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Briefing Note

**Antimicrobial Resistance:
An Emerging Water, Sanitation and Hygiene Issue**

**WASH FOR
HEALTH**

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1 Antimicrobial agents in the environment and antimicrobial resistance: an overview of the problem

The considerable overuse, careless use, inappropriate use and unregulated use of many antibiotics and other antimicrobial agents¹ in both human and veterinary medicine are well documented, as is the extensive and largely unregulated use of these agents in animal agriculture and aquaculture, including for growth promotion. Uncontrolled release and disposal of these agents to sanitary sewers and landfills and in effluent discharges from pharmaceutical production facilities are also known to occur.

These imprudent uses and abuses of antibiotics and other antimicrobial agents contribute to the extensive presence of their residues, their metabolites, multiple antimicrobial-resistant bacteria and their functional genes in human and animal wastes, in landfills and their leachates, in water, soil and sediments and in water-dependent food crops, such as seafood and produce. They persist for extended periods of time in many environmental compartments, even when antimicrobial use has ceased.

This briefing note is limited to consideration of antibacterial agents, antibacterial resistance and antibacterial resistance genes. Although it is recognized that antiparasitic, antiviral and antimycotic agents and resistance to them may also pose health risks, few studies have addressed the environmental health aspects of resistance to these agents.² With the recent trends in development and use of other antimicrobial agents, there may be an increase in parasitic, fungal and viral resistance, in which the aquatic environment is likely to play a role.

As a result of decades of use and abuse, antibiotics and other antimicrobial agents, their functional metabolites, antimicrobial-resistant bacteria and their antimicrobial resistance (AMR) genes are common and widespread contaminants in water and other environmental media, including wastewater and human excreta used for agricultural or aquacultural purposes or discharged to the environment, where they can persist for long periods of time. Although antibiotics and antibiotic resistance genes are considered natural components of the microbial communities that exist throughout the world's habitable environment, human impacts, including the introduction of synthetic antimicrobial agents, have radically changed their ecology.

Consequently, we now have further emergence and selection of new AMR traits in bacteria, including pathogenic bacteria of human health concern (Martinez, 2009a, 2009b; Wright, 2010), with well documented loss of antimicrobial treatment options for humans. The (aquatic) environment may play different roles in the emergence and spread of AMR, by (1) acting as a collecting vessel of resistant bacteria from animals and humans treated with antibiotics (i.e. anthropogenic resistance); (2) offering

¹ The term “antibiotic” is used here to represent any chemical substance produced by a microorganism or semi-synthetically that has the capacity to inhibit the growth of or to kill other microorganisms and is used to treat infections. The term “antimicrobial agent”, often abbreviated to “antimicrobial”, is used here to represent any chemical agent, including synthetic chemicals, that kills microorganisms or suppresses their multiplication or growth to prevent their pathogenic action and is used to treat infections.

² Low levels of the antiviral agent oseltamivir were detected in the aquatic environment by Söderström et al. (2009). They concluded that certain duck species may be exposed to the anti-influenza virus drug in water, which could promote the evolution of viral resistance. Azole resistance of the fungus *Aspergillus fumigatus* is an emerging problem for which there is evidence that its newly identified resistance mechanism probably develops in the environment (Verweij et al., 2012). This is because azoles are frequently used for crop protection and material preservation, and it is likely that breathing in the resistant spores of these *Aspergillus* strains from the environment leads to clinical infection.

direct and indirect exposure routes to humans and animals; (3) facilitating the spread of antimicrobial-resistant bacteria and resistance markers to other places (through surface water, groundwater, air, dust, wildlife); (4) acting as a reservoir for natural resistance markers; and (5) enabling the exchange of resistance markers between bacterial species.

Many enteric bacterial pathogens and associated faecal indicator bacteria, such as *Escherichia coli* and enterococci, are now multiple antimicrobial resistant, with some so resistant that infections cannot be effectively treated. A study has linked clinical isolates of multidrug-resistant enteric bacteria to the same bacteria found in environmental waters that were implicated in a possible waterborne community salmonellosis outbreak (Akinyemi et al., 2011), and there are other cases of increased human mortality and morbidity caused by antimicrobial-resistant bacteria (Barza & Travers, 2002; Travers & Barza, 2002; Helms et al., 2005; de Kraker, Davey & Grundmann, 2011). Therefore, there is a greater disease burden, measured as disability-adjusted life years (DALYs), from exposures to these bacteria via environmental media (water, wastewater, irrigated produce, etc.) and related pathways (e.g. faecally contaminated vectors such as flies, contact surfaces and contaminated hands). New strains or variants of highly resistant enteric bacteria of human health concern continue to emerge, are detectable in environmental media such as water and soil and are spreading globally, thus posing increased human health risks.

Among the Gram-negative enteric bacteria widely present in the environment and mammalian hosts, the development of extended spectrum beta-lactamase (ESBL) resistance in pathogens that cause considerable morbidity and mortality is recognized as a global public health concern (Ghafourian et al., 2014). An example of the continued emergence and spread of common enteric bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*, is the appearance of the bla_{NDM-1} gene to produce the New Delhi metallo- β -lactamase NDM-1, which is a carbapenemase beta-lactamase enzyme that hydrolyses and inactivates the therapeutically important carbapenem antimicrobial agents (Bushnell, Mitrani-Gold & Mundy, 2013). Various sources document evidence for the increased presence of these NDM-1 bacteria in human and animal populations and the environment. Their profound resistance prevents effective antimicrobial therapy of infected and ill people, as there are currently no new antibiotics available to combat bacteria resistant to carbapenems.

2 Environmental presence and exposure source hotspots

Human excreta and wastewater are recognized and documented as major sources of antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and their AMR genes because of the widespread and extensive use of antimicrobial agents by human populations. In many countries, facilities to treat municipal, community and household wastes that may harbour antimicrobial agents, antimicrobial-resistant bacteria and AMR genes are absent or inadequate, including ageing infrastructure such as leaking sewers that are often co-located with municipal water distribution pipes.

As a result, these contaminants are released directly into the environment where human exposures are likely and where antimicrobial-resistant bacteria and AMR genes are capable of persisting and spreading. Furthermore, human wastewater and excreta are used extensively in agriculture as sources of water and plant nutrients, and such use is encouraged by management practices such as ecological sanitation, municipal wastewater (re)use and water reclamation.

The potential for human exposure to such wastes is great. It is estimated that up to 90% of all wastewater is discharged untreated directly into rivers, lakes or the oceans (Corcoran et al., 2010). Therefore, the collection, prevailing management and purposeful or unplanned use of such wastes often result in increased prevalence and environmental release of antimicrobial contaminants, including antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes (Schwartz et al., 2003; Lupo, Coyne & Berendonk, 2012). Municipal wastewaters in particular are major environmental reservoirs for antimicrobial agents, antimicrobial-resistant bacteria and AMR genes, and they also provide an environment that is conducive to the transfer of resistance genes to other bacteria before or after being discharged into the environment (Rizzo, Fiorentino & Anselmo, 2013; Rizzo et al., 2013).

There is increasing evidence that wastewater treatment plants are hotspots that sustain and further promote the propagation and selection of antimicrobial-resistant bacteria and AMR genes within their systems as well as function as major point sources that release them into the environment, where they disperse (Jury et al., 2011; Bouki, Venieri & Diamadopoulos, 2013). Although wastewater treatment processes can reduce concentrations of pathogens in wastewater, wastewater treatment plant effluents do not show appreciable removal of antimicrobial-resistant bacteria and AMR genes in general (Okoh & Igbinosa, 2010; Leclercq et al., 2013). Although wastewater treatment was shown to reduce the discharge to surface waters, wastewater effluents and other sources are likely co-contributors to ESBL loads in recreational waters, representing a possible exposure route (Blaak et al., 2014).

It has been suggested that other specific hotspots for antimicrobial-resistant bacteria and AMR genes are the waste discharges of pharmaceutical production facilities, hospitals and other health-care facilities. People in hospitals are constantly and extensively being treated with antibiotics and other antimicrobial agents, and their solid, faecal and liquid wastes have been documented as important sources contributing to the release and subsequent spread of antibiotics and other antimicrobial agents, antimicrobial-resistant bacteria and AMR genes in the environment (Mach & Grimes, 1982; Korzeniewska, Korzeniewska & Harnisz, 2013; Leclercq et al., 2013; Varela et al., 2013; Zhang et al., 2013; Amaya et al., 2012).

3 Implications of environmental antimicrobial-resistant bacteria and AMR genes for human health

There is growing public health concern that antimicrobial-resistant bacteria and AMR genes in human waste could potentially enter water sources via untreated or treated wastewater effluent and result in the exposure of human populations that use such water as drinking-water sources, for bathing, washing and other domestic sources, for primary contact recreation and as irrigation water. The use of human excreta solids (such as latrine wastes, septage and biosolids) containing antimicrobial-resistant bacterial pathogens for food and other crops is also a health concern. Although human exposures to antimicrobial-resistant bacterial pathogens from various environmental sources and by various exposure pathways could cause infections resulting in illnesses and deaths, the extent to which human health risks are increased from such exposures is inadequately characterized, poorly documented and therefore of uncertain magnitude (Ashbolt et al., 2013). However, as noted above, a study has linked multidrug-resistant enteric bacteria to the same bacteria that were implicated in a possible waterborne community outbreak of an enteric disease (Akinyemi et al., 2011). Furthermore, it is well documented that infection with antimicrobial-resistant pathogens carries an increased risk of mortality, longer treatment and longer stays in hospital, and the use of more expensive and more toxic second-line therapies. The potential risks from antimicrobial-resistant organisms in the water environment include (1) infection by antimicrobial-resistant pathogens present in the water (e.g. resistant *Campylobacter* spp., *Shigella* spp., *Salmonella typhi* and other *Salmonella* spp.); (2) colonization and subsequent infection with opportunistic pathogens, such as *E. coli* and enterococci; and (3) transient colonization with antimicrobial-resistant organisms that can then be a source of AMR genes for the normal flora through horizontal gene transfer; should an endogenous infection occur, it may be with an antimicrobial-resistant strain. Overall, there is a lack of reliable, well documented and validated human health risk assessments for antimicrobial-resistant bacteria and AMR genes from such environmental exposures, and currently there is inadequate information based on quantitative microbial risk assessment to inform the development and implementation of appropriate risk management systems.

The direct use of antibiotics and other antimicrobial agents and wastewater and excreta laden with them in various food production systems, such as animal agriculture and aquaculture, is also a concern in terms of the widespread presence and spread of antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes in aquatic environments and in human food supplies. For example, an estimated 10% of the world's population is thought to consume wastewater-irrigated foods, and 20 million hectares of land in 50 countries are irrigated with raw or partially treated wastewater (Corcoran et al., 2010), much of which almost certainly contains antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes. As another example, aquaculture is a growing seafood production endeavour worldwide that has resulted in rapid, extensive and often imprudent increases in therapeutic and prophylactic usage of antimicrobial agents, including those important in human therapy.

The majority of antimicrobial agents used in aquaculture enter the environment, where their activity selects for and results in the extensive presence of antimicrobial-resistant bacteria and mobile AMR genes of human health concern in water, seafood and other aquatic life. For instance, high levels of resistance to chloramphenicol and tetracycline, high AMR indices and plasmid carriage have been observed in *Salmonella* serovars of human health concern that were isolated from catfish and tilapia from aquacultural production and markets. Evidence suggested that resistance was due to high and

unregulated use of antimicrobial agents for therapy and growth promotion (Budiati et al., 2013). The antimicrobial agents commonly used in aquaculture include several that are classified by the World Health Organization (WHO) as critical for human use, and resistance to them in human pathogens would severely limit therapeutic options.

Overall, the intensive, excessive and unregulated use of antimicrobial agents in aquaculture is a widespread practice that has led to the occurrence of antimicrobial-resistant bacteria and their mobile genetic elements in aquacultural systems and the environment, potentially leading to human health risks. However, such human health risks remain poorly documented and characterized. There is a need for greater attention and action to develop quantitative microbial risk assessments, risk management systems and supporting guidance (Cabello, 2006; Smith, 2008; Heuer et al., 2009; Park et al., 2012; Cabello et al., 2013; Pruden et al., 2013).

4 Environmental antimicrobial agents, antimicrobial resistance and risk-based guidelines for water and sanitation

Current WHO guidelines for drinking-water, recreational water and use of wastewater and excreta in agriculture and aquaculture contain no specific or even general information on antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria or their AMR genes.

Furthermore, they provide no specific guidance on how to assess, manage or minimize the potential human health risks associated with the presence of antimicrobial agents and antimicrobial-resistant bacteria and the various opportunities for human exposures via various water, sanitation and hygiene pathways and transmission routes. However, a growing body of scientific evidence suggests widespread global occurrence of antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes in wastewater systems, aquacultural systems, recreational water and drinking-water. The current lack of consideration of the human health risks from these contaminants in these various WHO guidelines is inconsistent with the harmonized health risk-based approach that has now become the basis for these various guidelines, known as the Stockholm Framework.

The Stockholm Framework provides a common conceptual framework within which to assess water quality hazards and manage associated risks from human exposure to water, wastewater and excreta. The key elements of the framework integrate risk assessment and the identification and setting of acceptable levels of risk, expressed as DALYs, the establishment of health targets for identified health risks of concern, the development and use of risk management systems, plans, policies and practices, the assessment of exposures and the monitoring of public health status, which are all part of an ongoing system for protection from health risks associated with water-related exposure.

For the different WHO guidelines, the framework and its elements are applied to the management of the health risks associated with that exposure medium and its pathways, such as the “Annapolis protocol”, applied to the management of recreational waters; the framework for safe drinking-water and its use of water safety plans for holistic drinking-water quality management; and the various guidelines for the safe use of wastewater and excreta in agriculture and aquaculture and their sanitation safety plans for integrated management of chemical and microbiological risks associated with such excreta and wastewaters.

Because the presence of antimicrobial-resistant bacteria and their AMR genes in water, wastewater, wastewater-irrigated foods and aquacultural systems is now widely recognized, greater and more harmonized consideration of them as an environmental health hazard is needed. This need should be addressed through a variety of integrated prevention and control measures supported by appropriate guidance for risk assessment and risk management (Ashbolt et al., 2013; Pruden et al., 2013). The lack of consideration of antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes in the environmental media addressed by the various WHO guidelines for drinking-water, recreational water and the use of wastewater and excreta in agriculture and aquaculture is a major gap in coverage of a class of contaminants of human health concern that requires more and better risk assessments, effective management approaches and systems, and specific guidance for management.

Greater and more focused efforts are needed to address the human health risks from environmental exposures to antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes from water and human excreta-related environmental exposures in the future development and implementation of revised and possibly new WHO guidelines in the area of water, sanitation and hygiene. It is suggested that WHO, its partners and stakeholders should bring together experts and various stakeholder representatives to examine the current evidence on environmental exposures and their health effects; explore approaches to quantify and estimate the risks; identify strategies to minimize and better manage the risks; and propose new and improved WHO guidance to support risk analysis and risk management efforts through integrated water safety plans, sanitation safety plans and related management plans linked to safe, prudent and responsible use of antimicrobial agents and the management of wastes and waters laden with antibiotics and other antimicrobial agents, antimicrobial-resistant bacteria and their mobile and functional genes.

A forum is suggested to facilitate the dialogue and discussion that will catalyse collective thinking and actions and provide the opportunity to develop strategies and plans for research and demonstration, risk analysis and risk management plans, policies, procedures, guidance, regulations and improved practices for directed and more effective management of antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes in the water, sanitation and hygiene context.

5 Proposed directions for risk assessment, management, policies and research

The following activities and actions are proposed to better address antimicrobial agents, antimicrobial-resistant bacteria and AMR genes in the environment as human health risks that need to be assessed and managed.

5.1 Risk assessment

- For exposure assessment, there is a need for improved identification of the types and sources of antimicrobial-resistant bacteria and their AMR genes in human and animal wastes, the movement of those antimicrobial-resistant bacteria and their AMR genes through the environment (e.g. water, soil, irrigated crops, aquaculture food products) and the pathways for human exposure (e.g. ingestion of contaminated food products) that can potentially lead

to infection and adverse health effects, with a focus on known as well as emerging bacterial pathogens.

- For health effects assessment, there is a need to develop approaches to estimate health risks associated with exposure to antimicrobial-resistant bacteria and their AMR genes in environmental media via routes such as ingestion, inhalation, skin and eye contact, and food contact and consumption. There is a need to encourage and support new research and demonstration projects to assess and estimate the human health risks through field epidemiological–microbiological studies and quantitative microbial risk assessments.
- There is a need to assess the current status of governments and other (international and commercial) regulations and policies to prevent or minimize the presence of antimicrobial agents and their metabolites and antimicrobial-resistant bacteria in humans, animals and environmental media impacted by human and animal wastes and to prevent or minimize the further selection for and propagation of antimicrobial-resistant bacteria that could lead to further human exposures and possible health effects.

5.2 Risk management

- There is a need to identify possible solutions to the problems caused by the presence of antimicrobial agents, antimicrobial-resistant bacteria and their AMR genes in environmental media. These efforts should include the identification of approaches to the development of management systems and plans to overcome and combat the widespread and uncontrolled use and abuse of antibiotics and other antimicrobial agents and the conditions that contribute to the production and dissemination of antimicrobial-resistant bacteria in people, animals and environmental media.
- There is a need to identify approaches to the development and implementation of systems for tracking and monitoring antibiotics and other antimicrobial agents, their metabolites and antimicrobial-resistant bacteria in environmental media. These efforts should focus on sources, source mitigation and minimization, supported by the development of management strategies and systems to minimize use, improve containment and treatment processes, and minimize subsequent environmental release and spread.
- There is a need to develop specific management objectives, policies, plans, procedures and practices to prevent and control the risks from exposure to antimicrobial agents, antimicrobial-resistant bacteria and their mobile and functional genes within water safety plans and sanitation safety plans, as presented in existing and possibly new, revised and better harmonized WHO water quality guidelines. The recognition that AMR is now widespread among the bacteria present in human and animal wastes and environmental waters now provides yet another important health-related basis to further encourage effective management systems and best practices to minimize such contamination of water and wastes and reduce human exposures.

Efforts are needed to adapt and apply the WHO water quality and health framework and strategy to specifically address antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes, according to the existing strategic objectives of the WHO Water Quality and Health Strategy – 2013–2020:

1. Obtain the most rigorous and relevant evidence regarding water quality and health related to antibiotics and other antimicrobial agents, their metabolites, antimicrobial-

resistant bacteria and AMR genes in water, wastes and other relevant exposure media.

2. Provide up to date, harmonized water quality management guidelines and supporting resources to address these contaminants of health concern.
3. Strengthen the capacity of Member States to most effectively manage water quality to protect public health.
4. Facilitate implementation of water quality and health activities through partnerships and support to Member States.
5. Monitor the impact of these activities on policies and practices to more effectively inform decision-making.

5.3 Policy / global level actions

- There is a need to identify and suggest ways to overcome the challenges faced in policies, practices and regulations for the availability, sale and distribution, monitoring, tracking and control of indicated and unapproved uses of antimicrobial agents and for the management and disposal of unwanted or expired antimicrobial agents and in creating and managing surveillance and other systems to track their production, environmental distribution and fate.
- There is a need to develop new WHO guidance to inform and support efforts to control the presence of antibiotics and other antimicrobial agents, their metabolites and antimicrobial-resistant bacteria in human and animal wastes and environmental media and reduce or minimize the routes of human and animal exposure through water, sanitation and hygiene policies, plans, practices and regulations.

5.4 Research needs

- Research is needed to identify and quantify the sources, occurrence and transport of antibiotics and other antimicrobial agents, antimicrobial-resistant bacteria and AMR genes in environmental media, especially water, wastewater and other media to which humans are exposed. There is a need to develop and implement an “indicator” system to identify and quantify sentinel antimicrobial-resistant bacteria in water, wastewater and other exposure media regularly and widely on a global basis and to communicate such data for the purpose of monitoring status, trends and unusual increases or emergence phenomena.
- Research is needed to identify water and waste treatment technologies, including physical removal and destruction, physical and chemical disinfection as well as biological treatments, to minimize the presence of antibiotics and other antimicrobial agents, their metabolites, antimicrobial-resistant bacteria and AMR genes in human and animal wastes and in environmental media for which WHO provides specific guidance.
- Research is needed to develop practical risk management systems and tools to minimize the release or introduction of antibiotics and other antimicrobial agents, antimicrobial-resistant bacteria and AMR genes into the environment by the establishment and use of policies, programmes and practices to eliminate and minimize use and to contain or destroy these contaminants at their source.
- Research is needed to identify and encourage policies, practices and tools to minimize human exposure to antibiotics and other antimicrobial agents, antimicrobial-resistant bacteria and AMR genes from environmental media, such as the use of personal protective equipment and other on-site or point-of-use application and use systems that minimize uncontrolled and excessive release and optimize collection, containment and the use of physical barriers to minimize human contact and exposure.

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