# RISK ASSESSMENT AND RISK MANAGEMENT OF ANTIMICROBIAL RESISTANCE IN THE ENVIRONMENT

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Although the environment as a player in antimicrobial resistance (AMR) seems to have finally come to the attention of policy-makers and research funds, we are far from implementing cost-effective intervention measures. A major issue lacking in the evidence-based research is the involvement of the environment in the emergence and spread of antimicrobial resistance. The lack of insight into the severity and impact of different types of pollution, both with regard to selective agents and the bacteria themselves, prevents society from identifying the most efficient health-based targets for intervention.

## Policy arena

Only recently has the role of the environment in the emergence and dissemination of antimicrobial resistance (AMR) come to the attention of policy-makers at the global level (WHO *(1)*), the regional level (EU *(2)*), and through national initiatives (e.g., the Uppsala Health Summit *(3)* and the UK O'Neill review *(4)*). The World Health Organization's (WHO) Global Action Plan on AMR *(1)* was launched at the recent World Health Assembly in May 2015 to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way and accessible to all who need them. To achieve this goal, the global action plan sets out five strategic objectives. With respect to the environment i.e., Water, Sanitation and Hygiene (WASH), three of those five objectives were prioritized:

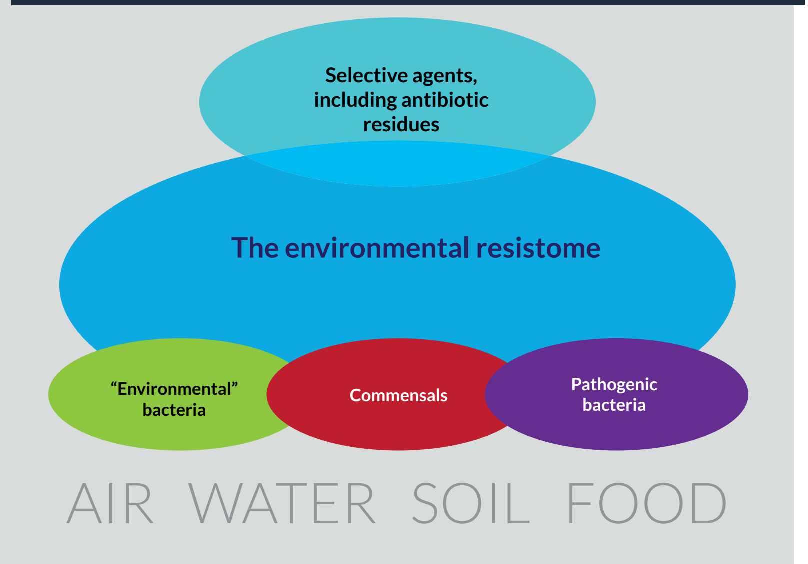
- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research; and
- to reduce the incidence of infection.

Moreover, Member States committed to finishing a national plan by 2017. The Joint Programming Initiative (JPI) on AMR published their Strategic Research Agenda *(2)* early in 2014 with the environment being one of the six priority topics. At the Uppsala Health Summit "A World Without Antibiotics" *(3)*, the environmental dimension of antibiotic resistance was one of the six aspects addressed in light of combating resistance and of the reasonable use of antibiotics, focusing on which steps to take next towards implementing the WHO Global Action Plan on AMR. Similarly, the O´Neill review, commissioned by the British government, recently published their report on the animal and environmental dimensions *(4)*. Their recommendations were very explicit in terms of reducing the most severe types of antibiotic pollution, i.e., those found at certain manufacturing sites. Other concerns that were brought to the attention of the G20 included sanitation, and, specifically, the proper disposal of wastewater, especially at antibiotic resistance hotspots *(5)*. An international conference series dedicated to the Environmental Dimensions of Antibiotic Resistance (EDAR) has received much attention with successful events so far held in Canada, China and Germany.

## Genetics, microbiology and chemistry

Although antimicrobial resistance is a broader term involving resistance of bacteria, viruses, fungi and parasites, the focus here is on antibiotic resistance (ABR) in bacteria and specifically the role of the external environment. Humans, animals and the external environment all can play a role in the emergence and spread of antibiotic resistance, although the interconnections differ widely depending on the specific bacterial species and

Figure 1: The environmental dimension of antibiotic resistance involves a complex interplay between harmless environmental bacteria, bacteria able to colonize the human body and eventually those that can also cause disease. Under a sufficient selection pressure from e.g., antibiotics, genes providing resistance may be selected for, enriched and move across species boundaries and ecological niches. The resistant bacteria, as well as selective agents, may be transported through water, soil, food and sometimes air




mechanism of resistance. So far, the clinical, veterinary and environmental domains have often been studied separately. In the future, we think more focus should be directed to the complex interplay of environmental, commensal and pathogenic bacteria, the flow of resistance factors and the role of selective agents in different environments.

Antibiotic molecules, as well as a plethora of mechanisms for resistance, occur naturally in the environment. Although resistance genes appear to be omnipresent, they are relatively rare in pristine environments. Still, the huge diversity of environmental niches and bacterial species across our planet provides an almost endless repertoire of genes, together forming the "environmental resistome" *(6)*. Most likely, this largely unexplored source of genes is considerably greater than the resistance genes that up until now have found their way into pathogens. Genes providing resistance to antibiotics may be carried on the chromosome of harmless environmental bacteria, and at times on mobile elements. The latter provides an opportunity for horizontal transfer under the right conditions. Previously unknown forms of resistance may therefore emerge in environments where environmental bacteria meet bacteria capable of colonizing the human body (commensals or pathogens), particularly if there is a selection pressure favouring the acquisition of resistance (Fig. 1). Such selective agents can be antibiotic residues from human or animal use, or from direct discharges from manufacturing. In addition, antibacterial biocides and metals have been put forward as being responsible for the co-selection of antibiotic-resistant bacteria *(25)*. Waste water treatment plants provide one of several environments where selective agents, environmental bacteria and human pathogens are found together, providing arenas for the potential development of new forms of clinically relevant resistance. Importantly, resistant bacteria, genes and residues can spread from environmental and anthropogenic sources and reservoirs to the soil and air, and to surface and ground water. This may lead to exposure of humans and animals to antibiotic-resistant bacteria via these environmental matrices, and hence contribute to the dissemination of resistance *(7)*.

## Environmental transmission pathways

Clinically relevant, antibiotic-resistant bacteria, such as extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-Ent), Carbapenemase-Producing Enterobacteriaceae (CPE); methicillin-resistant S. *aureus* (MRSA), and vancomycin resistant *Enterococcus* spp. (VRE), have been detected in the different environmental compartments including water, soil and air *(8–10)*. Antibiotic residues, e.g., fluoroquinolones, macrolides, aminoglycosides and tetracyclines, have also been identified broadly *(11)*, as holds true for resistance genes *(12)*. ABR in the environment may originate from humans, animals or the environment itself. Major sources of contamination for antibiotic-resistant bacteria and resistance genes in the environment include wastewater and faecal waste (in some areas via open defecation), animal husbandry and wildlife. The concomitant release of both resistant bacteria and antibiotics often complicates assessments of how big a role the residual antibiotics play in the selection of resistance in the environment. Although it is a gross oversimplification, animal and human transmission pathways tend to be shifted towards terrestrial and aquatic contamination, respectively. A particular concern is the widespread sewage sludge application on to land as a soil fertilizer and its role in the spread of resistant bacteria, genes and antibiotics *(13)*. The highest levels of both antibiotics and ABR are found in environments contaminated with direct discharges from antibiotic manufacturing *(14)*.

## Risk assessment

Assessing risks for emergence versus transmission of resistance are two fundamentally different exercises. A novel form of resistance in a pathogen in principle only needs to emerge once, then Pandora's box is opened *(15)*. It is intrinsically difficult to assess risks for such unknown, one-time events to occur, particularly as our knowledge is still limited in terms of how, where and under what circumstances known forms of clinically important resistance emerged, limiting our ability to make inference to previous, related events. Importantly, risk scenarios still deserve to be ranked and priorities made with regard to risk-reducing actions. Understanding the selective ability of sub-inhibitory concentrations of antibiotics is one aspect that would put us in a better position to identify where actions would be most urgent and cost-efficient. Recent attempts have been made to predict selective concentrations for a broad range of antibiotics *(16)*, but experimental data are also warranted. The ability of microorganisms and genes to move across physical niches and taxonomic boarders is another critical aspect to consider, sometimes covered by the term "ecological connectivity" *(17)*.

Transmission, on the other hand, can be subject to a more quantitative assessment *(18)*, with different challenges depending on both the environmental transmission routes involved as well as the type of pathogen. Exposure to antibiotic-resistant bacteria through water has been described more frequently as compared with soil or air *(8)*. The latter exposures seem likely in light of described exposures to airborne pathogens e.g., for Coxiella in air and dust particles leading to Q-fever *(19)*. The aquatic routes of transmission have been more extensively studied, including exposure to recreational waters and drinking water from surface water or ground water sources. A quantitative exposure assessment for ESBL-producing bacteria showed that human exposure to ESBL *E.coli* through swimming is likely, if recreational waters are located downstream from poultry farms and municipal wastewater discharge points *(20)*, but whether the predicted ingested dose is sufficient for colonization is not yet clear. More quantitative assessments are needed to assess both exposure and potential impact *(20)*. Currently a lot of debate has arisen on what levels of resistance in the environment should cause concern with regard to transmission *(15, 16)*. The relative contribution of environmental exposure to ABR as compared to exposures through the clinical and veterinary transmission routes is still open for discussion, since quantitative data in the environment are largely lacking *(8)*. This black box with respect to attribution of ABR infections to different sources and their severity and impact on public health is, accordingly, problematic. From that, it follows that it is difficult to judge to which extent intervention measures are cost-effective, practical and feasible, particularly in resource-limited settings.

## Risk management

Despite uncertainties with regard to the role of environmental contamination in resistance development and the ultimate consequences in the clinic, risks with contamination still need to be managed. We argue that there is so much at stake that the precautionary principle needs to be applied in many situations, even if we are not yet in the position to quantify the benefits of specific management actions *(21)*. There is already compelling evidence for environmental transmission of several types of bacterial infections, which to a large extent may be extrapolated to the corresponding resistant pathogens. Reducing environmental transmission of non-resistant pathogens is also an important measure, as fewer infections, regardless of the resistance profile of the pathogen, are expected to lead to less use of antibiotics, a known driver of resistance *(1, 10)*. About 15% of the world's population practice open defecation *(26)* without any wastewater collection or treatment. In such regions, even the most basic measures to contain and treat faecal matter would probably make a considerable difference. Given the way many resistant bacteria tend to spread across the world, local investment in improved sanitation could benefit everyone at the end of the day. Evaluating existing waste and wastewater management with respect to efficiency for the reduction of ABR and selective agents is also warranted. Process control at waste and wastewater treatment facilities may need to be enforced as well as maintenance and renovation. Innovative treatment options should be explored if current treatment processes prove to be insufficient. Examples of such processes have already been developed but are thus far only piloted at some specific locations instead of being implemented broadly.

Overall, the largest challenge is probably less a technological one, but more an issue of lack of awareness and incentives for actions. Regulatory systems that take into account risks for resistance promotion need to be put in place *(1, 23-24)*. In parallel, other economic incentives need to be created to stimulate risk-reducing actions *(3)*. While more research is clearly valuable to direct actions and to make better cost-benefit decisions, the lack of awareness about the environmental dimensions to the global threat of antibiotic resistance is probably the single most critical point hindering action on a global scale. Here, the WHO plays a crucial role. By providing accessible and understandable information to promote action, the WHO could capacitate regional and local centres and networks. With respect to risk governance, many Member States have already taken some first steps towards taking their responsibilities by drawing up national strategies and action plans strengthened by the WHO GAP and the JPI-AMR strategic research agenda. Existing comprehensive risk assessment and risk management frameworks such as the WHO water safety plans and sanitation safety plans can play a crucial role in global antibiotic resistance prevention and intervention programmes (WHO 2011). To speed up action, Woolhouse and colleagues suggested that an intergovernmental panel, akin to the Intergovernmental

Panel on Climate Change, could be an appropriate vehicle to actively address the antibiotic resistance problem *(22)*. Still, giant leaps are required with respect to setting health-based targets for antibiotic resistance and to translate these into operational targets for environmental faecal and antibiotic residue levels. While setting up such targets, we should also bear in mind that the palette of management options and their feasibility are strongly dependent on context (social, economic, political etc.). ■

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