Linking EPA to a One Health Focused National Scale Monitoring of Antimicrobial Resistance

Problem

Antimicrobial resistance (AMR) is one of the major public health threats of the 21st century. Antimicrobial resistance occurs naturally; however, resistance is accelerated by the misuse and overuse of antibiotics for humans and animals. In 2019, 2.8 million Americans were infected with antibiotic resistant bacteria, leading to more than 35,000 deaths and $21-24 billion in health care costs. Global deaths directly attributable to AMR infections were 1.27 million in 2019, with estimates of over 10 million (more than from cancer) by 2030. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

The magnitude of the AMR public health issue impelled the worldwide development of multifaceted action plans to combat AMR, including improved stewardship of antibiotics, development of new antimicrobials, and advanced surveillance. The U.S. federal government established a national surveillance system to monitor antimicrobial resistance in zoonotic bacteria from food animals and humans. Led by the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM), the National Antimicrobial Resistance Monitoring System (NARMS) for enteric pathogens is a collaboration with the Centers for Disease Control (CDC) and the U.S. Department of Agriculture (USDA). A consensus has emerged among the greater public health profession to adopt an interdisciplinary one health model of infectious disease monitoring and control. The One Health paradigm recognizes 1) that human and animal health are linked to environmental health, and 2) the need to better understand the role of the environment in the spread of disease. Following recommendations of the FDA Science Board in 2017, NARMS has been transitioning to an integrated One Health model of surveillance to include animal pathogens and environmental testing.

Approach

The FDA as the lead agency for NARMS, teamed up with EPA-ORD to leverage ORD's experience and existing programs to conduct a pilot environmental AMR monitoring effort. Since 2020, EPA-ORD has led an interagency NARMS Environmental Working Group to define and implement this pilot effort. Surface water was selected as an initial environmental component for monitoring because of its integration of various anthropogenic impacts within a watershed. Following guidance from many international working groups on the environmental dimensions of AMR, a three-phase research plan was defined, involving 1) standardized sampling and analysis to facilitate comparison of these data to rapidly expanding analyses across the globe, 2) development of a statistically robust study at the watershed scale to serve as a template for further efforts across the country, and 3) national scale

Phase 1	SWAM Pilot	Statistical Design Subgroup discussions	Initial testing of methodologies	FY21-1st half FY22
Phase 2			Watershed based assessment to evaluate methodologies before national sampling and serve as a demonstration project for future watershed studies	Spring FY22-Spring FY23
Phase 3			Probabilistic national survey to provide statistically valid estimates of AMR status and trends in surface water, using methods tested in the other phases	Summers 2023-24,
Phase 4			Continued probabilistic national monitoring together with expanding number of (partner-led) intensive watershed studies across the country	2024+

Table 1. Table showing the phases of the surface water pilot program and the associated timeline of events.

assessment to provide long term trends. Phase I focused on developing three major types of methods, including 1) culture based approaches for isolating antibiotic resistant bacteria (ARB) of interest *(E. coli, Enterococcus, and Salmonella*), 2) quantitative measures of dozens of antibiotic resistant genes (ARG), and 3) broader sequencing of the overall microbiome in water (i.e metagenomics). Phases II and III utilize existing EPA water quality monitoring efforts at the watershed (East Fork of the Little Miami River in Southeast Ohio, CY22-23) and national (National Rivers and Streams Assessment, CY23-24) scale.

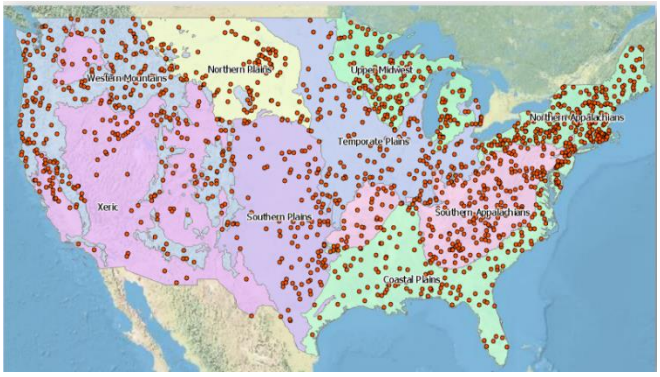

Figure 1. Map showing the National Rivers and Streams Assessment (NRSA) sites.

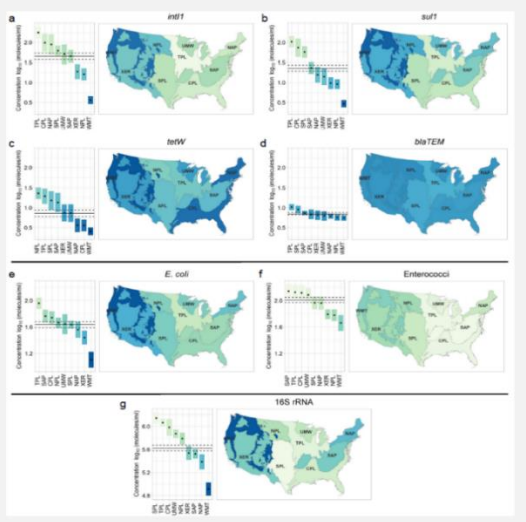

Figure 2. Mappring of ARG in preliminary testing as part of NRSA

Costs and resources necessary to accomplish the ambitious goals of the projects are shared across agencies. ORD provides staff (including a dedicated federal post-doc within CEMM and portions of staff in CEMM and CESER) and the significant overhead associated with planning and implementing the existing watershed and NRSA study designs. USDA-ARS provides staff for research planning and method development. FDA-CVM committed resources to perform the metagenomic analysis of samples and whole genome sequencing of isolates. In addition, FDA-CVM provided resources to USDA-ARS to support method development and EPA-ORD to collect, process, and analyze the samples via interagency agreements. Total funding to ORD was $300K in FY22, with projections of ~$1M total in FY23 and 24.

Results

The proposed work will analyze ~800 surface water samples from the East Fork watershed and nearly 2,000 from across the Nation as part of NRSA using the multilevel assessment approach

(isolation of key types of ARB to quantification of ARG to whole genome assessment) described above. *Salmonella* will be enriched, isolated, and genetically sequenced. Antimicrobial resistant and pan-susceptible *E. coli* and *Enterococcus spp*. will be enumerated, isolated, and sequenced. Nucleic acids will be extracted and analyzed for a set of ARG and fecal source tracking genes using methods developed and vetted by the Environmental Working Group. Extracts will be shipped to FDA for metagenomic analysis.

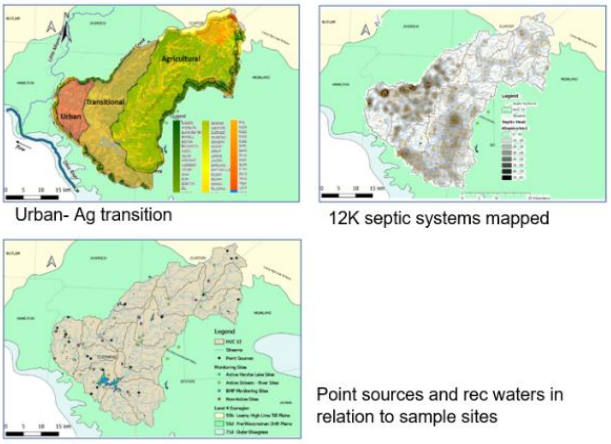

Figure 3. Maps of East ForK Watershed with relevant characteristics and study sampling sites

Impact

The national scale assessment of ARG and ARB prevalence in U.S. rivers and streams, based on a statistically valid design, will form a baseline for measuring long term environmental trends as a pilot component of the NARMS surveillance program. Additionally, it will provide information on which types of aquatic systems, environmental conditions, and landscape factors tend to be associated with higher ARG and ARB prevalence. However, since most sites are visited once during the summer and are tens to hundreds of kilometers apart, the national survey will provide little detail about seasonal patterns, the importance of storm events, and the dynamics of AMR as it moves from sources to receptors.

The watershed study is complementary to the national survey in that it addresses these questions of seasonal and interannual dynamics and local-scales processes that modify ARGs and ARBs in the environment. Importantly, One Health linkages between humans, animals, and the environment are more visible at the watershed scale, allowing for more direct assessment of specific exposure risks, occurrence drivers, and mitigation strategies. While the watershed study will increase our understanding of both risk and intervention control points based on the characteristics of this pilot system, it cannot explain AMR dynamics in other watersheds. Combining the watershed study with the national probabilistic survey allows inference to watersheds that share common characteristics and AMR drivers and will inform how to design and implement future studies focused on other watersheds.

Overall, these data will help the agencies better assess and prevent waterborne risks associated with AMR pathogens in surface water, drinking water, irrigation, and water reuse. Because work will be coordinated with the existing NARMS surveillance programs of CDC, USDA, and FDA, analyses will provide a fuller picture of how resistant strains are related spatially and temporally among human, animal, and environmental systems, as well as of how anthropogenic drivers and intervention strategies impact the transmission of AMR between them. Developed study designs and analytical methods will also provide consistent methodologies for other researchers in the field, facilitating broader data comparison and integration. Together, this effort will aid the broader national efforts to combat antimicrobial resistant bacteria by supporting a comprehensive One Health AMR monitoring strategy.