Meeting report: Antimicrobial resistance and urban waste water treatment.

Held at the European Environment Agency, 2nd-3rd October 2018.

1) Executive Summary

Antimicrobial resistance (AMR) is a worldwide, increasing threat to human health. International cooperation to tackle it started with the transatlantic taskforce on AMR in 2009[1], growing to a UN High Level Meeting on AMR in 2016[2] and G20 Berlin Declaration in 2017[3]. Its threat level is now considered to be on a par with climate change[4].

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. Sewage sludge arising from UWWT spread to land may also allow pollutants to reach the environment. Treatment taking place at UWWTPs represents the last chance to prevent pollutant releases into sewers reaching the environment.

The meeting summarised key findings for the topics of: monitoring; the release of treated urban waste water and transmission of AMR; options for reducing the potential of transmission. There was wide variation in the current state of knowledge – 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 cases of AMR due to direct or indirect exposure to urban waste water treatment discharges, e.g. leisure activities in rivers or lakes; irrigation of crops with water containing discharges from UWWTPs;
- Quantification of benefits from potential measures vs cost of implementation or cost of non-action;
- Understanding evolution and selection in collection and sewerage systems, urban waste water treatment plants and hospitals.

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[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 AMR 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. Opportunities for transmission to humans result from discharges from urban waste water treatment plants (UWWTPs) and from other sources that serve as habitat for bacteria, such as livestock or antimicrobial production facilities. 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 2017[5]. 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 has been launched by the European Commission under the Environmental Quality Standards Directive (2008/150/EC) as a daughter of the WFD[6]. 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 bacteria 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. Antimicrobials are used to treat microbial infections.

AMR is a natural phenomenon that has evolved over evolutionary time, but also develops rapidly when bacteria are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). New AMR 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)[7].

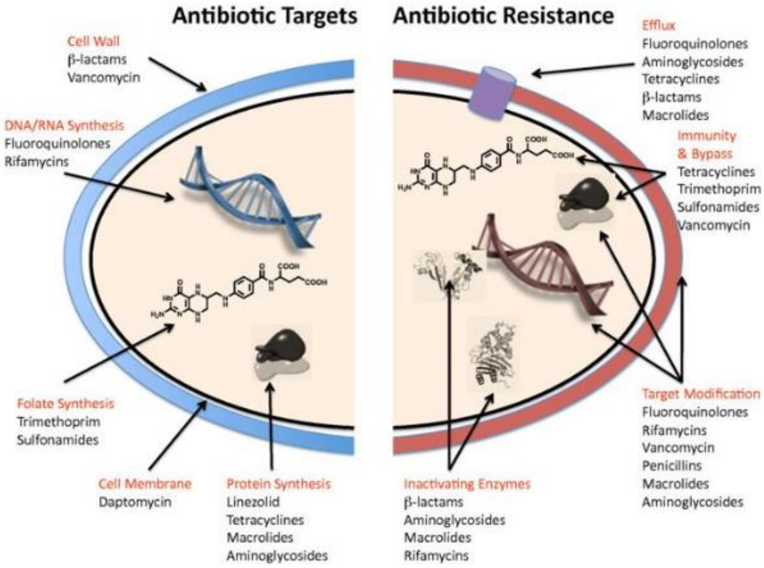
AMR is an ancient phenomenon. Even "pre-Antimicrobial era" permafrost samples show genes encoding for resistance against antimicrobials. There are two basic types of resistance: i) Intrinsic, where the resistance is usually related to structural features of the cell; ii) Acquired, where resistance is caused by mutation or acquisition of novel genes which can happen via a variety of mechanisms, together termed "horizontal gene transfer".

Figure [1] shows various ways in which antibiotics work ("antibiotic targets") and ways in which AMR 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. AMR 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://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF

[7] http://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance accessed 03/12/18.

Fig [1]: Antibiotic targets and mechanisms of resistance

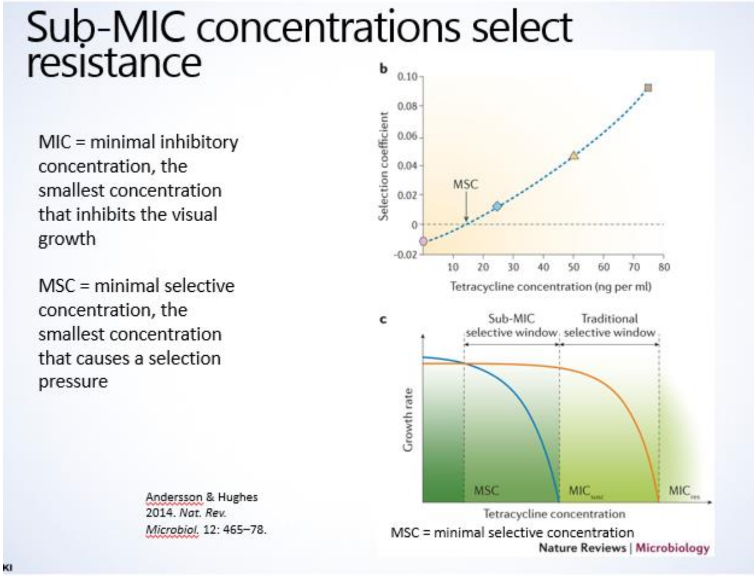


Source: Wright, GD, 2010 https://doi.org/10.1186/1741-7007-8-123

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, bacteria 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 the influent, natural processes can cause some bacteria to resist the bactericidal action. Once developed, AMR genes can be transferred between bacteria, though in the environment there is also the possibility for AMR to occur naturally.

Pressures that select for AMR include antimicrobial 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 [2])

Fig [2] Concentrations below the minimal inhibitory 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 removal of particles before effluent 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, combined or advanced treatment options 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 density (per volume) of bacteria in sewage. This reduction is most important in limiting the abundance of bacteria. While secondary treatment reduces the bacterial load, further disinfection treatment through processes such as UV radiation, ozonation or chlorination, may be of additional value for lowering the bacterial load in effluents discharged into the environment.

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 high[8]. 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 antimicrobials 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 antimicrobials is difficult, because currently there is limited toxicity information available. A PNEC is only available for a limited number of antimicrobials, and for a very limited range of species[9]. Setting quality standards without information for an adequate range of organisms can lead to conservative risk factors, which may produce very challenging standards with limited supporting evidence. Moreover, current scientific knowledge cannot provide evidence that the elimination of antimicrobial residues would reduce the load of bacteria with AMR, which have high self-replicative capacity and environmental fitness.

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

[9] Le Page et al., 2017. Environ. Int. 109:155-169. doi: 10.1016/j.envint.2017.09.013

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*[10]. 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 antimicrobials 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 antimicrobials 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 levels of AMR genes, based on the principle that AMR genes are classified as pollutants;
- Limiting the number of cefotaxime resistant *E. coli*: This builds upon existing bathing water standards by looking at enteric (intestinal) bacteria with AMR;
- Limiting concentrations to thresholds determined by Minimal Selective Concentrations (MSCs).

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

The European One Health Action Plan against AMR, launched in 2017, aims at making the EU a best practice region on AMR[11]. 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;
- the processing of waste water and sludge;
- the study of environmental sources of bacterial clones with AMR;
- the transmission of AMR affected by ecological variables including environmental, food and wastewater contamination.

[10] https://www.eea.europa.eu/publications/public-health-and-environmental-protection

[11] https://ec.europa.eu/health/amr/antimicrobial-resistance_en

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 themselves excreting bacteria with AMR, or taking medicine and excreting some of the active ingredient, which may allow bacteria in the environment to develop AMR.

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 sludge is stored, the more opportunity there may be for AMR to be generated. The retention time for sludge (4-12 days) and any subsequent treatment can allow bacteria with AMR to grow.

Disinfection can affect different genes in different ways (Fig [3]). Particularly in the context of urban waste water, the presence of other substances, such as some metals, can co-select for AMR. Exposure to heavy metals or disinfectants can, for example, induce bacterial adaptions resulting in reduced susceptibility to antibiotics[12]. It is important to improve understanding of the development of AMR during UWWT: effluent composition can vary significantly, so identifying co-selection factors may help to target appropriate measures.

A method to assess disinfection efficacy could be based on the quantification of ARGs (Fig [3]). Some genes can even be used as proxy to assess water quality in terms of AMR load - examples of these are the *intI1* integrase gene, or the *sul1* gene.

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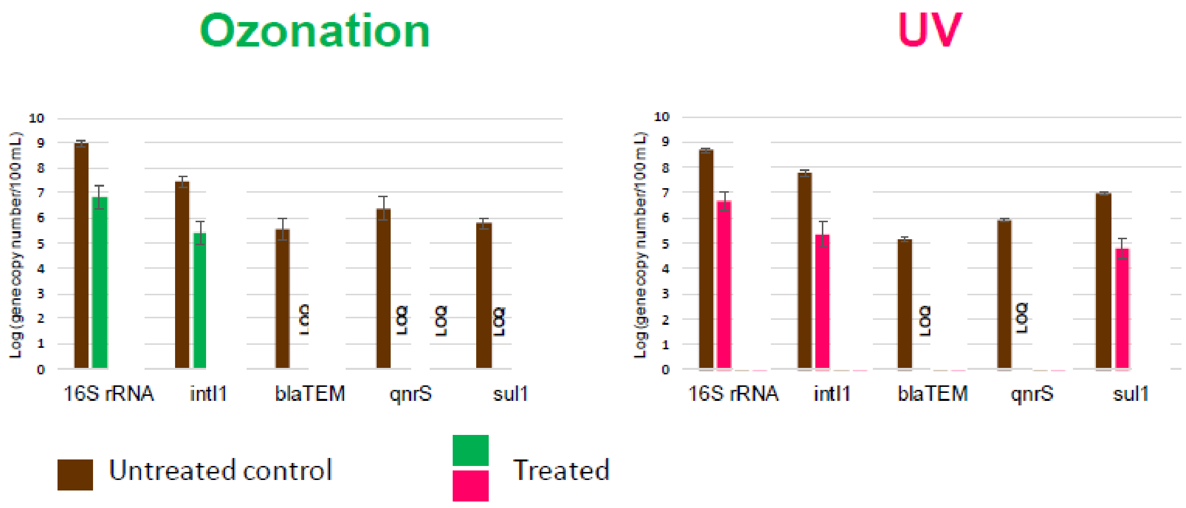
[12] Wales, A.D. and Davies, R.H. 2015. Co-selection of resistance to antibiotics, biocides and heavy metals, and its relevance to foodborne pathogens. Antibiotics 4: 567-604.

Fig [3] Number of AMR 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 *intI1* gene (maker for class 1 integrons, common in Gram-negative bacteria), the *bla$_{TEM}$* gene (marker for beta-lactamase resistant Gram-negative bacteria) and the AMR 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 country[13]. 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. The study showed that hospital effluents were not usually a very significant proportion of influent concentrations (below 10%), although some showed antibiotic concentrations over the minimum inhibitory concentration. It is important to recognise hospitals as important sources of emerging AMR genes and bacteria, often multidrug-resistant.

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 bacteria with AMR and AMR genes released each day varied between plants with a range of 6 orders of magnitude (10^{12}-10^{18})[14]. While this is still a large number, significant reduction of the loads released was considered an adequate strategy to mitigate AMR.

[13] rivm.nl/bibliotheek/rapporten/2017-0058

[14] Manaia et al., 2016. Applied Microbiology and Biotechnology. 100:1543–1557

4.2 Pathways and exposure in the environment

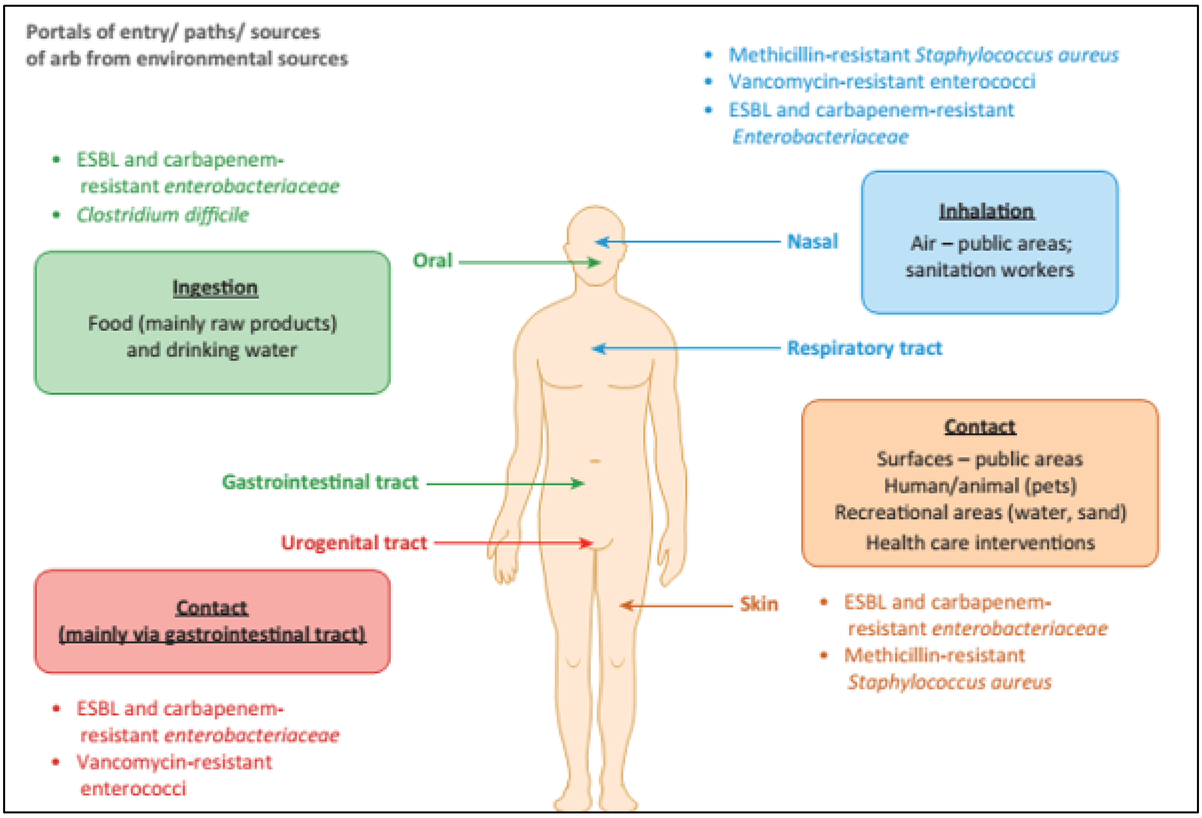
There is limited information on the pathways for and significance of AMR in the environment to reach humans. Because genes can be so readily transferred between bacteria, there may be several stages involved in any pathway.

A reservoir of AMR may exist in bacteria 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 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 bacteria with AMR. Fig [4] provides examples of these different pathways.

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)[15] suggest that environmental exposure and transmission does occur. Better understanding of the drivers for AMR propagation and persistence is required, and we need to identify which AMR determinants should be of most concern.

[15] https://doi.org/10.1016/j.envint.2017.11.003

Fig [4] 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 antimicrobials and are one way that bacteria develop AMR. Certain groups of people have greater exposure to such bacteria with AMR, principally those swimming in coastal waters e.g. surfers[16].

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. A monitoring system for the environment is necessary as currently there are no baseline data – so we cannot quantify how much AMR has changed in the environment, and without monitoring data that will remain impossible to assess.

[16] Leonard et al, 2015, Human recreational exposure to with AMR bacteria in coastal bathing waters, Environment International 82. DOI: 10.1016/j.envint.2015.02.013

Definition and harmonisation of the monitoring purpose are essential. For AMR in the environment, there are different possibilities. To collect relevant data to protect human and animal health, monitoring could assess occurrence/prevalence of AMR, the use of antibiotics, or the transmission or evolution of AMR, 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.

Wastewater AMR monitoring should be framed within the One-Health perspective - humans, animals and the environment, requiring a dialogue among the different actors addressing AMR issues.

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 d ischarges 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 antimicrobials, with AMR genes and co-contaminants such as metals (co-selective agents). Risk-based targets are needed, which recognise AMR 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 AMR, transmission and exposure are required. Cost/benefit analysis on potential additional measures for UWWT (collection and treatment) are required to justify investment and political decisions.

Table 1: Monitoring

Topic	State of knowledge
Monitoring purposes	**Agreed:** Monitoring can be used for surveillance; for the assessment of exposure risk for human health; and for site comparison. Antimicrobial 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). **Unknown:** Baseline occurrence, spatial and temporal trends in the environment. **Notes:** An obligation to monitor is considered important. For the identification of novel genes, a research-based approach to monitoring is more appropriate.
What should be monitored	**Agreed:** AMR bacteria and genes, to inform understanding of their levels in the environment. Method comparison is required. **Unknown:** Impact of waste water treatment on levels of AMR; the gradient from a point source in the environment.
Where to monitor	**Agreed:** For risk assessment, at sites of greatest exposure – bathing waters; For surveillance in human population – influent to UWWTPs; For evolution - within UWWTPs. **Unclear:** Sites which indicate effectiveness of measures, such as from waste water treatment or agriculture. Impacted sites. Screening of unofficial bathing waters.
When to monitor	**Agreed**: Both dry and wet weather; Statistically significant sampling required.

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

Topic	State of knowledge
Human waste contributes to the transmission of AMR	**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. UWWT reduces the risk of transmission. UWWTPs are not designed to tackle AMR. **Unclear:** Whether the waste gets back to humans. Whether UWWT amplifies particular genes or bacterial groups. **Unknown:** Currently in early research stage of quantification of the risk of infection or colonisation. Significance in overall infection burden relative to other sources.
Carriage	**Agreed:** Can occur through occupational exposure, travel and environment. **Unknown:** The risk of infection; Routes through the natural environment.

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

Topic	State of knowledge
Reduce use of antimicrobials	**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. **Unclear:** Use of antimicrobials as biocides etc could be reduced rather than patient use. There were different views on the scope for source control, depending on whether the amount of change required was considered acceptable.
Collect human waste containing newly launched antimicrobials separately and incinerate	**Agreed:** This approach is possible, though expensive. **Unclear:** Application to which antimicrobials? This would need case-by-case assessment.
Reduce microbial load of UWWT discharges **(which methods work?)**	**Unclear:** Reducing the contaminant load from UWWT applies not only to AMR – micropollutants and other risks to be considered. **Unknown:** Suitability of different techniques (both industrial and municipal). Integrating different risks into studies (eg AMR and chemicals). Relative risks, margins of safety.
Industrial production	**Agreed:** On-site treatment of antimicrobial residues. Not mixing effluent into municipal waste water. Good practice not to release large quantities of antimicrobials: need for regulation to ensure it happens in all cases. Role for responsible procurement (WW treatment costs). Include environment in Good Manufacturing Practice. Don’t allow production sites to discharge to UWWTPs, especially at development stage for new antimicrobials: alternatively, set discharge standards to UWWTPs. **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.

(Table continues on next page)

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

Hospitals as hotspots	**Agreed:** There are known releases of antimicrobials only used in hospitals e.g. carbapenams. Possible collection and separate treatment, or even incineration, of human waste (urine and faeces) for patients receiving treatment with new antimicrobial agents. **Unclear:** Could undertake regulation on release of antimicrobials and other medicinal products by hospitals and other healthcare facilities.
Developments	**Unclear:** Potential offered by “benign-by-design” pharmaceuticals.
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 antimicrobials 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. Travellers eg airports. Where should effort be put? Impact and significance of combined sewer overflows.
Urban waste water treatment (UWWT)	Suitability of different UWWT techniques to reduce AMR. Relative risks, margins of safety for UWWT techniques. Increased risk of industrial production to municipal UWWT in relation to pollutants and co-selection. 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.
Manufacture of antimicrobials	Relative risks of industrial losses vs release from patients. Measure of production (in kg) in Europe. Consideration of effluent management for production of new antimicrobial agents.
General	Assessment of costs and benefits. Identification of success criteria: e.g. a reduced no. of enterics, or of infections…? Integrating different risks into studies (eg AMR and chemicals).

6) List of participants

Name	Organisation
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*	European Centre for Disease Prevention and Control (ECDC)
ROSENSTOCK, Nele-Frederike	European Commission, DG Environment
ROSKOSCH, Andrea	German Environment Agency (UBA)
*	Dutch National Institute for Public Health and the Environment (RIVM) / Utrecht University
*	EFPIA
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*	University of Helsinki
WHALLEY, Caroline	EEA

Note * - a representative participated (but name withheld under GDPR).