UC Irvine
UC Irvine Previously Published Works

Title
Emerging issues in the environmental context of antibiotic-resistance

Permalink
https://escholarship.org/uc/item/1m33d7vw

Authors
Petrillo, Jessica E
Ogunseitan, Oladele A

Publication Date
2018-07-01

DOI
10.1016/j.envint.2018.03.049

Peer reviewed

Correspondence

Emerging issues in the environmental context of antibiotic-resistance

Jessica E. Petrillo[a], Oladele A. Ogunseitan[a, b, *]

[a] Office of International Health and Biodefense, Bureau of Oceans and International Environmental and Scientific Affairs, U.S. Department of State, Washington, DC 20520, United States
[b] Department of Population Health and Disease Prevention, University of California, Irvine, CA 92697, United States

ARTICLE INFO

1. Introduction

The intuitive position that natural biotic and abiotic environmental processes play roles in the development of antibiotic resistance is undisputed, but there is a general lack of understanding of the significance and magnitude of the international environmental context of this major threat to global health. The influence of antibiotics on individual and population health has been revolutionary; however, another revolution is now needed to ensure this transformative influence persists. Throughout the world, significant pathogens are rapidly becoming resistant to the drugs used to treat the diseases they cause (Centers for Disease Control and Prevention, 2018a; World Health Organization, 2017). The potential implications are significant and wide-reaching – negatively impacting health, economic and social development, and national and food security (Food and Agricultural Organization of the United Nations, 2016). Left unaddressed, by 2050 the global burden of drug-resistant disease is projected to become a leading cause of mortality and have the potential to result in annual direct costs (attributable to the impact on the labor supply) in the range of 2–3% of global output GDP (Taylor et al., 2014). Drug-resistant disease also is threatening medical advances made over the past century including services such as surgeries and chemotherapy (out of concern over an inability to control infections) and progress made on infectious disease such as Tuberculosis. While drug resistance is a natural phenomenon, human actions can accelerate the development of "avoidable" resistance (Centers for Disease Control and Prevention, 2018b). Limiting the emergence and spread of avoidable resistance calls for whole-of-society action.

Concerns over the emergence and spread of drug-resistant disease are driving national and international action to reduce avoidable resistance. The past few years have witnessed significant political support by specific sectors (e.g., through the World Health Organization, Food and Agriculture Organization, and World Organization for Animal Health) and groups of countries (e.g., through G7 and G20, and via the Global Health Security Agenda). In a rare demonstration of urgency on health issues, world leaders at the 71st United Nations General Assembly issued a political declaration on drug-resistant disease (United Nations, 2016). Nations and international agencies, the private sector, and civil society organizations are also increasingly taking action (World Health Organization, 2015a; FAO/OIE/WHO, 2016). The core elements of these efforts include: increasing awareness of drug-resistant disease and steps that can be taken to address it; improving the state of knowledge to inform evidence-based interventions; improving stewardship of antimicrobials; and accelerating research and development of new antibiotics, point of use diagnostics, and alternative therapies to antibiotics (World Health Organization, 2015b; National Action Plan for Combatting Antibiotic-Resistant Bacteria, 2015). Despite such international attention, key environmental components of the threat remain under-represented in political prioritization and public awareness, availability and implementation of effective interventions, and basic science (Food and Agricultural Organization of the United Nations, 2016; Yelin and Kishony, 2018).

2. Knowledge gap: the environmental context of antibiotic resistance

The coexistence in the same ecological niche of anthropogenic antibiotic pollution and antibiotic-producing, -sensitive, and -resistant bacteria is one of the more intractable subjects of environmental microbiology and biochemical evolution (Ogunseitan, 2005; Garbisu et al., 2018). It is also a critical, yet under-represented field of study that is needed to implement effective measures to limit the emergence and spread of avoidable drug-resistant disease (Ogunseitan, 2016).

The conversion of sensitive bacteria to antibiotic resistance is influenced by the concentration of antibiotics to which bacterial popula-

* Corresponding author at: Department of Population Health and Disease Prevention, University of California, Irvine, CA 92697, United States.
Email address: Oladele.Ogunseitan@uci.edu, Ogunseitano@state.gov (O.A. Ogunseitan).

tions are exposed, and the density of antibiotic-resistance genes present in the immediate environment (Sommer et al., 2017). The artificial introduction of antibiotics into the environment and natural ecosystems has the potential to tilt the balance of selection toward increased survival and proliferation of resistant bacteria, with potential impacts for humans and animals living in or near these ecosystems. A schematic diagram of the pathways through which anthropogenic sources impact environmental concentrations of antibiotics is presented in Fig. 1. These sources represent potential opportunities to design interventions against the putative selective pressures that drive the evolution and spread of antibiotic resistance in pathogenic bacterial populations.

While the determinations of pathogens of greatest concern vary by location, the top three pathogens on the WHO "priority pathogen" list, *Acinetobacter baumannii, Pseudomonas aeruginosa,* and bacteria belonging to the Enterobacteriacea family (World Health Organization, 2017) serve as a useful illustrative example of this phenomenon. The diseases caused by these bacteria pose a significant threat in hospitals and nursing homes particularly given their increasing resistance to carbapenems – an antibiotic of last resort. All three pathogens are abundant in the environment, including polluted water and soil ecosystems. So is *Streptomyces cattleya*, a species that naturally synthesizes carbapen-

ems (Surette and Wright, 2017) placing antibiotic-producing and antibiotic-sensitive bacteria in the same ecological niche. Recent data also show high concentrations of carbapenems in wastewater effluents, (Szekeres et al., 2017) underscoring the potential for the co-localization of anthropogenic carbapenems and carbapenem-producing and carbapenem-sensitive bacteria.

To compound the issue, new data suggest environment-mediated transmission of carbapenem resistance genes. Carbapenem-resistant bacteria have recently been found in farm animals in the United States (Mollenckopf et al., 2017) despite the fact that in the United States, carbapenems are approved for – but rarely used in – clinical settings and are not approved for usage in livestock.

Despite the theoretical understanding of environmental selective pressure to the emergence of antibiotic resistant pathogens, little data and few conceptual frameworks exist to support effective locally-relevant interventions. The collection of necessary field data to convert theory into action at specific locations is a daunting task that will likely require a distributed strategy for data collection, analysis, and communication.

Although the general pace of work on drug-resistant disease is quickening, research on the environmental life cycle of antibiotics, in-
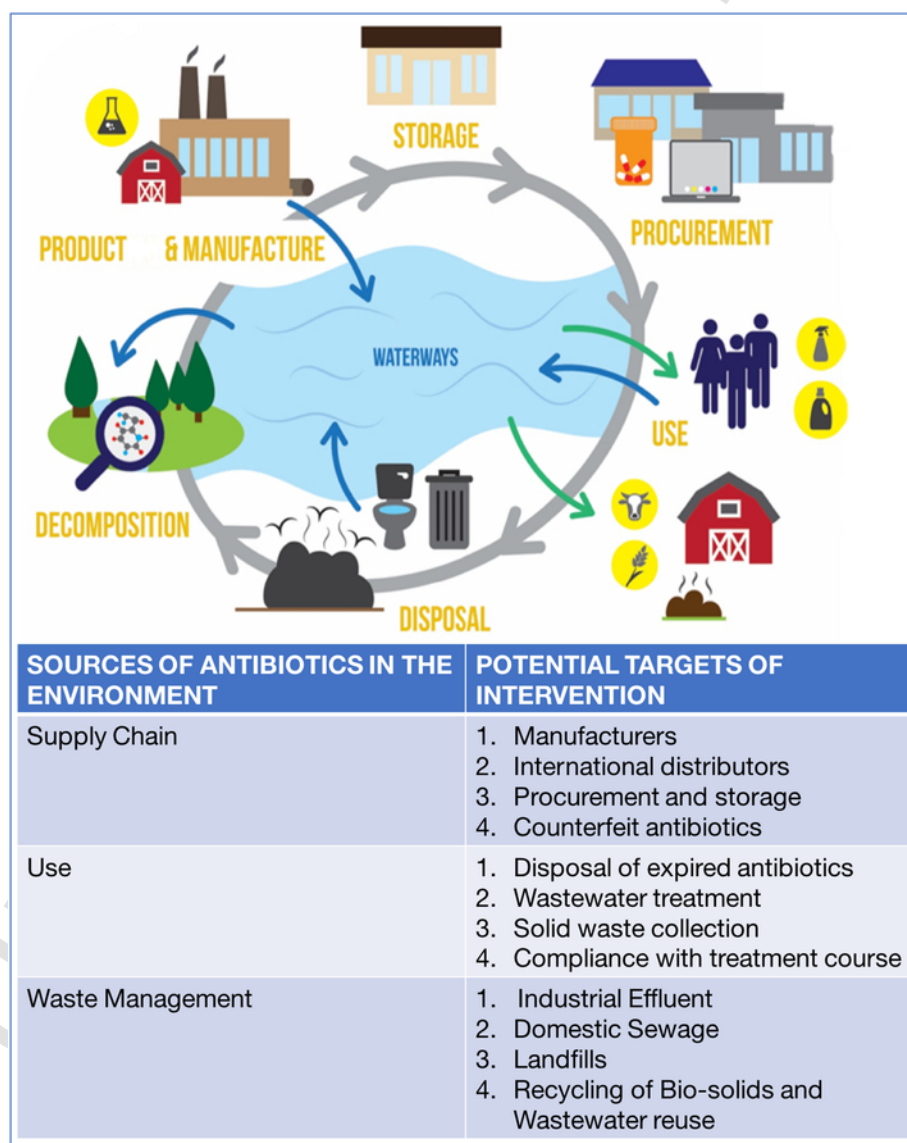

SOURCES OF ANTIBIOTICS IN THE ENVIRONMENT	POTENTIAL TARGETS OF INTERVENTION
Supply Chain	1. Manufacturers 2. International distributors 3. Procurement and storage 4. Counterfeit antibiotics
Use	1. Disposal of expired antibiotics 2. Wastewater treatment 3. Solid waste collection 4. Compliance with treatment course
Waste Management	1. Industrial Effluent 2. Domestic Sewage 3. Landfills 4. Recycling of Bio-solids and Wastewater reuse

Fig. 1. Generalized representation of the antibiotic life cycle architecture.

cluding those of last resort such as carbapenems, remains slow and sparse. Researchers often lack collaborators or professional networks in-country. The options for sample collection and processing are limited. The use of molecular approaches to elucidate the emergence and spread of genetic determinants of resistance is increasing (World Health Organization, 2017), but low-cost methods for detecting the presence of antibiotics in environmental samples is limited, and when advanced equipment is available, the systems to collect, transport, and analyze samples to be processed are often insufficient. The potential geographic scale of field sampling is formidable, covering diverse waterway systems (natural and man-made) and terrestrial environments. And while chemical life cycle modeling is a mature field of study with extensive regulatory applications in other arenas, there are few instances of the application of modeling chemical life cycles to the issue of drug-resistant disease. Moreover, the results of research in this topic area are not yet adequately linked to the decision-making processes that can inform national or international policies and actions.

3. Policy options

Successful integration of the environmental component into international, national, and local action to limit the avoidable emergence of drug-resistant disease will depend on strategies to coordinate political will and to translate science to operational capacity.

1. Garnering Political Will: Individual efforts have raised the profile of the environmental component of drug resistant disease (e.g., the U.N. Environment Program's participation in the UN Ad Hoc committee on AMR and the pharmaceutical industry commitment (International Federation of Pharmaceutical Manufacturers and Association, 2016) to support measures to reduce environmental impact from production of antibiotics). However general awareness and high-level support among policymakers (e.g., Ministries of the environment, interior, and science), scientists, professional societies, civil society, and industry remains low. Critical gaps include a lack of understanding of and connection among relevant sectors and stakeholders.

2. Fostering Scientific Knowledge and Catalyzing Operational Capacity: The robustness of multi-media modeling needed to support decision-making is limited in part due to (a) the paucity of data; (b) the complexity of simultaneously modeling the changing concentrations and population densities of the antibiotics and the microbes, respectively, and the interactions between them; and (c) the insufficient integration of methods for assessing toxicity, cell proliferation, and genetic determinants of resistance.

Traditional and innovative approaches – including citizen science approaches that more vigorously engage the public in affected areas – are needed to improve the scientific knowledge base, and to improve the operational capacity to collect and analyze samples and data, and to effectively communicate significant findings in a timely, relevant manner.

As an initial step toward meeting these objectives, the U.S. Department of State and the U.S. Geological Survey co-sponsored a workshop titled "Mapping the Life cycle of Antibiotics in Southeast Asia" with key participation from the Society for Environmental Toxicology and Chemistry. The purpose of the workshop was to develop an initial framework that diverse communities can use to understand and systematically address the environmental component of the emergence and spread of avoidable drug-resistant disease. The workshop focused on three potentially transformational questions in the environmental nexus of antibiotic-resistance (a) The application of chemical lifecycle assessment strategies to the mapping and modeling of environmental

fate of antibiotics, and identification of hotspots to prevent the rise of antibiotic resistance among pathogenic bacteria; (b) The development of methods to conduct antibiotic lifecycle mapping and modeling for low-resource, low-infrastructure settings, at ecologically vulnerable locations such as the Ganges River and the Lower Mekong delta, and (c) The inclusion of individuals, communities, and public participation in the development of tools, and in collection, integration, analysis and communication of data.

The workshop drew about fifty participants from twelve countries with expertise in complementary disciplines of agriculture, ecology, environmental science and engineering, health care system analysis, manufacturing and product development, mathematical modeling, public health policy, social and behavioral science, and crowdsourcing and citizen science.

The workshop highlighted opportunities for innovative, multi-sectorial participatory approaches in addressing current and forecasted challenges and gaps underlying the effective integrations of the environmental domain into local, national and international action plans to address drug-resistant disease. Future directions for this work include:

(a) Developing broad participatory approaches to collect data from various constituencies to improve understanding of routes by which antibiotics enter the environment, and to provide insights regarding off-label use and prevalence of counterfeit antibiotics. Solicitation of local knowledge of illicit or prohibited practices will be enhanced by engaging local participants in developing survey instruments in a manner that can contribute to the elucidation of global antibiotic reservoirs, flows, and disposals; (b) Distributed model sampling to engage citizens in the collection of water and soil samples from their environments. Hackathons (Global Health Hackathon, 2017) offer avenues for innovative tools development, and programs, such as the Local Environmental Observers Network, (LEO Network, 2015) provide models on how participatory methods can be used for physical data or sample collection; (c) Crowdsourcing data analyses of expectedly large, complex, and varied data sets that are not well suited to traditional computing (Open Street Maps, 2018). This technique could be applied to identify and respond to potential hotspots in antibiotic life cycle mapping exercises.

As the international community seeks to address the emergence and spread of drug-resistant disease, innovative approaches and trans-disciplinary collaborations are needed to ensure that the environmental dimension is effectively integrated into local, national, and international action plans and policies. A distributive approach – grounded in the methodologies of chemical lifecycle mapping and modeling – that connects individuals, communities, science, and policy will help overcome existing challenges presented by complex, multidisciplinary, multi-ecosystem threats.

References

Centers for Disease Control and Prevention, 2018a. Antibiotic/Antimicrobial Resistance. "Biggest Threats". In: https://www.cdc.gov/drugresistance/biggest_threats.html, (Accessed 16 March 2018).
Centers for Disease Control and Prevention, 2018b. Antibiotic/Antimicrobial Resistance. "About Antimicrobial Resistance". In: https://www.cdc.gov/drugresistance/about.html, (Accessed 16 March 2018).
FAO/OIE/WHO, 2016. Tripartite Collaboration on AMR. In: http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/, (Accessed 4 August 2017).
Food and Agricultural Organization of the United Nations, 2016. Antimicrobial Resistance 101. In: http://www.fao.org/zhc/detail-events/en/c/451065/, (Accessed 12 September 2017).
Garbisu, C., et al., 2018. Mobile genetic elements and antibiotic resistance in mine soil amended with organic wastes. Sci. Total Environ. 621, 725–733.
Global Health Hackathon, 2017. https://www.bcm.edu/global-health/innovation-center/hackathon/2017-hackathon, (Accessed 16 March 2018).
International Federation of Pharmaceutical Manufacturers & Association, 2016. Industry Roadmap for Progress on Combating Antimicrobial Resistance. In: https://www.ifpma.org/resource-centre/industry-roadmap-for-progress-on-combating-antimicrobial-resistance/, (Accessed 16 March 2018).

LEO Network, 2015. The Eyes, Ears, and Voice of Our Changing Environment. In: https://www.leonetwork.org/en/docs/about/about, Accessed 16 March 2018.

Mollenckopf, D.F., et al., 2017. Carbapenemase-producing Enterobacteriaceae recovered from the environment of a swine farrow-to-finish operation in the United States. Antimicrob. Agents Chemother. 61 (2), e01298–16.

National Action Plan for Combatting Antibiotic-Resistant Bacteria, 2015. National Action Plan for Combatting Antibiotic-Resistant Bacteria. In: https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf, (Accessed 4 August 2017).

Ogunseitan, O.A., 2005. Microbial Diversity. (Foreword by Lynn Margulis). Blackwell Publishing, Oxford, England, 308, ISBN 0632047089.

Ogunseitan, O.A., 2016. Bacterial diversity, introduction to. In: Kliman, R.M. (Ed.), Encyclopedia of Evolutionary Biology. Vol. 1, Academic Press, Oxford, pp. 114–118.

Open Street Maps, 2018. www.openstreetmap.org, (Accessed 16 March 2018).

Sommer, M.O.A., et al., 2017. Prediction of antibiotic resistance: time for a new preclinical paradigm?. Nature Reviews Microbiology(nrmicro-2017).

Surette, M., Wright, D.G., 2017. Lessons from the environmental antibiotic resistome. Annual Review of Microbiology 71, https://doi.org/10.1146/annurev-micro-090816-093420.

Szekeres, E., et al., 2017. Abundance of antibiotics, antibiotic resistance genes and bacterial community composition in wastewater effluents from different Romanian hospitals. Environ. Pollut. 225, 304–315.

Taylor, Jirka, Hafner, Marco, Yerushalmi, Erez, Smith, Richard, Bellasio, Jacopo, Vardavas, Raffaele, Bienkowska-Gibbs, Teresa, Rubin, Jennifer, 2014. Estimating the Economic Costs of Antimicrobial Resistance: Model and Results. The Wellcome Trust https://www.rand.org/pubs/research_reports/RR911.html.

United Nations, 2016. Draft Political Declaration of the High-level Meeting of the General Assembly on Antimicrobial Resistance. In: https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf, (Accessed 4 August 2017).

World Health Organization, 2015a. Global Action Plan on Antimicrobial Resistance. In: http://apps.who.int/iris/handle/10665/193736, (Accessed 4 August 2017).

World Health Organization, 2015b. Antimicrobial Resistance: National Action Plans. In: http://www.who.int/antimicrobial-resistance/national-action-plans/en/, (Accessed 4 August 2017).

World Health Organization, 2017. Global Priority List of Antibiotic-resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics. In: http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/, (Accessed 20 April 2017).

Yelin, I., Kishony, R., 2018. Antibiotic Resistance. Cell 172 (5), 1136.