Integrating Environmental Dimensions of "One Health" to Combat Antimicrobial Resistance: Essential Research Needs

Ling Jin, Amy Pruden, Alexandria B. Boehm, Pedro J.J. Alvarez, Lutgarde Raskin, Tamar Kohn, and Xiangdong Li*

ACCESS | Metrics & More | Article Recommendations

Antimicrobial resistance (AMR) is undoubtedly a vital "One Health" challenge underpinned by the interdependence of humans, animals, and the environment. The consequences of AMR—the failure of antimicrobials to cure infections in humans and livestock—directly affect human and animal health and wellbeing and result in socioeconomic loss. As a result, it is insufficient to only study AMR in the environmental compartments of water, soil, and air without an anthropocentric etiological perspective. Any investigation should consider the mechanisms and risks of AMR transmission to humans from what we eat, drink, breathe, and touch. Similarly, investigations on the evolution and transmission of antimicrobial resistance genes (ARGs) in environmental media are most relevant when there is a connection to preserving the efficacy of medically important antimicrobials.[1]

The recent exponential growth in environmental AMR research has often been narrowly focused and lacking the relevance and impact to health outcomes. This limits the applicability of the findings and can result in an over- or underestimation of the role of the environment. For example, focusing merely on quantitative or real-time polymerase chain reaction (qPCR)-based or metagenomics-based measurements of ARG abundances renders many health-irrelevant ARGs mistargeted; overlooking the aggregate exposure pathways constituting a population-level acquisition of AMR can lead to an underestimation of overall exposure. In this Viewpoint, we highlight several critical issues for researchers working in this field and invite a "Letter to Editor" response in order to better define impactful contributions from the environmental dimension of AMR as part of a broader "One Health" vision.

■ AMR RISK ASSESSMENT REQUIRES A HOLISTIC UNDERSTANDING OF ENVIRONMENT-HUMAN CONNECTIVITY

A number of studies investigating pollution over a range of environmental reservoirs have well documented catchment- and regional-scale patterns of anthropogenic inputs of antimicrobials, ARGs, and antimicrobial resistant bacteria (ARB) and other agents suspected to impose selection pressure and contribute to the evolution of AMR.[1] What is now needed is a means to translate such measurements into exposure and risk scenarios. A few studies have attempted to determine the genetic relationship between environmental and human isolates recorded in public databases to infer the dynamics of transmission. However, disentangling the underlying physical processes mediating transmission is challenging, and thus our understanding of the environment-human connectivity remains weak. Exposure/risk modeling is needed to consider relevant exposure scenarios and complexities based on empirical monitoring data combined with realistic thresholds for health protection. Aggregate exposure pathways to AMR should also be considered (e.g., ingestion of animal- and plant-based food and drinking water, inhalation of indoor and outdoor air, and contact between humans and with animals and high-touch surfaces, Figure 1). This would inform health interventions and enable source mitigations.

Occupational exposures also represent a key exposure scenario for assessment. Approximately 8% of the global population is employed in healthcare, waste management and recycling, and aquaculture and livestock rearing.[2] Priority should be given to assessing the risk of AMR in frontline workers, particularly in low-income countries where poor sanitation and hygiene conditions create an increase in probabilities and magnitudes of exposure. While evidence of the occupational acquisition of certain resistant pathogens has been emerging for workers in livestock farms[3] and wastewater treatment plants,[4] it is yet to be established for other sectors. The increased likelihood of resistant pathogens in the nasal carriage of nonoccupationally exposed family members of livestock workers[2] also supports the hypothesis that the occupational population may carry ARB from their workplace
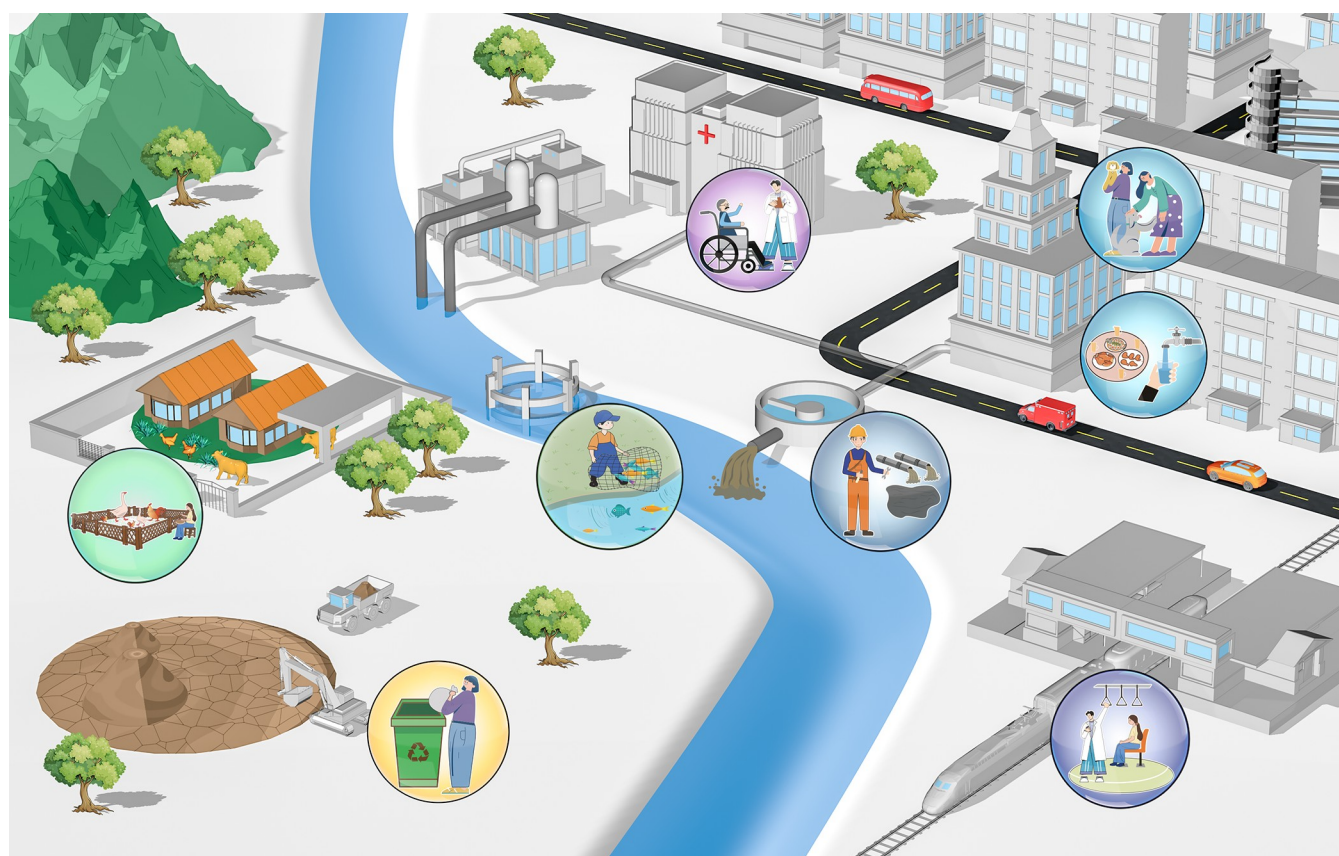
Figure 1. Environment-human, animal-human, and human-human transmission routes of antimicrobial resistance in occupational and general population.

back to households and communities. Such secondary transmission routes merit further investigation.

Lower-level chronic exposure scenarios include (a) ingestion of vegetables irrigated by reclaimed water or grown on soil fertilized by biosolids/manure, (b) raw food products from aquaculture or livestock farm animals, (c) contaminated tap water, and (d) inhalation of bioaerosols. Secondary transmission routes include short-range airborne transmission between humans as well as via high-touch surfaces in public spaces (e.g., mass transportation, street markets), particularly in densely populated urban regions, where fomite transmission of ARB (e.g., multidrug-resistant strains of *Mycobacterium tuberculosis*) may be favored. Contact with pets may also constitute an important pathway of AMR transmission considering the global pet population and ownership (e.g., 471 million dogs in 33% of households and 370 million cats in 23% of households[5]) and frequent use of antibiotics in these companion animals. Including social-environmental networks into a broader environmental exposure framework is therefore highly encouraged to probe the complex dynamics of microbial exchange and ARG acquisition.

To further unveil the role of environmental sources in the transmission of ARGs and ARB to humans, it is also vital to uncover the mechanistic processes that mediate progression from colonization to infection.[6] In healthy individuals, silent colonization may be caused by the resident vector of ARGs or by the commensal microbiota receiving ARGs from transiently colonizing vectors. Silent colonization over a long period may evolve into an endogenous infection if the host reaches an immunocompromised state. In immunocompromised individ-

uals, acute colonization from external sources may occur with the immediate invasion of the host. The development of high-throughput culturomics, functional metagenomics, and biofilm assays in *in vivo* animal and human exposure studies will aid in the elucidation of mechanisms underlying host−microbe interactions and host responses. The mechanisms of transmission to colonization and infection need to be translated into the strain-specific infectious dose of a certain ARB to advance quantitative assessments of microbial risk.[7,8] Such a framework should contain both culture-dependent and culture-independent measurements to include under-appreciated resistance phenotypes. A quantitative microbial risk assessment framework incorporating the aggregate exposure pathways, infectious dose, and effect mechanisms of colonization and infection is also in line with the well-established risk assessment framework for chemical pollutants, thus contributing to the development of a human exposome framework.

■ TAILORED SOURCE CONTROL REQUIRES A CONTEXT-SPECIFIC UNDERSTANDING OF SELECTIVE FORCES FOR ARG DISSEMINATION

On the source side, a causal understanding of which selective agents drive the emergence, evolution, and dissemination of resistance in environmental reservoirs is needed to enable engineering controls to limit ARG/ARB proliferation in environmental reservoirs, for example, the treatment of ARG-laden waste, disinfection of public spaces, ventilation design for closed spaces, or antimicrobial material in personal protection. Correlations with concentrations of suspect chemicals (e.g., antimicrobials, heavy metals) cannot fully explain the environ-

mental mechanisms driving the abundance of ARGs, mobile genetic elements, or bacterial taxa in environmental samples. In recent laboratory-based studies, a range of emerging non-pharmaceutical agents (e.g., nanoparticles, artificial sweeteners, microplastics) were discovered to stimulate the conjugative transfer of ARGs between bacteria or the transformation of extracellular ARGs into bacteria. Despite these advances, still lacking is a fundamental understanding of what roles the chemical cocktail of excreted antimicrobials and other nonpharmaceutical agents play in AMR selection in real environments. Such understanding can be advanced, for example, by an effect-directed analysis (EDA), a widely adopted approach in ecotoxicology for identifying the responsible agents contributing to the mixture effects of a given environmental sample on a biological end point. Microfluidic platforms, for example, can house high-throughput screening of active fractionations of extracts of environmental samples that can stimulate ARG evolution. A high-throughput (non)target analysis of the active fractions and mixture-effect modeling can help in prioritizing the selection agents.

Horizontal gene transfer (HGT) is itself a target tunable by engineering controls. Conjugation between bacteria is often considered to dominate the dissemination of ARGs in the environment due to the high transfer efficiency and general abundance of plasmid-borne ARGs. Transduction via bacteriophages and transformation via free DNA uptake are generally treated as negligible. Among the growing body of studies that are challenging such assumptions, a recent study[9] conducted in a suspended growth system clearly demonstrates that the phage delivery of ARGs can reach transfer frequencies comparable to those of conjugative plasmid-mediated transfer at relatively low bacterial cell concentrations under either quiescent or turbulent conditions that hinder conjugation. These emerging findings underscore the need for systematic investigations of HGT events to unravel what chemical (e.g., specific pollution, trophic status) and physical (e.g., hydrodynamics, UV radiation) conditions determine the relative importance of HGT mechanisms in environmental reservoirs. Novel approaches are needed, such as labeled assays and bioinformatic pipelines, to detect genetic exchange and HGT events in system-specific mesocosms or real-world source settings. A holistic understanding of the complex genetic dynamics in relation to physicochemical conditions will aid efforts to devise tailored strategies to mitigate the overall loading of high-risk ARGs and ARB.

◼ WASTEWATER-BASED EPIDEMIOLOGY OF AMR REQUIRES FURTHER DEVELOPMENT

During the COVID-19 pandemic, the value of sewage surveillance for SARS-CoV-2 RNA as a proxy of disease occurrence in a community was realized, prompting the establishment of corresponding research and infrastructure around the world for wastewater-based epidemiology (WBE). This development coincides with sewage surveillance for AMR.[10] Sewage can contain signals that reflect community-level dissemination of AMR. WBE is advantageous because it provides an integrated view of AMR dynamics carried across the human population, and community level surveillance may be more cost-effective and efficient than sampling from individuals. Information on ARGs prevalent in sewage could also inform medical doctors with respect to which antibiotics are likely to remain effective within a given population. The

WBE approach for population-level AMR surveillance is still in its infancy. Extensive research and benchmarking are required to understand the potential and limitations of this surveillance strategy for AMR, in view of its great complexity. Ensuring that the data are actionable is a prerequisite for the full benefits of WBE to be realized.

◼ ONE ENVIRONMENT FOR ONE HEALTH

Two decades of research on the environmental dissemination of AMR has highlighted more complex scientific questions than were initially considered when ARGs were defined as emerging contaminants. While the Precautionary Principle is advocated for assessing the risks of AMR, it is technically and economically infeasible to eliminate all environmental AMR reservoirs. A holistic, causal understanding of AMR transmission from environments to humans is needed to prioritize mitigation and control strategies.

Novel insights into the environment-human connectivity will inform cost-effective intervention measures (e.g., disinfection, personal protection) at key checkpoints along the chain of transmission. The environmental research community can contribute by developing different models adapted to an anthropocentric context of microbial transfer at the environment-human interface and advanced antimicrobial materials/technologies for protective equipment and decontamination measures. A system-specific understanding of the selective forces for ARG dissemination will lead to more precise engineering solutions to constrain the entry of ARGs into the environmental transmission chain. The environmental research community can also contribute by developing analytical approaches to identify responsible agents or conditions that select for AMR evolution and fit-for-purpose treatment technologies for mitigating high-risk ARGs and ARB at key sources. Cross-fertilization between environmental disciplines (e.g., chemistry, toxicology, microbiology, fluid dynamics, and engineering) and other disciplines (e.g., medical microbiology, immunology, infectious disease epidemiology, and data/network science) is needed and encouraged in this course. Mechanisms to achieve cross-national participation and coordination, such as the Tripartite Integrated System for Surveillance on AMR and Antimicrobial Use, are needed to realize the benefits of environmental AMR surveillance. Only in this way will the environmental significance of AMR be understood and managed as a meaningful contribution to the "One Health" approach to combatting this silent pandemic.

◼ AUTHOR INFORMATION

Corresponding Author

Xiangdong Li − *Department of Civil and Environmental Engineering, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong;* orcid.org/0000-0002-4044-2888; Email: cexdli@polyu.edu.hk

Authors

Ling Jin − *Department of Civil and Environmental Engineering and Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong;* orcid.org/0000-0003-1267-7396

Amy Pruden − *Department of Civil & Environmental Engineering, Virginia Tech, Blacksburg 24060 Virginia, United States;* orcid.org/0000-0002-3191-6244

Alexandria B. Boehm − *Department of Civil and Environmental Engineering, Stanford University, Stanford 94305 California, United States;* ◉ orcid.org/0000-0002-8162-5090

Pedro J.J. Alvarez − *Department of Civil and Environmental Engineering, Rice University, Houston 77005 Texas, United States;* ◉ orcid.org/0000-0002-6725-7199

Lutgarde Raskin − *Department of Civil and Environmental Engineering, University of Michigan, Ann Arbor 48109 Michigan, United States;* ◉ orcid.org/0000-0002-9625-4034

Tamar Kohn − *Laboratory of Environmental Chemistry, School of Architecture, Civil and Environmental Engineering, École Polytechnique Fédérale de Lausanne, Lausanne CH-1015, Switzerland;* ◉ orcid.org/0000-0003-0395-6561

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.est.2c01651

Notes

The authors declare no competing financial interest.

Biography

Prof. Li is Chair Professor of Environmental Science and Technology in Department of Civil & Environmental Engineering and Ko Jan Ming Professor in Sustainable Urban Development at The Hong Kong Polytechnic University. He is recognized for his innovative and dynamic work in environmental biogeochemistry, including research in the fields of regional contamination, urban air $PM_{2.5}$ pollution, and the origin and dissemination of antimicrobial resistance. Professor Li serves as an Associate Editor for Environmental Science & Technology (ES&T) and as Deputy Editor for ACS Environmental Au.

■ REFERENCES

(1) Vikesland, P. J.; Pruden, A.; Alvarez, P. J. J.; Aga, D.; Bürgmann, H.; Li, X. D.; Manaia, C. M.; Nambi, I.; Wigginton, K.; Zhang, T.; Zhu, Y. G. Toward a comprehensive strategy to mitigate dissemination of environmental sources of antibiotic resistance. *Environ. Sci. Technol.* **2017**, *51*, 13061−13069.

(2) World Bank. 2022. Moving towards sustainability the livestock sector and the world bank. http://www.worldbank.org (Accessed on 2022-02-26).

(3) Nadimpalli, M. L.; Stewart, J. R.; Pierce, E.; Pisanic, N.; Love, D. C.; Hall, D.; Larsen, J.; Carroll, K. C.; Tekle, T.; Perl, T. M.; Heaney, C. D. Face mask use and persistence of livestock-associated *Staphylococcus aureus* nasal carriage among industrial hog operation workers and household contacts, USA. *Environ. Health Perspect.* **2018**, *126*, 12.

(4) Rodríguez-Molina, D.; Berglund, F.; Blaak, H.; Flach, C. F.; Kemper, M.; Marutescu, L.; Gradisteanu, G. P.; Popa, M.; Spießberger, B.; Weinmann, T.; Wengenroth, L.; Chifiriuc, M. C.; Larsson, D. G. J.; Nowak, D.; Radon, K.; de Roda Husman, A. M.; Wieser, A.; Schmitt, H. Carriage of ESBL-producing Enterobacterales in wastewater treatment plant workers and surrounding residents — the AWARE Study. *Eur. J. Clin. Microbiol. Infect. Dis.* **2021**, DOI: 10.1007/s10096-021-04387-z.

(5) Petfood Industry. 2021. INFOGRAPHIC: Most of world owns pets; Dogs are tops. http://petfoodindustry.com (accessed on 2022-02-26).

(6) Casadevall, A.; Pirofski, L. Host-pathogen interactions: Basic concepts of microbial commensalism, colonization, infection, and disease. *Infect. Immun.* **2000**, *68*, 6511−6518.

(7) Schoen, M. E.; Jahne, M. A.; Garland, J.; Ramirez, L.; Lopatkin, A. J.; Hamilton, K. A. Quantitative microbial risk assessment of antimicrobial resistant and susceptible *Staphylococcus aureus* in reclaimed wastewaters. *Environ. Sci. Technol.* **2021**, *55*, 15246−15255.

(8) Nayfach, S.; Pollard, K. S. Toward accurate and quantitative comparative metagenomics. *Cell* **2016**, *166*, 1103−1116.

(9) Sun, R. N.; Yu, P. F.; Zuo, P. X.; Alvarez, P. J. J. Bacterial concentrations and water turbulence influence the importance of conjugation versus phage-mediated antibiotic resistance gene transfer in suspended growth systems. *ACS Environ. Au* **2021**, *2*, 156−165.

(10) Pruden, A.; Vikesland, P. J.; Davis, B. C.; de Roda Husman, A. M. Seizing the moment: now is the time for integrated global surveillance of antimicrobial resistance in wastewater environments. *Curr. Opin. Microbiol.* **2021**, *64*, 91−99.