Updated research agenda for water, sanitation and antimicrobial resistance

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ABSTRACT

The emergence and spread of antimicrobial resistance (AMR), including clinically relevant antimicrobial-resistant bacteria, genetic resistance elements, and antibiotic residues, presents a significant threat to human health. Reducing the incidence of infection by improving water, sanitation, and hygiene (WASH) is one of five objectives in the World Health Organization's (WHO) Global Action Plan on AMR. In September 2019, WHO and the Health-Related Water Microbiology specialist group (HRWM-SG) of the International Water Association (IWA) organized its third workshop on AMR, focusing on the following three main issues: environmental pathways of AMR transmission, environmental surveillance, and removal from human waste. The workshop concluded that despite an increase in scientific evidence that the environment may play a significant role, especially in low-resource settings, the exact relative role of the environment is still unclear. Given many antibiotic-resistant bacteria (ARB) can be part of the normal gut flora, it can be assumed that for environmental transmission, the burden of fecal-oral transmission of AMR in a geographical area follows that of WASH-related infections. There are some uncertainties as to the potential for the propagation of particular resistance genes within wastewater treatment plants (WWTPs), but there is no doubt that the reduction in viable microbes (with or without resistance genes) available for transmission via the environment is one of the goals of human waste management. Although progress has been made in the past years with respect to quantifying environmental AMR transmission potential, still more data on the spread of environmental AMR within human communities is needed. Even though evidence on AMR in WWTPs has increased, the reduction in the emergence and spread of AMR by basic sanitation methods is yet unresolved. In order to contribute to the generation of harmonized One Health surveillance data, WHO has initiated an integrated One Health surveillance strategy that includes the environment. The main challenge lies in rolling it out globally including to the poorest regions.

Key words | antimicrobial resistance bacteria, environmental surveillance, One Health, transmission pathway, wastewater treatment, water environment

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HIGHLIGHTS

- Workshop on antimicrobial resistance (AMR) and water environments was organized by the World Health Organization and International Water Association Health-Related Water Microbiology Specialist Group at the Medical University of Vienna in September 2019.
- There are three main issues, including environmental surveillance, removal from human waste, and environmental pathways of AMR transmission.
- In order to contribute to the generation of harmonized One Health surveillance data, WHO has initiated an integrated One Health surveillance strategy that includes the environment.
- The exact relative role of the environment on AMR dissemination is still unclear, especially in low-resource settings.
- Even though evidence on AMR in wastewater treatment plants has increased, the degree of the reduction in the emergence and spread of AMR by most basic sanitation is yet unresolved.

INTRODUCTION

Antimicrobial resistance (AMR) has been raised as an important issue on the international agenda for over a decade. AMR is not only a major threat to global health but also to our future economies (O'Neill 2016; Interagency Coordination Group on Antimicrobial Resistance 2019). In the United States alone, more than 2.8 million cases of antibiotic-resistant infections occur annually while 35,000 people are estimated to die (CDC 2019), and these numbers are expected to be higher in more resource-limited settings. However, studies on the AMR have mainly focused on the clinical and animal settings and the environment has been largely neglected until recently (Wellington *et al.* 2013; Bloomer & McKee 2018). While the relative role of the environment in AMR transmission is unclear at this stage, an important step is to identify hotspots of AMR spread and human exposure, and explore possible benefits of actions to reduce the load of AMR agents into water environments (Bengtsson-Palme *et al.* 2018; Amarasiri *et al.* 2019). This is reflected in the World Health Organization's (WHO) Global Action Plan on AMR, in which reducing the incidence of infection by improving water, sanitation and hygiene (WASH) is included as one of the five objectives (WHO 2015), and in the recent WHO, Food and Agriculture Organization of the United Nations (FAO), and World Organization for Animal Health (OIE) publication of a technical brief on WASH and wastewater management to prevent infections and reduce the spread of AMR (WHO *et al.* 2020). Moreover, the United Nations Ad Hoc Interagency Coordinating Group (IACG) on AMR repeatedly highlighted the need for increased waste management including access to WASH (Interagency Coordination Group on Antimicrobial Resistance 2019).

WHO and the Health-Related Water Microbiology specialist group (HRWM-SG) of the International Water Association (IWA) have cooperatively addressed the AMR and environment issues, mainly from the viewpoint that water environments provide important hotspots for AMR dissemination. Since 2014, WHO and HRWM-SG collaboratively organize a workshop on AMR and water environments as an associated event of the biennial international symposium of HRWM, and share up-to-date information related to AMR and water environments (Wuijts *et al.* 2017). On 20 September 2019, the third workshop on AMR and water environments was held as a post-event of the 20th International Symposium on HRWM at the University of Vienna, Austria. Three main issues related to AMR in water environments were discussed during the workshop: environmental pathways of AMR transmission, environmental surveillance, and removal from human waste. The workshop explored the potential contribution of environments to the spread of AMR by evaluating the state of knowledge on the relationship between AMR and aquatic environments.

The workshop was opened by Dr Astrid Louise Wester (recently WHO focal point for AMR and WASH, currently at the Norwegian Institute of Public Health). Dr Wester presented updated information on WHO activities on global AMR progress, including WASH in AMR National Action Plans (NAPs; WHO *et al.* 2016), IACG-AMR recommendations (Interagency Coordination Group on Antimicrobial Resistance 2019), ongoing discussions on the Global Framework for Development and Stewardship to combat AMR, and on waste management in the WHO Good Manufacturing Practices system. Professor Paul Hunter (University of East Anglia, Norwich, UK), provided an overview of the links between AMR and WASH in healthcare facilities and the contribution of international travel on the dissemination of AMR (Arcilla *et al.* 2017). Dr Gernot Zarfel (Medical University of Graz, Austria) discussed the isolation of antibiotic-resistant strains of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. (collectively known as ESKAPE pathogens) from the Danube River (Kittinger *et al.* 2016a, 2016b, 2018).

The main component of the workshop was the discussion in three breakout groups:

Group 1: Environmental surveillance – the WHO extended-spectrum *β*-lactamases (ESBL) *Escherichia coli* tricycle project – status, lessons from piloting and next steps (Session Coordinator: Dr Heike Schmitt, RIVM, The Netherlands).

Group 2: Wastewater treatment technologies – practical implementation of the precautionary principle (Session Coordinator: Dr Mohan Amarasiri, Tohoku University, Japan).

Group 3: Environmental pathways for AMR – decision tree for prioritizing WASH and environment actions (Session Coordinator: Dr Amy Kirby, CDC, USA).

In this article, discussion and conclusions derived from the breakout group discussion are summarized.

GROUP DISCUSSION

Group 1: Surveillance – the WHO extended-spectrum beta-lactamase (ESBL) *E. coli* tricycle project – status, lessons learned from piloting and next steps

Firstly, the session coordinator Dr Heike Schmitt described the WHO Tricycle project (Matheu *et al.* 2017). The project aims to engage environmental, animal production, and medical stakeholders in participating countries. In the suggested protocol, samples are collected from humans (blood samples from hospital surveillance and feces from pregnant women), animals (chicken), and the environment (human and wet market wastewater and river water upstream and downstream of a city, in one or two cities in a country). Usually, the capital and/or a smaller city next to the capital city were selected for sampling because of easier transport access and the availability of laboratory facilities. For environmental sampling, ideally, 8 sampling sites per country (4 locations per city and 2 cities per country) are selected, and 8–10 samplings per location per year are conducted. Analysis of environmental samples is based on quantitative determinations of ESBL *E. coli* and total *E. coli* by use of tryptone bile X-glucuronide (TBX) agar plates. The project is performed over a 1-year time-scale, to account for possible seasonal variability. Acquired data are the prevalence (% carriage) of ESBL-resistant *E. coli* in animals and humans, the occurrence (counts) of ESBL-resistant *E. coli* and total *E. coli* per volume of river water, and the ratio of ESBL *E. coli* to total *E. coli*. Chicken was chosen as a target animal because they are globally available, cheap, and easily accessible. Countries can also opt for drinking water as a target sample. At the moment, five countries (Ghana, Indonesia, Madagascar, Malaysia, and Pakistan) have piloted the Tricycle protocol, and application in more countries is ongoing. Collected data are used by the countries to define intervention strategies where appropriate. The costs per country for reagents are modest.

After the project explanation, it was discussed which reservoirs the participants of the workshop group would suggest for inclusion in environmental surveillance. There were three representative suggestions from participants. The first one is pristine areas as baseline/background conditions because scientists may have a bias toward focusing on hotspots. The second one is prioritizing because they have high concentrations of AMR observed in the environment, which have high population densities, and people live in close proximity with animals and share water systems (Nigeria Centre for Disease Control 2017; Taneja & Sharma 2019). The third point is the need to pay attention to socially deprived areas (e.g. slums) rather than capital cities. It is important to compare between urban and rural areas, and poor and rich populations.

Then, the group voted on suggested surveillance targets as AMR reservoirs, based on what would be feasible and desirable. The voting results are presented in Table 1. The currently suggested target of human wastewater ranked first, followed by sampling to acquire a representative baseline of surface water (e.g. average), hospital wastewater and animal abattoir/slaughterhouse wastewater. The representative baseline of surface water may involve pristine surface water sites, which represent the background level of AMR in nature. There were several antibiotic-resistant bacteria (ARB)/antibiotic resistance genes (ARGs) targets related to animal waste, which included the animal abattoir/slaughterhouse wastewater, densely populated areas in which animals and humans share the same space and water (e.g. India, Nigeria), and zoos/wildlife reserves/aquariums. Totally different targets from the current project are landfills and aquaculture. Based on this voting, the group reached the conclusion that human wastewater is important to inform general prevalence and concentration of ESBL-resistant *E. coli*. Hospital wastewater was suggested for discussion as an additional target of the Tricycle project. Animal wastewater and representative samples of surface water were also deemed important.

Table 1 | Proposed surveillance targets and vote count by group 1 participants

Proposed surveillance target	Vote count
Human wastewater	10
Representative baseline of surface water (e.g. average)	8
Hospital wastewater	5
Animal abattoir/slaughterhouse wastewater	5
Densely population areas in which animals and humans share the same space and water (e.g. India, Nigeria)	4
River water	4
Landfills, as antibiotics might be dumped with waste	3
Aquaculture	3
Drinking water (source water)	3
Irrigation water/wastewater reuse for agriculture[a]	2
Urban vs. rural surface waters	2
Antibiotics production sites	1
Drinking water (after production)	1
Pristine surface water sites	1
Zoos/wildlife reserves/aquaria (Singapore)	1
River before and after human wastewater treatment plants	1

[a]Probably depends on the country what type of water is used for irrigation.

The second question discussed in this breakout group was: What kind of sample metadata are needed to make better use of the data? Suggestions from the participants were climate information (wet vs. dry season, precipitation, river flow, water/air temperature, tidal influence), water quality (pH, dissolved oxygen, biochemical oxygen demand, conductivity, total suspended solids, total coliforms, 16S sequence counts for normalization, antibiotics, toxicity), geographical information (land use, population density, antibiotics use/sales), operational information from wastewater treatment plants (WWTPs; number of people serviced, animals serviced, discharge volume), watershed information (source tracking), and sampling strategy (taking multiple samples to account for variability, high flow situation sampling, comparison with low flow sampling, sediments/biofilms, good documentation on sampling location (GPS location), type of water body (river/lake)). These can be classified as variables to assure that the sample was taken correctly and research would be repeatable, as well as to identify underlying causative factors.

Group 2: Wastewater treatment technologies – practical implementation of the precautionary principle

The session coordinator was Dr Mohan Amarasiri. Dr Amarasiri first asked the following question: Which kind of wastewater treatment systems should be developed/implemented to remove ARB and ARGs? In addition, group 2 participants raised the following questions: What does AMR release into environment mean? Why should we worry about ARB from WWTPs? Dr Amarasiri employed a brainstorming approach to extract answers to the questions and collected ideas on the role of wastewater treatment for preventing the dissemination of AMR. The following were the important discussion points.

Since ARB are not different from susceptible bacteria physiologically, no particular selection occurs at any point in the treatment. In less economically developed countries (LEDCs), it is important to change from open defecation to improved systems such as double pit latrines and septic tanks with proper soil absorption as the basic sanitation systems such as pit latrine are better than open defecation in terms of the reduction of ARB/ARGs emission to environments (Graham *et al.* 2019). Based on the emergency response experience from Ebola virus and cholera outbreaks, slaked lime (calcium hydroxide) has been shown to reduce fecal coliforms and intestinal enterococci by more than 4 logs (da Silva *et al.* 2018). It is important to understand the extent to which systems applicable in LEDCs would reduce ARB/ARGs with the potential use of high pH lime.

Concerns about the use of different qPCR methods, including the location and length of the target in addition to not understanding the real taxonomic coverage to determine the selection of ARGs in WWTP were raised. Different studies use different primer sets to target the same ARG, which makes it impossible to compare the outputs. It is important to develop standardized protocols for quantification of ARGs. We cannot assess the removal effectiveness of ARGs at WWTPs if not attributed to specific phyla because of insufficient information of methodology. Primers should cover 3 or 4 phyla for the quantification of ARGs in WWTPs to overcome the bias among phyla. Presenting the relative abundance means of detected ARGs may facilitate to communicate with clinical researchers to convey the message with regards to the importance of wastewater survey for ARGs. Besides these points, it is also important to culture ARB, rather than only measuring ARG copy number.

In addition to municipal wastewater, wastewater from combined sewer outflows, hospitals, daycare centers, and other sources, which are commonly regulated by BOD and coliforms, may be hotspots of AMR (Amarasiri *et al.* 2019). In high-income countries, systems such as ozonation are performing well for the removal of ARB, although there are concerns that the use of ozonation with micropollutants, including antibiotics, may not be appropriate due to the formation of by-products which are more toxic than the micropollutants themselves (Zimmermann *et al.* 2011). Therefore, it is important to have a balance between improving sanitation and removal/transformation of micropollutants.

Current technologies may be quite selective regarding ARB removal (different outcomes from different technologies). Several chemicals can promote the selection for certain AMR, such as heavy metals and detergents (Amarasiri *et al.* 2019). Physicochemical analysis is necessary in addition to the ARB/ARGs detection. The efficacy of decentralized systems in the removal and release of ARB/ARGs in the aquatic environments must be evaluated. Peracetic acid seems to be effective against ARB (Kitis 2004). Systems, such as algae ponds with high pH, may be useful for the elimination of ARB in LEDCs. However, operation and maintenance of waste stabilization ponds in LEDCs with high population growth is a major concern.

According to the global database on country progress in the implementation of the global action plan on AMR, all countries except for six countries (Angola, Guinea, Nauru, San Marino, Tuvalu, and Yemen) are at different stages of developing or implementing their NAP on AMR. These NAPs are developed based on the Global Action Plan by WHO in 2015 and focuses on surveillance, education, monitoring and regulating consumption, and use of antimicrobials in humans, animals, and production, as well as plants and the environment (https://amrcountryprogress.org/). Multiple stakeholders, including engineers and practitioner, need to be involved in the development and implementation of NAPs in each country (Pruden *et al.* 2018).

It is also suggested to leverage opportunities, such as polio or typhoid fever outbreaks, to involve stakeholders on the AMR issue. An additional trigger in LEDCs may be to advocate that whatever is released in the environment is going to be present in food they consume. It may be possible to use an indicator ARB throughout WWTPs to assess the removal of ARB at each stage similar to other pathogens like viruses (Amarasiri *et al.* 2017). ESBL-resistant *E. coli*, included in the WHO tricycle project, may be a good indicator in evaluating the removal efficiency of ARB by WWTP unit processes. Temporal variation in the performance of WWTPs can be monitored by ARGs.

Finally, this group reached several conclusions. It is important to monitor AMR, metals, and metadata such as physicochemical analysis at WWTPs. In centralized systems, the application of ozonation and the use of oxidation ponds and waste stabilization ponds with sufficient retention time (with high pH level to prevent ARGs moving to algae and sediment) must be effective to reduce the environmental pollution with AMR. In decentralized systems, lime and peracetic acid are effective for AMR reduction. The separation efficiency of solid and liquid waste also affects the AMR reduction efficiency.

The group also made several recommendations based on their discussion: (1) to determine effectiveness of basic sanitation such as pit latrines toward reduction of emergence and spread of AMR; (2) to obtain data from other locations under other circumstances if you cannot evaluate locally; sharing data should be stimulated and facilitated; collaboration among institutions is needed; (3) to use ESBL *E. coli* as an indicator for treatment effectiveness evaluation using the Tricycle protocol; if the treatment is not effective, to add another treatment step; (4) to confirm if ARBs and susceptible bacteria behave similarly in wastewater treatment; (5) to consider AMR in wastewater guidelines and its cost-effectiveness; (6) to establish standardized detection methodologies for AMR in wastewater; (7) to clarify AMR terminology across One Health domains; (8) to involve engineers in NAPs on AMR; (9) to establish the impact of AMR release into the environment; and (10) to raise public awareness of AMR.

Group 3: Environmental pathways for AMR – decision tree for country prioritization of WASH and environment actions

The group 3 coordinator Dr Amy Kirby pointed out that in LEDCs where antibiotic use is poorly regulated, easy access to antibiotics is an important reason for the increased presence of antibiotics/ARB/ARGs in the environments. The discussion in group 3 proceeded as a conversation between the coordinator and the group participants.

The first question from the coordinator was: Are there potentially important transmission routes other than commonly recognized ones? There were several responses from the participants, which included indoor airborne transmission, and fecal sludge. The latter route is of interest due to the use of fecal sludge for agricultural purposes.

The second question was: How to prioritize WASH and environmental interventions? There were several suggestions from the participants, including (1) by country/region based on income level, (2) by types of existing regulations on antibiotic use, (3) by resistance emerging vs. resistance spreading, and (4) by type of and access to sanitation, specifically in healthcare facilities.

The coordinator called to attention that fungal infections are often left out of the discussion. The potential transmission routes of antimicrobial fungi were suggested by participants, which included agricultural settings, ice machines, and shower water.

The coordinator raised another concern about the control of AMR in food, in which livestock have been focused as one of the possible drivers of AMR, but the infection from produce items are often overlooked. There were several suggestions from the participants as follows: Risks are location-specific (e.g. due to varying irrigation water quality), and washing of vegetables is not always effective (e.g. due to root uptake, variable treatment performance in production facilities, e.g. due to inconsistent chlorine levels). Therefore, it is important to focus on the release of pathogens rather than treatment efficiency.

Also, several important points for discussion were raised by the participants. One of them is the disconnection between the research in clinical and environmental settings. The importance of better communication and coordination between clinical researchers and water engineers was emphasized. It was also highlighted that the knowledge of *Pseudomonas* ecology is limited to spread in hospitals (Lutz & Lee 2011; Vaz-Moreira *et al.* 2012; Zanetti *et al.* 2013; Luczkiewicz *et al.* 2015).

Another point was that sustainability interventions could also carry risks; for example, green buildings and water conservation can increase the stagnation potential and dead-ends in distribution systems (also major issues in older hospitals where water distribution systems may be poorly mapped). The other main knowledge gap/action point raised by the participants was the importance of distinguishing between home and hospital to consider how AMR spreads within communities. It was suggested that future research should link dissemination of AMR to specific behavioral factors (e.g. swimming in surface water vs. fountain mist exposure). Another point was the measurement of antibiotic residues levels in water used for different purposes.

Finally, group 3 reached the following conclusions. (1) Action priority should be based on a location-specific priority organism list. (2) *Pseudomonas* deserves more attention. (3) Quantitative microbial risk assessment (QMRA) can aid in prioritization. (4) For LEDCs, focus should be mainly on waste treatment and drinking water treatment.

OVERALL DISCUSSION

Following the group discussion, the coordinators presented the discussion summary of each group followed by a general discussion time with all the workshop participants (Table 2). The latter was focused on the issues including the definition of AMR, the health risk of ARGs/ARB from human exposure to aquatic environments, and the need for standardized methods for the analysis of AMR in aquatic environments to compare results. The workshop concluded that fundamental questions are not new, but the unity of language is very important and the reduction of the spread

Table 2 | A brief summary of discussed questions and the suggested research directions

Discussion points	Suggestions
Group 1: Surveillance – the WHO extended-spectrum beta-lactamase (ESBL) E. coli tricycle project – status, lessons learned from piloting and next steps	
AMR surveillance in humans, animals and the environment. What are the suitable surveillance targets as AMR reservoirs?	• Areas with high population densities, and people live in close proximity with animals and share water systems • Measurements in socially deprived areas • Human wastewater • Surface water (baseline concentrations) • Hospital wastewater • Animal abattoir/slaughterhouse wastewater
What are the necessary sample metadata to make good use of AMR surveillance data?	• Climate information • Water quality • Geographical information • Operational information from WWTPs • Watershed information • Sampling strategy
Group 2: Wastewater treatment technologies – practical implementation of the precautionary principle	
Which kind of wastewater treatment systems should be developed/implemented to remove antibiotic resistance genes (ARGs) and antibiotic-resistant bacteria (ARB)?	• For low- and middle-income countries (LMICs), basic sanitation systems such as pit latrines are better than open defecation in terms of the reduction of ARB/ARGs emission to environments • It is important to understand the extent to which systems applicable in LMICs would reduce ARB/ARGs with the potential use of high pH lime • Importance in developing standardized protocols for quantification of ARGs • Importance of having a balance between improving sanitation and removal/transformation of micropollutants • Evaluating the contribution of decentralized systems in the removal and release of ARB/ARGs in the aquatic environments • The necessity for data sharing and collaboration
Group 3: Environmental pathways for AMR – decision tree for country prioritizing WASH and environment actions	
Are there potentially important transmission routes other than commonly recognized ones?	• Indoor airborne transmission, and fecal sludge • The potential transmission routes of antimicrobial fungi including agricultural settings, ice machines, and shower water • Livestock have been focused as one of the possible drivers of AMR, but the infection from produce items are often overlooked
How to prioritize WASH and environmental interventions?	• Importance of better communication and coordination between clinical researchers and water engineers • Linking dissemination of AMR to specific behavioral factors (e.g. swimming in surface water vs. fountain mist exposure • Quantitative microbial risk assessment (QMRA) can aid in prioritization

and emergence of AMR would benefit from a harmonized and interdisciplinary approach.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

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