AMERICAN SOCIETY FOR MICROBIOLOGY

Policy Pathways to Combat the Global Crisis of Antimicrobial Resistance

Executive Summary

Antimicrobial resistance (AMR) is a top public health threat and national security issue, projected to cause 10 million deaths by 2050. As antimicrobial resistance grows, it will create increasingly complex challenges in the hospital, the lab, on the farm and in communities. A multifaceted problem like AMR requires a multidimensional approach, and microbiologists must be a part of the solution.

Policymakers need to understand the key components to tackling AMR and carefully coordinate policies to save lives. This report lays out clear, science-based solutions that, if taken together through a One Health framework, will address this problem from every angle. As the leading organization advancing the microbial sciences, the American Society for Microbiology (ASM) has identified areas where policies should be strengthened, emphasizing the role that microbiology plays in assessing the challenges and creating solutions. This paper aims to provide concrete action steps that policymakers, working together with microbiologists, can take to turn the tide.

Our recommendations for policymakers that prioritize science and the roles of microbiologists are:

1. Support innovative research into antimicrobial resistance to better understand the science of microbes, how resistance emerges and is spread and how pathogens react to countermeasures.
2. Champion bold solutions to the challenging antimicrobial marketplace and work with regulators to create a straightforward approval pathway for antimicrobials and other countermeasures.
3. Support and strengthen the microbiology workforce in public health, laboratory, veterinary and research settings.
4. Address data modernization to ensure that testing and tracking in humans and animals keeps pace with rapidly evolving microorganisms.
5. Improve detection models, especially rapid detection, for antimicrobial resistance to identify outbreaks before they spread, whether on the farm, in the hospital or in communities.
6. Foster stewardship models for antimicrobial prescribing that ensure the right person, animal or crop gets the right drug for the right infection while preserving the effectiveness of currently available antimicrobials long term.
7. Harmonize domestic and global policy frameworks to bolster antimicrobial stewardship and increase lab capacity in low- and middle-income countries, in coordination with the United Nations, the World Health Organization and global partners.
8. Promote and fund efforts with partner countries to develop a global assessment of AMR and provide technical assistance to researchers navigating global research frameworks.

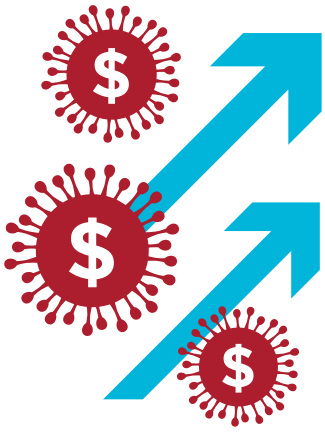
This paper addresses these issues in further detail below by examining the challenges, illuminating the complicating factors, and providing clear solutions that, when taken together, create a robust response to antimicrobial resistance that can protect the health of Americans and ensure that we have the tools to combat AMR for decades to come.

Introduction

The World Health Organization lists AMR as one of the top 10 global public health threats facing humanity, associated with the deaths of 4.95 million people in 2019 and a potential economic impact of $100 trillion by 2050[1]. AMR increases incrementally, which makes efforts to combat AMR vulnerable to deprioritization due to other emergent and existential threats. Current policies at both the domestic and international levels are falling short of the need to treat resistant infections and to prevent both the development and spread of resistance.

ASM has made addressing the AMR crisis a top priority. Our members around the world are at the forefront of efforts to combat antimicrobial resistance, investigating how microbes interact and persist in living organisms and the environment, how they develop resistance, and how we can prevent, detect and treat antimicrobial resistant infections. Microbiologists have significant roles to play in addressing these gaps, by conducting research at the basic, translational and clinical levels, developing diagnostics and vaccines, strengthening infrastructure for the surveillance of resistance development and antibiotic use, promoting the responsible use (stewardship) of antimicrobials and advocating for a One Health approach. Tackling AMR through research funding, preventive strategies, improved diagnostics, public health surveillance, therapeutics and novel countermeasures across humans, animals and our shared environment is imperative.

The CDC reported a higher excess expenditure of

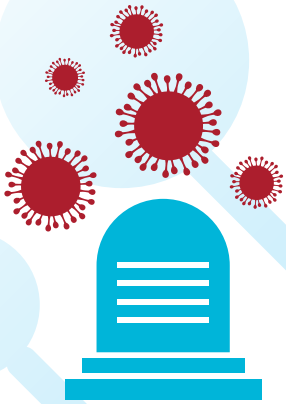


$20 billion
in annual health care costs

$35 billion
in societal costs due to AMR

Innes et al., 2020

According to a 2022 Lancet study, antimicrobial resistance itself caused



1.27 million
deaths in 2019

4.95 million
deaths where antimicrobial resistance played a role

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext

[1]World Health Organization. 2022. Antimicrobial Resistance. Retrieved from https://www.who.int/health-topics/antimicrobial-resistance

Foundations of AMR Policy in the U.S. and Abroad

Progress against antibiotic resistance will require an unprecedented level of collaboration both domestically and abroad. The foundation for the current global AMR agenda was laid in 2015, with the adoption of the Global Action Plan on AMR at the WHO World Health Assembly. This plan was the culmination of a strategic approach led by the U.S. and others. In the U.S., an Executive Order issued by President Obama in 2014 established the Presidential Advisory Commission on Combating Antibiotic Resistant Bacteria (PACCARB). ASM successfully advocated for PACCARB to be authorized in law with bipartisan support under the 2019 Pandemic and All-Hazards Preparedness Act (PAHPA). PACCARB is tasked with advising the Secretary of Health and Human Services regarding programs and policies to support and evaluate the implementation of U.S. government activities related to combating AMR, including the National Action Plan to Combat Antibiotic Resistance (CARB)[2].

The most recent CARB Action Plan was released in October 2020 and expands on the original plan by emphasizing evidence-based AMR reduction activities, such as antibiotic stewardship in humans and animals, as well as an increased focus on resistance in the environment, while continuing to prioritize infection prevention and control and innovative approaches to diagnostics and treatments. While these updates are a step in the right direction, significant challenges remain to achieving the goals set forth in the Action Plan. The COVID-19 pandemic illuminated the most pressing gaps in the U.S. public health response, including staffing shortages, the lack of rapid diagnostics to guide treatment decisions, and shortages of routine medications and supplies, that will inform our response to the next viral or bacterial pandemic and likewise, the likely accompanying exacerbation of AMR.

Policy Recommendations:

- Reestablish the Federal Interagency Antimicrobial Resistance Task Force to coordinate and develop efforts addressing antibiotic resistance and pursue the goals of the National Strategy for Combating Antibiotic-Resistant Bacteria.
- Collaborate with the World Health Organization, the Food and Agriculture Organization of the United Nations, World Organization for Animal Health, the U.N. Environmental Program and other multinational organizations on strategic initiatives to combat AMR.
- Ensure that global and domestic AMR policies address all forms of antimicrobial resistance development.
- Establish an interagency One Health working group to harmonize policies and clarify U.S. agency roles in addressing zoonotic diseases and advancing public health preparedness.

[2]U.S. Department of Health and Human Services. 2020. National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025. Retrieved from https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-2020-2025

Investing in Fundamental and Translational Research to Combat AMR

Perhaps more than anything else, the ability to reach the CARB goals depends on sustained public and private sector investment and a strong scientific workforce. Predictable support ensures the continuity of research into how we can prevent, detect and treat antimicrobial resistant infections across the spectrum of microbes. It starts with ensuring that our federal science agencies that support microbial science research, including the National Institutes of Health (NIH), U.S. Department of Agriculture (USDA), the Department of Energy (DOE) and National Science Foundation (NSF) receive robust and sustained funding increases, that discovery research is supported and that predictable pathways from discovery to development are ensured.

Funding authorities like the Biomedical Advanced Research and Development Authority (BARDA), which counters threats, the Advanced Research Projects Agency – Health (ARPA-H), which provides funding to combat specific diseases, and the Agriculture Advanced Research and Development Authority (AgARDA), which is authorized to fund advanced research on long-term and high-risk challenges for food and agriculture, should be leveraged to spur innovation in the AMR space in order to bring countermeasures more quickly to market. DOE and the NSF innovation, workforce and bioeconomy provisions of the recently passed CHIPS and Science Act present an opportunity to advance the science underlying AMR countermeasures and to bolster the microbiology workforce.

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, is one example of successful collaboration among government and private funders. As a global non-profit that focuses on enhancing the preclinical antibacterial and diagnostic product pipeline, it is partially funded by the U.S. through BARDA under the Administration for Strategic Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS). Between 2016 and 2020, CARB-X received $483 million from funders to support the development of new classes of antibiotics, non-traditional therapies, vaccines, and rapid and novel diagnostics.

Policy Recommendations:

- Provide robust and sustained funding for fundamental research on microbial genomics and mechanisms that lead to drug resistance through the NIH, USDA, NSF, the DOE Office of Science and the Department of Defense.
- Expand investments in BARDA, ARPA-H and AgARDA and continue to support CARB-X to focus on innovative preventatives, diagnostics and therapeutics.
- Establish loan forgiveness programs and training grants for the microbiology workforce that include medical microbiologists, the veterinary workforce and other medical laboratory scientists and professionals, both in and outside of public health settings.

Policy Pathways to Combat the Global Crisis of Antimicrobial Resistance

Basic Research

Basic biological research is largely federally funded and addresses mechanisms that underlie the formation and function of living organisms, ranging from the study of single molecules to complex integrated functions of humans and contributes to our knowledge of how disease, trauma or genetics alter normal physiological and processes.

Discovery Research

Discovery research is the process through which potential new therapeutic entities are identified, using a combination of computational, experimental, translational and clinical models. Drug discovery is funded through a mix of public and private funding (e.g., Carb-X, BARDA. ARPA-H and AgARDA). In antibiotic drug development this stage includes testing for compounds that have antimicrobial properties.

Development

Clinical trials in humans go through several phases and must first be approved by regulatory agencies. "Drug development" is a term used to define the entire process of bringing a new drug or device to market and is largely carried out by private entities. This includes characterizing the key features of the drug and testing for safety and efficacy.

Regulatory Approval

In the U.S., drug developers must apply to the FDA for product approval; once approved, clinical trials can begin. Clinical trial data must be submitted to the FDA, along with proposed labeling and directions for use.

Delivery and Post-Market Monitoring

Once FDA reviews and approves the application, it works with the drug developer to develop and refine prescribing information. Once a drug is on the market, the FDA continues to collect and review reports regarding product safety.

Stimulating Antibiotic Discovery and Development

Antimicrobials play a crucial role in the current and future success of modern-day human and veterinary medicine, but the current pipeline of products is insufficient to meet the continued threat of resistance. Every new antibiotic that has been approved for use in humans is a member of a chemical class discovered before 1987; the time to resistance for subsequent generations of these compounds is much shorter than a novel antibiotic. There is a dire need to discover novel mechanisms of action that can overcome resistance. However, the current economic model for antimicrobial discovery and development is dysfunctional. Few private companies invest in this research because it is challenging to demonstrate its value to investors.

Currently, there is no incentive structure for antimicrobials to be brought along the development process after the initial discovery phase of research, leading to a significant dearth of pre-clinical products in the pipeline. Creating an incentive structure for antimicrobial development is one approach to addressing the gap between discovery and product development to encourage continued research, development and introduction of new antimicrobials. A new antibiotic drug can take over a decade to develop and can cost hundreds of millions of dollars without any guarantee of safety and/or efficacy, and it must be used sparingly to maintain its effectiveness, limiting profitability in a volume-based market. There are even fewer antibiotics available for food animal use than for humans, with more new antibiotics being approved for companion animals than for food animals. Even with an incentive structure for antimicrobial development in place, this gap will take years to fill.

Policy Recommendations:

- Incentivize the development of antibiotics, antihelmintics and antifungals as well as other countermeasures through a subscription program that would provide a predictable return on investments for critically needed new antibiotics.
- Renew and strengthen the NIH-funded Antibiotic Resistance Leadership Group clinical trials network on antibacterial resistance to conduct clinical research; deploy a similar approach for food animals through the appropriate federal agencies.

Advancing Alternatives to Antimicrobials

The need for antimicrobials and alternatives to antimicrobials to treat infections, protect crops and promote animal growth and health is acute. As uses of antimicrobials, fungicides and pesticides are further restricted to preserve human health, there will be a proportionate increase in the demand for alternatives. For example, probiotics have gained popularity in production agriculture as a replacement for antibiotics for growth promotion, but without a solid foundation of research, producers are bound to an inefficient trial-and-error approach. The continued dearth of new antimicrobial agents and approaches requires continued efforts to develop novel targets and new drugs, improved diagnostic tests and modalities, and alternative treatment methods such as immunotherapy, phage therapy and antibody-based therapy. Alternatives to antibiotics and antifungals, including probiotics, microbiome therapeutics and phage therapy have the potential to delay or halt AMR development, but they face additional development and regulatory hurdles and the need for antimicrobials and alternatives to antimicrobials to treat infections, protect crops and promote animal growth and health is acute. Additional support is needed for innovative research and new approaches, including further investigation of bacteriophages as antimicrobial agents, microbial communities, new diagnostic tool development or the use of artificial intelligence (AI) to better understand resistance patterns.

For example, bacteriophage therapy, also known as phage therapy, is an alternative approach to combating antimicrobial resistance, but this therapy comes with challenges[3]. Phages are viruses that infect bacteria in nature and have been utilized in the laboratory setting for research purposes for decades. They can be engineered to infect and kill specific types of bacteria which makes this approach particularly promising. Phage therapy has the advantage of leveraging 3.5 billion years of evolution, which made phages not only extremely abundant, outnumbering bacteria ~10:1, but also extremely specific in the recognition of a target. Unlike antibiotic drugs, this therapy would allow "phages-as-drugs" to be made specific to a given pathogen, avoiding problems like dysbiosis and general killing of beneficial microbes. The complexity of phage mixtures, the risk of evolution, the challenges associated with demonstrating safety and efficacy are all hurdles that this area of research is facing. To capitalize on phage therapy's promise, more clinical trials are needed to demonstrate efficacy for FDA approval. With more evidence, phage therapy may become a serious alternative to traditional antibiotics.

[3]Barron M. 2022. Phage Therapy: Past, Present, and Future. https://asm.org/Articles/2022/August/Phage-Therapy-Past,-Present-and-Future

Microbiome therapy represents another alternative approach to preventing infection and combating resistance (See Harnessing the Microbiome). Microbiome therapeutics are designed to modulate the gut microbiome to generate certain therapeutic molecules or antitoxins. Significant advances have been made thanks to the Human Microbiome Project, including FDA approval of two microbiome therapeutics. While these are both targeting treatment for a gut microbe infection, there is preliminary evidence that this approach can be used both to treat and prevent antimicrobial resistance. In addition, new evidence demonstrates the diverse sources of antimicrobial resistant microbes in our gut. For this reason, more basic research is needed to advance our understanding of microbiome modulation and of microbial communities, including antimicrobial resistant genes, in humans, animals and our environment[4] (See Harnessing the Microbiome).

The pathway to FDA approval is complex for microbiome-based treatments. The FDA classifies microbiome therapeutics as foods, drugs or biologics, depending on the product. Fecal microbiota transplants (FMT), for example, are classified as biologics, and the only FDA-approved FMT was granted Fast Track, Breakthrough Therapy and Orphan designations[5]. Recent FDA guidance for FMTs for recurring infection with *Clostridioides difficile* (often called *C. diff*) divides the category between FMTs that were developed with stool banks and those that were not, with an FMT developed without a stool bank being subject to less rigorous oversight due to safety concerns with stool banks. As the industry for microbiome products grows in both human and veterinary medicine, we urge the FDA to develop clear guidance that sponsors can use to inform their drug development process. The FDA should also recognize the important role microbiome products can play in combating AMR and other health conditions by conducting more workshops and public outreach to stakeholders.

Policy Recommendations:

- Through cross-cutting funding and coordination across federal science agencies, study the impact of antibiotic and antifungal therapy on human and animal gut microbiomes, environmental microbiomes and agricultural microbiomes.
- Clarify FDA regulatory requirements for development of FMT products for humans and animals.
- Address gaps in the research-to-market pipeline through federal incentives and public-private partnerships.
- Streamline the Combined Regulatory Framework for Biotechnology to increase clarity and decrease the amount of time needed for new countermeasures to reach the market.

[4]Willms IM, Kamran A, et al. 2019. Discovery of novel antibiotic resistance determinants in forest and grassland soil metagenomes. Front. Microbiol. 10:460. Retrieved from https://www.frontiersin.org/articles/10.3389/fmicb.2019.00460/full

[5]U.S. Food and Drug Administration. 2022. FDA Approves First Fecal Microbiota Product. https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product

Tracking the Threat of AMR

Access to accurate and timely data is critical to prevention, detection and treatment. More support is needed for real-time global surveillance of specific antibiotic resistance genes in humans, animals and the environment[6], as well as the emergence and spread of antibiotic resistant infections. Monitoring antimicrobial use in human health, agriculture and consumer products will help state and local public health departments more quickly identify and respond to emerging threats.

Public health surveillance programs in the U.S. continue to face challenges[7], and they are unable to collect, systematize and harmonize data across jurisdictions due to a lack of infrastructure; data modernization is needed for a systematic approach to detecting and tracking antimicrobial resistance. The Centers for Disease Control and Prevention (CDC) leads the U.S. public health response to AMR through its Antimicrobial Resistance (AR) Solutions Initiative, Lab Network and AR Isolate Bank (in coordination with FDA) which supports activities in all 50 state health departments, several local health departments, Puerto Rico, Guam and the U.S. Virgin Islands. Despite these efforts, most public health laboratories are not equipped with the trained personnel needed to translate antimicrobial resistance findings into rapid identification of emerging threats.

Detecting the Presence of Antimicrobial Resistance

The U.S. has recently made significant investments in genomic sequencing partnerships and programs to increase our capacity to detect existing and emerging antibiotic-resistant organisms through the CDC Advanced Molecular Detection Program (AMD). Programs like AMD are critical to addressing AMR and complement the research and development taking place in academic centers and in the private sector. Using AMD technologies, scientists can study the emergence of resistance and pathogen transmission. Because antimicrobial resistance often emerges in hospitalized patients, partnership and collaboration between clinical and public health laboratories will be critical. The recently established Pathogen Genomics Centers of Excellence (PGCoEs) can play a role in advancing the use of genomic technologies to addressing AMR; however, the success of the Centers and the work depends on stable funding.

[6]Berglund F, Ebmeyer S, et al. 2023. Evidence for wastewaters as environments where mobile antibiotic resistance genes emerge. Commun Biol 6:321. Retrieved from https://www.nature.com/articles/s42003-023-04676-7

[7]U.S. Government Accountability Office. 2023. Antibiotic Resistance: Federal agencies have taken steps to combat the threat, but additional actions needed. https://www.gao.gov/assets/gao-23-106776.pdf

Understanding how resistant organisms spread also requires identifying reservoirs and emergence of resistant organisms in the environment. Wastewater surveillance is commonly used in the U.S. and other countries to monitor pathogen and chemical levels in communities through municipal sewer systems. It gained public attention during the COVID-19 pandemic as a useful metric for measuring viral presence and prevalence, and the establishment of the National Wastewater Surveillance System (NWSS) at the CDC helped inform local responses to COVID-19. The NWSS could be deployed to monitor spatial and temporal trends for a variety of health threats, including AMR, but its future is uncertain as the current network is funded through emergency supplemental funding[8]. Wastewater surveillance can be combined with other surveillance data to inform public health; additional research is needed to determine its effectiveness in determining the potential spread of resistance to humans, animals and the food supply[9].

In partnership with the Environmental Protection Agency (EPA), the USDA, the FDA and the CDC are working to address AMR using a One Health approach. FDA's National Antimicrobial Resistance Monitoring System (NARMS) was established in 1996 as a partnership among FDA, CDC and USDA to track antibiotic resistance in foodborne bacteria from retail meats, human illnesses and food producing animals. In partnership with FDA's Veterinary Laboratory Investigation and Response Network (Vet-LIRN) and USDA's National Animal Health Laboratory Network (NAHLN), NARMS was expanded to encompass select animal pathogens, and they are currently working with the EPA to understand AMR in the environment. Separately, USDA's Animal and Plant Health Inspection Service (APHIS) is currently developing bacterial diagnostics to track AMR in wildlife and studying the potential of certain species to transmit disease to livestock and crops. In coordination with the CDC, NARMS or a similar approach should be leveraged to move the U.S. toward a comprehensive rapid response network.

With stronger requirements and increased investment in surveillance systems, along with greater use of technologies like AMD, we can help our health care and veterinary providers make informed decisions that improve antimicrobial stewardship and reduce infections.

Policy Recommendations:

- Provide robust and sustained funding for the CDC's Antibiotic Resistance Surveillance and Laboratory Network and Advanced Molecular Detection program to maintain pathogen genomic sequencing and surveillance programs in public health, as well as sustain public-private and academic partnerships.
- Provide robust and sustained funding for the National Healthcare Safety Network, the National Animal Health Laboratory Network and the Veterinary Laboratory Investigation and Response Network.
- Coordinate data collection through existing systems at USDA, FDA, CDC and EPA to identify and track emerging human, animal and plant pathogens and resistance.
- Authorize and fund the CDC National Wastewater Surveillance System for AMR, in coordination with the Environmental Protection Agency and other relevant agencies.

[8]Chau KK, Barker L, et al. 2022. Systematic review of wastewater surveillance of antimicrobial resistance in human populations. Environ. Int. 162:107171. Retrieved from https://www.sciencedirect.com/science/article/pii/S0160412022000976

[9]Berglund F, Ebmeyer S, et al. 2023. Evidence for wastewaters as environments where mobile antibiotic resistance genes emerge. Commun. Biol. 6:321. Retrieved from https://www.nature.com/articles/s42003-023-04676-7

The Importance of Diagnostics and Challenges to Detecting Resistance

Diagnostic tests are the primary means of identifying infectious disease in humans and animals and detecting resistance in microorganisms. Novel diagnostic tools and approaches are needed to detect resistance and assist in appropriate prescribing of antimicrobials. While optimizing use of current diagnostics is critical, developing the next generation of low-cost diagnostics that can provide rapid analysis of resistance and differentiation of infection type remains elusive. We are woefully behind in the development of rapid, accurate diagnostic tests that 1) determine infectious from non-infectious syndromes, 2) distinguish among bacterial, fungal, parasitic and viral infections; 3) identify the specific pathogen; and 4) test for antimicrobial susceptibility patterns.

Beyond the research and development needed to create better infectious disease diagnostic tools (See Investing in Fundamental and Translational Research to Combat AMR), another challenge is the timeliness of implementation of updates to antimicrobial susceptibility test (AST) breakpoints, which are the interpretive criteria used for determining efficacy of an antibiotic against a specific bacterium. Accurate antimicrobial susceptibility testing and reporting is essential for guiding appropriate therapy for patients and for collecting timely data to inform prevention and stewardship efforts.

Breakpoints are subject to continuous adjustment and updating to best reflect current clinical outcome data, but these changes can only benefit patients and public health if adopted in a timely manner by clinical and public health laboratories that perform AST. A recent survey identified that up to 70% laboratories accredited by the College of American Pathologists (CAP) and up to 45% of CAP-accredited laboratories outside the U.S. use various obsolete clinical breakpoints to interpret AST results to guide patient care. Furthermore, some laboratories indicated that they were unaware of breakpoint changes or the need to update breakpoints[10]. This results in serious patient safety concerns and hampers the ability to track and contain the worldwide threat of AMR, as pathogens of serious or urgent concern can go undetected and spread to additional patients and across healthcare systems and communities.

The FDA's Center for Drug Evaluation and Research (CDER) is tasked with updating breakpoints in the U.S., and one of the biggest challenges to making the changes in a timely manner is the lack of robust clinical trial data, especially for older antimicrobials. Recognizing this challenge, Congress included language in the 21st Century Cures Act (Cures) Act in 2016 to improve the process. The Cures provisions made it easier for FDA to accept update requests and scientific rationale from entities other than drug sponsors such as standards development organizations (SDO), specifically the Clinical Laboratory Standards Institute. However, the change has not resulted in as significant an increase in the FDA's acceptance of updated breakpoints

[10]Simner PJ, Rauch CA, et al. 2022. Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints. Open Forum Infect Dis 9:ofac007.

as was hoped. Solving this complex problem and creating a smoother process to ensure more timely and broader application of updated breakpoints will require cooperation from all stakeholders, from AST device manufacturers to regulatory agencies, to laboratories and clinical associations, to laboratory accreditation groups and SDOs.

Diagnostics and susceptibility testing are also important to animal health. Broad-spectrum antimicrobials are used in livestock before, or in place of, a confirmed diagnosis (for example, before undertaking any antimicrobial susceptibility testing) due to logistical considerations. The problem is compounded by the number of animal species and different pathogens of interest that are common in one species but not others. While market research indicates that the animal AST market is growing, more work is needed; in addition, it is important to educate veterinarians on how to correctly interpret AST results[11]. Though the FDA does not currently regulate breakpoints for animal ASTs, calibrating tests to the latest breakpoints and ensuring timely breakpoint revisions continues to warrant additional attention.

Policy Recommendations:

- Address data modernization and laboratory capacity for veterinary, clinical and public health laboratories.
- Support the generation of updated clinical data, streamlined review and timely adoption of updated Antimicrobial Susceptibility testing (AST) breakpoints for new and existing agents to support both human and animal health.
- Establish improved guidance for optimal use of diagnostics in all health care settings to optimize clinical care and antibiotic utilization.
- Support research and development of novel, rapid and more accurate diagnostic tools and approaches.
- Streamline the process to ensure more timely and broader application of updated breakpoints through stakeholder engagement.

Prevention and Stewardship

Even with concerted efforts to develop and market novel treatments, we are unlikely to identify new, broad-spectrum antibiotics with the utility of those that have been the mainstay of medical care for decades. In other words, we may never find another penicillin, so prevention of AMR transmission and stewardship of existing antimicrobials is critical.

One key aspect of prevention is the use of vaccines. Vaccines have a crucial role in decreasing rates of infections, which in turn reduces the need for antibiotics. For example, a highly effective tuberculosis vaccine could significantly cut back on cases of multidrug-resistant TB, which is the leading cause of drug-resistant infectious disease deaths globally, but the most readily available TB vaccine is only effective in infants. Just as has been proposed for antimicrobials, an incentive program focused on the development of vaccines that target tuberculosis, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* infections could stimulate investment in these critical public health tools.

[11]Clinical and Laboratory Standards Institute. 2019. Understanding Susceptibility Test Data as a Component of Antimicrobial Stewardship in Veterinary Settings. CLSI report VET09. Retrieved from https://clsi.org/standards/products/veterinary-medicine/documents/vet09/

Stewardship also requires provider and public education efforts to modify expectations of antimicrobial use. Antimicrobials often eliminate symptoms before they eliminate infection, and patients may choose to end their course early despite proper use protocols. In addition, out of date practice can lead to longer courses of antimicrobials than needed. Meanwhile, clinicians sometimes prescribe broad spectrum antibiotics for an infection that could be treated with a more targeted antimicrobial with less antimicrobial resistance selection pressure. Historical approaches such as proposed bans on certain antimicrobials or chemicals make partnerships with the private sector challenging and have not resulted in the desired policy outcomes. Instead, education on appropriate antimicrobial use and best practices in stewardship should be incorporated into professional school curricula to educate our next generation of physicians, veterinarians and pharmacists.

In addition to educational campaigns, federal agencies have developed guidelines that encourage judicious prescribing of antimicrobials to preserve their effectiveness. The FDA recently implemented a plan to require veterinary oversight for all animal drugs that contain antimicrobials important in human medicine. Known as the veterinary feed directive, the new policy takes effect in June 2023. As of June 2023, therapeutic antibiotics for food producing and companion animals must now be administered under the supervision of a licensed veterinarian. The FDA is also looking to change policies on duration of use for medically important antimicrobials in animals, though no draft guidance has been published since the initial concept paper was released in 2021.

Understanding Antimicrobial Use

Tracking antibiotic prescriptions and use is a tool that can be leveraged for stewardship efforts, and stakeholders have called for national data on antibiotic use across settings. Pharmacists can track the antibiotics that are prescribed and request that providers limit inappropriate prescribing to their patients. However, these efforts will fail without educating consumers on the importance of using antibiotics only when needed and only as directed.

Hospital-based monitoring systems can slow the spread of resistant infections by arming health care practitioners with data that would enable more effective infection control policies, allowing for fewer cases of drug resistant infections and prolonging the effectiveness of current therapies. Despite being included in the initial CARB action plan, monitoring antibiotic use and health-care-associated infections remains an area where there are gaps in data that, if addressed, would allow for better prevention of AMR spread and more effective treatment of infected patients. The Centers for Medicare and Medicaid Services (CMS) has created incentives for hospitals to reduce health-care-associated infections, but this effort has been stymied by the fact that many hospitals do not have effective tools to easily monitor antibiotic use or AMR emergence. In 2022, the CMS finalized a rule that will require hospitals and critical access hospitals to report antimicrobial use and resistance data into the National Healthcare Safety Network (NHSN), which is housed by CDC[12].

[12]Department of Health and Human Services. 2022. Medicare program; Hospital inpatient prospective payment systems for acute care hospitals. Retrieved from https://www.govinfo.gov/content/pkg/FR-2022-08-10/pdf/2022-16472.pdf

On the animal side, the National Animal Health Monitoring System (NAHMS) monitors antimicrobial use in domestic livestock and the underlying reasons for their use, while also documenting alternatives used for treatment and prevention. Linking to this system is the National Animal Health Laboratory Network (NAHLN), which tracks AMR in animals. NAHLN analyzes samples submitted by veterinary clinics and diagnostic laboratories for resistant pathogens in food animals and companion animals.

Additional stewardship efforts should be considered in the consumer products sector. Household product manufacturers have responded to increasing consumer demand for antimicrobials in products like soap and paint, but scientists warn that the overuse of these chemicals could lead to antimicrobial resistance, negative health effects and environmental harm. For example, they have raised concerns regarding the overuse of quaternary ammonium compounds (QACs), including benzalkonium chloride which is a common component of antibacterial wipes and hand sanitizers[13]. Although the use of QACs is regulated by the EPA, it does not always require manufacturers to label specific antimicrobials for certain products and use cases, limiting awareness of what antimicrobials are being used[14,15]. In addition to promoting stewardship among manufacturers, policymakers should consider requiring disclosure of QACs and their potential impacts to promote judicious use by consumers.

Finally, building public trust and communicating the threat posed by AMR to health care providers, producers and the public is key. Educational interventions aimed at the public can cover a wide range of infection control practices and AMR awareness, from thorough handwashing to teaching when antibiotics may or may not be appropriate. These efforts should leverage expertise from multiple disciplines to address the social, structural and behavioral dynamics that typically limit uptake of public health interventions.

Policy Recommendations:

- Ensure health care facilities have the capabilities to meet the CMS guidance implementing antimicrobial stewardship programs to improve infection control measures, evaluate and improve the use of antimicrobial drugs.
- Support efforts and practices to reduce the non-therapeutic use of medically important antibiotics in food-producing animals to preserve the effectiveness of antibiotics used in the treatment of human and animal disease.
- Highlight best practices and stewardship success stories in the U.S. and abroad, as well as fund efforts to promote effective communication among researchers, clinicians, product manufacturers, veterinarians and the public.
- Increase educational efforts funded by the USDA and CDC through trainings and workshops on the impact of vaccines, hygiene and stewardship on AMR in human health, agriculture and veterinary settings.
- Expand efforts to monitor antibiotic prescribing, continue to build and require measurement of healthcare-associated infections and leverage these data to ensure optimal infection prevention measures are being implemented.

[13]Zhang Y, Zhang Y, et al. 2023. Quaternary ammonium compounds: a chemical class of emerging concern. Environ. Sci. Technol. 57: 2c08244. Retrieved from https://pubs.acs.org/doi/10.1021/acs.est.2c08244

[14]Environmental Protection Agency. 2021. Label Review Manual Retrieved from https://www.epa.gov/sites/default/files/2021-02/documents/full-lrm_2-22-21.pdf

[15]Environmental Protection Agency. 2023. Data Requirements for Pesticides. 40 CFR Part 158 Subpart W. Retrieved from https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158/subpart-W

Global Perspective

A global challenge like AMR demands global collaboration. Many low- and middle-income countries (LMIC) struggle with laboratory capacity, limited public health resources, inadequate wastewater infrastructure and a higher burden of infections. These same countries are also bound to intensive agriculture processes that rely on antibiotics to feed the world. They also hold some of the most promising natural resources for the discovery of novel antimicrobials and other drugs, and we must ensure that they benefit from those resources.

Microbiology is an interconnected discipline, with researchers and clinicians all over the world sharing samples and genetic data. Yet lesser-resourced countries have historically not benefited in proportion from their contribution of genetic resources. In 2014, the Nagoya Protocol was established to ensure that benefits arising from research and development of genetic resources are shared in a fair and equitable way. Although the U.S. has not ratified the Convention on Biological Diversity and hence the Nagoya Protocol, our researchers are obligated to follow the agreement when working with one of the more than 100 countries that ratified it. Despite the spirit of the Protocol, this has created administrative hurdles to AMR discovery research that academic researchers are not equipped to navigate. One proposed solution is for the U.S. State Department to designate a liaison to support researchers in negotiating agreements with countries that have ratified the Nagoya Protocol. This approach would lower the barrier to research while protecting against exploitation.

Globally, laboratory availability and capacity are limited. Many countries, particularly LMICs, lack the infrastructure to perform the basic surveillance and testing required to assess AMR. According to the Mapping AMR and AMU Partnership, a multiorganization and multinational consortium led by the African Society for Laboratory Medicine, only 1.3% of the 50,000 medical laboratories forming the laboratory networks of its 14 participating countries conduct bacteriology testing.[16] The U.S. can strengthen health systems and build laboratory capacity through programs funded by CDC and the U.S. Agency for International Development (USAID). ASM works with local, state and national governments to strengthen laboratory capacity in resource-limited settings and empower microbiology laboratories to integrate clinical care and population surveillance in remote and underserved areas. ASM, with its Global Public Health program and international membership, can play a leading role in advocating for addressing global policy challenges and play an intermediary role in building local expertise that can lead to local solutions that can be scaled up.

Another element of the global landscape that warrants more consideration is the challenge of financing medical products and diagnostic development for diseases endemic in LMICs. AMR does not respect geopolitical borders, so efforts to combat AMR domestically should also consider diseases with a significant global burden. In addition to updated breakpoint uptake for diagnostics available and accessible globally, new diagnostics that work within the framework of global delivery challenges are an important part of the solution. Having an accurate assessment of the global AMR burden can influence product development and point industry and government partners in a direction that can lessen the global AMR burden. This will link back to the importance of policies that encourage more discovery and development of antibiotics and

[16]African Society for Laboratory Medicine. 2022. The Crisis within the Crisis. https://aslm.org/wp-content/uploads/2022/09/ASLM_MAAP-Policy-Brief_Embargoed-until-15-Sept-6AM-GMT.pdf?x26552

prophylactics like vaccines while also ensuring that those products can stay on the market and be accessible when necessary. Coupling new technologies with stronger infrastructure in LMICs will help bend the AMR curve.

Aligning U.S. domestic AMR policy with the global policy infrastructure is critical to mitigating AMR. Whereas stewardship is a necessary component of global AMR strategies, antibiotics are still commonly used for growth promotion in many countries to meet the demands of the global agricultural marketplace. Recognizing these economic and infrastructure demands, support for stewardship should be a key component of international efforts when paired with appropriate alternatives. Reducing and eventually phasing out all use of antibiotics for animal growth promotion should be a global goal to ensure that both animal and human health are preserved[17].

Policy Recommendations

- Support and consistently fund CDC's global health programs and the Antibiotic Resistance Solutions Initiative. This includes the AR Lab Network, which was authorized in 2022 to focus on global laboratory capacity to provide technical assistance to countries around the world to address AMR.
- Sustain consistent funding for the U.S. Agency for International Development's global health security programs, including PEPFAR, which assist with addressing AMR and other pathogens for which we have seen highly resistant strains emerge.
- Study and promote wastewater infrastructure to understand and reduce the emergence of AMR in LMIC.
- Provide technical assistance to researchers navigating Nagoya Protocol requirements to promote the fair and equitable sharing of benefits arising from genetic resources.

Conclusion

Antimicrobial resistance poses serious threats to human, animal and plant health. It is not solely a health problem, an environmental problem, a diagnostic problem or a drug development problem. It is all of the above and microbiologists, from basic science to environmental monitoring, to diagnostics and surveillance, can provide solutions. ASM joins with our colleagues in global public health, science and industry to support research funding, stewardship and preventive strategies, improved diagnostics, public health surveillance and the development of novel countermeasures. As AMR increases in the U.S. and around the world, ASM and its members stand ready to work with Congress, federal agencies and global governing bodies to develop a One Health approach to advance science and practice to protect human and animal health, the economy and society at large.

[17]Food and Agriculture Organization of the United Nations. 2023. Animal production. Antimicrobial Resistance. Retrieved from https://www.fao.org/antimicrobial-resistance/key-sectors/animal-production/en/

AMERICAN SOCIETY FOR MICROBIOLOGY

Companion Piece #1

Harnessing the Microbiome to Understand and Reduce Resistance

Microbiome research aims to advance understanding of microbial communities and how they interact with the world around us. Understanding of the microbiome has evolved significantly since the concept of the human microbiome emerged roughly two decades ago. Today it is understood that microbial communities exist on, in and around people, plants, animals and the environment and have symbiotic relationships that protect against disease and, in some cases can be leveraged to treat it. The rapid pace of discovery has led to greater technology needs, data sharing infrastructure and approval pathways.

Thanks to federal investment in microbiome research, including the Human Microbiome Project (HMP), we now know that antibiotics and other antimicrobials leave their mark on both the microbiome and host immunity. Antimicrobials expand the host-specific pool of antimicrobial-resistance genes and organisms, degrade the protective effects of the microbiome against invasion by pathogens and may impair vaccine efficacy. Microbiome research has captured the attention of the public as well and has generated a booming demand for prebiotic and probiotic dietary supplements. Recently, the FDA approved the first microbiome therapeutic to prevent recurrent *Clostridium difficile* (AKA *C. diff*), which causes a potentially life-threatening diarrheal disease.

Looking across species, broader adoption of microbiome research will both support health and treat infections. Understanding plant, soil and animal microbiomes will help inform the spread and persistence of AMR in agriculture and food production systems in addition to providing new tools to address it. The federal government has directed resources to soil and plant microbiome research in recent years but lacks sustained support for research on agriculturally important animals, where microbial interventions have shown to be effective in maintaining livestock health. ASM encourages additional support for microbiome research in food animals in response to increasing pathogen resistance in the meat, milk and egg supplies.

With increasing pressure to reduce antibiotic use in food production, the need to leverage the microbiome as a tool to promote healthier and more productive livestock and plants is now greater than ever. Similar to the Human Microbiome Project, a Livestock Microbiome Project could advance our understanding of antibiotics' impact on animal microbiomes, catalyze development in precision feeding, support best practices in probiotic development and help industries understand the effect of probiotics, prebiotics and competitive exclusion on animal health and productivity. Producers know that specific feed supplementation (nutraceuticals, botanicals, prebiotics, probiotics and tailored symbiotics) improves production performance in food-producing animals; however, a better understanding of the specific organisms and mechanisms involved in this improvement would have broad implications for agriculture and its sustainability. A coordinated effort to evaluate livestock animal microbiomes could propel the food industry to the next level and address the most pressing concerns in health, food safety and antimicrobial resistance.

Stewardship is a key component in the fight against AMR. In the U.S., medically important antibiotics are no longer allowed in feed or water for the purpose of growth promotion in food-producing animals. This creates a market for viable, FDA-approved alternatives, and a growing body of research indicates that microbiome research can positively impact animal production as well as animal health while making it less reliant on antibiotics. The pathway to regulatory approval for microbiome-based interventions is complex, and ASM supports efforts to streamline the Coordinated Framework for the Regulation of Biotechnology.

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Companion Piece #2

The Unique Challenges of Fungal Resistance

While most of the attention on AMR revolves around bacterial infections, antifungal resistance remains underrecognized[18]. Fungal infections are becoming increasingly widespread, causing an estimated 2 million deaths per year[19]. Over the past several decades, multiple new pathogenic species have emerged, including *Candida auris* in humans, *Batrachochytrium salamandrivorans* in salamanders and multiple new species of plant pathogens. With continued global warming, ecosystem perturbation, and global movement and trade, it is likely that novel fungi will continue to emerge as disease agents. Continued diligence is necessary to identify new and emerging pathogens and then to study these organisms to provide insights relevant to prevention, diagnosis and treatment.

The increasing threat of antifungal resistance is driven by limited discovery of new antifungal agents, fungicide overuse in agriculture, overuse and overprescription of antifungals in health care and failure of patients to finish the entire course of antifungal treatments when administered. In addition, the incomplete removal of pharmaceutical antifungals in wastewater treatment systems compounds environmental factors that drive evolution in fungal species and contribute to geographic expansion. For example, the resistant fungus causing Valley Fever (*Coccidioides immitis*) has spread beyond its usual range in the southwestern United States into southern Washington State.

The underlying genetic similarities between the fungal and animal kingdoms makes it challenging to identify drugs that kill the fungus without causing serious side effects and toxicity in patients. *C. auris* is often resistant to the most effective antifungals, leading to significant risk of severe infection and death. Clinical resistance to every class of antifungal drug has emerged, and multidrug-resistant pathogens are now spreading around the globe.

The direct threat posed by fungi to human health, alarming as it is, is exceeded by the indirect effect of fungal diseases of plants that jeopardize food security worldwide[20]. In addition to killing crops, fungi produce toxins that contaminate food supplies, such as toxins that lead to the development of cancers. Included among these toxins are those with acute effects that have been considered for deployment as biological weapons against humans and crops. In recent years, there have been an unprecedented number of fungal diseases causing extinctions of wild species, with mass mortalities seen in bats and amphibians, that threaten biodiversity[21].

[18]American Society for Microbiology. 2022. Combatting Antifungal Resistance. Retrieved from https://asm.org/Articles/2022/November/Combatting-Antifungal-Resistance

[19]McDermott A. 2022. Drug-resistant fungi on the rise. PNAS 119: e2217948119. Retrieved from https://www.pnas.org/doi/10.1073/pnas.2217948119

[20]National Center for Biotechnology Information. n.d. One health: Fungal pathogens of humans, animals, and plants. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK549988/

[21]Fisher MC, Alastruey-Izquierdo A, et al. 2022. Tackling the emerging threat of antifungal resistance to human health. Nat Rev Microbiol 20:557-571. Retrieved from https://www.nature.com/articles/s41579-022-00720-1

Companion Piece #2

The Unique Challenges of Fungal Resistance

Support is urgently needed to address fungal resistance.
Researchers are developing new and innovative strategies to thwart fungal pathogens, but it is a race against time and regulatory hurdles[22] because fungi can rapidly evolve resistance. Innovative funding strategies are needed to transform basic research into applied innovation, but fungal threats are excluded from major funding sources—for example, CARB-X authority is limited to bacteria, and they do not develop antifungals. This should be addressed by establishing a similar effort in antifungals or by expanding the scope of CARB-X authority.

Additionally, public health officials and policymakers should address the absence of fungal diseases in AMR surveillance systems. Until recently, antifungal surveillance was largely done on an ad-hoc basis, and was nonexistent in low-resource settings. This has started to change; for example, the WHO recently published the first-ever Fungal Pathogens Priority List[23] and the CDC's Antimicrobial Resistance Laboratory Network has increased the funding to state, local and territorial public health departments to support susceptibility testing capabilities for *C. auris*. Opportunities remain to expand capacity to detect additional priority pathogens.

[22]U.S. Government Accountability Office. 2022. Drug Development: Pathway for Approving Antibacterial and Antifungal Drugs for Patients with Limited Treatment Options is Infrequently Used. GAO-22-105042. Retrieved from https://www.gao.gov/products/gao-22-105042

[23]World Health Organization. 2022. WHO Fungal Priority Pathogens List to Guide Research, Development and Public Health Action. https://www.who.int/publications/i/item/9789240060241

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While this statement is an important step to make sure that American Society for Microbiology members and leadership have a seat at the table in discussing AMR policies, it is by no means all encompassing. To facilitate continued dialogue, the ASM Policy and Advocacy Team would like to encourage all Society members to submit feedback at **advocacy@asmusa.org.**