about:
    (i) the diagnosis (when known);
    (ii) the nature and purpose of recommended interventions;
    (iii) the burdens, risks, and expected benefits of all options, including foregoing treatment
(c) Document the informed consent conversation and the patient's (or surrogate's) discission in the medical record in some manner. When the patient/surrogate has provided specific written consent, the consent form should be included in the record.[4]

As with any treatment, physicians should explain to patients the risks of overprescribing antimicrobial medications.

Inequity in Health Care

Antimicrobial resistance is also relevant to existing disparities in US health care, as it has many effects on microbiological, individual, societal, and ecological levels. In particular, antimicrobial resistance poses a danger to medically disadvantaged populations. The main drivers of antimicrobial resistance are the misuse and overuse of certain drugs, lack of access to clean water, poor sanitation and hygiene (in animals and humans), and lack of access to affordable medicines.[1] Many of these drivers arise in poor, marginalized communities.

Physicians have an ethical duty to increase awareness of these disparities and to strive to improve outcomes in medically underserved communities. Opinion 8.5 discusses how physicians should go about addressing disparities and how to avoid perpetuating them further. Specifically, Opinion 8.5 states that the medical profession has an ethical responsibility to:

(g) Help increase awareness of health care disparities
(h) Strive to increase the diversity of the physician workforce as a step toward reducing health care disparities
(i) Support research that examines health care disparities, including research on the unique health needs of all genders, ethnic groups, and medically disadvantaged populations, and the development of quality measures and resources to help reduce disparities.[5]

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

How Should Health Care Respond to Threats Antimicrobial Resistance Poses to Workers?

Majd Alsoubani, MD, Maya L. Nadimpalli, PhD, MS, and Shira Doron, MD

Abstract

Antimicrobial resistance (AMR) is a looming pandemic whose poor health outcomes are unlikely to be equitably distributed. This article focuses on intersections between AMR and inequities in health care workplaces in the United States and identifies the following as key problems: lack of published data on task-specific occupational health risks related to colonization and infection with antimicrobial-resistant pathogens, limited scientific literature reporting on race and ethnicity, and poor access to infection control educational opportunities for minoritized health care workers. This article argues that an equitable approach to remediating these problems requires improving surveillance and expanding research on how AMR is likely to influence health outcomes among members of the US-based health care workforce.

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Antimicrobial Resistance and Structural Racism

Antimicrobial resistance (AMR) is a growing global threat that poses significant challenges to public health. AMR arises when bacteria or fungi undergo genetic changes that render them unresponsive to antibiotic treatments, leading to infections that are more likely to cause severe illness or death. In the United States alone, nearly 3 million infections annually are attributable to resistant pathogens.[1] AMR is associated with not only increased risk of severe infections but also longer hospital stays and increased mortality.[1,2]

If AMR is an upcoming pandemic, it is now abundantly clear that it will not affect us all equally. Certain racial and ethnic groups in the United States are disproportionately impacted by the burden of AMR.[3,4,5] As an example, Black patients have higher rates of hospital onset and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections than White patients.[6] These disparities may be due to Black patients having less access to affordable medical care, a higher likelihood of poverty and crowded living conditions, and more documented chronic medical comorbidities than White patients, all of which contribute to extended hospital stays.[6] Studies have also

shown that MRSA colonization and infection are more common in patients with public health insurance and those with low socioeconomic status.[7,8] This trend has been documented in other antimicrobial-resistant infections, such as drug-resistant tuberculosis, penicillin-resistant *streptococcus pneumoniae*, and urinary tract infections with multidrug-resistant pathogens.[4,9,10]

Health care workers are on the front lines of the fight against AMR, as they are responsible for prescribing and administering antibiotics and implementing infection prevention and control measures. Health care workers who belong to racial or ethnic minority groups often hold the lowest-paid and most physically demanding jobs in health care.[11,12] For example, Dill and Duffy showed that Black women have the highest likelihood of working in the long-term-care sector and in nurse aide positions.[13] Racial and ethnic minority groups are overrepresented in health care positions that are not only underpaid but also often under-resourced, require overtime work, or involve tasks that may greatly increase occupational exposure to antimicrobial-resistant pathogens.[13] This manuscript examines the intersection of AMR and health care workplace equity in the United States and proposes measures to study and combat these challenges.

AMR Transmission

Workplace inequities can impact health care workers' occupational exposure to AMR. Workers concentrated in health care positions that do not require an advanced medical degree (nursing aides, transport staff) are often responsible for tasks that involve prolonged patient contact, such as bathing, which could increase risks of occupational exposure to AMR pathogens. These positions are often disproportionately filled by workers from racial and ethnic minority groups.[14,15] A multinational study conducted in Europe from 2008 to 2011 demonstrated that personnel who feed patients had increased risk of colonization with extended-spectrum beta lactamase-producing *Enterobacterales* compared to other health care workers.[16] We suspect that workers who handle bathing, toileting, mobilizing, and transporting patients might be similarly at higher risk. However, there are limited data on health care workers' occupational risk of colonization or infection with multidrug-resistant organisms (MDRO) and limited reporting on race and ethnicity.[17] In a meta-analysis on occupational infection risk due to MDROs in health care workers that included 22 international studies, 4 of which were conducted in the United States, only 1 reported results by participants' nationality.[16]

Health care workers in long-term care facilities, acute care, and intensive care units might be especially at risk. These settings have been found to carry MDROs like multidrug-resistant *Candida auris*, which has become a global threat and is often transmitted nosocomially.[18] MDROs like carbapenem-resistant *Enterobacterales* are highly prevalent among residents of long-term care facilities due to the acuity of their medical conditions, frequent antibiotic exposures, and use of gastrointestinal devices and indwelling catheters; moreover, residents tend to harbor these organisms for extended periods of time, which increases risk of transmission.[19,20] Barriers to consistent infection control measure implementation in long-term care facilities were unmasked by the COVID-19 pandemic. In addition to shortages in personal protective equipment and staff, lack of organizational communication and teamwork have been highlighted as underlying causes.[21]

Another category of health care workers who might be more impacted by AMR are those providing care in low-resource settings, such as rural areas or low-income neighborhoods. These settings often have limited financial resources and may have

shortages of personal protective equipment.[22] Furthermore, due to staff shortages, rural health care staff are more likely than their urban counterparts to have multiple job responsibilities in addition to direct patient care, which might include infection control and AMR education.[23]

AMR Education Equity

Adequate knowledge of AMR and AMR prevention is essential to combat the threat of resistance. Health care workers who have not received advanced degrees in medicine, such as nursing aides or transport staff, often do not receive the same level of AMR education and training. In the United States, health care workers in nursing homes have reported lack of knowledge, training, and continued medical education opportunities as key barriers to effectively implementing infection control measures.[24] Nursing home staff who lack advanced medical degrees have also reported less frequent training and orientation on infection control measures than their medically trained counterparts.[25] For example, a multicenter study conducted in the French health care system that evaluated the knowledge and attitudes of health care workers regarding MDROs found that those who lacked advanced medical degrees (eg, nursing assistants) scored significantly lower on knowledge of AMR and infection control measures than health care workers with advanced medical degrees (eg, physicians).[26] Educational interventions targeted to different staff members, such as environmental services members, have been shown to be effective in improving overall knowledge of risk of pathogen transmission and necessary cleaning practices in addition to preventing the transmission of MDRO.[27,28] Moreover, workers' compliance with infection control measures has been found to be influenced by their knowledge of infection control practices and modes of MDRO transmission.[25,29]

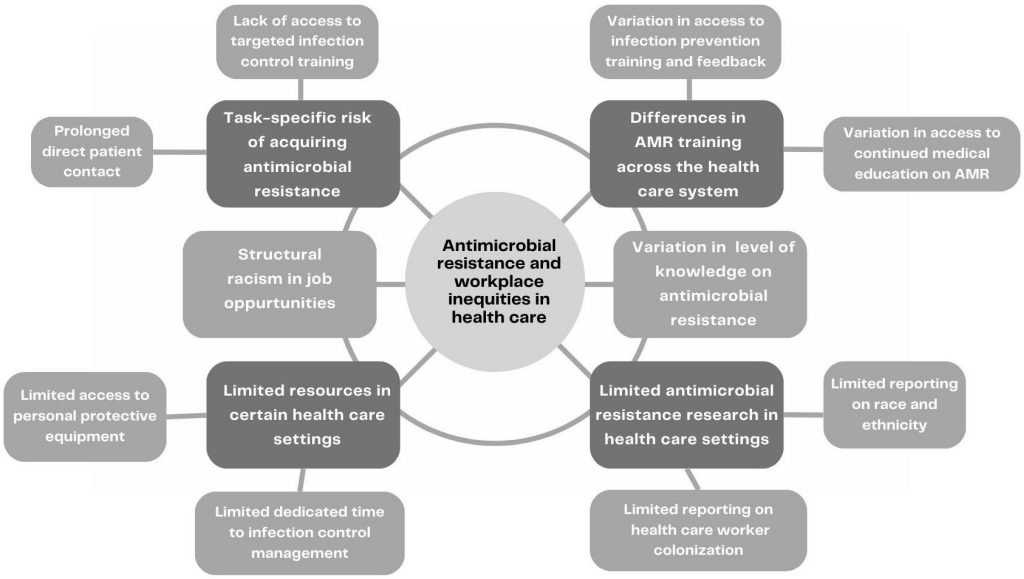
Education on AMR and safe antibiotic use for health care workers who lack advanced medical degrees could have added benefits for certain minority communities. Low-income and Latinx communities commonly report self-medication with nonprescription antibiotics, the use of "left-over" antibiotics, and the purchase of foreign-made products, all of which could exacerbate the risk of AMR.[30,31,32] Providing health care workers with education on AMR not only would improve adherence to infection control measures but also could lead to dissemination of this knowledge to their communities. However, it is important to acknowledge that the drivers of antibiotic misuse are complex and therefore may not be mitigated solely by improved knowledge about antibiotic resistance.

Recommendations

As health care workers and scientists, all of us have a responsibility to prioritize understanding the impact of health care workplace inequities and to acknowledge the intersectionality of workplace disparities, race, ethnicity, and AMR risk (see Figure). Currently, there is a clear gap in AMR research evaluating health care worker exposures and occupational risk. For instance, to our knowledge, there are no large longitudinal or multicenter US studies evaluating health care workers' occupational risks of exposure to MDROs. Future research should include tracking and surveillance of MDROs among health care workers across the spectrum of health care settings to identify populations at the greatest risk. In addition, the medical profession needs to advocate for policies and practices for consistent data collection on race and ethnicity in AMR research on a national scale to better understand the impact of AMR on vulnerable communities and racial and ethnic minorities. With regard to institutional and policy changes, we recommend that health care institutions strive to provide equitable educational

opportunities for all health care employees by using targeted AMR education and infection control training in order to promote effective infection prevention and responsible antibiotic use. Because nursing homes and long-term care facilities play a crucial role in providing essential health care services to communities and vulnerable populations, fostering partnerships with these facilities to establish opportunities for continued education on AMR and infection prevention is an important goal that will benefit minoritized health care workers as well.

Figure. Contributors to Antimicrobial Resistance and Heath Care Workplace Inequity



However, implementing new policies and expanding educational programs require funding support and allocation of resources to the most vulnerable sectors in health care. Expanding budgets dedicated to combating AMR requires action from health care systems and, on a larger scale, from governments. This manuscript calls for collaborative efforts among policy makers, employers, workers, and other stakeholders to safeguard workplace equity in the face of AMR.

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

Why We Need to Change How We Talk About Infectious Disease

Frank Kronenberg, PhD and Sipho Dlamini, MBChB

Abstract

This article builds a case for raising occupational consciousness by critically questioning ahistorical and apolitical uses of battle language, especially when referring to infectious diseases. Words such as *invasion*, *colonization*, and *resistance* are particularly ethically troubling, and this article considers why the social practices our language brings about matter in health care. Dynamic relationships among humans and microbes, as well as metaphor, are considered here in historical context and through the lens of Derrida's portmanteau *hostipitality*, which invites reconsideration of an infectious disease notion of *host* and how conceptions of hospitality have been institutionalized and commodified. This article argues that language used in infectious disease care settings should be informed by coexistence as a guiding value of clinical and ethical relevance.

I had been talking to a patient. We had found drug-resistant bacteria in her lungs, and she was understandably worried. I tried to reassure her that the bacteria were not causing any problems and didn't need any treatment, they just happened to be there. The language I used to do this was "it's just a colonizer." This particular patient was Native American.
Olivia S. Kates, MD, MA

Word Choices Are Ethics Choices

The epigram reveals the ethical importance of interrogating geopolitical terminologies and analogies (eg, *invasion*, *colonization*, *resistance*) in how we talk about the dynamic relationships among humans, microbes, and their shared environment. Our thinking about this topic is informed and guided by our Global South-based research involvement in decolonizing global health—a subdiscipline within public health and medicine—and our recognition that colonialism and global health are inextricably linked. As Nunn and Qian pointed out, the worldwide expansion of European presence has resulted in the transmission of new diseases and demographic, ecological, and economic changes to the Global South.[1] The field of infectious disease is significantly shaped by the historical origins and evolution of global health, previously known as colonial or imperial medicine (1500-1800), missionary medicine (early 1800s), tropical medicine (late 1800s) and international medicine (after 1950), and, as Cator and Borrell note, "each synonym has nuances in its goal and the period in which the term predominated."[2] Acknowledging

that it is impossible to comprehensively address the complex subject of geopolitical terminologies and analogies in the field of infectious disease, our main aim is to illustrate how use of geopolitical battle language legitimizes outdated and potentially harmful colonial practices and mindsets in infectious disease. We approach and engage this topic through 2 conceptual lenses: *occupational consciousness* and Derrida's deconstructionist portmanteau *hostipitality*.

Occupational Consciousness

We first wish to briefly speak to why language and *languaging* in particular matters. Swain defines languaging as "a process of making meaning and shaping knowledge and experience through language."[3] *Language* can be approached from the perspective of structural and generative linguistics, whereby it is conceived as "an autonomous system of science" and "a mental grammar," whereas *languaging* allows for language to be viewed through a critical linguistics lens as "a series of social practices and actions."[4] *Occupational consciousness*, a concept coined and theorized by Ramugondo, also applies to the terminologies we use in our practices. It is defined as "ongoing awareness of the dynamics of hegemony and … [how] through what people do every day" we can either sustain or disrupt "dominant practices … with implications for personal and collective health."[5] In other words, without being critically and sensitively conscious of the ends of our daily occupations, including languaging,[6,7,8,9] we may unintentionally cause or perpetuate harm, which we are ethically obliged to mitigate.[10,11,12,13] For example, Cox and Fritz have highlighted that "Some commonly used language in healthcare confers petulance on patients, renders them passive, or blames them for poor outcomes"; "Such language negatively affects patient-provider relationships and is outdated"; "Research is needed to explore the impact that such language could have on patient outcomes"; and lastly, "Clinicians should consider how their language affects attitudes and change as necessary."[14]

The definition of the occupational consciousness concept in terms of "dynamics of hegemony" and "dominant practices" prompts us to acknowledge and interrogate the ahistorical and apolitical use of the "battle" metaphors *invasion*, *colonization*, and *resistance* in languaging the dynamic relationships among humans, microbes, and their shared environments.[15,16,17,18,19,20,21,22] Given that biomedicine is predominantly occupied with diagnosing and treating symptoms and diseases rather than their underlying causes,[23] it seems apt to adopt a historicizing approach to understanding why geopolitical terminologies are problematic. This approach allows us to consider that the use of battle language[24] may originate from what Maldonado-Torres identifies as "a 'master morality' of dominion and control at the heart of western modernity … [which] constitutes the centre of a warring paradigm that inspires and legitimizes racial policies, imperial projects, and wars of invasion."[25]

Biomedicine Remains a Tool of Empire

It is imperative to underscore that, historically, the practice of modern medicine and its specialization, infectious disease, are deeply embedded in and held in check by colonial thinking in Western modernity[23] in partnership with white supremacy. The American sociologist Barbara Katz Rothman goes so far as to suggest that biomedicine is today's "ruling empire, colonising the planet."[23] Horton points out in the *Lancet* that though Rothman does not deny that biomedicine has saved lives, her concern is with the growing economic, governmental, and religious power of biomedicine in society.[10] In particular, health and health care in the biomedical empire have come to mean commodified medical services, which Rothman describes as "very individualised and

very professionalised."[10,23] Biomedicine is *not* preoccupied with understanding and advancing people-planet health but, arguably, at best with preventing death and at worst with determining who lives and who dies. The latter commitment is manifest, for example, in practices of using drugs on certain populations without their consent (eg, AZT trials conducted on HIV-positive African subjects by US physicians in 1994[26]) and privileging and withholding treatment (eg, Tuskegee Study of Untreated Syphilis in the Negro Male from 1932 to 1972[27]).

Keeping in mind the deep embeddedness of biomedicine in colonial thinking and practices, we now critically and ethically review the prevailing understanding in infectious disease of humans, microbes, and their dynamic relationships in a shared environment.

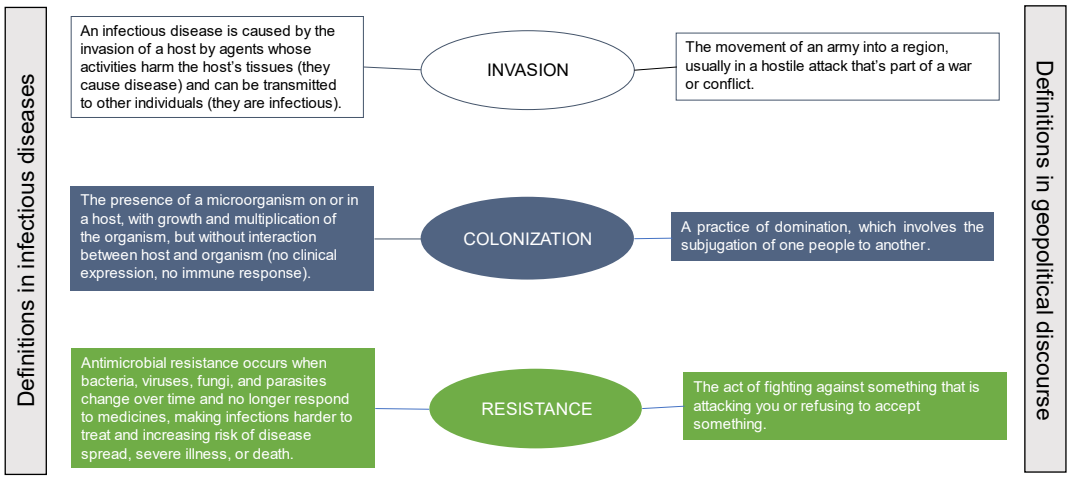
All Humans Are Counted, But Not Treated as Equals

In infectious disease, the thesis (ontological assumption) that underlies the dominant understanding of humans appears to be that "*being human is a given for all* [italics added]."[28] This apolitical and ahistorical premise is supported by the ongoing tracking of our rapidly growing global population.[29] Literally every human body counts as human, given the logic that the earth's human inhabitants, currently over 8 billion,[30] (are to) share the same planetary environment. Additionally, microbes do not discriminate among humans they select as hosts. However, across centuries, a political review of human history irrefutably evidences that not *every body* that is counted as a human also gets treated as one. Frantz Fanon languaged this disturbing historical reality in terms of a man-made division of humanity along "the racialized line of the human": above the "Zone of Being" (superior "whiteness") and below the "Zone of Non-Being" (inferior "blackness").[31] Fanon basically produced the antithesis that *being regarded as human is not a given for all*. In his doctoral research, the first author (F.K.) offers the synthesis that "Being [regarded as] human … [is] not a given but a political potentiality which manifests on a continuum of enacted harmful negations and salutogenic affirmations of our humanity."[28] Based on this decolonial, historicized perspective on humans, we problematize the use of battle and geopolitical analogies in explaining antimicrobial resistance in infectious diseases.

Bacteria-Like Ancestors of Humans

The other core concept for understanding dynamic relationships in infectious disease is microbes, or microorganisms, which are viruses, bacteria, and fungi. In the human body, the ratio of bacteria to human cells is close to 1:1.[32] Most evolutionary biologists agree that bacteria-like organisms are the ancestors of humans.[33] Sometimes microbes (pathogenic ones) cause sickness, but, most of the time, microorganisms (non-pathogenic ones) are in a symbiotic relationship with their human hosts.[34,35,36] They have adapted to parts of the body (skin, gut, other organ systems and mucous membranes) and provide vital functions essential for human survival. Foreign microbes from the atmosphere, other people, and other sources (including biological weapons) must gain entrance to the body for infections to occur. It is at this point that battle and geopolitical terminologies are used: when microbes enter through the respiratory, gastrointestinal, urogenital tracts, or breaks in the skin surface (see Figure).

Figure. Terminologies Used in Infectious Diseases and Geopolitical Discourses



Relationship Between Humans and Microbes

In infectious disease, the relationship between humans and microbes is premised on the former being host to the latter. Given that microorganisms can either be "friendly" or "enemy-like," it seems useful to consider the etymology of the word *host*. *Host* is derived from the Latin *hospes* and *hospit* (guest). The similar-sounding *hostis* means stranger or foreigner and, in classical use, enemy.[37] You may also hear these Latin words' relation to the words *hostility* and *hostage*. In infectious disease, this category of hostile or unfriendly microbes would be called pathogens.[38]

Other apt terms derived from *host* are *hospitality*, from the Latin *hospitalitem* (friendliness to guests) and *hostility*, from the Latin *hostilis* (inimical and warfare).[39] Hospitality and hostility are etymologically interlinked yet seemingly contradictory concepts. Jacques Derrida, the Algerian-born French philosopher and principal exponent of deconstructionism, coined the term *hostipitality*, which merges the word *hospitality*—"being friendly or welcoming to strangers"—and its antonym *hostility*—"being unfriendly or hostile to strangers."[40] Hospitality, it has been argued, is always conditional and includes within it the potential for hostility, just as hostility includes within it the potential for hospitality; both imply "the possibility of the other."[41] Indeed, Derrida famously argued that hospitality is a word of "a troubled and troubling origin, a word which carries its own contradiction incorporated into it,"[40] by which he refers to hostility.

As a case in point of how languaging can be harmful, we share why Derrida coined the word *hostipitality*. In 1997, the French government had imposed the Debre bill on immigrants and those without rights of residence, the so-called *sans-papier*. At the time, Derrida wrote: "I remember a bad day last year: It just about took my breath away, it sickened me when I heard the expression for the first time, barely understanding it, the expression crime of hospitality." Derrida was reacting to the Debre Bill, which concerned a law permitting the prosecution, and even the imprisonment, of those who take in and help foreigners whose status is held to be illegal. Derrida continued: "What becomes of a country, one must wonder, what becomes of a culture, what becomes of a language when it admits of a 'crime of hospitality,' when hospitality can become, in the eyes of the law and its representatives, a criminal offense?"[42]

Taking a cue from Derrida, from an ethics perspective, are we not compelled to ask, *What becomes of health care when it admits of battle analogies—when invasion, colonization, and resistance can become, in the eyes of biomedicine and its representatives, an acceptable way of talking about infections?* The notion of *hostipitality* may serve to ignite health care practitioners' occupational consciousness, prompting them to be mindful of and mitigate the risk of languaging, of using language in everyday practices that may cause or sustain harm done to those in need.

Coexistence: A Guiding Value of Clinical and Ethical Relevance

Although the context of Derrida's thinking about *hostipitality* was worldwide mass-scale migrations,[42] the term arguably does have a real bearing on antimicrobial resistance challenges, particularly for Western countries grappling with pressing migration problems: the influx of refugees and asylum seekers due to armed conflict, natural disasters, or economic hardship. The perpetual political-historical reality is that some populations of humans are hosted whereas others are treated with hostility.[31] What we are exploring here is a juxtaposition of geopolitical and infectious disease analyses: on the one hand, relationships between humans in the Zone of Being and othered ones in the Zone of Non-Being *and*, on the other hand, between humans and invading, colonizing, and resisting microbes in their environments.

The instance that triggered the writing of this article was the generatively disruptive realization that the use of the phrase "it's just a colonizer" may not be innocent but rather ambivalent, ethically and logically speaking. Therefore, the idea of humans hosting microbes as "strangers" may present as an alternative to languaging microbes as "invaders" who turn out to be "just colonizers." Again, we draw from Derrida, who speaks of "unconditional" and "conditional" hospitality. Unconditional hospitality refers to the law of real hospitality as a moral attitude to others, demanding the unconditional reception of strangers; conditional laws of hospitality impose conditions by translating the unconditional law into a reciprocal right to receive and a duty to offer hospitality.[40,42,43] Historical accounts suggest that at times Indigenous peoples' first response during the earliest encounters with Europeans was consistent with Derrida's definition of unconditional hospitality. Only when Indigenous peoples realized that these Europeans had come to take advantage of their original welcome in the most brutal ways did they start to resist. Metaphorically speaking, their "social immune system" kicked in and fought back, resisted. In other words, if we invert the infectious disease use of geopolitical terminologies in a historicized way, "the European colonizers were the ultimate pathogens" who caused mass-scale death and destruction of other cultures and civilizations.[44] Grounded in Western modernity they deemed superior (Zone of Being), the conquerors, invaders, and colonizers also benignly regarded themselves as "explorers," "Christianizers," and "civilizers," which in our contemporary age is languaged as bringing or spreading "development," "democracy" and "human rights"[45] to othered human populations in the south, the geopolitical peripheries of our global and local societies (Zone of Non-Being).

However, ultimately our argument is not to throw the baby out with the bathwater but to identify and pursue other guiding values of clinical and ethical relevance. The pioneering environmentalist Rachel Carson suggested that *"Man is a part of nature, and his war against nature is inevitably a war against himself* [italics added]."[46] The latter part of this quotation resonates with Maldonado-Torres' "'master morality' of dominion and control at the heart of western modernity,"[25] while the former prompts us to draw from other worldviews, those that are based on the principle of coexistence.[47,48] In the context

of infectious disease, appreciating and tapping into humans' capability to ethically negotiate coexistence with and discernment among friendly and enemy-like pathogens and people could indeed present as a more evolved intelligence for critical practical judgments than the ahistorical and apolitical logic and use of battle language.

Conclusion

The current way of languaging infectious disease, along with its geopolitical context, is problematic: it frames microbes alone as pathogens (nonhuman and therefore harmful) and Europeans as colonizers (human and therefore not harmful). This characterization, however, creates confusion for some, as we have not all experienced the world in the same way. Colonization constituted a dehumanization exercise across the world, and therefore using this term with reference to microbes in human bodies may create further distress for those who have been colonized, necessitating new language or terminology in infectious disease. The term coined by Derrida, *hostipitality*, provides the possibility of both hostility and hospitality with respect to people as well as pathogens. As such, it calls for us to become and remain occupationally conscious of biomedicine's colonial mindset of empire and geopolitical use of language and to bring about a shift from merely preventing death to embracing unconditional and conditional coexistence.

In closing, we revisit the epigraph that opened the article, with the infectious disease practitioner saying in effect to her Native American patient: *"Don't worry, it's just a colonizer."* One wonders what this patient would have said or done in response.

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Examining Antimicrobial Stewardship Program Implementation in Carceral Settings

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Abstract

Antimicrobial resistance is a global threat that inequitably affects minoritized populations, including Black, Latinx, and Indigenous people—especially in carceral settings—and is largely driven by inappropriate antimicrobial prescribing practices. People whose identities are minoritized are more likely to be incarcerated, and people who are incarcerated experience higher disease risk than people who are not incarcerated. This article draws on a case of dental infection suffered by a woman who is incarcerated to consider key ethical and clinical complexities of antimicrobial prescribing in carceral settings.

Antimicrobial Resistance in Carceral Settings

Antimicrobial-resistant (AMR) infections are an increasingly common cause of hospitalization and death, but programs preventing the development of antimicrobial resistance are incompletely implemented in low-resource health care settings.[1] Examples of such settings include carceral settings like jails and prisons, which have focused for several years on improving infection control for respiratory, viral, bloodborne, and foodborne pathogens through isolation, quarantine, and testing protocols,[2] but have devoted considerably less attention to preventing the emergence and decreasing the spread of AMR pathogens.

Given the intersection of poverty, mental illness, trauma, and racism, infectious disease epidemics and pandemics disproportionately take root in carceral settings where residents are already at increased risk for negative health outcomes. In one study of probationers and people recently released from prison in Connecticut, Black individuals reported a greater number of impacts of incarceration on their well-being than White individuals.[3] The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) is a clear example of the impacts of incarceration on the dissemination of AMR pathogens in minoritized communities. The first outbreak of MRSA was reported in 1968 at Boston City Hospital[4]—a safety-net hospital renowned for providing care to financially disadvantaged persons in the greater Boston area—and outbreaks of MRSA infection and MRSA colonization were reported nationally in carceral settings in the early 2000s.[5]

As a result, incarceration is viewed as a well-recognized risk factor for MRSA infection.[5,6,7,8,9,10,11]

Antimicrobial stewardship programs (ASPs) are evidence-based interventions designed to optimize antimicrobial usage and to decrease the emergence of new AMR pathogens while reducing harm caused by unnecessary antimicrobial use and improving patient outcomes.[12,13,14] The US Federal Bureau of Prisons, a system of 121 prisons housing about 200 000 people, developed and implemented an ASP program that led to a 26% decrease in antimicrobial use from fiscal year 2010 to fiscal year 2015.[15] Outside of this publication—and despite a federal rule requiring US hospitals that participate in Medicare or Medicaid to implement ASPs[16]—we know of no other published reports of jail, state prison, or federal efforts to implement ASP programs. Most of the 1.8 million individuals who are incarcerated in the United States[17] do not have stewardship programming to protect them against antimicrobial resistance.

Previous work by the fourth author (C.Y.) and colleagues has explicitly discussed the intersectionality of ethics and antimicrobial stewardship.[18] The goal of this paper is to utilize Beauchamp and Childress' 4 principles to assess ethical issues that arise in connection with stewardship of antibiotics in carceral settings. The 4 principles are (1) autonomy (having the ability to make one's own decisions independently of external control), (2) nonmaleficence (avoiding harm), (3) beneficence (conferring benefit to the patient), and (4) justice (making choices that focus on fair distribution to maximize the welfare of society). In particular, we want to reflect on the complexities of the term *justice*, especially in discussions of ethics and carceral health.

Carceral Settings and Ethics

To illustrate both the strengths and the limitations of the 4 principles framework, we will utilize a hypothetical patient scenario.

Case. Cynthia is a 45-year-old Black woman detained (pretrial) in jail who has faced barriers to routine dental cleanings and has a painful tooth. After finding that the tooth pulp is exposed and the tooth is not salvageable, the dentist in jail recommends the removal of the tooth. Cynthia is concerned because her cellmate had her teeth pulled and reported that the dentist did not give her enough pain medications. Cynthia asks for antimicrobials to treat the infection. When asked about allergies, Cynthia says that her mother told her she had a rash to penicillin as a child. She receives 14 days of clindamycin, and the pain improves with antimicrobials but returns after antimicrobial completion. Cynthia continues to decline tooth extraction and asks for a prolonged course of antimicrobials. She hopes to be out on bail soon and plans to get the tooth pulled after release. After 2 months of antimicrobial treatment, the jail clinician is conflicted as to whether to continue the antimicrobials.

Analysis. Dental infections are common in criminal-legal involved populations.[19,20] A short course (less than 5 days) of antimicrobials is recommended when treating limited odontogenic infections, although there is variation in dental prescribing patterns.[21] Dental extraction is widely accepted as the necessary procedure for a necrotic tooth, as it can be a nidus for extensive, life-threatening infection. This case brings up several important points.

First, the jail clinician wanted to respect Cynthia's autonomy by honoring her request for antimicrobials instead of tooth extraction, but how autonomous is Cynthia? Based on

Beauchamp and Childress' analysis, competence in the form of insight and capacity are essential to autonomy. Cynthia's explanation of why she is concerned about tooth extraction (and her request for antibiotics) demonstrates a reasonable understanding of her medical choices; she does not show any signs of incapacitated decision making; and her fears are consistent with those regularly expressed by patients experiencing incarceration in similar circumstances. Yet the oppression intrinsic to carceral systems is explicitly designed to limit autonomy and liberty, as evident in investigations of reproductive and transgender health injustices,[22,23] the findings of which can be extrapolated to other health care scenarios, such as the case above. In this case, Cynthia faces oppression in several ways. She has limited power to advocate for pain medications to make a necessary tooth extraction more comfortable. The stigma of her incarcerated identity has resulted in limited access to otherwise commonplace health care interventions like penicillin allergy de-labeling for optimal medical treatment. Her pretrial detainment in jail and her history of being unable to access dental care suggest that she cannot afford bail and has limited financial resources, leaving her exposed to financial exploitation. If she is housed in a for-profit facility, her ongoing detainment pretrial may even be generating revenue for those who own the jail. These kinds of oppression mean that though Cynthia may have the competence to make her own medical decisions, her range of and access to available choices is profoundly limited, as is typical of other patients experiencing incarceration.[23,24] As such, a jail clinician must acknowledge and accommodate the imperfect autonomy of a patient who is incarcerated. Shared decision making about treatment—and, in this case, the clinician's agreeing to provide Cynthia with antibiotics even if to do so is not the evidence-based course of action—is a sign that the clinician recognizes patients' limited autonomy. Prescribing antibiotics could thus foster greater trust.

Second, the benefits of honoring Cynthia's autonomy do come with the potential to engender harm. The clinician wants to alleviate Cynthia's suffering and to prevent further harm from delaying tooth extraction (eg, worsening abscess formation or further involvement of bone or other teeth) by administering antimicrobial therapy. But this option risks promoting *Clostridioides difficile*-associated colitis (a secondary infection precipitated by antimicrobial exposure), antibiotic-associated diarrhea, and other adverse effects, including the emergence of drug-resistant strains of pathogens. People who are incarcerated receive both hidden and direct messaging that treatment for the disease should be delayed until release.[24,25]

Third, Cynthia's report of a penicillin allergy highlights the harms faced by patients experiencing incarceration who have limited access to commonplace stewardship interventions such as penicillin allergy de-labeling that promote patient safety and optimize clinical care. Incorrectly reported penicillin allergies can lead to more expensive, less effective, and broader-spectrum antimicrobial prescriptions, and, as a result, penicillin de-labeling is a key component of ASPs, although there have been barriers to such programs' equitable implementation.[26,27,28] Those with penicillin allergies are also reported to have greater morbidity and mortality for a wide variety of infectious processes, including—but not limited to—bacterial pneumonia and bacteremia.[29,30] To our knowledge, penicillin allergy de-labeling is not routinely offered in carceral settings; however, there are validated systems to determine if people are at high, medium, or low risk that can assist in the evaluation of a patient with a reported drug allergy.[31]

In addition to facing barriers to penicillin allergy de-labeling as part of robust ASP programs, patients who are incarcerated unjustly face limited resources to maximize their outcomes because of logistical barriers of de-labeling and limited quick-return financial incentives.[32] One strategy in the community is a "watch-and-wait" approach to infections, wherein antimicrobials are prescribed but patients only take the medication if they get worse or antimicrobials are not prescribed but patients are encouraged to contact the clinician if they get worse. When we use a watch-and-wait approach in the community, we do so because there is relatively easy access for certain patients to health care. Patients who are incarcerated do not enjoy such access. Clinicians have limited hours, and most jails and prisons require a "sick slip" or written application for health care,[33] which is then reviewed by a nurse and potentially triaged to clinicians for evaluation. This process can take a lot of time, which can increase the risk of worsening infection. If departments of health and infectious disease organizations hope to leverage de-labeling and a watch-and-wait approach to avoid antibiotic resistance development, these programs must not continue to overlook carceral systems, which may be target areas for such programs.

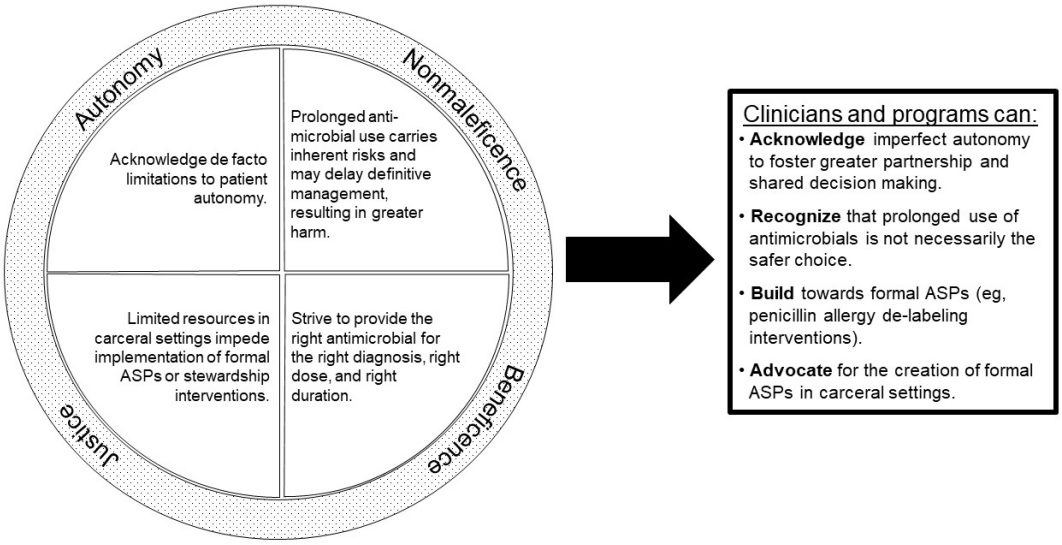
A fourth point is that prescribing medications in carceral settings represents a loaded interaction between patient and clinician. Even small interactions, like an antimicrobial prescription, can feel meaningful to someone who is incarcerated. People who are incarcerated may view the prescription as a token of trust and respect. Clinicians in the carceral setting may also see prescribing antimicrobials as a beneficent act of a compassionate physician-advocate that provides not simply medical help but emotional and psychological support to marginalized patients. In Cynthia's case, the clinician may be reluctant not to prescribe antimicrobials because of concerns that the dental infection might worsen and there would be no system for rapid evaluation. Prescribing antimicrobials in a questionable case like this is a reflective harm reduction strategy, given the prolonged period it takes for people who are incarcerated to access health care. Withholding antimicrobials can be seen by patients as a reflection of unjust practices rooted in inequitable societal, medical, and carceral practices. Further complicating the patient-clinician dynamic, some clinicians may see antimicrobial prescribing as personal protection; carceral settings are often highly litigious environments, and so prescribing antimicrobials "just in case" often represents the practice of defensive medicine. While it is a noble desire to address patient concerns with the medical tools available, having too low a threshold for prescribing antimicrobials is very often more harmful than beneficial, even while it might feel like doing something is kinder than doing nothing.

Next Steps

As clinicians working at the intersection of antimicrobial stewardship and health equity—with a specific interest in serving as advocates for incarcerated populations within the United States—we, the authors, ask ourselves: "Is an unnecessary antimicrobial prescription the best way to practice our advocacy and push against injustice?" The core ethical principles are helpful for dissecting and identifying how ethical issues are embedded in daily clinical interactions between clinicians working in carceral settings and their patients (see Figure). To continue to ignore conversations about antimicrobial prescribing in carceral settings violates core ethical principles of health care delivery to a vulnerable population. ASPs are needed in carceral settings to provide a best-practices framework that can balance concerns about the development of antimicrobial resistance and ensuring the highest level of evidence-based antimicrobial prescribing

and ensuring that both people who are incarcerated and clinicians working in carceral settings feel supported.

Figure. Applying Bioethical Principles to Antimicrobial Prescribing and Stewardship in Carceral Settings



Abbreviation: ASPs, antimicrobial stewardship programs.

Lack of ASPs in jails and prisons is likely related to several intertwined factors. Health care services in carceral settings are under-resourced for increasingly complex chronic care patients whose cost of care is also rising. While individuals who are incarcerated are among the very few populations in the United States with a constitutionally guaranteed right to health care,[34,35] there are no mandates for ASPs in carceral settings. *Estelle v Gamble* (1976)[36] ruled that correctional settings that failed to provide people who are incarcerated with medical care "reasonably commensurate with modern medical science" was a violation of the Eighth Amendment and set the standard to prevent "deliberate indifference" to the harm caused by lack of provision of health care to people in jails and prisons. The prescription of unnecessary antibiotics with potential risks of side effects or multidrug-resistant infection, we believe, does not clearly qualify as "deliberate indifference." Indeed, we maintain that these decisions are not indifferent to the patient's goals and desires but deliberately working to address them. Yet the broader community, a group that does not have the same identified constitutional right to health care, may ultimately face the consequences of increasing antimicrobial resistance that stems from the health care challenges within carceral settings outlined above. Another reason for the lack of ASPs in carceral settings is that, without clear accreditation standards, carceral facilities do not have the same incentives as health care facilities to identify and prevent drug resistance. Moreover, political stakeholders may be unwilling to provide any investment in quality improvement in carceral health care facilities due to stigma against individuals with criminal-legal exposure, who are often stigmatized and marginalized in other ways due to mental health conditions, addiction, poverty, or being a person of color.

Critical next steps include cross-disciplinary participation in creating ASP programs in carceral settings. Stakeholders can include specialists in ASP implementation, carceral

health care professionals, jail or prison administrators, and national health care accreditation organizations. As ASPs are implemented, it behooves the interdisciplinary team to proactively consider how such programs can help guide ethically challenging patient conversations in ways that ensure minimizing development of antimicrobial resistance while also ensuring that patients feel supported. Given the porous nature of jails and prisons, ASPs have the potential to decrease community transmission of AMR pathogens. They may also offer the potential to provide higher-quality, more cost-effective care to vulnerable patients, similar to ASP programs in other health care settings.[37,38]

Implementation of ASPs in jails and prisons, however, is a short-term solution to help improve the conditions of confinement. In parallel, we support legislative and policy reforms that seek to address and reverse the harms of incarceration. Preventing people from being incarcerated through improved access to housing, food, job opportunities, and mental health treatment without involving the carceral or judicial system should be the ultimate goal.

Implementing ASPs in carceral systems would be not only an impetus for greater equity and access to care in the carceral system, but also an act to fight the injustice of disproportionate harm to patients in carceral settings from inappropriate prescribing, to decrease the spread of AMR organisms, and to work around the dearth of advocates within carceral health care fighting for change. To best support patients like Cynthia, prevent community spread of resistant infections, and ensure high-quality care to a vulnerable population, ASP programs must go to jail.

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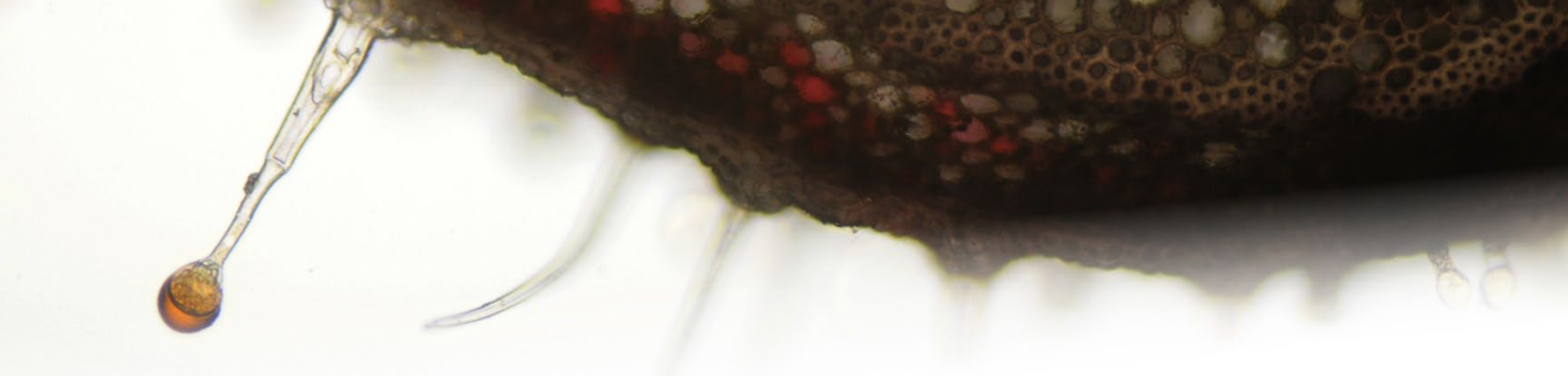

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HISTORY OF MEDICINE: PEER-REVIEWED ARTICLE

A Brief History of Antimicrobial Resistance

Devin Hunt and Olivia S. Kates, MD, MA

Abstract

Despite mounting attention in recent years, health threats posed by antimicrobial resistance are not new. Antimicrobial resistance has dogged infectious disease treatment processes since the first modern antimicrobials were discovered.

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An Evolutionary Arms Race

When recounting the history of medicine, few triumphs compare to the emergence and widespread use of antimicrobials. Alexander Fleming's serendipitous discovery of penicillin on his petri dish[1] brought about a new era in biomedicine. Suddenly, pathogens that had wreaked havoc for generations—spreading untold morbidity and mortality in their wake—were at the mercy of our chemical armamentarium. Seemingly overnight, infectious diseases receded before the ever-rising tide of antimicrobials, and optimistic observers in the United States and Europe predicted a swift and righteous victory over the scourge of infection.

Of course, such a victory was not achieved. Antibiotics are derived from the evolutionary arms race between microbes and their ecological competitors (fellow microbes, fungi, plants, and animals), and, as a result, the emergence of resistance is entirely predictable. As swiftly as we claimed new victories, microbes began evading our latest weapons, altering their cell walls, upregulating drug efflux systems, and dismantling and detoxifying our new wonder drugs.[2,3]

This story of innovation and setbacks is as old as time, familiar to anyone who works with pathogens, cares for patients, or develops new drugs. It begins with the early investigators and innovators who first recruited naturally occurring and synthetic chemicals in the fight against infectious diseases, and it continues toward an uncertain future.

Humans Harness Modern Antimicrobials

In 1907, Paul Ehrlich, a German physician-scientist, delivered a lecture to the Royal Institute of Public Health in London on the effect of aminophenylarsenic acid on

trypanosomes (a type of single-cell parasite).[4] In his address, Ehrlich detailed the synthesis of arsenicals, or arsenic-derived compounds, and their selective toxicity in treating sleeping sickness. In a moment of prescience, Ehrlich noted that while these medicines were remarkably successful in controlling the disease in mice, resistance to these compounds could be cultivated, passed on to new generations of trypanosomes, and maintained after sustained treatment. Despite this forewarning of the difficulties to come, the first battle in the war against infectious diseases had been won. The race to develop more of these compounds had begun.

It is perhaps the closest thing to a modern biomedical fairytale: Fleming's plates of *Staphylococci* exposed to the air during laboratory work were contaminated by a mold and began to die.[1] The 1929 discovery and isolation of penicillin ushered in a new era of biomedical research and discovery. Penicillin's potency and limited side effects in humans—especially when compared to contemporaneous chemical antiseptics, such as carbolic acid—led to its immediate recognition as a potential topical and systemic treatment for pyogenic infections. Its use as a selective agent in bacterial culture media also allowed for the reliable isolation of penicillin-tolerant microorganisms for the purposes of diagnosis and scientific research.[5]

Early Uses of Penicillin

Unsurprisingly, Fleming's work was recognized by antimicrobial researchers for its revolutionary potential. At Oxford, a team assembled by Howard Florey and Ernst Chain set out to isolate penicillin and assess its antimicrobial effects. In 1940, Florey's team published its study of the efficacy of penicillin *in vivo*. The effect of this new wonder drug could not be understated: among mice infected with relevant human pathogens, all untreated animals succumbed to their infections within 10 days, but those treated with penicillin had dramatically improved survival rates.[6] With the knowledge that penicillin was both efficacious and well tolerated in mice, Florey's team set its sights on human trials.

In 1940, a 43-year-old police officer, Albert Alexander, was admitted to the Radcliffe Infirmary at Oxford for an infection of the face, scalp, and orbits. He was treated with first-generation sulfonamide antibacterials; however, over several months, his condition continued to worsen. On February 12, 1941, Florey's team started an infusion of penicillin and saw rapid clinical improvement. Unfortunately, by the fifth day the supply of penicillin had been exhausted, and Alexander's clinical status again began to decline. On March 15, 1941, Alexander succumbed to his infection. His autopsy indicated staphylococcal infection and osteomyelitis as the cause of death.[7]

The first use of Fleming's wonder drug was a disappointment. Despite efficacy in mice, tolerability in humans, and transient improvement in the patient's infection during treatment, there simply was not enough supply to meet the needs for effective, curative dosing and duration in a human patient. Scarcity—not lack of efficacy—led to the failure of the first therapeutic regimen of penicillin.

Florey's team, however, was undeterred. In the same report published in 1941, Florey's team detailed remarkable advances in the ability to purify, concentrate, and deploy penicillin at therapeutic doses. Florey's team had determined that, after intravenous administration, penicillin was excreted in the patients' urine. This penicillin could then be recovered, purified, and reinfused, momentarily overcoming the problem of scarcity. With the ability to essentially recycle penicillin and maintain bacteriostatic

concentrations of penicillin in the blood, clinical outcomes improved, and patients began to be cured of penicillin-susceptible infections.[7] While barriers to the widespread use of the drug—scarcity, access, and deployment—remained, the first true superweapon in the fight against infectious diseases had emerged.

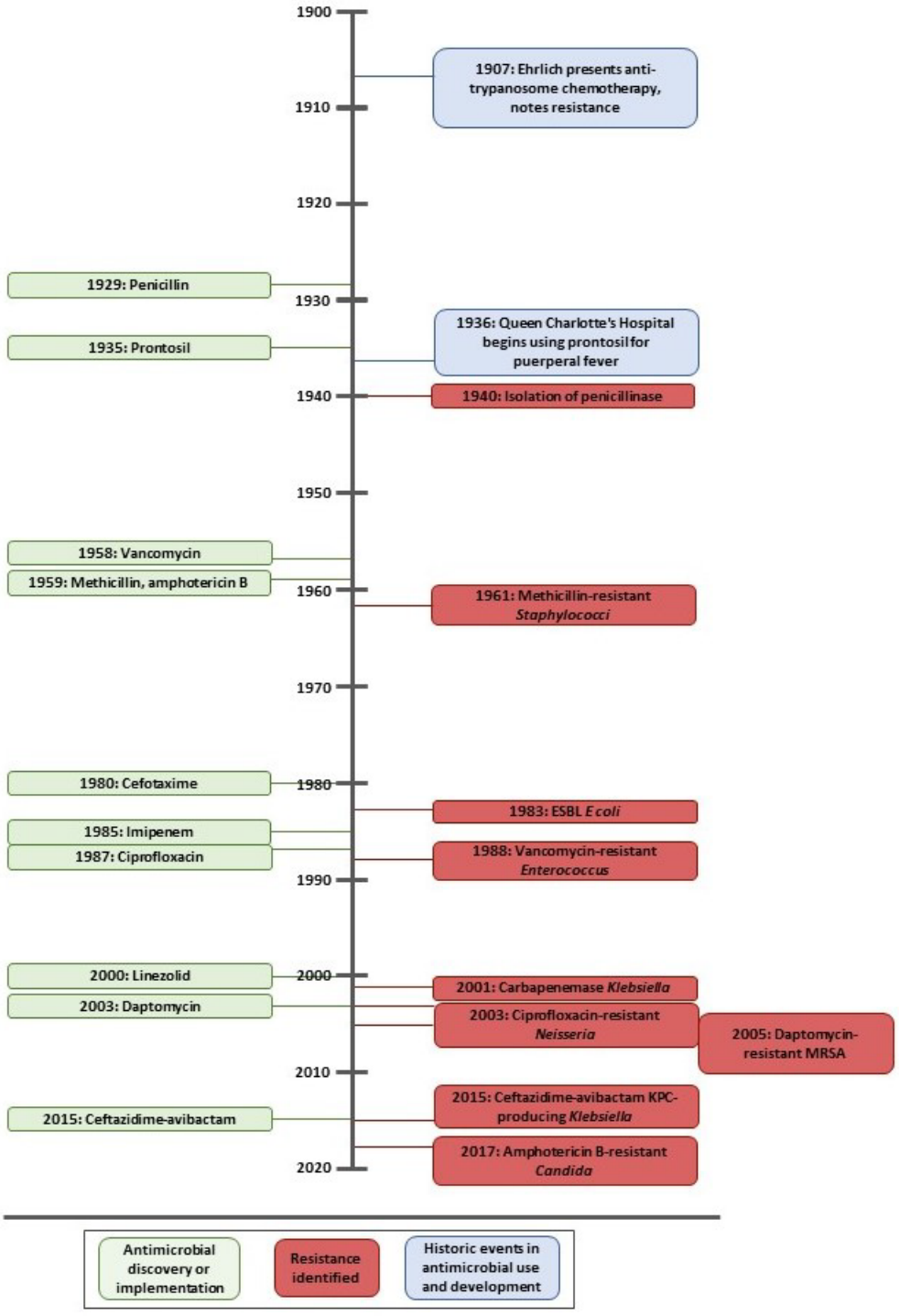
Resistance Evolves

As soon as this new antimicrobial was discovered—and even before the successful treatment of patients at the Radcliffe Infirmary in London—researchers were beset with the problem of resistance. In a 1940 letter to the editor of *Nature*, Oxford biochemists Edward Abraham and Chain reported a startling discovery: an enzyme isolated from penicillin-insensitive *Escherichia coli* could break down penicillin and hamper its bacteriolytic functions.[8] Researchers next sought to understand how resistance developed and whether the antimicrobials themselves played a role in their own inconsistent or waning efficacy. Milislav Demerec demonstrated that antibacterial resistance arose spontaneously in bacterial cultures as a function of random genetic mutations, although the mutations themselves were not a direct result of antibiotic exposure. However, exposure to antibiotics selected for resistant bacterial strains and allowed them to persist.[9]

Antimicrobials in the Modern Era

The decades following the implementation of penicillin saw incredible research and innovation in the field of antimicrobials.[10] An escalating cycle of discovery, implementation, and emergence of resistance drove the development of new classes of antibacterials, including the modified beta-lactams, cephalosporins, fluoroquinolones, and aminoglycosides still used today (see Figure). Despite the emergence of resistance to new antibacterials, scientists and pharmaceutical companies were generally able to keep pace through the mid-20th century, deriving new compounds from natural products and modifying them to suit clinical needs.

Figure. Key Events in Antimicrobial Discovery and Resistance



Data sources: Fleming A[1]; Erlich P[4]; Abraham EP, Chain E[8]; Colebrook L, Kenny M[11]; Little JS, Dedrick RM, Freeman KG, et al[12]; Schooley RT, Biswas B, Gill JJ, et al[13]; Barber M[14]; Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S[15]; Leclercq R, Derlot E, Duval J, Courvalin P[16]; Yigit H, Queenan AM, Anderson GJ, et al[17]; Fenton KA, Ison C, Johnson AP, et al; GRASP collaboration[18]; Mangili A, Bica I, Snydman DR, Hamer DH[19]; Humphries RM, Yang S, Hemarajata P, et al[20]; Lockhart SR, Etienne KA, Vallabhaneni S, et al.[21]
Abbreviations: ESBL, extended spectrum beta-lactamase; *E coli*, *Escherichia coli*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Against this backdrop of innovation and resistance, antimicrobials found another application: agriculture. With the rise of industrial farming, animals were kept in increasingly crowded and often unsanitary conditions, and antimicrobials were utilized prophylactically in livestock to increase growth rates and prevent illness.[22,23] Unlike in the clinical setting, in agriculture the use of antimicrobials is not subject to the same oversight or guidelines for prescribing. The lack of consistent regulation permits wide variation in terms of the classes and concentrations of antimicrobials used in agriculture. Often, livestock are given subtherapeutic doses of antibacterials, which creates an environment of selective pressure that fosters emergence of resistance among the bacteria in the animals' bodies.[23] Despite early research indicating the potential for antimicrobial resistance to spread from bacteria in livestock to bacteria in human hosts,[24] the use of clinically important antimicrobials in agriculture persists into the present, and demand for meat continues to rise. In 2021, an estimated 54% of the 11 million kilograms of antimicrobials sold for use in domestic agriculture in the United States belonged to the "medically important" category.[25]

While widespread use of antimicrobials in both health care and agricultural settings created an environment for resistance to flourish, the discovery of new antibiotics slowed.[26] Soon enough, antimicrobial drug development began to clash with the realities of an economic system predicated on supply and demand.[27] As death rates from cancer and heart disease rose to replace deaths from infectious diseases, pharmaceutical companies faced slimmer economic margins for developing new anti-infectives. The rate of discovery of new antibiotics slowed, and those few specialized drugs that were developed to overcome antimicrobial resistance (eg, carbapenems, lipopeptides, oxazolidinones, novel tetracyclines, and novel beta-lactam/beta-lactamase inhibitor combinations) were expensive to use.[28] With the latest antimicrobials often only available in highly resourced settings, low- and middle-income countries (LMICs) face a disproportionate burden of antimicrobial resistance and associated deaths. An antimicrobial resistance research group estimated that 1.27 million deaths globally in 2019, including over a million in LMICs, were attributable to antimicrobial-resistant bacteria.[29] If the affected individuals had had the same type of infection but with an antimicrobial-susceptible pathogen, they would have survived.

Mycobacteria, Retroviruses, and Fungi

Typical bacteria like streptococci or *Escheria coli* are neither the only pathogens to be targeted by antimicrobials nor the only ones able to evade those antimicrobials through development of resistance. In fact, the cycle of discovery and resistance has occurred and continues in every area of infectious disease medicine, driven by microbial evolution, human behavior, and market forces that dictate drug development and dissemination.

The first effective anti-tuberculosis drug, streptomycin, was discovered shortly after penicillin. Selman Waksman won a Nobel Prize for systematic research into antimicrobials produced by soil bacteria, culminating in the discovery of streptomycin.[30] This history is complicated by the conflicting perspective of graduate student Albert Schatz, who made significant contributions to the discovery of streptomycin but had been persuaded to sign away his rights to patents or royalties before suing to have these restored.[31]

The next chapter in anti-tuberculosis drug discovery is perhaps more collegial. In 1951, 3 drug companies reported the almost simultaneous discovery that the compound

isoniazid was able to kill *Mycobacterium tuberculosis*.[32] None of these companies would receive a patent for their "new" drug, however. Two doctoral candidates in Czechoslovakia (now the Czech Republic) had already published, back in 1912, a method for producing isoniazid as an example of organic chemical synthesis, completely unaware that it would become a cornerstone of tuberculosis treatment. With industry researchers unable to lay claim to the drug as a "novel invention," multiple companies took up production of isoniazid, resulting in lower costs and easier dissemination.[33]

But strains of *Mycobacterium tuberculosis* quickly developed resistance to either drug, streptomycin or isoniazid, when used alone. Even when used in combination with each other and with other anti-tuberculosis medications, *Mycobacterium tuberculosis* has proved a challenging target. When researchers began studying drug-resistant tuberculosis, they hypothesized that resistance mutations would make the mycobacterium less fit and less able to spread, limiting drug resistance to treatment-experienced patients.[34] But they soon discovered that drug-resistant tuberculosis not only develops in patients receiving partial or sporadic tuberculosis treatment but also spreads, resistance intact, to others. In 2012, nearly 4% of new tuberculosis infections were already resistant to isoniazid *and* rifampicin, the 2 most important drugs for treatment.[35] The rate is as high as 20% in Eastern Europe and Central Asia, while the rates may be underestimated in parts of Africa and the Middle East due to missing data and barriers to comprehensive laboratory assessment for drug-resistant tuberculosis.[35]

Person-to-person spread of drug-resistant tuberculosis was first described in the context of another infectious disease, human immunodeficiency virus (HIV). In the early 1990s in New York City, public health officials observed an increase in the prevalence of drug-resistant tuberculosis, particularly in patients with HIV, even in the absence of prior treatment.[36] They hypothesized that close networks of patients with overlapping risk factors for HIV and tuberculosis, as well as impaired immune function leading to more severe, rapidly progressive tuberculosis infections, might explain these findings.[36]

The first antiretroviral drug to treat HIV—zidovudine, or AZT—was approved in 1987.[37] Treatment with AZT provided little reprieve in the HIV epidemic, however, because the same story of antimicrobial resistance played out for antiretrovirals as had for anti-tuberculosis drugs: first discovery, then resistance, then discovery again, leading to combination therapy. Durable suppression of HIV became possible with the use of triple-drug therapy after 1995, and newer options continue to offer durable suppression with fewer side effects and simpler regimens adapted to individual patients' needs and preferences. But despite a growing number of options and a greatly improved understanding of HIV viral dynamics, drug resistance remains a challenge for many patients who lived through the early days of less effective antiretroviral therapies or for patients who have experienced sporadic or incomplete treatment.[38] As with antibacterial resistance and anti-tuberculosis drug resistance, antiretroviral resistance disproportionately affects people living in LMICs, where HIV is more prevalent and where reliable access to the latest treatments (as well as tools for diagnosis, monitoring, and detecting resistance) depends on global resource sharing as well as economic and infrastructure development.[39]

As with HIV and tuberculosis, patients with compromised immune systems who deal with more severe or prolonged infections are at increased risk for antimicrobial resistance. Patients with compromised immune systems due to cancer, organ transplantation, HIV, or other conditions bear the greatest burden from serious infections due to fungi. Like

humans, fungi are eukaryotes, meaning they rely on similar cellular machinery for survival and growth. For antifungals to be clinically useful, they must target factors unique to fungi and absent in or nonessential to human cells to avoid off-target toxicity in the patient being treated.[40] This narrow set of therapeutic targets contributed—and continues to contribute—to the relative lack of antifungals. Emergence of resistance to even one class of antifungals, where alternatives are limited, can have devastating consequences for patients with serious fungal infections.[40]

A Future of Antimicrobial Resistance

Antimicrobial resistance is a pressing threat to global health. The unifying themes across pathogen types are clear: the discovery of antimicrobials has driven down mortality from infectious diseases, including bacteria, fungi, mycobacteria, and viruses. Pathogens undergo mutations that, with the selective pressure from exposure to antimicrobials, lead to emergence and persistence of antimicrobial resistance. Where the burden of infection is greatest—whether because of compromised immunity or geopolitical forces—and where access to antimicrobials is inconsistent or unstable, resistance thrives. As a result, our victories against death from infectious diseases are inequitably distributed and tenuous.

Beyond the ethical and moral imperatives to reduce suffering and disease, the COVID-19 pandemic has illustrated that infectious threats *anywhere* are infectious threats *everywhere* and that one threat (a virus) can have downstream implications for a wide range of infectious diseases and their treatments.[41] Colonial-era mentalities regarding borders and the segregation of illness and poverty are incongruent with the reality of antimicrobial resistance as a global health threat. Preserving past successes and advancing our battle against infectious diseases requires continued discovery, novel therapeutics, improved global health infrastructure, and robust collaborations among stakeholders in the antimicrobial development process. We must act now to ensure that the wonder drugs of yesteryear remain viable options for treating the patients of today and to ensure that the wonder drugs of tomorrow will be available worldwide, wherever they are needed most.

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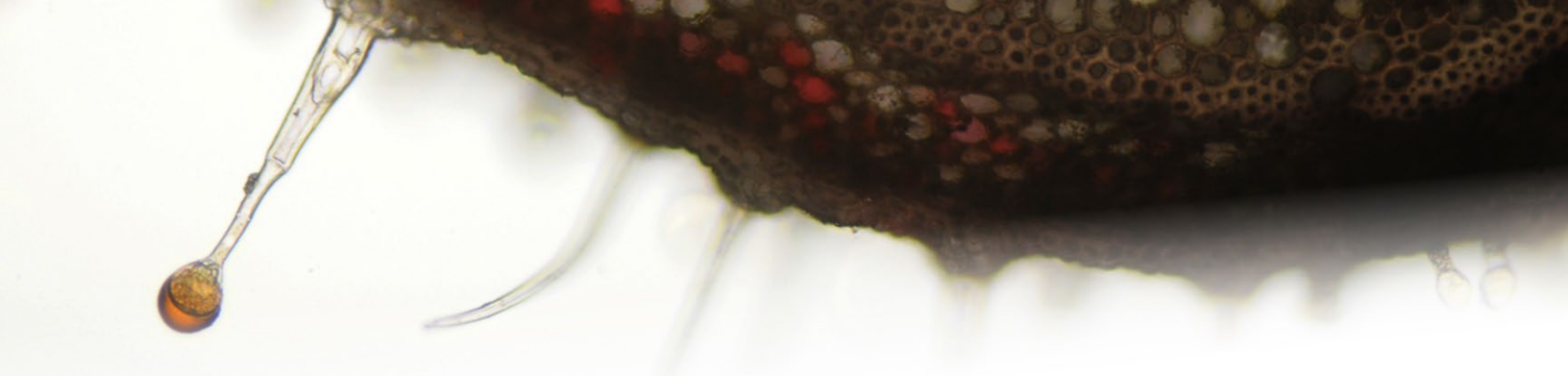

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HISTORY OF MEDICINE: PEER-REVIEWED ARTICLE

Why We Should Reexamine the "Golden Age" of Antibiotics in Social Context

Karen M. Meagher, PhD

Abstract

Economics is the primary discipline used to understand supply chain design, scale-up, and management. For example, antibiotics can be compared to other forms of "tragedy of the commons," whereby a common good (effective treatment of infections) is jeopardized by individual consumption and lack of community oversight and stewardship. While economic analysis can explain innovation decline in terms of market failure, one pitfall of an early-stage focus on research and development is a failure to challenge the discovery narrative. Ethics also has a distinct place in helping us envision alternatives to what markets can produce. This article advances a more contextualized view of how science and technology policy has shaped antibiotic supply chains over many years, emphasizing how shifting the story we tell about past successes is central to securing a reliable antibiotic supply chain in the future.

Effectiveness Paradox

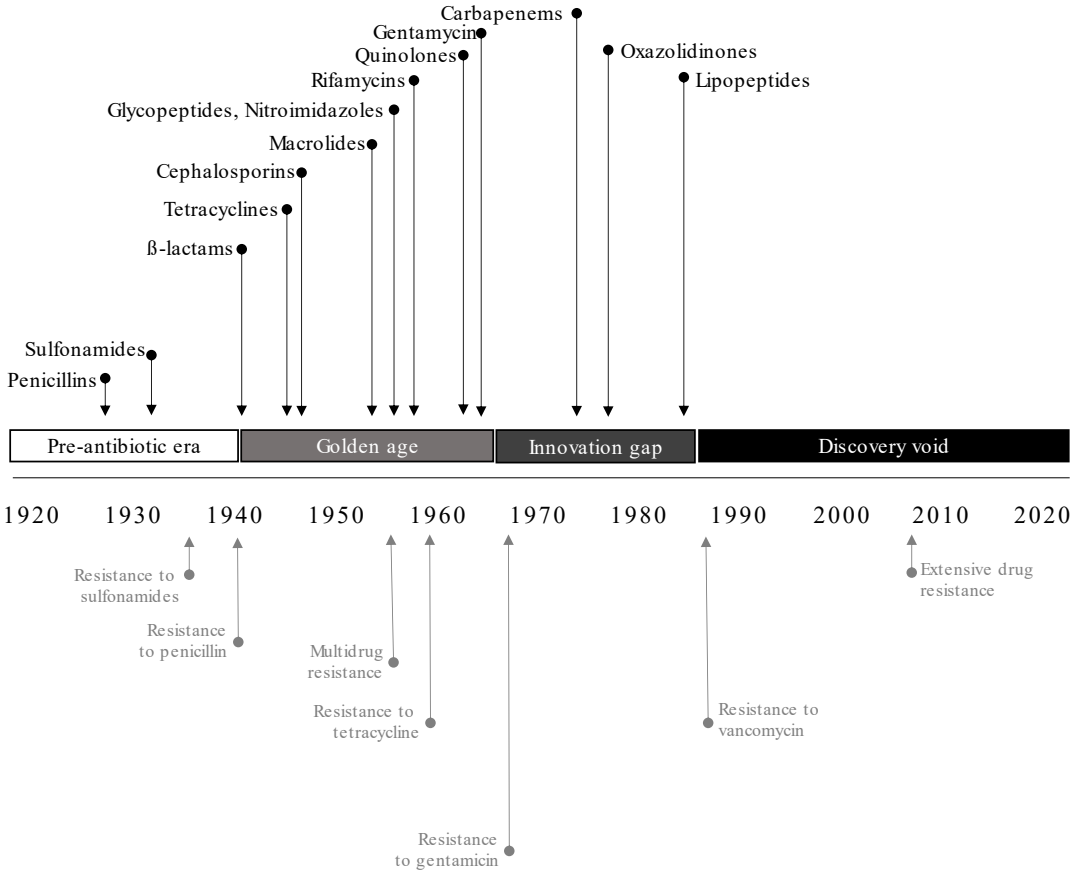
Antimicrobials are treatments for microbial infections caused by bacteria, viruses, and fungi. Antibiotics are medicines especially used to treat bacterial infections. Penicillin was the first antibiotic and effective treatment developed for bacterial infections encompassing pneumonia, gonorrhea, and rheumatic fever.[1] Penicillin's reduction in human suffering is neither qualitatively nor quantitatively simple to capture, but the medicine has saved millions of lives and improved human life expectancy for many. However, antibiotics present an "effectiveness paradox": the more they are used, the less effective they become. Repeat exposure of bacteria to an antibiotic can generate the conditions that select for resistance, or the capacity of colonies to survive despite treatment. One recent study estimated that over 1.27 million deaths in 2019 were attributable to bacterial antimicrobial-resistant infections.[2] As antibiotic resistance is increasing globally, so, too, is demand for last-resort medicines that can effectively treat resistant infections.[3] The effectiveness paradox can be compared to other forms of "tragedy of the commons," whereby a common good (eg, effective treatment of infections) can be jeopardized by individual consumption.[4] However, as Hardin recognized, ethics has a distinct place in helping us envision alternatives to the tragedy of the commons.[5] This article advances a more contextualized view of how value-driven

science and technology policy has shaped antibiotic supply chains over the years,[6] emphasizing how the story we tell about past success is central to securing access to antibiotics in the future.

A Story of Antimicrobial Innovation

The sheer magnitude of lives saved by antibiotics is a staggering public health, medical, and humanitarian achievement. It is unsurprising, then, that the advent of antibiotics is among the historical developments that have the hallmarks of heroic stories. The discovery narrative is linear, simple, and marked by regular innovations of distinctive scientific personalities. Commonly depicted along a timeline, the 1950s to 1970s period of antibiotic development is often referred to as the "golden age" of antibiotics (see Figure).[7,8]

Figure. Dominant Narrative of Antibiotic Discovery



Data sources: Iskandar K, Murugaiyan J, Hammoudi Halat D, et al[7]; Silver LL[8]; Ventola CL[9]; National Research Council[10]; Davies J, Davies D[11]; Rahman MM, Alam Tumpa MA, Zehravi M, et al.[12]

The discovery narrative is in keeping with Paul De Kruif's depiction of big scientific personalities as primary enactors of scientific achievement, which he chronicled in his 1926 influential book, *Microbe Hunters*.[13] De Kruif focused on microbiologists of the 19th century, and his account is one of steady progress: "it is sure as the sun following the dawn of tomorrow, that the high deeds of microbe hunters have not come to an end; there will be others to fashion magic bullets."[13] Independently of who merits credit for the achievement of identifying penicillin's medical utility and refining its production,

Alexander Fleming's ability to fit within the discovery narrative might partly explain the messy media storm that characterized him as the sole scientific genius who revolutionized medicine with penicillin.[14,15] In contrast, Howard Florey's more reserved personality and his team's collective efforts to purify and test the effectiveness of penicillin at the University of Oxford garnered much less public attention and received delayed recognition.[15]

Diverging from De Kruif's vision of steady progress, contemporary drug development is frequently depicted as an era of a "discovery void" following an "innovation gap" in which new antibiotic drug development petered out in the 1980s and 1990s (see Figure). The same timeline of bygone halcyon days followed by a fallow period has been presented across popular media, pharmacology, microbiology, and policy.[7,8,9,10,11,16] The failure of the 21st century to live up to the promise of progress clashes with a protagonist-driven account of how scientific success occurs. For antibiotics, the oft-unexamined link between discovery and scientific heroism is so tight that, for the last decade, the phase following the "lean years" on timelines has been depicted as one of "disenchantment,"—a future that is oddly anachronistic, given that it is often explicitly depicted as a post-antibiotic return to the 1800s and the time of Semmelweis, a physician from 200 years ago with no antibiotic armamentarium except his (widely ignored) advocacy of hand hygiene.[11,12] It is notable that within the discovery narrative, there is little examination of how scientific heroism accords with a profit motive. (See Supplementary Appendix on economic concepts related to antibiotic resistance.) This lacuna in the dominant narrative of penicillin is especially striking, as patent debates marked disagreements within the scientific community from the very beginning.[17] Timelines like those in the Figure demonstrate how discovery narratives continue to shape popular understanding of how science progresses. Gaps in our understanding of what drives functional antibiotic supply chains are partly due to this tendency to decouple the history of science from its social and political context.

Some turn to economics to account for the contrast between antibiotics' profound contributions to human well-being and the current period of innovation stagnation, seeking a solution to the tragedy of the commons in a market-driven pricing model.[18] It has long been widely recognized that markets confront serious limitations in their ability to supply medical services efficiently.[19] Antibiotic market failures that lead to the detriment of social well-being are depicted as "deviations" from ideal economic market dynamics that concern only 2 parties (producers and consumers) and a range of stipulated conditions that enable markets to efficiently meet consumer needs. More specifically, economic analyses emphasize how, since the 1970s, the lack of landmark antibiotic discoveries is due to sudden or newly emerging market failures such as lack of large profit margins (when compared to treatment for chronic diseases), price deviations from social value, and stewardship practices that undermine sales by volume.[20] A perception that market incentives for antibiotics are misaligned has led to developments such as CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), a nonprofit organization that funds preclinical and early phase novel antimicrobial research.[21]

Economics does provide one way to understand the market failures that contribute to a paucity of innovation and can be consonant with ethical perspectives.[22] Antibiotic resistance is a prime example of an externality that contributes to market failure: a cost borne by society as a whole as infections become more difficult to treat. Industrialized agriculture pollution of waterways that results in antibiotic resistance is another form of

externality.[23] However, lumping together many structural failures under the label of "externalities" can conflate the value of antibiotics as prevention and treatment, obfuscate the responsibilities of states to protect public health, and evade identification of social structures that supply goods in ways that go beyond consumer satisfaction and efficiency (eg, equitably and sustainably). Other examples of market failure in antibiotic supply include monopoly (oligopoly) power of biopharmaceutical companies, which is sustained by high up-front innovation costs and control over manufacturing processes that leads to noncompetitive drug pricing and inadequate geographic dispersion of production capacity and supply chains.

In the next section, I explore how redirecting attention to science and technology policy provides a more comprehensive account of our past than economic explanations of market failure consonant with the discovery narrative's focus on early-stage antibiotic research and development. I also discuss obstacles to policy change and recommended policies for moving forward.

Early Antimicrobial Production and Distribution

It was not only novel discoveries but also innovative approaches to science, technology, and health policy that rendered penicillin effective, available, and accessible both during and after the Second World War. For a short but incredibly intense period in the 1940s, the US government scaled penicillin production by modifying policies on trade secrets, property rights, antitrust regulations, and drug licensure.[5,13,14] The US War Production Board (WPD) broke down the barriers of trade secrets by creating consortia of private companies, academic partners, and government agencies whose members were incentivized to share and develop industry-wide best practices for antibiotic quality and scalable production. Moreover, in contrast to the narrative of scientific heroism, it was highly collaborative cross-industry and multinational structures that led to rapid innovation and scaling up of manufacturing.[5] This section provides an overview of how functional antibiotic supply for some populations was previously achieved through strategic national objectives combined with shifts in domestic and global policy encompassing science, trade, and humanitarianism.

Strategic national objectives. During the Second World War, the US government's compelling interest was to prevent and treat infections of Armed Services personnel on the front line. The WPD consortium increased penicillin supply in part by creatively utilizing American farmers' know-how and existing resources. For example, an agricultural research laboratory in Peoria, Illinois, helped adapt deep fermentation processes using corn-steep liquor to increase the penicillin content in each production batch.[24] Meanwhile, in the United Kingdom, penicillin was such a precious resource that its use was restricted to objectives integral to the war effort. In 1941, Florey himself provided some doses to veterinarians addressing mastitis infections in cows; dairy farms were crucial to a populace whose diets were severely limited by international shortages.[25]

Domestic trade policy. Notably, intellectual property policies were also rearranged to support domestic penicillin development and manufacturing scale-up. Scientists in the Oxford group disagreed about the wisdom and ethics of obtaining a patent, including about whether products as opposed to processes could be considered intellectual property. Such disagreements are especially pertinent to bioethics, as it was an ethical obligation to serve humanity that shaped Florey's decision not to patent the Oxford team's process for producing penicillin.[13,14] Meanwhile, most US process patents were

held by the US Department of Agriculture and widely licensed without royalties. Quinn contends that it was the absence of product patents that enabled commercial pharmaceutical companies to create novel reciprocal licensing arrangements, engage collaboratively in ways that were far superior to competitive research and development, and share information more effectively.[5] With scientific cooperation surreptitiously hidden from Nazi occupying forces, a distinct Netherlands research group refined its own process. After the war, the group's separate patent led to both more supply and lower prices.[13]

Global trade policy. During the postwar era, antibiotic availability was driven by other global policy shifts that sought to recognize the distinctive global value of antibiotics. US intellectual property arrangements may have supported scalability to meet needs within the Global North, but access in the Global South still lagged. The 1970 Indian Patents Act reshaped drug manufacturing globally, in part by abolishing product-based drug patents, enabling generic versions of drugs to be produced through reverse engineering of pharmaceuticals in India.[26] Antibiotics have also been at the center of determining international implications of the rule of law. For example, India, Iran, and the Philippines filed suit against Pfizer for violation of the Sherman Act by establishing monopoly practices. In 1978, in *Pfizer, Inc v Government of India,* the US Supreme Court recognized the status of sovereign nations to sue under US domestic law.[27] India's subsequent rapid development of pharmaceutical manufacturing, combined with a US regulatory abbreviated new drug application process in the 1980s, allowed Indian manufacturers to avoid repeating clinical trials or marketing comparable generics in the United States, resulting in India becoming a current leader in world antibiotic manufacturing and the United States becoming the largest importer of their antibiotic exports.[26]

Global health policy. Because antibiotics are lifesaving, ensuring access to them has been a high priority in global health policy. However, global access to antibiotics is highly variable and fragile,[27,28,29] both with and without a prescription.[30] The World Health Organization (WHO) included antibiotics on its essential medicines list (EML) for the first time in 1977.[31] Although the WHO definition of essential medicines and its processes for listing medicines has changed over time, by 2002 the EML prioritized infectious disease health needs and articulated adequate antibiotic supply as a criterion of functional national health systems.[32] More recently, the WHO has proposed categorizing antibiotics on the essential medicines list as Access, Watch, or Reserve, depending on their lifesaving potential and likelihood of generating resistance.[33]

Many of the economic strategies suggested by a discovery void narrative rely on leveraging policy to serve economic goals. Conversely, economics can be a tool by which we ascertain how well we are achieving antibiotic clinical and stewardship goals (eg, monitoring WHO Access-Watch-Reserve antibiotics). For example, Orubu and colleagues identified 16 indicators across the antibiotic supply chain that can be used to assess national capacity to ensure population access to antibiotics and mitigate inappropriate use, in part due to dispensaries outside the control of pharmacists.[34] They found that over half of the licenses for antibiotic products in Bangladesh belonged to the WHO Watch group rather than the Access group; the authors contend that the proportion of licensed WHO Watch antibiotics on the market provides one way to measure misuse of antibiotics that might be replaced by treatment options with fewer risks of producing resistance.[34]

Moving Forward

Current policy interventions for mitigating the rise of antibiotic resistance are wide-ranging, including price controls, taxation, improved surveillance, legal reform, health services infrastructure investment, public and expert educational initiatives, pharmacy guidance, and regulatory oversight of agricultural or human use.[35,36,37] Bioethics and social science have also offered a variety of contributions that draw on economic, anthropological, sociological, historical, and normative approaches.[25,38,39,40,41,42,43,44] These discourses share the insight that the drivers of resistance are sufficiently complex that coordinated policy solutions that cross national and geographic boundaries are needed.[45,46] As the Bangladeshi study demonstrates, attending to policy and socio-behavioral dynamics of antibiotic resistance also redirects attention to the evidence base for stewarding antibiotics, including both facilitators and barriers.[47,48,49] Collaborative effort could leverage multidisciplinary insights, with cultural analysis[50] and ethical analysis helping to identify values reflected in policy alternatives, values-based attitudes of stakeholders, and justificatory grounds of policy change. The resources listed in the Table focus specifically on policies that can improve antibiotic supply and distribution. These resources provide initial insight into formulating multidisciplinary research questions that can advance more contextualized approaches to antibiotic supply chain policy.

Table. Contextualized Approach to Antibiotic Supply Chain Improvement

Source	Policy interventions	Values	Stakeholders
Afari-Asiedu[a] (2022)[51]	• Improving antibiotic dispensing practices in community pharmacies through: - Education - Practice guidelines - Local consensus process - Distribution of supplies - Performance monitoring	• Engagement • Ownership over the process • Stakeholder buy-in • Sustainable interventions	• International organizations • Health system personnel • Professional associations • Academics • Health trainees • OTC medical sellers associations
Kamere (2023)[52]	• Quality assurance processes • Investment in transportation and distribution systems • Accurate forecasting of needs	• Strong and secure supply chains • Access lifesaving therapies • Constant availability	• National organizations • Regional alliances • Local community programs and committees • Pharmacists
Mendelson[a] (2016)[53]	• Integrated community case management • Sharing task of prescribing • Health systems strengthening	• Access • Equity • Human rights	• Physicians • Pharmacists • Patients • Health leaders • Policy makers
Frid-Nielsen (2019)[38]	• Integrating social science AMR research into scientific discourse	• Integration of relevant multidisciplinary discourse • Collaboration • New forms of epistemic community	• Researchers • Policy makers • Patients • Clinicians

Smith (2020)[22]	• Decoupling profitability and sales volume • Intervening in failed markets	• Affordability • Long-term sustainability • Reducing reliance on antibiotics • Distributive justice	• Farmers • Veterinarians • Doctors • Patients • Industry • Governments
Ho and Lee (2020)[54]	• Global and national stewardship guidelines • Manufacturing quality assurance • Collective governance • Cross-sectoral integration	• Collective action • Responsible use • Stewardship • Research and development • Fair competition • Equitable access • Transparency • Availability • Quality assurance • Affordability	• WHO • UN Food and Agriculture Organization • WOAH • G20 leaders • National governments • Health sector • Agricultural sector • Economic experts • Security experts • Environmental experts • Regulatory agencies

[a] Limited to low- and middle-income countries.
Abbreviations: UN, United Nations; WHO, World Health Organization; WOAH, World Organisation for Animal Health.

Conclusion

In sum, the "golden age" of antibiotics is arguably a sociopolitical story, one that recapitulates the tendency to nostalgically view the 1950s through 1970s as a bygone heyday of the United States' rise to global dominance, including through strategic advancement of science and technology. The discovery narrative, however, fails to explicate how the benefits of antibiotics were and continue to be accrued by some groups while excluding others. Governments have *always* intervened in antibiotic production, and therefore the "innovation gap" does not reflect a novel state of market failure in antibiotic supply chains. Rather, the benefits and harms of antibiotic usage extend well beyond the innovation stage. Relinquishing the dominant, ahistorical discovery narrative is the first step to redirecting our analyses appropriately: toward questioning how the rise of antibiotics resistance has failed to generate the political will necessary to propel science and technology policies that prioritize access, equity, and sustainability.

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VIEWPOINT

Uptown Squirrel Does Not Eat That

Christy A. Rentmeester, PhD

Abstract

This essay plays out a few ethics reasons we have to reconsider what's really being marketed to us in some free offers that distract us from questions of ethical, cultural, and clinical importance, for example. Possible points of focus for bioethics as a field are related to antimicrobial resistance and stewardship.

Will Work for Food

There's a place in Lincoln Park in Chicago where I used to regularly see the same leucistic female Eastern gray squirrel—she was nearly all white except for the middle of her head—eating horse chestnuts. There are usually 2 to 4 chestnuts in each leathery, coarse, green capsule that falls from a tree. Most capsules are about the size of a tennis ball and the weight of a lacrosse ball. In late September or early October, a wise person won't stand too long under a horse chestnut tree without a helmet. The capsules fall heavily, with a thud, and a hungry squirrel has to apply substantial force of jaw and paw to break the capsules, find the fruit, and finally eat.

Day after day, same squirrel, same place. *She has to work hard for her food*, I thought to myself when I watched her, *I wonder why she doesn't investigate that pile of easy free stuff over there.* Within 20 minutes, she found the too-white heap of gluten I had spotted. She sniffed at what was nearly a whole loaf. She raised, lowered, then again raised her head. She was not tempted and resumed her struggles with the horse chestnuts strewn under broad crowns of 3 tall trees. *You are discerning, squirrel*, I observed and, inspired by the privileged heroine of Billy Joel's famous song, named her Uptown Squirrel.

Litter and Masquerade

As I left the park, I walked past the pile of what Uptown Squirrel did not eat and what is commonly marketed to humans (for purchase) as bread. This litter confirmed my respect for the numerous posted alerts to not feed wild animals in the park.[1] Nutritionally vacuous foodstuffs can, in some cases, help some wild animals consume enough calories to meet their energy demands, but they do not help them meet the profile of vitamins, proteins, and minerals they need for long-term well-being. Although micronutrient fortification improves some food items' nutritional index, harms of feeding poor human foodstuffs to wild animals are well-known. One condition common among

Canada geese and other wild birds attracted to human-littered, nutritionally poor food is called Angel Wing Syndrome,[2] which is caused by malnutrition and is irreparable and eventually fatal because the birds' improperly formed wings compromise their capacity for takeoff and flight.

A hard lesson of scarcity is that many animals have to eat what's available in their environments, regardless of whether it meets their nutritional needs. Many humans, too, are pressed to eat poor-quality food when nutritionally dense food is scarce, too costly, or too hard to access. Under different conditions, any of us, including Uptown Squirrel, might eat that too-white heap. Conditions of scarcity are topics to which bioethics literature attends widely and well. What gets far less attention from bioethics, however, is why we are not more outraged by nutritionally poor food that is aggressively marketed to us. Shouldn't we regard as deeply ethically problematic, for example, some cereal companies' mockery of their corporate citizenship obligations (to not exploit children's sweet teeth, for example) when colorful bits of cleverly spun sugar are masqueraded on supermarket shelves as food?

Food Products

Michael Pollan urges us to carefully distinguish between food and food products in our diets.[3] So, let's start with what I'm going to go out on a horse chestnut limb and call a clear case of a food product that does indeed make too-white gluten loaf look like a wonder.

Two months after last seeing Uptown Squirrel, I learned that humans were recently invited to order chicken feed . . . to eat. "Chix Mix, a snack inspired by antibiotics-free ingredients,"[4] was a limited-time free promotion by one prominent agribusiness industrialist. I have not read a nutrition label for this product, but I'm guessing it contains vitamins and minerals this company selects for their chickens (not for you or me) to grow (preferably as fast as possible) to some saleable size and flavor profile.

Also odd is that this product is vegetarian. In jest, I suppose this could be important to vegetarians who eat chicken. In earnestness, I suppose this could be important to people concerned about prions—even though that's mainly a potential problem in poor cattle feed,[5] not poultry feed. In any case, advertising forced vegetarianism of chickens or chicken feed seasoned for human consumption seems a strange marketing priority. Like many birds, wildfowl (eg, turkeys, prairie chickens, ducks, geese, swans) forage for items like grains, seeds, fruits, grasses, eggs, and insects; they have not evolved to be and are not, generally, vegetarians, at least not by choice. Perhaps we might at least take some comfort in that Chix Mix product "contains grains, primarily consisting of corn and soybeans and is mixed with vitamins, minerals and amino acids"[4]? Thankfully, fortification comes to our dietary aid in this product, just as it does in a pile of too-white gluten loaf.

Joke Time

C'mon, though, you might wonder: *Humans eat many snack foods we joke about as junk food. Why single out Chix Mix for ethical scrutiny?* OK, I'll ease up. Even if the joke is on us, this product is, after all, a "seasoned blend" that the packaging invites us to regard as "chicken feed that's good enough for humans."[4]

Yes, you read that right: *good enough*.

Perhaps, like me, you are unsure whether this phrase is amusing, humiliating, or both. In any case, *good enough* should prompt us to recall habits of discernment expertly modeled by Uptown Squirrel. She would stop, sniff, paw, and maybe wonder, *Are there antibiotics in this?*

Darn good question, Uptown Squirrel! As it turns out, "Chix Mix is designed as a marketing opportunity as the industry faces controversy about antibiotics in chicken feed and treatment of its animals."[4] While it is grand to see an agribusiness industrialist nod to growing global public concern about problems such as concentrated agricultural feeding operation (CAFO) chickens' welfare and antimicrobial resistance, it's a vast logical leap from (a) eating a seasoned version of what their chickens eat to (b) mitigating threats to humanity posed by a rapidly growing list of pathogens resistant to the best available antimicrobial agents that once effectively stifled their growth, adaptation, and transmission.[6] But, yes, this company would like you to order (for free!) and enjoy, as a token of this agribusiness industrialist's antimicrobial stewardship, this package of yardbird mash'n'pellets.

C'mon, though, you might still wonder: *Isn't it good that agribusiness industrialists aren't using antibiotics?* There is a vast literature on antimicrobial uses in CAFOs that any reader can easily engage to further explore whether and when not using antimicrobials is good agribusiness practice. For purposes herein, however, an upshot is this: Chix Mix packaging specifies that antibiotics are not being used *in the chicken feed*; this tells us nothing about this company's actual use, nonuse, overuse, or selective use of antimicrobials. Chix Mix packaging tells us nothing meaningful about this company's antimicrobial stewardship practices.

Marketing for Distraction

Some have likely been beguiled by Chix Mix. So, let us recall how Uptown Squirrel, though momentarily distracted, realized that her time and precious physical energy were wasted on the free white litter and far better spent keeping to the business of wrestling horse chestnuts into edibility. We might follow her lead and resist being distracted by Chix Mix's oddity, if not novelty, from the urgency and severity of antimicrobial resistance.

Strangely, the *CNN* story about Chix Mix I cite in this essay says that the US Department of Agriculture (USDA) and the World Health Organization (WHO) "allow for the use of antibiotics that are not crucial to the treatment of human diseases."[5] But we have good reasons to be suspicious of a claim that these agencies see agribusiness uses of antimicrobials as not undermining the effectiveness of these same antimicrobials' applications in human health. In fact, neither the USDA nor the WHO view human animal and nonhuman animal pathogen vulnerability as so neatly, tidily, or clearly distinct.

Focus, Bioethics.

In fact, the USDA and WHO view agribusiness practices as clearly within the scope of things they find relevant and potentially threatening to human health. We've long been wary of zoonotic spillover and spillback threats,[7] and we have good reasons to suspect that any proffered wall between microbes that affect nonhuman animals and microbes that affect human animals is illusory, or at least as permeable as a row of extra chairs that used to separate the smoking and nonsmoking sections of my favorite pizza place in the early 1990s. We know that "73% of all antimicrobials sold on Earth are used in animals raised for food [and that] … [a] growing body of evidence has linked this

practice with the rise of antimicrobial-resistant infections, not just in animals but also in humans."[8] We also know that the WHO ranks "medically important antimicrobials for risk management of antimicrobial resistance due to non-human use" in its most recent (sixth) edition of *Critically Important Antimicrobials for Human Medicine.*[9] Furthermore, the USDA National Institute of Food and Agriculture articulates as a goal of its antimicrobial resistance programs to "reduce or negate any potential negatively adverse impact of antimicrobials used in agriculture that may have potentially adverse effects on the treatment of human diseases."[10]

One job of bioethics is, at least, to clarify federal and international agencies' public policy stances when needed. Another job of bioethics should likely be to help draw out ethics and policy reasons to be suspicious of when and how *good enough* is offered to glibly joke about food product quality or drug effectiveness. We might also consider the moral psychological value of feeling insulted when agribusiness industrialists' food products pose as antimicrobial stewardship tokens; specifically, we can channel our responses to such insults into resisting distraction generated by food products marketed with jocular tone about antimicrobial resistance or marketed as actual food.

Uptown Squirrel's food selection behaviors might be taken as her wise suspicion that "free" is a currency of foolery. For humans, getting something for nothing can have momentary appeal as a gleeful surprise that satisfies our need, sometimes, for things to come easily to us. But "free" might be better viewed—at least in ethics terms—as a test of how cheaply one's participation and complicity in the quiet-creeping harms of nonsense can be bought.

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