AMERICAN SOCIETY FOR MICROBIOLOGY

# Policy Pathways to Combat the Global Crisis of Antimicrobial Resistance

## Executive Summary

a straightforward approval pathway for antimicrobials and other countermeasures.
3. Support and strengthen the microbiology workforce in public health, laboratory, vet settings.
4. Address data modernization to ensure that testing and tracking in humans and anim rapidly evolving microorganisms.
5. Improve detection models, especially rapid detection, for antimicrobial resistance to before they spread, whether on the farm, in the hospital or in communities.
6. Foster stewardship models for antimicrobial prescribing that ensure the right perso gets the right drug for the right infection while preserving the effectiveness of curre antimicrobials long term.
7. Harmonize domestic and global policy frameworks to bolster antimicrobial stewards capacity in low- and middle-income countries, in coordination with the United Natio Organization and global partners.
8. Promote and fund efforts with partner countries to develop a global assessment of technical assistance to researchers navigating global research frameworks.

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

## 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 scien66t support microbial scien66esearch, including the National Institutes of Health (NIH), U6.S. Department of Agriculture (USDA), the Department of Energy (DOE) and National Scien66oundation (NSF) re66e robust and sustained funding increases, that discovery research is support6t predictable pathways from discovery to development are ensured.

Funding authorities like the Biomedical Advan66esearch and Development Authority (BARDA), which counters threats, the Advan66esearch Projects Agen665 (y – Health (ARP)70.1 (A)40 (-H), which pr)25.1 (o)30 (vides which is authoriz6o fund advan66esearch on long-t6or food and agriculture, should be leveraged to spur innovation in the AMR spac6e in order to bring 66ermeasures more quickly to market. DOE and the NSF innovation, workforce and bioe66y provisions of the recently passed CHIPS and Scien66ct present an opportunity to advan66es and to bolster the microbiology workforce.

The Combating Antibiotic-Resistant Bacteria Biopharmac6eutical Accelerator, or CARB-X, is one example of successful 66ation among government and privatofit that focuses on enhancing the preclinical antibacterial and diagnostic product pipeline, it is partially funded by the U.S. thrA under the Administration for Strategic Preparedness and Response (At the Department of Health and Human Servi66es (HHS). Between 2016 and 2020, CARB-X re66ed $483 million from funders to support the development of new classes of antibiotics, non-traditional therapies, va66 and rapid and novel diagnostics.

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- **Expand investments in BARDA, ARPA-H and AgARDA and 66o 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 laboratts and professionals, both in and outside of public health settings.**

### 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 e□cacy.

### 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

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

## 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

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.

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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 )

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].

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.

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[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

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

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].