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Emerging issues in the environmental context of antibiotic-resistance



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, dangerous 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 populations 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 Enterobacteriaceae 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 carbapenems (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, (Szekeress et al., 2017) underscoring the potential for the colocalization of anthropogenic carbapenems and carbapenem-producing and carbapenem-sensitive bacteria.

To compound the issue, new data suggest environment-mediated

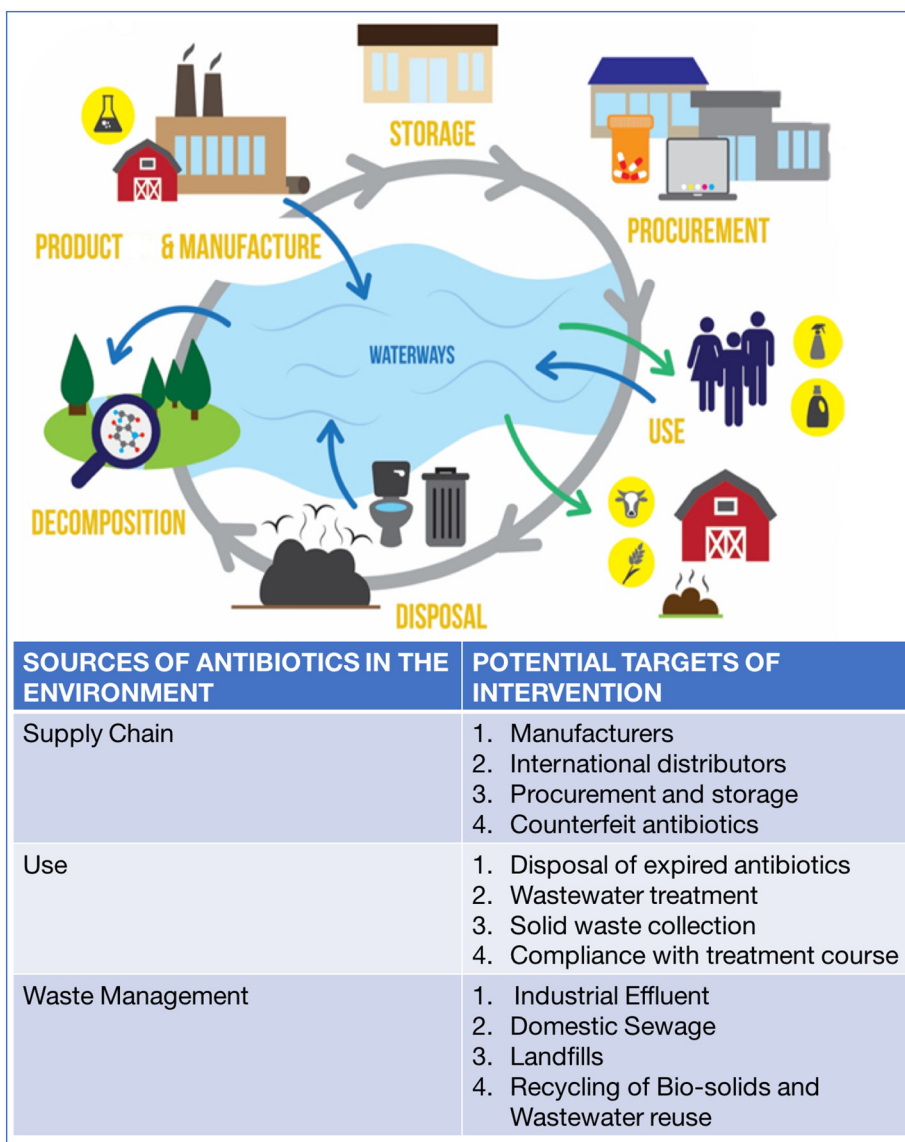


Fig. 1. Generalized representation of the antibiotic life cycle architecture.

transmission of carbapenem resistance genes. Carbapenem-resistant bacteria have recently been found in farm animals in the United States (Mollenkopf 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, including 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.

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