

Meeting report: Antimicrobial resistance and urban waste water treatment,
Held at the European Environment Agency, 2nd-3rd October 2018.

1) Executive Summary

Antimicrobial resistance is a worldwide, increasing threat to human health. International cooperation to tackle it started with the transatlantic taskforce on AMR in 2009¹, growing to a UN High Level Meeting on AMR in 2016² and G20 Berlin Declaration in 2017³. Its threat level is now considered to be on a par with climate change⁴.

Health and food sectors are heavily involved in action to mitigate the risk but there has been limited action in third part of the potential exposure/transmission pathway, environment.

Urban waste water treatment (UWWT) is key to protecting environment and human health. The investment in UWWT is substantial, with a planned lifetime of many decades. Urban waste water treatment plants (UWWTPs) receive waste waters from many upstream sources but act as a point source, from where pollutants can enter rivers, lakes and coastal waters. Treatment taking place at UWWTPs represents the last chance to prevent pollutant releases into sewers reaching the environment.

Key findings were summarised for the topics of monitoring, the release of treated urban waste water and transmission of AMR, and options for reducing the potential of transmission. Knowledge levels varied – from those where general agreement could be reached, to unclear and unknown situations. Priority knowledge gaps were identified as being:

- Impact of urban waste water treatment on AMR;
- Monitoring for information on spatial and temporal trends in the environment;
- AMR exposure from the environment to humans;
- Quantification of risk, or contribution to acute cases of AMR, from urban waste water treatment discharges;
- Understanding evolution and selection in collection and sewerage systems, urban waste water treatment plants and hospitals.

¹ <https://www.cdc.gov/drugresistance/tatfar/index.html> accessed 04/12/18

² <https://digitallibrary.un.org/record/845917> accessed 04/12/18

³ <http://www.g20.utoronto.ca/2017/170520-health-en.html> accessed 04/12/18

⁴ <https://www.gov.uk/government/speeches/antimicrobial-resistance-needs-an-urgent-global-response>

2) Introduction

The meeting was held to discuss current knowledge and the level of risk represented by urban waste water treatment in the transmission of antimicrobial resistance in the environment. It brought together researchers, industry stakeholders, European Commission and European agencies, with differing experience, with the aim of building a broader understanding of the issues. The organisers are very grateful to the participants for their input.

While there has been significant effort put into understanding transmission of AMR in the health and food sectors, understanding the role the environment may play is at an early stage, in part due to the complexity of the environment. Major opportunities for transmission to humans result from discharges from urban waste water treatment plants (UWWTPs) and from the use of antibiotics in agriculture for veterinary and biocidal use. This meeting focused on urban waste water treatment, as the “simple case” where we have known point sources.

The aim of this report is to summarise the discussion, which was focused firstly on introducing the topics to a range of stakeholders and then to consider on which issues there was general agreement and on which where further information was required. It should be seen as a starting point for a discussion which needs to continue and develop.

3) Key concepts

3.1 Policy context

The European One Health Action Plan against AMR was launched in 2017⁵. The Plan acknowledged the environment as a contributor to the development and spread of AMR in humans and animals, but that strong evidence was required to better inform decision-making.

In the European Union (EU), the legislation governing urban waste water treatment is largely set by the Urban Waste Water Treatment Directive (91/271/EEC) (UWWTD), which requires certain levels of treatment depending upon the size of the population being served and the sensitivity of the waters into which the effluent is discharged. The aim of the UWWTD is to protect human health and the environment, with requirements for reduction in of organic matter, nitrogen and phosphorus (but not bacteria). The Bathing Water Directive (2006/7/EC) (BWD) applies where waters are designated for bathing and sets bacteriological standards for the water, which may require additional treatment at UWWTPs. The overarching Water Framework Directive (2000/60/EC) (WFD) provides a common approach to managing European waters and includes both the UWWTD and BWD as “basic

⁵ https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf accessed 03/12/18.

measures” towards achieving the objective of good status in all waters. A strategic approach to pharmaceuticals in the environment is being developed by the European Commission under the Environmental Quality Standards Directive (2008/150/EC) as a daughter of the WFD. At the time of the meeting, both the WFD and the UWWTD are undergoing evaluation to assess whether they are delivering as intended and whether there are gaps in the legislation.

3.2 Microbial ecology and antimicrobials

There are an enormous number of microorganisms on earth and they form a vital part of a healthy ecosystem. Antimicrobials are medicines used that treat infections caused by microorganisms such as bacteria, fungi, viruses, and parasites.

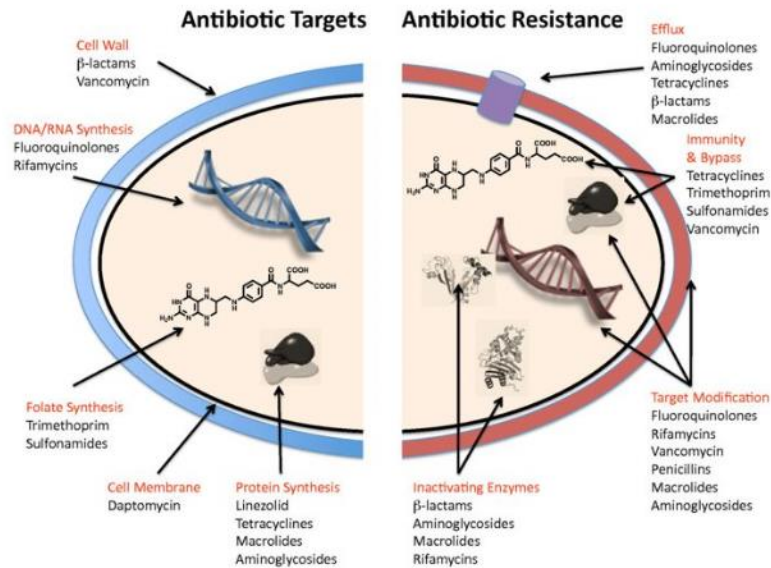
AMR is a natural phenomenon that has evolved over evolutionary time, but also develops rapidly when microorganisms are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). New resistance mechanisms are emerging and spreading globally, threatening the ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. Without effective antimicrobials for prevention and treatment of infections, medical procedures such as organ transplantation, cancer chemotherapy, diabetes management and major surgery become very high risk (WHO, 2018)⁶.

One type of AMR, specifically antibiotic resistance is an ancient phenomenon and even samples from permafrost, “pre-Antibiotic era” show resistance genes against modern antibiotics. There are two basic types of resistance: i) Intrinsic, where the resistance is usually related to structural features of the cell; ii) Acquired, where resistance is caused by mutation or acquisition of novel genes which can happen via a variety of mechanisms, together termed “horizontal gene transfer”.

Figure [A] shows various ways in which antibiotics work (“antibiotic targets”) and ways in which resistance may be generated. Antibiotics work by interfering with enzymes involved in forming the cell walls, nucleic acid metabolism and protein synthesis, or by disrupting membrane structure, for example. Resistance mechanisms include reducing the amount of antibiotic taken up or increasing the amount expelled, producing non-sensitive enzymes, changes (“mutations”) to the target site, or changes to the antimicrobial itself.

⁶ <http://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance> accessed 03/12/18.

Fig [A]: Antibiotic targets and mechanisms of resistance

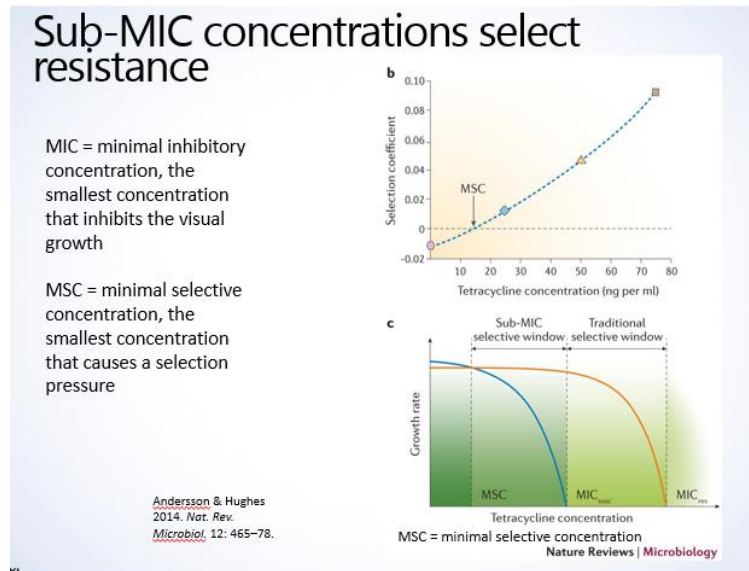


Source: Wright, GD, 2010 <https://doi.org/10.1186/1741-7007-8-123>

Resistance is part of evolution. It occurs when the bacteria are subjected to a pressure that has the effect of selecting individuals that can resist that pressure. Those that are resistant tolerate the pressure better than those that are not, and go on to parent successive generations. For urban waste water treatment, microorganisms provide an important ecosystem service at the treatment plant. Able to resist the range of pollutants that enter, they can break down the organic matter in the effluent. As antimicrobials form part of that influent, it is a natural process that causes some microorganisms to resist the bactericidal action. Once developed, resistance genes can be transferred between microorganisms, though in the environment there is also the possibility for resistance to occur through natural processes.

Pressures that select for resistance include antibiotic residues as well as contaminants like some metals. Traditionally, the smallest concentration that causes a selection pressure was considered to be the “minimal inhibitory concentration” (MIC) which inhibits growth of susceptible or non-resistant bacteria. More recently, the importance of the “minimal selective concentration” (MSC) has been recognised. This is the lowest concentration at which a selection pressure may have an effect on the relative growth rates of resistant and susceptible bacteria, and can be several times lower than the MIC. (Fig [B])

Fig [B] Concentrations above the minimum selective concentration select for resistance



3.3 Urban waste water treatment

Urban waste water treatment protects surface waters from the adverse effects of waste water discharges, such as organic pollution, the associated development of bacteria and fungi, and oxygen depletion, which degrade aquatic life. This is achieved through the collection and treatment of waste water in settlements and areas of economic activity. The installation of waste water treatment facilities first requires a sewage collection system be established and then the provision of facilities to treat the collected waste water. “Primary treatment” refers to simple sieving of the effluent, to remove large objects, before discharge into the environment. “Secondary treatment” subjects the effluent to microbiological breakdown to reduce the oxygen demand on the receiving water. More stringent or tertiary treatment may be applied where the receiving water is particularly sensitive, and there is a need to substantially reduce nitrogen and phosphorus concentrations, for example. Disinfection techniques, such as ozonation, chlorination or UV treatment, may be applied to reduce the bacterial load, for instance to protect bathing waters. Typically, higher levels of treatment will involve higher costs, owing to higher energy and infrastructure costs.

Collection and sewerage systems are built to deal with a maximum capacity. Heavy rainfall can exceed the capacity in systems combining both household

and surface drainage, so “storm water overflows” enable the excess, untreated effluent to be directed to rivers etc., bypassing sewage treatment.

Application of sewage sludge to land is an important destination for large quantities of organic material, acting as a fertiliser and improving soil condition. In this way, it contributes to a circular economy, but may represent another way for AMR to be spread into the environment.

Urban waste water treatment significantly reduces the numbers of bacteria in sewage. This reduction is most important in limiting the numbers of resistant bacteria. While secondary treatment reduces the bacterial load, further intensive treatment such as disinfection using UV oxidation or chlorination is needed for significant destruction of microorganisms.

3.4 Protection Goals

Protection goals specify what to protect, where to protect it and over what time period. At this stage, protection goals for AMR in the environment are unclear.

The precautionary principle, enshrined in the Treaty of the Functioning of the European Union, underpins the approach to policymaking when an environmental or human health hazard is uncertain and the stakes are high⁷. Such is the situation with AMR and the environment.

There is a long history of regulating chemical compounds in the aquatic environment. In the current context, environmental quality standards under the Water Framework Directive provide a useful model for monitoring concentrations of antibiotics in water, while monitoring fecal indicators under the Bathing Water Directive provide one for microbiological pollution.

Environmental quality standards set a concentration of a particular chemical that should not be exceeded in a water body. The standard is set based on the toxicity to the most sensitive species in a range from algae, through invertebrates, to fish and predators like otters, birds or humans. The toxicity assessment considers the predicted no effect concentration (PNEC) i.e. that at which no adverse effects are expected. It is similar in concept to the MSC used in microbiology, though the MSC is the lowest concentration at which selection pressure may occur.

Setting environmental quality standards for antibiotics is difficult, because currently there is limited toxicity information available. A PNEC is only available for about 20 out of a total 111 antibiotics, and for a very limited range of species. Setting quality standards without information for an

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[http://www.europarl.europa.eu/RegData/etudes/IDAN/2015/573876/EPRS_IDA\(2015\)573876_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/IDAN/2015/573876/EPRS_IDA(2015)573876_EN.pdf)

adequate range of organisms can lead to conservative risk factors, which may produce very challenging standards with limited supporting evidence.

Good bathing water quality is achieved if the 95th percentile of all samples at the site in the most recent assessment period is lower than defined limits of intestinal enterococci and *E. coli*⁸. Limits are set for the number of colony-forming units in a set volume of water, with lower limits for coastal and transitional waters than inland waters.

For limiting the release of antibiotics themselves in the environment, quality standards for concentrations in water would be relevant both to effluents released during manufacture, and to those from UWWTPs where the substance has been neither metabolised nor degraded during treatment. Reducing the concentrations of antibiotics in the environment from manufacturing relies on good practice to control releases, with a theoretical limit of zero releases. Those arising from medical or veterinary use however, can only be limited to “necessary use”.

For AMR in the environment, various protection goals can be envisaged, depending upon the aim of the monitoring programme. Examples are:

- Limiting the levels of antimicrobial resistance genes (ARGs): This treats genetic determinants for resistance as pollutants;
- Setting activity-based assessments: For example, antibiotic residues tests for food and drink;
- Limiting the number of cefotaxime resistant *E. coli*: This builds upon existing bathing water standards by looking at resistant enteric (intestinal) microorganisms;
- Limiting concentrations to thresholds determined by Minimal Selective Concentrations (MSCs): Similar in concept to environmental quality standards.

3.5 Environmental elements of European Commission R+D funding for AMR

The EU One Health Action Plan, launched in 2017, aims at making the EU a best practice region on AMR⁹. It commits to closing knowledge gaps on AMR in the environment and on preventing transmission. In an international collaboration, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) supports One Health research.

The EU Horizon 2020 work programme for 2018-20 commits nearly 200mEuro to AMR, and there are industry and joint industry-government initiatives to address AMR. Via ERA-Net co-funding the Commission supports 7 research projects studying environmental aspects of AMR including:

- the dynamics of AMR in the urban water cycle;

⁸ <https://www.eea.europa.eu/publications/public-health-and-environmental-protection>

⁹ https://ec.europa.eu/health/amr/antimicrobial-resistance_en

- the processing of waste water and sludge;
- the study of environmental sources of resistant clones;
- the transmission of resistance affected by ecological variables including environmental, food and wastewater contamination.

4) Discussion

4.1 Urban waste water treatment and AMR

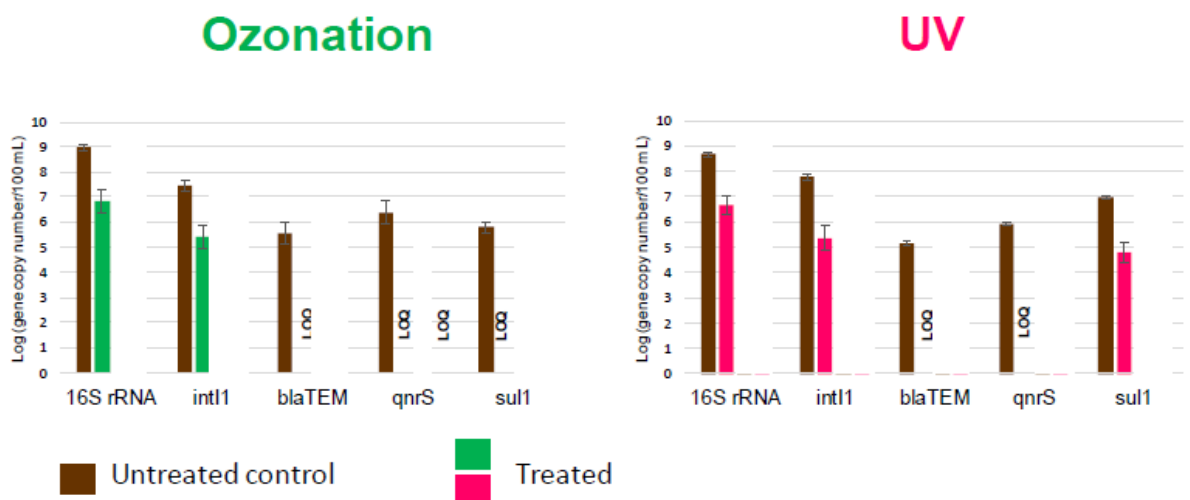
The major known sources and transmission routes for AMR are through health and food applications. Pathways to the environment through urban waste water treatment largely arise from people excreting resistant bacteria themselves, or taking medicine and excreting some of the active ingredient, which may allow bacteria in the environment to develop resistance.

Gene transfer can take place in urban waste water treatment plants, though the rate and extent may be dependent on a range of factors, including the type of treatment applied. The longer the effluent is stored, the more opportunity there may be for AMR to be generated. This creates challenges: for instance, while disinfection is used to reduce the bacterial load, the waiting time between secondary treatment and disinfection can allow resistant bacteria to grow.

Disinfection can affect different genes in different ways (Fig [C]). Particularly in the context of urban waste water, it should be noted that the presence of other substances, such as some metals, can co-select for resistance

[EDITING NOTE - WHY DOES THIS MATTER? SUPER-RESISTANT BUGS OR SOMETHING ELSE?]

Fig [C] Number of antibiotic resistant genes following disinfection treatment of urban waste water effluents – ozonation and UV



Source: Sousa et al, J. Hazard Mater. 2017 5;323(Pt A):434-441.

LOQ = below limit of quantification.

Selected genes 16S rRNA gene (marker for bacteria), the *intl 1* gene (marker for class 1 integrons, common in Gram-negative bacteria), the *bla*_{TEM} gene (marker for beta-lactamase resistant Gram-negative bacteria) and the antibiotic resistant genes *qnrS* and *sul1*.

A study in the Netherlands considered 100 UWWTPs (a third of all Dutch UWWTPs) and loadings in the context of well-characterised understanding of water across the country¹⁰. UWWT reduced the number of bacteria 100-1000 times and was significantly correlated with *E. coli*. Most of the differences in removal efficiency can be explained by rainfall, where increased rainfall can flush more waste into sewers but can also dilute the influent.

Some work suggests that urban waste water from hospitals represents a potential hotspot for AMR. However, the study showed that usually hospital effluents were not a very significant proportion of influent concentrations (below 10%), although some showed antibiotic concentrations over the minimum inhibitory concentration.

In a study considering treated effluents from UWWTPs in six countries (China, Estonia, Finland, Portugal, Spain and USA), Manaia *et al.* (2016) found that the numbers of antibiotic resistant bacteria and antibiotic resistant genes released each day varied between plants with a range of 6 orders of magnitude (10^{12} - 10^{18})¹¹. While this is still a large number, significant reduction of the loads released was considered an adequate strategy to mitigate antibiotic resistance.

4.2 Pathways and exposure in the environment

There is limited information on the pathways for and significance of AMR in the environment to reach humans. Because genes can be so readily transferred between microorganisms, there may be several stages involved in any pathway.

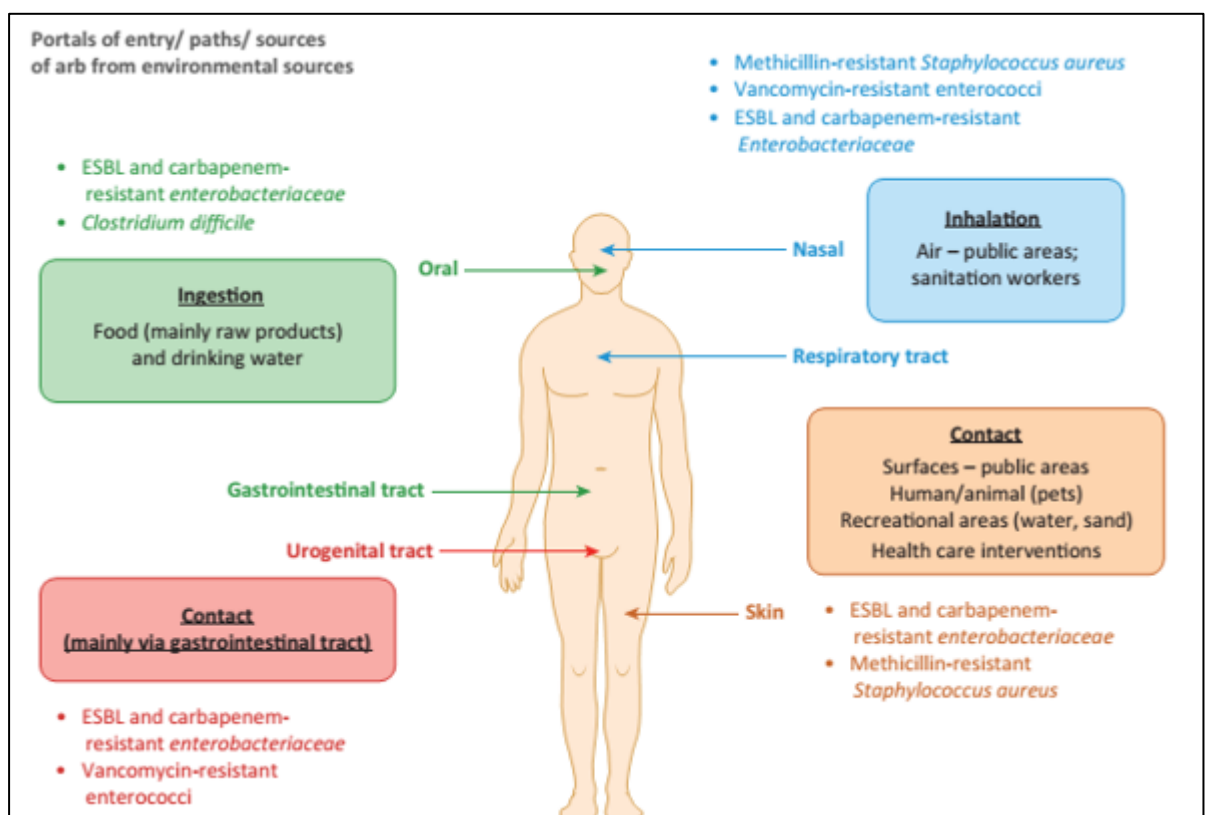
A reservoir of AMR may exist in microorganisms that rarely reach humans, but these may interact with “carriers” which readily acquire and transfer genes. These carriers can interact with “vectors” which are widespread, human associated bacteria which can pass on genes to pathogens which have high capacity to infect and cause disease. The physical routes back into humans or animals, then, are through ingestion of contaminated (raw) food and drinking water; physical contact between people/animals, or from surfaces in public areas, recreation (water, sand) or health care. The remaining way is through inhalation, where sanitation workers would be most at risk of inhaling droplets, or populations downwind of intensive farms which have been shown to be more likely to be colonised by animal associated AMR bacteria. Fig [D] provides examples of these different pathways.

¹⁰ rivm.nl/bibliotheek/rapporten/2017-0058

¹¹ Manaia *et al.*, 2016. *Applied Microbiology and Biotechnology*. 100:1543–1557

A key knowledge gap is the significance of environmental exposure of AMR to humans, relative to health and food pathways. However this issue is complicated by the fact that relatively rare gene transfer events from environmental bacteria may lead to pandemic spread of AMR in human associated bacteria. The threshold for environmental levels becoming of concern in terms of acute exposure risk needs to be assessed, although studies such as that by Leonard et al., (2018)¹² suggest that environmental exposure and transmission does occur. Better understanding of the drivers for resistance propagation and persistence is required, and we need to identify which resistance determinants should be of most concern.

Fig [D] Possible routes of transmission of AMR back into humans



Source: Manaia, Trends Microbiol. 2017 25(3):173-181.

Escherichia coli (*E. coli*) are widely used as indicators of fecal pollution of water. Extended spectrum beta-lactase (ESBL)-producing *E. coli* are representative of enzymes produced by bacteria to destroy antibiotics and are one way that bacteria develop resistance. Certain groups of people have

¹² <https://doi.org/10.1016/j.envint.2017.11.003>

greater exposure to such resistant bacteria, principally those swimming in fresh or coastal waters e.g. surfers¹³.

4.3 Monitoring

Robust monitoring procedures are key to ensuring the reliability and comparability of results between different workers and sites. The relative novelty of AMR in the environment means broadly applicable monitoring methods and strategies applicable have yet to be agreed.

Clarity of the monitoring purpose is essential. For AMR in the environment, there are different possibilities. To protect human and domestic animal health, monitoring could assess prevalence of the level of resistance, the use of antibiotics, or the transmission or evolution of resistance, for example. For environmental protection, some measure of ecological effect would be more appropriate. Selection of suitable sites follows the purpose. Monitoring programmes also need to consider costs, method robustness and skills required to implement the methods.

5) Conclusions and further research needs

While there have been research projects and national initiatives into AMR and the environment, there is as yet nothing available at European level to assess the risks presented. The meeting agreed on several points regarding needs around monitoring and options for reducing the risks of transmission from discharges from urban waste water treatment plants and identified a number of gaps in knowledge which should be addressed (Tables 1-4).

In summary, there is a need to establish the role that UWWT has in limiting environmental and human health risks, focusing on antibiotics, antibiotic resistant genes and co-contaminants such as metals (co-selective agents). Risk-based targets are needed, which recognise resistance poses a human health risk as well as providing an ecosystem service. Surveillance data are needed to support management options. Methods of assessing relative risk presented by UWWT in terms of selection for resistance, transmission and exposure are required.

¹³ Leonard et al, 2017, Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters, Environment International 82. DOI: 10.1016/j.envint.2015.02.013

Table 1: Monitoring

Topic	State of knowledge
<p>Monitoring purposes</p>	<p>Agreed: Monitoring can be used for surveillance; for the assessment of exposure risk for human health; and for site comparison.</p> <p>Antibiotic concentration in water does not act as a proxy for AMR. It can provide information on risks driving evolution of AMR (i.e. not transmission).</p> <p>Unknown: Baseline occurrence, spatial and temporal trends in the environment.</p> <p>Notes: An obligation to monitor is considered important. For the identification of novel genes, a research-based approach to monitoring is more appropriate.</p>
<p>What should be monitored</p>	<p>Agreed: Antibiotic-resistant bacteria and genes, to inform understanding of their levels in the environment. Method comparison is required.</p> <p>Unclear: spatial consumption data across use categories <i>[EDITING NOTE – WHAT DOES THIS MEAN?]</i></p> <p>Unknown: Impact of waste water treatment on levels of AMR; the gradient in the environment (cf in the clinical setting) <i>[EDITING NOTE – WHAT DOES THIS MEAN?]</i></p>
<p>Where to monitor</p>	<p>Agreed: For risk assessment, at sites of greatest exposure – bathing waters; For surveillance in human population – influent to UWWTPs; For evolution - within UWWTPs.</p> <p>Unclear: Sites which indicate effectiveness of measures, such as from waste water treatment or agriculture; impacted sites <i>[EDITING NOTE – PLEASE PROVIDE EXAMPLE]</i></p>
<p>When to monitor</p>	<p>Agreed: Both dry and wet weather; Statistically significant sampling required.</p>

Table 2: Release of treated urban waste water and transmission of AMR

Topic	State of knowledge
<p>Human waste contributes to the transmission of AMR</p>	<p>Agreed: It does. Urban waste water treatment (UWWT) is very important in reducing coliforms etc. in water but it still releases large numbers of ARBs.</p> <p>UWWT reduces the risk of transmission. The majority of UWWTPs are not designed to tackle AMR.</p> <p>Unclear: Whether the waste gets back to humans; Whether UWWT amplifies particular genes or bacterial groups.</p> <p>Unknown: Currently in early research stage of quantification of the risk of infection or colonisation; Significance in overall infection burden relative to other sources.</p>
<p>Carriage</p>	<p>Agreed: Can occur through occupational exposure, travel and environment.</p> <p>Unknown: The risk of infection; Routes through the natural environment.</p>

Table 3: Options / measures for reducing potential for AMR transmission via UWWT

Topic	State of knowledge
Reduce use of antibiotics	<p>Agreed: Economic model for antibiotics should include the environment. Use can only be reduced to certain point e.g. c.20% patients in hospitals. Technological developments could reduce need eg implants.</p> <p>Unclear: Use of antibiotics as biocides etc could be reduced rather than patient use.</p> <p>There were different views on the scope for source control, depending on whether the amount of change required was considered acceptable.</p>
Collect human waste containing newly launched antibiotics separately and incinerate	<p>Agreed: This approach is possible, though expensive.</p> <p>Unclear: Application to which antibiotics? This would need case-by-case assessment.</p>
Reduce microbial load of UWWT discharges (which methods work?)	<p>Unclear: Reducing the contaminant load from UWWT applies not only to AMR – micropollutants and other risks to be considered.</p> <p>Unknown: Suitability of different techniques (both industrial and municipal). Integrating different risks into studies (eg AMR and chemicals). Relative risks, margins of safety.</p>
Industrial production	<p>Agreed: On-site treatment [of antibiotic residues]; mixed into municipal waste [EDITING NOTE – WHAT DOES THIS MEAN?].</p> <p>Good practice not to release large quantities of antibiotics: need for regulation to ensure it happens in all cases. Role for responsible procurement (WW treatment costs). Include environment in Good Manufacturing Practice.</p> <p>Don't allow production sites to discharge to UWWTPs: alternatively, set discharge standards to UWWTPs.</p> <p>Unknown: Increased risk of industrial production to municipal UWWT; Relative risks of industrial losses compared to release from patients; Amount of production (in kg) in Europe.</p>
Hospitals as hotspots	<p>Agreed: Known releases of antibiotics only used in hospitals e.g. carbapenams. [EDITING NOTE – PLEASE CHECK]</p> <p>Unclear: Could undertake regulation on hospitals.</p>
Developments	<p>Unclear: Potential offered by “benign-by-design” pharmaceuticals.</p>

Topic	State of knowledge
Reducing load to UWWTP	Unclear: Practicality and efficacy of separated sewer systems or within-toilet systems.
Reducing load from UWWTP	Unclear: Development of sludge management processes to reduce potential transmission route from sludge to land.
Precautionary principle...?	Unknown: Application of the principle in relation to AMR and the environment

Table 4: Knowledge gaps

4.1 Priority knowledge gap	Notes
Monitoring for information on spatial and temporal trends in the environment	Needs consistency in approach. Intercomparable robust methods not yet available. Needs data architecture that can be applied at different scales
Impact of urban waste water treatment on AMR	
(AMR exposure from the environment to humans	
Quantification of risk, or contribution to acute cases of AMR, from urban waste water treatment discharges	Need to understand whether it is significant in overall infection burden
Understanding evolution and selection in collection and sewerage systems, urban waste water treatment plants and hospitals	

4.2 Other knowledge gaps	Notes
Environment	Standing stock of AMR in the environment and significance of results. Catchment approach needed to reflect receiving environment - not limited to a single UWWTP. How to apply precautionary principle with respect to antibiotics and environment.
Transmission of AMR	Exposure from environment through to colonisation/carriage in humans and infection; dose-response. Risk of infection via “carriage” – travel, occupation, environment.

4.2 Other knowledge gaps	Notes
	<p>Travellers eg airports. Where should effort be put?</p> <p>Impact and significance of combined sewer overflows.</p>
Urban waste water treatment (UWWT)	<p>Suitability of different UWWT techniques to reduce AMR.</p> <p>Relative risks, margins of safety for UWWT techniques.</p> <p>Increased risk of industrial production to municipal UWWT [<i>EDITING NOTE – is this in relation to pollutants and co-selection, and/or manufacture of antibiotics on the UWWTP?</i>].</p> <p>Direct measurements of effectiveness of UWWT on reducing risk of transmission of AMR, costs and benefits, ; also for new methods and alternative treatments eg within-toilet treatment.</p>
Manufacture of antibiotics	<p>Relative risks of industrial losses vs release from patients.</p> <p>Measure of production (in kg) in Europe.</p>
General	<p>Assessment of costs and benefits.</p> <p>Identification of success criteria: e.g. a reduced no. of enterics, or of infections...?</p> <p>Integrating different risks into studies (eg AMR and chemicals).</p>

6) List of participants

EDITING NOTE – DOES EVERYONE AGREE TO THEIR NAME AND AFFILIATION BEING INCLUDED?

Name	Organisation
BERENDONK, Thomas	University of Dresden
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MANAIA, Célia	Catholic University, Porto
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MONNET, Dominique	European Centre for Disease Prevention and Control (ECDC)
ROSENSTOCK, Nele-Frederike	European Commission, DG Environment
ROSKOSCH, Andrea	German Environment Agency (UBA)
SCHMITT, Heike	Dutch National Institute for Public Health and the Environment (RIVM) / Utrecht University
SNAPE, Jason	EFPIA
STELLA, Pietro	European Food Safety Authority
THORNBERG, Dines	Eureau
UHEL, Ronan	EEA
VALLET, Bertrand	Eureau
VAN HENGEL, Arjen	European Commission, DG Research
VIRTA, Marko	University of Helsinki
WHALLEY, Caroline	EEA