PERSPECTIVE

Water and sanitation: an essential battlefront in the war on antimicrobial resistance

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One sentence summary: This perspective synthesizes the roundtable discussion focused on water and sanitation aspects of antimicrobial resistance that took place at the 4th Environmental Dimension of Antibiotic Resistance conference.

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ABSTRACT

Water and sanitation represent a key battlefront in combating the spread of antimicrobial resistance (AMR). Basic water sanitation infrastructure is an essential first step towards protecting public health, thereby limiting the spread of pathogens and the need for antibiotics. AMR presents unique human health risks, meriting new risk assessment frameworks specifically adapted to water and sanitation-borne AMR. There are numerous exposure routes to AMR originating from human waste, each of which must be quantified for its relative risk to human health. Wastewater treatment plants play a vital role in centralized collection and treatment of human sewage, but there are numerous unresolved issues in terms of the microbial ecological processes occurring within them and the extent to which they attenuate or amplify AMR. Research is needed to advance understanding of the fate of resistant bacteria and antibiotic resistance genes in various waste management systems, depending on the local constraints and intended reuse applications. World Health Organization and national AMR action plans would benefit from a more holistic 'One Water' understanding. In this article we provide a framework for research, policy, practice and public engagement aimed at limiting the spread of AMR from water and sanitation in low-, medium- and high-income countries.

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Antimicrobial resistance (AMR) has been hailed as the 21st century’s top global health threat, and, without serious and immediate attention, a return to a pre-antibiotic era is predicted (WHO 2014). The inability to treat infectious diseases would result in negative public health consequences and a devastating global economic burden (WHO/Europe 2017). In recognition of this crisis, the World Health Organization (WHO) developed a Global Action Plan on AMR (GAP on AMR) which was subsequently ratified by the United Nations and is being translated by each member state into national AMR action plans (WHO 2015). The WHO GAP on AMR calls for the need to optimize the use of antimicrobial medicines in human and animal health and the development of standards and guidance for assessing risks from antimicrobial residues in water and wastewater (WW). Notably, while the GAP on AMR acknowledges the risks and the need to understand the role of the release of AMR microorganisms found in farmyards, food, water and the environment, specific advice on policy is not provided, particularly with regard to WW and reuse. Two years after the publication of the WHO’s GAP on AMR, the European Commission (EC) published A European One Health Action Plan against Antimicrobial Resistance (AMR). In this groundbreaking policy document, the EC called for research to address the knowledge gaps pertaining to AMR in the environment and transmission. Specifically, in Section 3.6, the EC calls on member states to support research into: (i) the release of resistant microorganisms and antimicrobials into the environment and their spread; (ii) risk assessment methodologies to protect human and animal health; and (iii) the development of technologies for the removal of antimicrobials in WW and the environment, with the aim of reducing the spread of AMR. It is the aim of this article to expand on the EC One Health Action Plan, as it is the only high level policy document to explicitly recognize many of the issues that need to be considered in the ‘One Water’ concept.

Sanitation, defined as the collection and treatment of human sewage, is a cornerstone of reducing the global burden of infectious disease, including those caused by antibiotic-resistant pathogens. Effective water and sanitation practices therefore must be central to any AMR action plan. Here we provide a framework for understanding the role of water and sanitation as a vital aspect in addressing the current AMR crisis. In particular, we focus on antibiotics (herein defined as antibacterial agents that kill bacteria or slow their growth and that are used to combat bacterial infections), antibiotic-resistant bacteria (ARB) (defined as bacteria with acquired resistance) and antibiotic resistance genes (ARGs) (which confer increased bacterial survival in the presence of antibiotics), particularly those that are mobilizable.

Wastewater treatment plants (WWTPs) are an essential feature of modern urban infrastructure, employing various physico-chemical and microbial ecological processes to biodegrade organic pollutants, remove nitrogen and phosphorus, and reduce pathogen loads before discharging the treated water into the environment. Centralized WW management systems collect and treat sewage containing human excrement and other waste streams, effectively mixing any excreted antimicrobials along with human microbiome-associated commensal and pathogenic ARBs bearing ARGs (Su, An and Li 2017). While the infrastructure of WWTPs has improved and increased over the last century, water sanitation and management systems have not been intentionally designed to manage AMR concerns. Understanding the fate of ARBs and ARGs through the spectrum of water sanitation and hygiene practices becomes particularly acute in the modern movement towards recovery of WW residuals for fertilizing and the use of treated WW for irrigating edible crops as well as augmenting potable water supplies (Pruden 2014). Here we provide a synthesis of an expert panel discussion that took place at the 4th International Environmental Dimension of Antimicrobial Resistance (EDAR) Conference, held in Lansing, Michigan, USA in August 2017, and review the relevant literature. We identify the most urgent research needs, while also proposing a path forward in terms of common sense practices and policies that prioritize investment based on the type of waste and likely risk that it carries and that consider local socioeconomic, geographic and other constraints.

**Modern wastewater management systems: a conduit or barrier to the spread of AMR?**

Wastewater management and treatment has been instrumental in reducing disease and death caused by faecal-borne pathogens such as typhoid and cholera (CDC 1999; WHO 2017b). Nevertheless, the degree of sanitation and access to safe drinking water varies widely on a global scale, with 80% of society’s wastewater still flowing untreated into terrestrial and aquatic ecosystems (UNESCO 2017). Hence, the United Nations Sustainable Development Goals #3 ‘Ensure Healthy Lives and Promote Well-Being for All at All Ages’ and #6 ‘Access to Water and Sanitation for All’ should help directly attenuate the spread of AMR. Indeed, appropriate collection, management and treatment of sewage is an essential step in preventing the spread of many human diseases, and would simultaneously reduce the need for antibiotics and limit the spread of ARB (WHO/Europe 2017).

WWTPs receive a full spectrum of human microbiome-associated bacteria, including ARBs and associated ARGs. Also, a substantial portion of antibiotics are excreted by humans in an intact form and they are routinely detected in the influent sewage, with partial removal during biological WW treatment (Batt, Kim and Aga 2007; Zhang and Li 2011; Rizzo et al. 2013). Sources of antibiotics to sewage include households, hospitals, clinics and pharmaceutical factories. It isn’t clear whether residual antibiotics exert selective pressure on human pathogens and commensal bacteria that pass through WWTPs (Bengtsson-Palme, Larsson and Kristiansson 2017). It is often assumed that the antibiotic concentrations in WW are below the minimum inhibitory concentration, but they may still be above the minimum selective concentration or minimum metabolic concentration, driving the evolution of AMR (Gullberg et al. 2014; Berendt et al. 2015). In addition, WW may contain other compounds such as metals and/or biocides, including disinfectants such as quaternary ammonium compounds that have been implicated in ARG selection via co- or cross-resistance (Wales and Davies 2015; Hegstad et al. 2010).

In WWTPs, the high concentrations of active bacteria and their rigorous mixing in the presence of selective agents might support the evolution of new resistant strains, e.g., through the capture of new ARGs by integrons coupled to horizontal gene transfer. The inability to treat infectious diseases would result in negative public health consequences and a devastating global economic burden (WHO/Europe 2017). In recognition of this crisis, the World Health Organization (WHO) developed a Global Action Plan on AMR (GAP on AMR) which was subsequently ratified by the United Nations and is being translated by each member state into national AMR action plans (WHO 2015). The WHO GAP on AMR calls for the need to optimize the use of antimicrobial medicines in human and animal health and the development of standards and guidance for assessing risks from antimicrobial residues in water and wastewater (WW). Notably, while the GAP on AMR acknowledges the risks and the need to understand the role of the release of AMR microorganisms found in farmyards, food, water and the environment, specific advice on policy is not provided, particularly with regard to WW and reuse. Two years after the publication of the WHO’s GAP on AMR, the European Commission (EC) published A European One Health Action Plan against Antimicrobial Resistance (AMR). In this groundbreaking policy document, the EC called for research to address the knowledge gaps pertaining to AMR in the environment and transmission. Specifically, in Section 3.6, the EC calls on member states to support research into: (i) the release of resistant microorganisms and antimicrobials into the environment and their spread; (ii) risk assessment methodologies to protect human and animal health; and (iii) the development of technologies for the removal of antimicrobials in WW and the environment, with the aim of reducing the spread of AMR. It is the aim of this article to expand on the EC One Health Action Plan, as it is the only high level policy document to explicitly recognize many of the issues that need to be considered in the ‘One Water’ concept.

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transfer (HGT). HGT can occur through conjugation, transformation or transduction, all processes facilitated by high concentrations of and close contact to bacteria that is inherent to biological WW treatment. However, measuring the rates at which HGT actually occurs in WWTPs remains an important knowledge gap. Conceptual and quantitative frameworks that describe HGT dynamics in microbial communities have long been proposed (Smets, Rittmann and Stahl 1990). They might be adapted, with suitable experimental estimators of HGT rates (e.g., Sørensen et al. 2005) and range (e.g., Musovic et al. 2010), to evaluate the role of HGT in maintaining plasmid-borne ARGs in microbial communities, such as those that might occur in WWTPs. Frequent HGT is likely in WWTPs (von Wintersdorff et al. 2016) due to high loads of antibiotics, ARBs and ARGs. Already, there are reports of the enrichment of certain ARBs, such as carbapenem-resistant bacteria (Hrenovic et al. 2017), and ARGs, such as blaNDM-1 (Luo et al., 2014), and their influence on impacted watersheds (Pruden, Arabi and Storteboom 2012; Amos et al. 2014) cannot be ignored. Furthermore, even rare transfer events occurring in sewage can be important, such as pathogens acquiring a new ARG.

WHAT TO MONITOR? DETERMINING SUITABLE TREATMENT ENDPOINTS

Overview

Effective monitoring schemes for AMR in water treatment systems are urgently needed in order to document baseline levels of resistance and to guide investment of resources towards combating AMR. However, there are numerous options in terms of what to actually monitor. Each option presents its own advantages and disadvantages and, where economically and technologically possible, monitoring multiple endpoints provides the most comprehensive evaluation. Through open collaboration and sharing of scientific information, it is possible to work towards a consensus in identifying simple yet meaningful monitoring schemes that are widely accessible to water utilities and low and middle income countries (LMICs) alike, and that will aid global comparison of the effects of WW treatment technologies.

Antibiotic residuals and selective agents

Monitoring antibiotic residuals is justified given their potential role in the evolution of AMR. Antibiotics have been associated with the selection of resistant strains as well as the stimulation of HGT, even below MICs (Shun-Mei et al. 2018). However, in WWTPs and other aquatic environments selective effects are often weak, not observed, or results are conflicting, indicating that causal links between environmental concentrations of antibiotics and selection for resistance may not be straightforward (Knap et al. 2008; Gao et al. 2012). Therefore, the benefit of intensive monitoring of antibiotics to assess risks of antibiotic resistance development and dissemination in domestic WW treatment systems is not clear. Antibiotics typically occur at very low concentrations in WW (< 1 μg/L) and monitoring requires a high level of expertise and expensive analytical equipment, such as LC MS/MS. Thus monitoring antibiotics might mainly be accessible to large water utilities. Currently, there is no guidance on which antibiotics to target, except for a combination of those defined as of “critical importance” by the WHO (WHO 2017a) such as macrolides, beta-lactams and fluoroquinolones, and whether they are readily detected in environmental matrices. With regards to other potentially selective agents such as metals and biocides, we likewise still lack detailed information on their selective potential for ARG retention in WW.

Culture-based techniques

Direct monitoring of ARBs is of interest because they represent viable strains with well-known traits that can be subject to phenotypic resistance determination. There are numerous ARBs that could potentially be targeted, both Gram-positive and Gram-negative. These can provide insight into classes of resistance of clinical relevance, which can be monitored either in faecal indicator organisms, in pathogens, or by using culture-independent methods. Recently, the WHO identified extended-spectrum beta-lactamase (ESBL) producing Escherichia coli as a candidate for global surveillance (Matheu, Aidara-Kane and Andremont 2017). The intention is that the approach relies upon faecal indicator monitoring as the most widely accessible method while focusing on a resistance phenotype of the utmost clinical concern.

Culture-independent techniques

The limitations of faecal bacteria as indicators of true pathogens are well established (Savichtcheva and Okabe 2006), as are the limitations of culture-based techniques for representing the actual microbial community composition of complex WW ecosystems (Gilbride, Lee and Beaudette 2006). Understanding microbial ecological processes is essential in assessing the potential of AMR to evolve and spread (Taylor, Verner-Jeffreys and Baker-Austin 2011). For example, ARGs encode the ability to resist antibiotics via various mechanisms such as efflux pump, target modification and antibiotic inactivation. Various ARGs have been widely monitored in WWTPs for research purposes, including those encoding resistance to beta-lactams, tetracyclines, sulphonamides, quinolones and glycopeptides (Zhang, Zhang and Fang 2009; Yang et al. 2012). ARGs may be present on the chromosomes, but are often associated with mobile genetic elements (MGEs) such as plasmids, phages and transposons which can facilitate HGT.

Several options are faced in determining which ARGs and/or MGEs to focus upon. ARGs providing resistance to critically-important drugs for human medicine; such as carbapenems, third and fourth generation cephalosporins, fluoroquinolones and colistins should be prioritized in line with efforts led by international organizations (WHO 2017a). These high-relevance genes are often rare in environmental systems. On the one hand, their rarity could be an advantage from a regulatory perspective. On the other hand, their low abundance could reduce the sensitivity of the monitoring approach. As such, more abundant but less clinically-relevant ARGs such as sulphonamide, tetracycline, or certain β-lactam-ARGs may be promising indicators of human contamination. Alternatively, the detection of MGEs defined to carry large numbers of ARGs may provide a more comprehensive and sensitive indication of AMR than individual ARGs. A particularly promising target indicator of anthropogenic ARG pollution are class 1 integrons, which hold a particularly high clinical relevance (Gillings et al. 2015). Another MGE-targeted approach that could be developed into monitoring bioassays to identify the presence of mobile ARGs is the exogenous plasmid isolation technique (Smalla, Jechalke, and Top 2015).

Quantitative polymerase chain reaction (qPCR) provides a means of precisely quantifying ARG or MGE targets in water matrices; qPCR has the advantage of being fairly accessible, particularly to larger water treatment utilities. Although classical
assays can only count a small number of genes at a time, the use of high-capacity PCR arrays can circumvent this problem (Zhu et al. 2013) as it allows parallel quantification of multiple ARGs. Quantitative data is crucial to assess effectiveness of mitigation and to relate ARG and MGE distributions to climate or socioeconomic conditions. However, scientific knowledge has not yet progressed to the point where there is agreement upon ARG targets to prioritize risks or to recommend admissible values for the abundance of ARGs in an effluent. However, there is movement towards prioritizing ARGs encoding resistance to clinically important antibiotics as well as their ability to mobilize into pathogens. Correspondingly, relative risk-ranking approaches are emerging as these targets into consideration, along with relative quantities compared to a comparable ‘background’ (Martínez, Coque and Baquero 2015; Manaia 2017).

The shot-gun metagenomic DNA sequencing approach is becoming more widely applied for profiling the thousands of ‘total’ ARGs, integrongs and MGEs that may be present in a sample, without a priori selection of targets (Yang et al. 2013; Li et al. 2015; Pal et al. 2016). This approach provides unique insights, e.g., into the overlap between the resistomes of different habitats (Munck et al. 2015). Accurate annotation of ARGs from metagenomic data remains a challenge. However, publicly available ARG databases, such as the Comprehensive Antibiotic Resistance Gene Database (CARD) (Jia et al. 2017) and the Structured Antibiotic Resistance Gene (SARG) database (Yang et al. 2016), are becoming more and more robust, while newer pipelines and tools are aiding in the enhancement of ARG identification and data interpretation (Arango-Argoty et al. 2016; Arango-Argoty et al. 2018). ‘Total ARGs’ have been observed to correlate with more traditional indicators of effective WW treatment (Yang et al. 2014). Further efforts to refine interpretation of metagenomic datasets and to identify which ARGs/MGEs are of concern and in which context will be valuable. While the metagenomic approach is not widely accessible for routine monitoring efforts because of cost, it has already provided a wealth of information that should be mined to identify the most useful indicators that can then be evaluated using other methods.

A combination of culture and culture-independent analysis is also possible; E. coli cultures used for microbial water quality assessment can be subjected to whole genome sequencing, yielding an ARG per E. coli metric that can be used with E. coli density data to estimate human exposure risk. This approach was used to estimate human exposure in bathing waters in England, with 2.5 million exposure events to 100 or more E. coli-borne ARGs estimated to occur in 2016 (Leonard et al. 2018).

**Integrated approaches**

Holistic approaches to monitoring and surveillance should include culture-based and culture-independent methods, along with monitoring of basic physico-chemical conditions and the presence of known chemical drivers of AMR such as antibiotics, metals and biocides. Such efforts can work towards identifying suitable targets for more unified monitoring in the field. In parallel, or potentially as an alternative, new integrative assays may be worth considering. For example, if the question is whether the treated water has the propensity to propagate resistance, then assays could be developed to assess the extent to which exposure to the water (and its constituent microbiome) can lead to transferred resistance (Klümpner, Dechesne and Smets 2014). Such approaches would be analogous to the Ames test, or other toxicity assays.

**RISKS ASSOCIATED WITH WATER AND SANITATION SOURCES OF AMR**

**Overview**

AMR risk is distinct from traditional pathogen risk assessment because antibiotic resistance does not fit the standard paradigms of dose-response and acute illness. Rather, the primary concern is the spread of resistance and the increasing likelihood of humans and animals acquiring antibiotic-resistant infections. Risk may be further subdivided into direct human health risk versus environmental risk of evolution and the dissemination of new strains of resistant pathogens containing new ARGs and MGEs. Including the consideration of HGT of ARGs among commensal and pathogenic bacteria is particularly challenging, but important, as is consideration of the potential for latent infection. A more holistic ‘microbiome’ perspective may aid in more comprehensive characterization. Here we evaluate existing knowledge and identify key research needs with regards to developing a comprehensive framework for risk assessment appropriate for AMR.

**Epidemiology**

Epidemiology is the study of sources, causes and control of disease at the population scale. There are numerous epidemiological methodologies available, including molecular source-tracking of outbreak strains. While scant effort has actually been made to link incidences of AMR infection to water and sanitation exposure (Ashbolt et al. 2013; Huijbers et al. 2015), epidemiological frameworks can provide useful guidance to the development of risk models. The release of ARBs derived from animal and human microorganisms deserves particular attention because these bacteria are also the best candidates for transmitting antibiotic resistance back to humans and animals (Harwood et al. 2014; Manaia 2017). The main sources of AMR from WWTPs to the environment are aqueous effluent and solid residuals. Humans can subsequently be exposed through ingestion, bathing or the inhalation of various media influenced by these sources (Ashbolt et al. 2013; Huijbers et al. 2015). For example, vegetables can be consumed that are irrigated either directly or indirectly with WWTPs’ effluent-influenced water or grown in biosolid-influenced soil (Christou et al. 2017; Zhu et al. 2017). Skin could be colonized when swimming in affected surface waters (Leonard et al. 2015) or the gut when water is ingested, and aerosols could be inhaled by operators in WWTPs or downwind of biosolids applications (Carey et al. 2016; Li et al. 2016).

**Risk definition**

Human health risk assessment serves to estimate the probability of illness or death among individual members of a population exposed to a given hazard. More broadly speaking, risk assessment serves to estimate probability and severity of an undesired event. For AMR, risk assessment must take into account and weigh multiple aspects: the current or expected future importance to human and animal health of the antibiotic to which resistance is conferred, the pathogenic potential of the specific bacterial populations carrying the ARG, and the expected ease of dissemination and exposure to affected populations. Furthermore, ecological mechanisms of resistance dissemination, such as HGT, are essential to consider. The potential hazards associated with AMR risk include antibiotics and other selectors (e.g.,

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metals, biocides), ARBs (both pathogenic and non-pathogenic), ARGs, integrons and various MGEs.

Many, if not all ARGs, integrons and MGEs, originated in environmental bacteria and did not evolve de novo in clinical pathogens (Poirel, Kämpfer and Nordmann 2002; Poirel et al. 2005). As ARGs became associated with MGEs they were transferred to pathogenic bacteria in a process that might have taken place several times during evolution, leading to today’s resistance crisis. In summary, a series of events contribute to the recruitment of ARGs from the environmental resistome into human and animal pathogens and these can be broadly classified into three general risk classes: (i) recruitment of ARGs by MGEs over evolutionary time; (ii) colonization/invasion of human or animal microbiomes by commensal bacteria carrying mobile AMR at medium timescales; and (iii) development of an infection by an AMR-carrying pathogen at short timescales (Ashbolt et al. 2013). Regarding (i), the initial associations between ARGs and MGEs are likely to be rare events, but are a prerequisite for spreading ARGs within microbial populations and transfer to other hosts, including pathogens. For example, two comprehensive studies indicated that the vast majority of the soil or WWTPs’ resistome components are not associated with MGEs (Forsberg et al. 2012; Munck et al. 2015). Given these bottlenecks and the specific conditions required for positive selection, these evolutionary processes may happen at timescales of years or decades. Regarding (ii), the colonization of human and animal microbiomes by mobile ARGs is a result of the exposure to individual human/animal/environmental-derived ARB. These bacteria may act as potential donors of ARGs associated with MGEs to human and animal gut microbiomes, even in the absence of active infections (Bengtsson-Palme et al. 2015). In this sense, human and animal microbiomes are ‘biological reactors’ for the emergence, HGT and proliferation of AMR of clinical relevance (Baquero, Martínez and Cantón 2008), in part due to the exposure to strong antibiotic selective pressures (Salyers, Gupta and Wang 2004; Woolhouse et al. 2015). Therefore, the invasion of animal and human microbiomes may lead to rapid dissemination and expansion of the pool of mobile ARGs within a medium timescale (for example, weeks to years). Upon acquiring an infection, transfers of ARGs from the host microbiome to the pathogen could be triggered by commencement of antibiotic therapy. This risk is defined as the ‘chronic exposure risk’, a class of risk not directly managed by current regulations pertaining to WWTPs’ effluents or biosolid residuals (LeBlanc, Matthews and Richard 2009; Jeong, Kim and Jang 2016). Finally, (iii), the risk of acquiring an infection caused by a pathogen carrying a mobile AMR gene is operating at the shortest timescale because a single event (infection onset) is necessary. This risk is defined as the ‘acute exposure risk’.

Exposure assessment

Exposure assessment identifies the media to which human populations may be exposed and determines the concentrations of the relevant contaminants. Relevant water and sanitation exposure to AMR includes: contact with raw sewage (e.g., open defecation areas; operators of sanitation facilities, particularly in locales with inadequate sanitation); aerosols generated during WW aeration and treatment (especially relevant to sanitation workers) (Laitinen et al. 1994; van den Broek et al. 2009); skin contact and aerosols generated when irrigating crops or recreational fields with reclaimed water (Carey et al. 2016); ingestion of produce influenced by affected irrigation water or biosolids (Christou et al. 2017); skin contact and particulate inhalation associated with biosolids (Dohmen et al. 2017); swimming/recreation in affected surface waters (Leonard et al. 2015, 2018; Dorado-García et al. 2017); and drinking water influenced by reclaimed or recycled water (Xi et al. 2009; Garner et al. 2016). It is also important to put such exposure in context with contributions from other sources such as agriculture, aquaculture, meat products, hospital visits and international travel. In this manner, exposure assessment will help identify and rank likely sources and move towards prioritizing management.

While little work has been done to precisely quantify human exposure, abundances of ARBs, ARGs and MGEs are fairly well quantified in sewage, WWTPs, WWTPs’ effluent and impacted natural waters (Ashbolt et al. 2018). There is also emerging literature on the colonization of the human and animal microbiome (Kozak et al. 2009) with environmental resistance carriers (Bengtsson-Palme et al. 2015). The factors that control and constrain the rates of resistance from various sources to human microbiomes remain largely unknown. Templates for such studies exist, e.g., work on the effects of occupational exposure of workers in slaughterhouses or farms on resistance carriage (Price et al. 2007; Dohmen et al. 2017). One study recently attempted to integrate AMR surveillance, human exposure risk assessment and relative risk of colonization in a cross-sectional study of surfers and non-surfers (Leonard et al., 2018). This study estimated that > 2.5 million exposure events to blaCTX-M-bearing E. coli occurred in UK bathing waters in 2015 and that surfers were > 4 times more likely to be colonized by blaCTX-M-bearing E. coli than the non-surfers control group.

Risk characterization

Risk assessment associated with ‘acute’ risks posed by AMR pathogens in the environment can be conceptualized within existing quantitative microbial risk assessment (QMRA) frameworks as dose response curves for exposure versus infection risk (Ashbolt et al. 2013). However, very little is known regarding the short- or long-term health risks posed by exposure to environmentally relevant bacteria carrying mobile ARGs that may be transferred to pathogens on skin or in the human gut. However, a recent systematic review of infection risk associated with colonization by carbapenem-resistant Enterobacteriaceae concluded that 16.5% of colonized individuals developed infections (Tischendorf et al. 2016). However, this was a study of adult hospital inpatients where the risk of infection may be greater than in the general population. It is difficult to envisage a risk assessment framework that can disentangle the complexity of very rare gene transfer events of ARGs from environmental bacteria to human or animal pathogens. The factors that lead to such rare events have global consequences but might be unknowable due to complexity, although risk factors for some steps in the chain of events leading to the emergence of uncharacterized ARGs in human and animal pathogens may be possible (Ashbolt et al. 2013).

Relative risk paradigm as a proxy

AMR in one form or another is now known to be a ubiquitous feature in microbial communities and ARGs can be found even in entirely pristine or pre-antibiotic era microbes (D’Costa et al. 2011). Furthermore, there is evidence that many resistance determinants that now occur in clinical isolates originated from
harmless environmental bacteria (Poirel, Kämpfer and Nordmann 2002; Poirel et al. 2005). Thus, it is impossible to expect to achieve ‘zero’ ARBs or ARGs in treated WW. At the same time natural ‘background’ ARGs can still present risk. However, until risk models are more developed, a reasonable benchmark is to compare AMR profiles in anthropogenically influenced environments with those of a relevant natural background. Anthropogenic sources like WW have repeatedly been shown to carry much higher loads of ARB and ARG than natural water (Pruden, Arabi and Storteboom 2012; Amos et al. 2014). In addition, human impact also tends to be associated with a high degree of mobilized resistance elements. For this reason, establishing background types and numbers of ARGs and MGEs as proxies is an important first step for prioritizing risk and selecting monitoring targets. While it is not necessarily trivial to find a suitable ‘natural’ analogue for WW, comparison to natural waters as a reference point (e.g., Czekalski et al. 2015) provides an estimate of the contamination potential relative to an accepted harmless environment.

Undoubtedly the individual risks of a particular ARG may vary widely (Bengtsson-Palme et al. 2014; Viklesand et al. 2017) and approaches to rank associated risks based on criteria such as importance to human health, mobility and novelty have been discussed (Martínez, Coque and Baquero 2015). However, exceptions have been noted in which chromosomally occurring ARGs of clinical importance are also sometimes highly mobile, as was illustrated by CTX-M progenitors to clinically important beta-lactamases that were mobilized repeatedly among Kluyvera spp. in different parts of the world (Poirel, Kämpfer and Nordmann 2002). Ideally, facilitated by next-generation DNA sequencing, ‘resistome’-based risk criteria could be developed. At the same time, for general regulatory purposes, routine monitoring, and for defining initial thresholds for action, simple criteria based on a few common and easily measurable endpoints interpreted against suitable background systems will likely be key. Correspondingly, it would be valuable to determine how simple indicators, such as the class 1 integrase gene intI1, more broadly represent resistome-level risk (Gillings et al. 2015).

WATER TREATMENT TECHNOLOGIES AND MANAGEMENT PRACTICES AS BARRIERS AGAINST THE SPREAD OF AMR

Overview

Treatment of WW streams is an essential tool for managing AMR risk associated with water and sanitation. The fate of ARBs and ARGs through various WW treatment processes has been an extensive area of research in recent years. However, a major challenge is now to synthesize information in a form accessible and informative to water and sanitation engineers. Given that risk-based or other standardized AMR monitoring targets have yet to be identified, studies vary in terms of measures by which they evaluate process performance. Effects of the treated water and sludge on corresponding aquatic and soil-based receiving environments is one approach to determining the effectiveness of WW treatment for reducing amplification of downstream AMR markers (Pruden, Arabi and Storteboom 2012; Amos et al. 2014; Burch, Sadowsky and LaPara 2014; Czekalski, Diez and Bürgmann 2014). The Global Water Pathogens Project (GWPP) provides an online compilation of faecal-based pathogens and includes a chapter that comprehensively summarizes the fate of ARBs and ARGs in a range of WW treatment systems (Ashbolt et al. 2018). For antibiotic compounds themselves, they may be subject to various transformation or phase-transfer processes such as sorption, biodegradation, chemical oxidation or photochemical transformation (Zhang and Li 2011). In this section we provide a brief overview of the range of various treatment options available and their pros and cons for AMR management, with particular attention towards economics and accessibility, given local constraints. Movement towards resource recovery and water reuse also place special considerations on WW treatment in the context of AMR and the level of treatment required.

Biological treatment

Aerobic biological treatments include various adaptations of activated sludge, such as enhanced nutrient removal, as well as biofilm-based processes, such as trickling filters. We cannot here provide a full review on the fate of AMR in WWTPs, but a general conclusion from the literature is that the situation appears complicated and biological treatment does not uniformly reduce total ARGs (Yang et al. 2013).

Extensive monitoring of WWTPs in Hong Kong using metagenomics indicated that 78 ARG subtypes persisted through the biological WW and sludge treatment process. A high removal efficiency of 99.82% for total ARGs in WW suggested that the sewage treatment process is effective in reducing ARGs (Yang et al. 2014). Microbial ecological processes that may be at play during typical biological treatment include persistence (i.e., pass-through from influent to effluent), attenuation and die-off due to non-native environment and active populations of bacterial predators, selection (i.e., enrichment) due to the ability of resistant strains to withstand stress, and HGT of ARGs to the resident WWTP microbial community. While continued research is of value to sort out the role of this tangled ecological web and the ultimate reduction of AMR risk in various contexts, it seems wise to present additional treatment barriers when possible, particularly when the water is intended for reuse.

Biosolids treatment and reuse

Aerobic biological treatment generally results in two products: treated water and residual sludge. The sludge is a consequence of the high growth rate microbes employ that actively convert organic carbon to biomass. This biomass is rich in nutrients and thus is commonly used as a ‘biosolid’ fertilizer, particularly in the USA, the UK, Germany and southern Europe. However, the risk carried by land-application of biosolids is widely debated and in some countries such as Switzerland, Sweden and other Nordic countries, they are largely incinerated and converted to energy. In terms of AMR, mass balance analysis reveals that approximately 90% of the ARGs leave WWTPs in the form of biosolids, while only 10% leaves though the aqueous effluent (Munir, Wong and Xagoraraki 2011; Yang et al. 2014). This suggests that biosolids warrant special attention. Anaerobic digestion is generally the norm for biosolids. Several studies have suggested that thermophilic anaerobic digestion, operated between 48C and 55C, is more efficient for removing ARGs (Diehl and LaPara 2010; Ma et al. 2011; Tian et al. 2016), but this is not always the case (Zhang, Yang and Pruden 2015). Anaerobic treatment also appears to be better for the removal of ARGs than aerobic treatment (Diehl and LaPara 2010; Ma et al. 2011), which may be a function of selecting for different bacteria and corresponding suites of ARGs. Overall, the complexity of biological treatment of biosolids still presents many unknowns. Additional precautions may be warranted, particularly when used as soil amendment for edible crops, such as extended wait times before harvest.
**Advanced treatment options**

Advanced treatment may be advisable in some circumstances, particularly where there is increased potential for human exposure, but it comes at a cost. Advanced oxidation processes (AOPs) such as various combinations of ozone, UV and hydrogen peroxide employ hydroxyl radicals to aggressively attack organic matter, including antibiotics and other pharmaceuticals (Klavarioti, Mantzavinos and Kassinos 2009; Homem and Santos 2011), reducing overall downstream selection pressure (Liu et al. 2017). In addition, AOPs also destroy pathogens. AOPs are particularly growing in popularity when the water is intended for reuse, including potable reuse (Schimmoller et al. 2015). While AOPs appear promising for the destruction of ARGs and minimizing AMR risk (Dodd 2012; Liu et al. 2017), this is not widely proven and research is needed to demonstrate that benefits persist into receiving environments and that they are not ultimately a selective pressure for resistant strains. For example, partly due to bacterial regrowth downstream from ozonation, resistance determinants may not be efficiently removed (Czekalski et al. 2016) and ARBs may even be differentially selected (Alexander et al. 2016).

Membrane treatments can range in size cut-offs, where even microfiltration can enhance DNA removal to a considerable extent (Riquelme et al. 2013). Reverse osmosis (RO) has become the norm for potable reuse in the USA state of California, as well as the Middle East and other parts of the world, and arguably is the strongest barrier available, essentially only allowing water molecules to pass through. Unfortunately, in addition to extreme cost requirements, RO also produces significant volumes of undesirable brine water, disposal of which is not insignificant. The resulting water is nearly equivalent to distilled water and thus can greatly overshoot the water quality needed for the intended purpose (Lee, Howe and Thomson 2012). Combining powdered activated carbon (PAC) sorption of antibiotics and other micropollutants followed by ultrafiltration, which is less costly and energy intensive than RO, appears to be particularly promising for reducing toxicity and selection pressure towards AMR (Margot et al. 2013), but does produce sludge that would need to be managed.

Disinfection, such as chlorination, is also commonly applied to treated WW. On one hand, it is a known entity that presents tremendous benefit for eliminating pathogen in water systems. On the other hand, the effectiveness of chlorine for AMR control remains unclear. A handful of studies have suggested that selection of some ARBs is favoured by chlorination (Murray et al. 1984; Shrivastava et al. 2004; Xi et al. 2009; Shi et al. 2013), but this has not been widely established and benefits have also been cited (Dodd 2012).

**Low-tech treatment**

In LMICs and regions with decentralized WW systems, treatment is often achieved using simple wetlands and oxidation ponds. These systems are more sustainable based on economic and infrastructure constraints but provide less complete treatment than a traditional, activated sludge WWTP. Few studies of the fate of AMR in such systems have been carried out (Anderson et al. 2013), indicating the need for research to establish the effectiveness of treatment technologies appropriate to LMICs (Ashbolt et al. 2018).

**Treatment focused on ‘hot spot’ sources**

Alarming levels of several antibiotics have been reported in surface water affected by pharmaceutical manufacturing discharge, as high as several tens of µg/L (Larsson 2014), and are a serious concern as ‘hot spots’ for AMR evolution. The release of antibiotics from manufacturing to public sewage streams and ultimately to the environment must be monitored and prevented at all costs, while hospitals may present an additional point-source of concern worthy of scrutiny. Hospital WW generally carries higher loads of ARBs of greater clinical concern (Varela et al. 2013; Music et al. 2017; Timraz et al. 2017). In addition, the range of antibiotics found in hospital WW can differ greatly from that of municipal sewage owing to the unique suite of antibiotics only available through intravenous injections (Szekeres et al. 2017). Where treatment is employed, biological processes are not uncommon (Liu et al. 2017; Yi et al. 2017), yet are not ideal because the treatment process is not optimized for the removal of the pharmaceuticals, nor are they engineered to reduce or remove ARGs from the WW. More extreme on-site treatment of hot-spot wastestreams aimed at destruction, mineralization or complete retention of antibiotics through AOPs (Hollender et al. 2009), sorptive processes (Li and Zhang 2010; Bonvin et al. 2016) and/or membranes is preferable (Li, Li and Wang 2004; Kovalova et al. 2012; Margot et al. 2013).

**TOWARDS GLOBAL ACTION IN COMBATTING WATER AND SANITATION ROUTES OF AMR DISSEMINATION**

The need for improved global sanitation

The absolute first step to combat environmental dissemination routes of AMR is to ensure that at least basic sanitation needs are met. Livestock management provides an illustrative example, where poor herd management results in elevated disease pressure necessitating greater antimicrobial use. Parallels to humans might be made in so much as disease transmission is more likely in areas where clean water, sanitation and hygiene (WaSH) are not rigorously maintained. The challenge from AMR is maximized in highly populated areas that have poor adherence to WaSH principles and have unregulated use of antimicrobials, characteristics that are found in many of the most populous nations, e.g., India. In 2015, 12% of the world population practiced open defecation, with the highest rates (~ 50%) found in Eritrea, Niger, Chad, South Sudan, Benin and Togo (WHO/UNICEF 2015). Rates of open defecation have been decreasing significantly worldwide, with India and Pakistan, for example, seeing declines from 66% to 40% and 40% to 12%, respectively. Open defecation is commonly found in countries where WaSH is poorly supported and antibiotics are poorly controlled, a combination that further exacerbates the transmission of AMR infections. This is exemplified in India where more and more powerful broad-spectrum antibiotics are being used in the clinic with diminishing effectiveness, resulting in an alarming mortality rate of 58 000 newborns per year due to AMR (Laxminarayan et al. 2013). Such a focus on treating infection, rather than prevention, is a false economy. Filice et al. (2010) showed that the cost of treating patients infected with methicillin-resistant Staphylococcus aureus (MRSA) was more than double that of treating patients infected with methicillin-susceptible Staphylococcus aureus (MSSA) ($34 657 compared with $15 923) (Filice et al. 2010). In a larger multinational study, O’Neill showed that improvements in water quality and sanitation across the four middle
income countries of Brazil, Indonesia, India and Nigeria could lead to a reduction in antimicrobial use by approximately 300 million cases per year (O’Neill 2016). It is critical to recognize that the spread of AMR does not recognize borders, with local actions putting the global population at risk as a function of global travel, contamination of food products, and even atmospheric dissemination (Mazar et al. 2016). Thus, such hot spots of epidemiological transmission require urgent attention to avoid global dissemination (Graham et al. 2014).

More developed countries are not fully protected against the spread of water-borne ARB as they grapple with ageing infrastructure along with the demand for more innovative and sustainable water treatment technologies. In the USA, the century-old water infrastructure, which is plagued by leaky sewers and overloaded WWTPs, most recently earned a grade of D+ on the American Society of Civil Engineers Infrastructure Report Card based on the physical condition and investment needed for improvement (ASCE 2017). ASCE further estimated that 271 billion dollars is required to meet sanitation needs in the USA over the next 25 years. Poor infrastructure in the form of leaking sewage pipes and their co-location with leaking potable water pipes is a sure way to degrade public health and exacerbate AMR (Karkey et al. 2016). The urgent need to invest in water infrastructure also presents the opportunity to do so in a more sustainable manner, such as advancing water reuse. Since 2008 in the USA, funding for recycled water distribution has increased by 21% (ASCE 2017). Water recycling brings obvious concerns for public health, including closing the loop for AMR to disseminate directly from sewage to drinking water (Pruden et al. 2013). However, these are generally being addressed proactively through requirements for aggressive water treatments and multiple barriers (EPA 2012; National Research Council 2012), including AOPs and membranes, which are as likely to provide benefits as barriers to AMR, though further research is needed to confirm this is the case. Still, it is critical to recognize that water reuse is happening all around us, whether we recognize it or not, and may be better as a planned, rather than de facto endeavour. For example, in London, a substantial portion of the drinking water supply is derived from the River Thames, which itself receives WW from over 2.5 million people by the time it reaches London (Singer et al. 2014). A discussion with the wider society about conserving and recycling water is needed given the scarcity of freshwater. The question is not if we will need to close the water loop, but when and how. With this in mind, focused scientific effort is needed to inform policy and support major societal decisions such as how to best prioritize and address mounting public health issues, where to invest in water infrastructure, how to effectively protect source waters, and what level of treatment is acceptable technologically, economically and socially. In addition to addressing concerns about AMR, improved and upgraded water treatment systems can address other concerns such as hormones, pharmaceuticals, personal care products, nanoparticles and microplastics, along with the myriad of other pollutants occurring in municipal WW.

Water and sanitation in the broader context: interconnections with livestock, agriculture and industry

Effort is needed to quantify the relative contributions of various anthropogenic and natural sources of AMR in a water sanitation context, including industry, landfills, livestock manure, agriculture, transportation, stormwater, greywater and mining (Singer et al. 2016). A geospatial and temporal inventory of antimicrobials, metals and biocides released into the environment would be beneficial towards understanding the relative role that each might play in driving AMR in the environment. This can help guide focused mechanistic research and mitigation efforts. MGEs must also be characterized for their roles in maintaining and disseminating existing and novel ARGs, cassettes, plasmids and bacteria (Pruden et al. 2006; Singer et al. 2016). While most antibiotic resistance assays are determined under idealized conditions, ideally consideration to chemical mixtures, along with co- and cross-selective pressures and in realistic environmental matrices is needed (Bengtsson-Palme and Larsson 2016; Le Page et al. 2017; Xu et al. 2017).

Agriculture accounts for 70% of all water withdrawn from aquifers, streams and lakes (FAO 2011). In many large rivers, only 5% of former water volumes remain in-stream, with some rivers having insufficient water to reach the sea all year round (Rutkowska, Raschid-Sally and Buechler 2007). This rapid increase in irrigation agriculture over the past 50 years represents a major driver for water reuse, e.g., grey and blackwater (Drechsel et al. 2008; National Research Council 2012). Wastewater residuals, such as biosolids, are also commonly applied as soil amendments (Qadir et al. 2010). The exposure of grazing animals to pasture amended with reclaimed WW and biosolids represents another poorly explored pathway between humans, the environment and animals (Eamens and Waldron 2008). Differences in the carriage of AMR genes between humans and animals could also be used to develop treatment endpoint criteria. For example, a Dutch meta-analysis found differences in the frequency of specific mobile AMR genes carried by ESBL-producing E. coli from human origin (including WW) and farm animal origins (Dorado-García et al. 2017). Similarly, a European-wide study found mobile fluoroquinolone-resistant genes carried by Salmonella to be present in humans and poultry but not in other farm animals (Veldman et al. 2011). Finally, a Czech study found the vast majority of $aac(6')-Ib-cr$ (mobile resistance to fluoroquinolones)-carrying E. coli isolates in samples of human (specifically clinical) origins, but not from poultry origins (Röderova et al. 2017). The identification of specific marker genes would likely need to be done on a regional basis, but the human and farm animal resistance surveillance data available in several regions could be used to provide necessary information to make adequate selections of indicator AMR genes.

Opportunities for policy

WaSH has been at the centre of many of the Millennium Development Goals (UN 2017) and remains core to the Sustainable Development Goals (UN 2015). Although sustainable access to safe drinking water and basic sanitation is a major goal proposed by the WHO, in 2015 2.4 billion people were still using unimproved sanitation facilities and 946 million people were still practising open defecation. The importance of proper sanitation for effective control of AMR was recently recognized by the WHO in their Global Action Plan (WHO 2015). Effective policy to limit AMR dissemination through appropriate handling of WaSH continues to go unrecognized, in LMICs and high income countries alike. While AMR is not the only problem in the world today, it is one that affects everyone in one form or another. Thus, it is reasonable to recommend investments based on the best available science and that are economically in harmony with other benefits to other systems providing fundamental needs such as food, water and healthy ecosystems. Continued advancement of
the science, such as identifying meaningful monitoring markers and developing appropriate risk models, will help guide the most fruitful focus of such investments. For example, should the focus be on what goes down the drain in the first place, or on targeted treatment of hot-spot point sources, like agricultural application, hospitals and pharmaceutical manufacturing? Furthermore, should the bulk effort be focused on water, which is more widely disseminated, or sludge, which contains higher loads of resistance determinants? Also, simply requiring the provision of basic information to consumers, such as where their drugs are coming from and under what conditions they were produced, can help support an informed populace in voting with their purchasing power if the goods do not comply with their environmental ethics and principles. In terms of water quality regulations, systematic documentation of the occurrence of various ARBs and ARGs is needed, and could help advance the simple faecal-source tracking frameworks that have long been recognized to be fraught with shortcomings.

While acute risks of human pathogens, including resistant strains, are, to some extent, considered by regulations on treated WW and biosolids applications (LeBlanc, Matthews and Richard 2009; Jeong, Kim and Jang 2016), broader risks on the ecology and evolution of new strains, and risks of colonization and delayed infection, are largely uncharacterized and unaddressed. It is especially difficult to pinpoint risks associated with releases of various ARB, ARG and selective targets without agreed upon and standardized assays. Still, given the enormous potential harm of an escalating antibiotic resistance crisis, it may be prudent to follow a precautionary principle, and assess where and how improvements to the current situation is feasible. Within the water sector, possible interventions include: (i) strengthening existing barriers to AMR dissemination, (ii) introducing new barriers, and (iii) reducing selective pressure for AMR (Fig. 1).

Communication, education and engagement

Scientific research plays an essential role in advancing the state of the knowledge, while scientists and scientific advisory panels can offer advice at local, global and national levels on how to most effectively harness water supply and sanitation practices as a means to limit the spread of AMR. However, concerted action requires buy-in from all stakeholders including pharmaceutical manufacturers, hospitals and medical practitioners, water and sanitation engineers, governments and the public.

Ultimately the public sways and prioritizes investment of public funds towards the myriad of problems in today’s world. Thus, keeping the public informed about the problem of AMR is essential. While a growing number of people experience the devastation of resistant infections, the problem remains often narrowly viewed as one of hospital ‘infection control’. Given the essential nature of antibiotics to public health, the incorporation of units on antibiotic resistance in the school curriculum, with emphasis on microbial ecological and evolutionary processes as well as environmental routes of dissemination, is warranted. In today’s globally interconnected society, working with the media is also an essential avenue to an informed public. However, the AMR problem is complex, and involves numerous unknowns and uncertainties, making it difficult to accurately boil down concepts into a simple message for a lay audience. Poorly managed communication can be disastrous if it induces fear without pointing out clear courses of action, eventually fueling growing mistrust in science. It is important to recognize that risk perceptions of stakeholders are often different from those of the scientists and that the majority of people rely on their own unique ‘lay theories’ to understand and make sense of the world (Science for Environment Policy 2014). Ultimately, improved public knowledge will be a driving force towards mitigating the spread of AMR. Pointing out the comprehensive benefits of related action, such as improving sanitation and conditions in developing countries, may help encourage and mobilize the public.

The education and training of professionals involved in water quality policies and management as well as experts in environmental conservation and protection can do much to translate science into practice. Engaging with various scientific communities is a necessary step towards improved water and sanitation practices considerate of AMR risk. Also, human health care and veterinary practices would benefit from more integrated knowledge of the ecology and evolution of AMR, moving beyond the confinement of the clinic or the farm and spanning people, animals and the environment.

Synergies with One Water/One Health

Managing the chronic risk of exposure of humans and animals to AMR by limiting the release of antibiotics, ARBs, ARGs and MGEs from human WW streams to the environment is worthy of immediate scientific and policy action. Ultimately, the reality is that our food, sanitation and potable water systems are intimately connected and interdependent systems that provide a foundation for public health. This is the essence of the One Water/One Health paradigm (One Health 2017; One Water 2017), which can provide a guiding principle for recognizing these interconnections and steering action. Success will require building and fortifying new channels of communication among multiple stakeholders and between stakeholders and science, and ensuring that they are engaged and understand their role in the larger AMR challenge (Singer et al. 2016). It is only through a holistic vision of the many interconnected threads that a robust and sustainable policy can be formulated.

As scientific guidance builds and strengthens, there are several avenues by which a precautionary principle rationally applies (Foster, Vecchia and Repacholi 2000; Maynard 2002). AMR concerns can be factored into already planned WWTP upgrades or water reuse plans. Policy pertaining to sludge disposal and land-application of biosolids can consider effects on the long-term persistence of ARGs and MGEs and their potential for dissemination in the air, into surface- or ground-water, and into food crops and animals (Singer et al. 2016). Ideally, a precautionary approach can be incorporated with minimal additional investment as synergistic opportunities with other initiatives and benefits are identified. The tension between rapid action and a need for evidence-based policy will remain a significant challenge for many years to come. Solutions to the AMR challenge in the environment will require technological, medical, behavioural and societal change. As a global society, it is critical to continue to seek to identify and implement such changes within a holistic framework, incorporating the perspectives of policymakers, regulators, scientists, industry and society. It is only through this inclusive holistic strategy, at the national and international level, that gains can be maximized and unintended consequences minimized. It will take a concerted effort by all nations to make this progress and ensure the continued benefits of antibiotics to public health for future generations.
Figure 1. Promising barriers to environmental dissemination of antimicrobial resistance along the water and sanitation continuum and ultimately to human exposure.

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REFERENCES


Timraz K, Xiong Y, Al Qarni H et al. Removal of bacterial cells, antibiotic resistance genes and integrate genes by on-site hospital wastewater treatment plants: Surveillance of...

Tischendorf Jessica, de Avila Rafael Almeida, Safdar Nasia. AMERICAN JOURNAL OF INFECTION CONTROL 2016;44:5:539–43.


