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The CDC response to antibiotic and antifungal resistance in the environment

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Abstract

Antibiotic resistance challenges public health on many fronts, and it is increasingly clear that it must be addressed in the environment to control emerging resistance and infections in humans and animals. Here, we outline how the US Centers for Disease Control and Prevention is addressing antibiotic resistance in the environment.

Antibiotic resistance (AR) is one of the greatest global public health challenges of our time. We once again live in an era when people around the world are dying from untreatable infections. AR is an ever-changing and increasing threat that has the power to undermine the technological advances and extensive progress made in modern medicine, food production, and life expectancy. To effectively counter this threat of AR, we must have a clear understanding of the sources and how it spreads. For all the knowledge we have acquired on this topic, there remain immense gaps and unknowns that still need to be filled and answered.

AR is a One Health issue affecting people, animals, plants, and our environment; the health of each is connected and contingent upon the other. Antibiotics save lives; however, any time antibiotics are used for people, animals, or plants, they exert ecologic pressure and contribute to the development of AR. The resistant organisms can then spread and share antibiotic resistance genes (ARGs) to affect nearly every aspect of life. A One Health approach with coordinated and aggressive action is critical to successfully fight this ubiquitous threat.

The environment (e.g., water, soil) can be a major reservoir of ARGs that impact human health and is affected by land use and waste management practices that vary around the globe.[1] The environment ultimately receives runoff and waste discharge from built environments including our homes, healthcare facilities, factories, public and private

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buildings and institutions, the runoff from stormwater and from animal and plant production, and the excrement from all wildlife it supports. This important role for the environment was highlighted in the November 2019 Centers for Disease Control and Prevention (CDC) second *Antibiotic Resistance Threats in the United States* report (AR Threats Report).[2] This report indicated that 18 resistant bacterial and fungal pathogens and *Clostridioides difficile*, categorized as urgent, serious, and concerning threats to human health, cause more than 3 million infections and close to 50,000 deaths in the United States each year. The report also highlighted three additional resistant pathogens on a watch list consisting of azole-resistant *Aspergillus fumigatus*, drug-resistant *Mycoplasma genitalium*, and drug-resistant *Bordetella pertussis*; these were included because, though the full burden of these pathogens in the United States or around the globe is not yet understood, there are increasing concerns about their potential to spread across borders resulting in morbidity and mortality akin to other AR threats. Among the 21 total AR human pathogens, many are also found in companion animals, food-producing animals, or the environment (e.g., water, soil). The AR Threats Report goes to great lengths to communicate that for AR, there is significant interconnection across the entire One Health spectrum, including humans (healthcare, community, travel), animals (companion, food, and wildlife), plants, and the environment (e.g., water, soil) (Figure 1).

Relative to the role of humans and animals, the role of the environment (e.g., water, soil) in the spread and amplification of AR is less understood. The CDC has teamed with international partners to delineate important gaps in how resistant organisms and antimicrobials from multiple sources contribute to the presence of resistance in the environment, the potential impact of environmental AR on human health, and what are next steps to address the risks posed.[3] Contamination of the environment with antibiotic residues, resistant organisms, and ARGs can occur through multiple pathways. Soil can become contaminated from animal waste on farms or when untreated or un-composted animal manure or pesticides are applied during plant production. Water resources can then becontaminated from these sources through seepage into groundwater and runoff into surface water. Human waste can contaminate soil, groundwater, and surface water in areas without appropriate sanitation or where wastewater treatment plants (WWTPs) are suboptimal or completely lacking, thereby not effectively removing antibiotic residues, organisms, and ARGs (Figure 1).

CDC has taken on a leadership role in advancing understanding of the role of the environment in AR, expanding a public health perspective that mirrors the major focus areas visually depicted in the figure and as described above.[4] CDC-led or -supported public health research spans from work on the development of AR in sink drains and wastewater plumbing of healthcare facilities to the passage of ARGs through wastewater treatment facilities, and the dissemination of ARGs in natural watersheds and waterways. Other projects focus on the risk of transmission of AR in the environment to humans, risks of antifungals used as plant pesticides on development of resistance, potential health risks of AR reaching watersheds from food animal production, and developing laboratory methods to detect ARGs in environmental samples and associating them with specific organisms.[5] What follows are examples of work led by CDC and its partners in several of these focus areas.

AR contamination of watersheds by human waste

Investigators from the University of Utah were funded by CDC to study three rivers comprising the Blue River watershed that straddles the states of Kansas and Missouri.[6] This watershed was selected on the basis of its high population density, long history of waste overflow from a combined sewage system, and the presence of multiple, high-capacity WWTPs. They found, on average, a 140-fold increase in ARG abundance in samples collected five km downstream of a WWTP discharge location, as well as a 30-fold increase in ARG diversity in samples collected from downstream sites. In another study, researchers from the University of Georgia intensively sampled a mixed-use watershed located in northeast Georgia and found *E. coli* contamination frequently exceeding the US Environmental Protection Agency (EPA) threshold for recreational water; AR was identified in 6.9% of isolates.[7] *E. coli* counts exceeded the EPA threshold more often in the spring and summer seasons. In general, rural streams had acceptable *E. coli* counts, while urban and suburban streams had higher levels of *E. coli* counts that may be attributable to surface runoff from built infrastructure, leaking sewer lines, and failing septic systems. Additionally, investigators from The Ohio State University investigated the potential uptake of carbapenem resistance (CR) genes in bacteria colonizing aquatic wildlife in the Ohio Scioto river.[8] They found specific CR genes in bacteria recovered from fish taken both upstream and downstream of WWTPs, suggesting the potential for AR to become integrated and disseminated in the environment through wildlife.

Hospitals and other healthcare facilities can be an important human source of the ARGs that make it into municipal sewage that then may pass through WWTPs. Colonization and amplification in healthcare facility drains and building wastewater plumbing by human-sourced ARGs may be a frequent initiating event. AR pathogens can become established in biofilms in sink drains, especially the p-traps, that then may become a source for AR healthcare-associated infections.[9] A driver in this early colonization and amplification are the nutrients that are often disposed along with the ARGs in sinks and healthcare plumbing.[10] Because further amplification can occur along the length and surface area of building and municipal sewage systems, a promising approach may be mitigation strategies applied early in the waste stream, such as heating of sink p-traps[9] or pulsed electric field application.[11]

Impact of antifungal use on plants

Another important focus to advance understanding of AR in the environment includes CDC's work on the fungal pathogen *Aspergillus fumigatus*. This mold can be found indoors and outdoors and is common in *soil. A. fumigatus* produce spores that spread through the air and are breathed in by humans frequently. This intake of spores is a risk for people with weakened immune systems and can cause serious lung or sinus infections, which can spread to other parts of the body, and can result in death. The first line treatment for these infections are the azole class of antifungal drugs. Azole fungicides, similar to lifesaving azole medications used in humans, are broadly used in agriculture on a vast array of crops to treat or prevent fungal plant diseases and subsequent crop loss. In the US alone, agricultural use of azoles has increased 4-fold since 2006.[12]

An increasing number of azole-resistant *A. fumigatus* infections are being identified in humans worldwide. It is expected that the use of azole medications to treat aspergillosis in humans would inevitably contribute to the development of resistance. However, the growing number of resistant *Aspergillus* infections identified among patients who never received azole treatment prompted the discovery of unique genetic resistance markers associated specifically with environmental azole fungicide use. This globally emerging occurrence of resistance prompted CDC to evaluate US patients and crop soil for the presence of these environmental markers. In 2011, CDC began passive monitoring from clinical microbiology laboratories across the nation, and in 2016 this system identified its first human isolate of this kind, with more to follow.[13] In 2017–2018, CDC funded investigators at the University of Georgia to collect and characterize azole-resistant *A. fumigatus* strains from agricultural and horticultural sites in multiple US regions to better understand the emergence and sources of azole resistance. In 2017, azole-resistant *A. fumigatus* isolates carrying the environmentally related markers were first detected in US soil samples obtained from a commercial peanut field treated with azole fungicides.[14] These findings help to establish the emergence of azole-resistant *A. fumigatus* strains among US patients likely caused by selection for resistance during environmental azole use.

Next steps

The CDC AR-related work in water (i.e., surface, ground, and drinking waters) will continue to expand to identify the main U.S. sources of pathogens and ARGs, gain a better understanding of how to prevent their transport and development in our water resources, and determine the true levels of impact on human health with regards to resistance carriage or infections. One focus will continue tobeonour health care facilities, as we advance our studies of biofilms, sink drains, premise plumbing, and disinfection methods, as well as on the effluent that is currently released from these facilities.

In 2020, CDC was able to leverage foundational work on AR in the environment to support the COVID-19 response. CDC originally funded investigators at the University of South Carolina to evaluate the role of bio-aerosols generated during wastewater treatment on the risk of AR infection or colonization in wastewater workers. Using additional CDC funding, the investigators were able to expand their study to include SARS-CoV-2 testing in wastewater, bio-aerosols, and wastewater workers. This work provided critical information on the COVID-19 risk from wastewater exposures and the utility of wastewater testing to track SARS-CoV-2 infection levels in the community. The National Wastewater Surveillance System (NWSS) is now collecting data from over 150 wastewater treatment plants across the country and provides actionable, community-level public health data to understand the spread of COVID-19. This work will again be expanding to include additional AR focus to track the presence of more bacterial and fungal pathogens and the ARGs they carry and share.

The CDC work on *A. fumigatus* is moving to a more structured surveillance methodology to collect, confirm, and characterize *A. fumigatus* clinical isolates and detect azole resistance from hospital-based laboratories, commercial and clinical laboratories, and state public health laboratories within their region. This standardization within the AR Laboratory

Network will aid public health departments and healthcare facilities in raising awareness that azole-resistant *A. fumigatus* may be increasing in the clinical setting in the US, and CDC will continue to expand these efforts and work with partners to more thoroughly evaluate the levels of human risk for AR infections and carriage generated by pesticide use on plants.

Tracking the movement of ARGs and pathogens through the One Health spectrum is of great importance. To address this focal area, projects are currently underway that will determine the full profile of all ARGs present in human stool samples and compare them to genes observed in healthcare, agricultural, and environmental settings. The organisms to be studied include extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and antibiotic-resistant *E. coli*. Researchers will evaluate risk factors including use of antibiotics and other prescription pharmaceuticals, age, housing, water source, lifestyle factors (e.g., travel, companion animals), bacteria spread within households, and diet.

The second US National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB 2.0) defines the focus of work proposed to be conducted from 2020–2025[15]. Among the many AR plans and topic areas to cover, several involve work on AR and the environment, including (1) coordinate with federal partners to expand AR surveillance from multiple sources across One Health, including establishment of new capacities for collecting AR data from the environment (e.g., water, soil); (2) map existing AR ecology across One Health and monitor shifts over time by establishing a pilot sampling strategy to collect human, animal, plant, and environmental (e.g., water, soil) specimens along with epidemiological data; (3) engage relevant stakeholders, including animal and plant production communities, to develop and implement strategies to foster the appropriate use of medically important antibiotics; (4) expand the CDC AR Laboratory Network internationally in key regions and establish capacity to receive and test isolates using standardized methods and deploy rapid responses to control and contain high-threat, human-relevant, antibiotic-resistant pathogens from across the One Health spectrum, including from the environment; (5) work internationally to assist governments, civil society, and the private sector in low- or middle-income countries to improve capacity and implement effective practices to prevent and control infection, including through the availability and proper use of water, sanitation, and hygiene (WASH); (6) assist international governments, civil society, and the private sector in low- or middle-income countries with capacity-building for antibiotic stewardship and regulation to address the appropriate use and availability of quality-assured antibiotics, including for use in agriculture; and (7) provide specimens, laboratory testing, data, and evaluations to collaborators and work with partners to promote alternatives to antibiotic and antifungal use, including vaccines, therapeutics, and infection control practices that promote healthy humans, animals, and plants so that infections and spread are prevented.

Some of this work is already underway domestically and internationally, with planning for potential expansion, and anticipating many collaborative opportunities with our partners to further advance the work on AR in the environment. It is critical that as we address the global problem of AR, we take a comprehensive One Health approach to understand and mitigate the impact of AR pathogens in humans, animals, and the environment.

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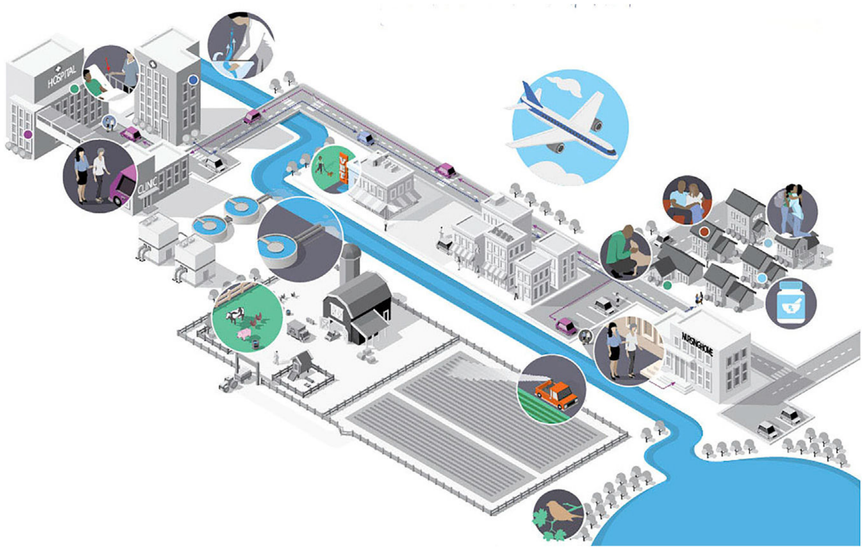

Figure 1. Interconnectedness of human, animal, and plant health and the critical role of the environment in the dissemination of antibiotic resistance

The figure highlights the complexity of the factors involved in emergence and spread of antibiotic resistance, including antibiotic use in medicine and farming, healthcare-associated infections, animal- and community-associated infections, land use, and wastewater management. The figure is reproduced from CDC's report on Antibiotic Resistance Threats in the United States.[2]