

Editorial: Antimicrobial resistance in the water environment

INTRODUCTION

It has been called ‘the next plague’ and has raised many eyebrows from both sides of the topic; namely, those who stand on the ‘we are all going to die’ side and those who simply state: ‘What is the problem?’ The facts are actually somewhere in the middle of these extreme statements. On the one hand, we cannot simply overlook the fact that some pathogens are resistant to all currently known antimicrobials, and that the data point to finding even more of these pathogens that are now resistant to the drugs of last resort. On the other hand, this topic has to be approached carefully, and the large volumes of data obtained need to be looked at closely. As biologists (environmental microbiologists), we should not be surprised that for the last several decades we have applied tremendous evolutionary pressure in the medical health environment, as well as in agriculture and animal raising, and that more bacterial populations have become increasingly resistant to the antimicrobial compounds being used. As data have shown, there always seems to be a small percentage of the bacterial populations that are resistant to low levels of some antimicrobials; as the levels are increased, the sensitive cells are eliminated and the resistant ones continue on their path, now being more numerous and more resilient because of their innate resistance. For several decades now, antibiotic resistance has been discussed in different forums because of the public health implications. At the current trajectory, the WHO (2020) estimates that by 2050 more than 350 million deaths would be caused by antimicrobial resistance globally. In the USA more than 2.8 million people become infected with bacteria that are resistant to antibiotics annually, resulting in at least 35,000 deaths. The use and abuse of these useful compounds have not been properly addressed politically in most cases. It is not unusual for physicians to use the latest generation of antibiotics instead of relying on older (and cheaper) drugs; however, these physicians have to make on-the-spot decisions and cannot

wait for resistance screening from the laboratory that takes days to complete. Besides the cost implications, such screening would be impossible in the already overburdened healthcare facilities in developing countries. Additionally, antibiotics are still seen as a ‘magic bullet’ by the lay public who do not fully appreciate the mode of action of each compound. The public should be made aware that they are part-and-parcel of the fight against antibiotic resistance. To date, most attention has been paid to antibiotic resistance; however, antibiotic sensitivity of the microbiota may be just as important. The use of (e.g.) oral antibiotics disrupts the intestinal microbiota, thereby eliminating sensitive microorganisms. This provides opportunistic pathogens that are members of the resident biota (e.g., *Clostridium difficile* infections), with a chance to cause dysbiosis and secondary infections, with possible long-term effects on the patient.

The development of oral antibiotics was an incredible advancement at first sight; however, this is a method that has its pros and cons: it is advantageous since the patient can self-medicate and not be dependent on the doctor, nurse or clinic for drug administration. The downside to this (and we are all likely guilty) is that we quit taking the drugs after a couple of days when feeling better, and thus unused antibiotics remain in homes, which are then either thrown away with the garbage or flushed in the toilet. The latter is an increasing concern, because sewage is teeming with enteric bacterial pathogens that are now exposed to the antibiotics and also to other cells containing antibiotic-resistance genes (ARGs) that can be transmitted horizontally; because of this, sewage treatment plants have been called ‘hotspots’ for antimicrobial resistance gene transfer. It used to be said that all antibiotics should be taken for the full course; however, new data have shown that precisely because of antibiotic resistance, it may be advisable not to take the full course. Obviously, then, the patient should be aware and should have a suitable place to get rid of the unused antibiotics. Any policy covering this should also consider the prohibition of

certain oral antibiotics in areas where there is a large prevalence of resistance to a specific drug; the latter drug could still be available in injectable form until the prevalence of resistance is lowered.

TESTING FOR THE PRESENCE OF ANTIBIOTIC-RESISTANCE GENES

It has been reported that wastewater from hospitals, animal farms, aquaculture farms and homes contain antibiotics, antibiotic-resistance bacteria, and extracellular antibiotic-resistance genes carried in plasmids, transposons and other mobile genetic elements. While the public health concern over antibiotic resistance emerged approximately a decade after the commercialization of penicillin, many currently used natural antibiotics are in fact produced by environmental microorganisms (e.g., *Penicillium* spp., *Streptomyces* spp. and *Streptococcus* spp.). In addition, the presence of antibiotic-resistance-like sequences, including vancomycin- and tetracycline-like resistance genes, as well as those expected to provide beta-lactam resistance, have also been detected in samples that pre-date antibiotic use, including thousand year-old mummies and coprolites (mummified feces). This has resulted in the presence of antibiotic-resistance genes (e.g. beta-lactam resistance) in many ecosystems, including ancient gut microbiomes, and isolated areas with unknown anthropological activity.

We now have the ability to test for the presence of antibiotic-resistance genes in a few hours, and even in the absence of growing the microorganisms in the laboratory. What has made this topic even more prevalent in the last few years is the ability to carry out culture-free identification and sequencing. For instance, the Polymerase Chain Reaction (PCR) and quantitative PCR methods (qPCR) are often the preferred methods to test for the presence and load of antibiotic-resistance genes in water environments, sewage and other sources; yet, while PCR and qPCR methods enable researchers to obtain results in a time- and cost-efficient manner, the method still involves a degree of *a priori* knowledge of the gene(s) of interest. This may pose the disadvantage of ignoring the presence of other important antibiotic-resistance genes in water, sewage and other sources.

Antibiotic-resistance genes can now be screened simultaneously with the advent of high-throughput sequencing technologies. This is in part possible by the availability of databases containing updated and curated antibiotic-resistance gene sequences, mostly from clinical isolates. High-throughput sequencing and sequence databases facilitate the identification of antibiotic-resistance genes, evolution of antibiotic-resistance bacteria in water and sewage environments, identification of the short- and long-term effects of antibiotics and antibiotic resistance to public health, and determine the dynamics and potential routes of transmission of antibiotic-resistance genes and related microorganisms.

ANTIBIOTIC RESISTANCE AS A PUBLIC HEALTH CONCERN

The public health concern should not rest only on the presence of these genes in a microbial population, but rather in the conditions of a given ecosystem for horizontal gene transfer of antibiotic resistance. Similar to PCR, high-throughput antibiotic-resistance gene sequence data should also be carefully considered. The detection of an antibiotic resistance gene sequence(s) in water, sewage or other sample types would need to be further validated using gene expression patterns and phenotypic characteristics. Although man-made ecosystems such as sewage treatment plants have been called 'hotspots' for such activity by some researchers, it would seem that the hotspots of greater concern are really the guts of the animals receiving oral antibiotics, either as therapeutic agents or at sub-therapeutic concentrations in the feed. It would seem that the ideal conditions for genetic transfer is the gut; perfect temperature, water content, slow movement and, in some cases, the presence of antibiotics (e.g., DNA synthesis interference compounds) that elicit lysogenic phage expression leading to a larger percentage of the population being the recipients of the resistance genes.

Nevertheless, proper treatment of wastewater before its release into the environment is essential to prevent the spread of antibiotic-resistant bacteria (ARB) and ARGs into the environment. Based on recent studies, the removal efficiency of ARGs depends largely on the type of genes

present and the treatment processes used. Low-energy anaerobic–aerobic treatment reactors, constructed wetlands, and disinfection processes are some of the various treatment options that have shown good removal efficiencies. Recently new strategies regarding antibiotic-resistance genes and antibiotic resistant bacteria making use of nanomaterials and biochar combined with other treatment methods and coagulation were investigated, but require additional research.

All-in-all, antibiotic resistance is a multifactorial problem that likely has multifactorial solutions: antibiotic use and abuse has to be reduced, oral antibiotic use has to be looked at carefully, and drastic measures may need to be taken to reduce the release of antibiotics into the environment. Resistance gene transmission conditions have to be duly elucidated and measures taken for its control. No control of antimicrobial resistance is possible without active participation of the lay public and extreme governmental regulations in regard to oral antibiotics.

Universal access to safe water, sanitation and hygiene (WASH) in households, healthcare facilities and schools remain critical elements to prevent infectious diseases and thereby limit the spread of antimicrobial resistance worldwide. With water scarcity on the rise in many countries, policy reviews regarding reuse of wastewater effluent and industrial water management to prevent or limit the spread of antimicrobials are urgently needed. Similarly, more attention should be given to the transboundary nature of antimicrobial resistance as poor countries are likely to bear the brunt of the problem.

The seven contributions to this special issue on ‘Antimicrobial Resistance in the water environment’ in *Journal of Water and Health* feature a mixture of primary research, reviews and commentaries, including but not limited to the detection, monitoring and surveillance of antimicrobial resistance (AMR) genes in various water types, sewage, activated sludge and in wastewater reuse. The occurrence and distribution of antimicrobials, ARB and ARGs was determined by a variety of techniques using the latest information available in both developing and developed

countries. It is in our best interest to continue to perform studies related to: the prevalence of antibiotic resistance in various water types and related sources across continents using various detection methods, the public health concerns of the prevalence and transmission of antibiotic-resistance genes from and to various environments, as well as to determine the appropriate interventions and policies that can be applied to limit the horizontal transmission of antibiotic-resistance genes. This special issue highlights the current AMR problem in the water environment, the importance of ongoing surveillance and monitoring efforts, but most of all the role of each person in combatting antibiotic resistance issues in the future, the importance of WASH, the need for continuous monitoring efforts and policy reviews needed to curb the problem, especially in developing countries. More research is also needed on the economic impacts (direct and indirect costs) related to AMR and the transboundary impacts of antimicrobial use. Inclusion of AMR impacts on DALYs in the Global Burden of Disease report will further highlight the importance of AMR and track the public health implications over time.

Finally, we hope that this special issue raises awareness and identifies more research questions to likely inspire more researchers to explore ARGs in water sources and come up with solutions to solve those problems inherent to the use of these important compounds.

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