

JPIAMR Workshop

Environmental Dimensions of AMR

Summary and recommendations

Gothenburg, Sweden, 27-28 September 2017

Co-hosted by

JPIAMR

University of Gothenburg

Swedish Research Council

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Introduction

The workshop, initiated by JPIAMR and the Swedish Research Council VR, was led by Professor Joakim Larsson at the University of Gothenburg. Over 20 scientists with core expertise on the Environmental Dimensions of Antibiotic Resistance, met in Gothenburg, Sweden, to discuss the steps needed to create a JPIAMR roadmap for research on AMR within the environment (see Appendix for participant list). The steps discussed may contribute to the initiated update of the Environment section of the JPIAMR Strategic Research Agenda (SRA) and a potential upcoming research calls with a focus on the environmental dimensions of AMR.

Executive summary

The experts attending the workshop concluded that the current environmental priority topic section in the existing SRA (2013) requires revision to better reflect the current state of knowledge. Moreover, previous omissions were identified, such as the need to evaluate and develop social interventions (not just technical solutions), a greater clarification of the need to understand the role of selective agents and anthropogenic input on evolutionary processes in the environment leading to resistance, and a quantitative assessment on the exposure of humans to antibiotic resistant bacteria via different routes and the impact this has on human and animal health. The attendees suggest a revision of the priority topic text, taking into account recommendations listed in this report.

There was a strong consensus among the participants to promote a future call covering the environmental dimensions listed below. All parts were considered necessary to address, although individual proposals could focus on one or more of the following broad questions:

1. *What is the relative contribution of different sources of antibiotics and antibiotic resistant bacteria into the environment?*
2. *What is the role of the environment, particularly anthropogenic input (e.g. pollution and other activities), on the evolution (mobilization, selection, transfer, persistence etc.) of antibiotic resistance?*
3. *How significant is the exposure of humans to antibiotic resistant bacteria via different environmental routes, and what is the impact on public health?*
4. *What are the technological, social, economic and behavioral interventions that effectively could mitigate the emergence and spread of antibiotic resistance via the environment, and what interventions would be desirable, based on cost-benefit evaluations and feasibility, in different contexts?*

Such a call would have a strong environmental focus, but would have clear connections to other priority topics (e.g. transmission and intervention). Furthermore, the suggested call should engage not only environmental scientists but also clinical researchers and expertise from within widely different areas, from evolutionary microbiology to economics and health ethics. The group recognized that such a call would cover most of the relevant aspects related to AMR and the environment, thereby not limiting the ability to fund excellence, while still maintaining a focus on solution-oriented research. The topic could also be part of a joint call with the JPI on WATER, should such an opportunity arise. The value of addressing different regional and societal perspectives was acknowledged, as well as the opportunity to take advantage of the multinational involvement in research consortia.

Structure of the workshop

Participants were either invited directly by VR or recommended by the individual JPIAMR member states (the majority), some in their roles in the different organs of JPI (e.g. management board, steering committee, scientific advisory board). After a welcome and presentation of the JPIAMR by Patriq Fagerstedt, an introduction of all participants and summary of the scope of the workshop, Professor Joakim Larsson gave a brief presentation on AMR and the environment (see illustration) and some of the related research challenges. This was followed by a brief summary by Professor Edward Topp

(Canada) on some of the outcomes of a recent conference (Environmental Dimensions of Antibiotic Resistance) held in Michigan, USA in August 2017. This was followed by discussions in breakout groups, dealing with knowledge gaps related to evolution, transmission, and interventions led by Professors Joakim Larsson, Ana-Maria de Roda Husman (the NL) and Ramanan Laxminarayan (India), respectively. The breakout groups then reported back in the form of summary bullet points to the whole group. This was followed by discussions on how to clarify and structure the identified knowledge gaps. The identified knowledge gaps from the three thematic areas (evolution, transmission, interventions) were used to describe research needs (see below). During day two, there was also a discussion with all participants on what to bring forward as a potential call-topic for the nearer future (outcome given in the executive summary).

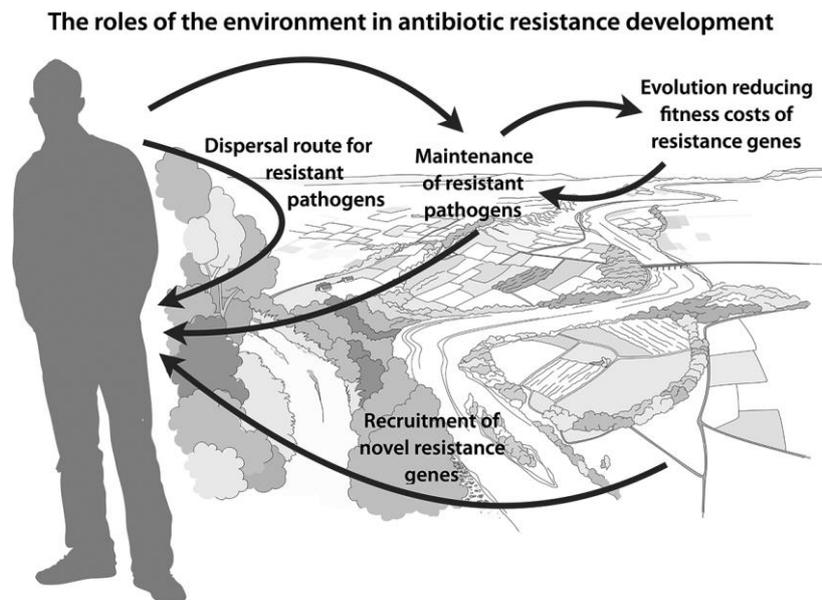


Illustration from: Bengtsson-Palme J, Kristiansson E, Larsson DGJ. (2017). Environmental factors influencing the development and spread of antibiotic resistance. FEMS Micro Rev. doi: 10.1093/femsre/fux053

Knowledge gaps to be addressed

1. What is the relative contributions of different sources of antibiotics and antibiotic resistant bacteria into the environment?

Although still far from clear, there is a growing body of knowledge on how both selective agents and resistant bacteria reach the external environment, intentionally and non-intentionally. Despite that this is possibly the most investigated environmental dimension of AMR to date, better quantification of such pathways would help populate models and stratify risks. It should be noted here that the risks for human health depend both on processes in the environment (point 2) and the probability for resistant bacteria in the environment reaching humans (point 3). Also, it is not necessarily total mass flows, of e.g. antibiotics, that decide the importance of different sources, but also the concentrations reached, the opportunities for growth of bacteria (including elevated temperatures, nutrients and other permitting physiochemical conditions, thus allowing for selection), duration of the exposure etc.

By defining baseline data with regards to the natural variability of resistance genes, mobile genetic elements and mobilization/transfer frequencies in different types of environments, the role of anthropogenic activities can be better assessed. Such data are also central when evaluating effects of interventions and intervention experiments (point 4). It is important to understand that many events in microbial communities are not constant but rather stochastic and change over time, resulting in quantification challenges. Standardized surveillance methods (for selective agents, bacteria and DNA in matrices such as manure, wastewater and surface water) and reporting formats would be valuable in

this context. Surveillance of resistance in fecal bacteria in e.g. untreated sewage could potentially also serve as an indicator (or early warning) of (changes in the) the regional clinical resistance situation.

2. *What is the role of the environment, particularly anthropogenic input (e.g. pollution and other activities), on the evolution (mobilization, selection, transfer, persistence etc.) of antibiotic resistance?*

There is a critical gap in understanding the relation between exposure concentrations to antibiotics and selection for resistance in bacterial communities. Similar gaps also exist for non-antibiotic, co-selective compounds (metals, antibacterial biocides), where additional challenges involve the extent of their co-selective ability and the mechanisms involved. Understanding exposure-effect relationships are further complicated by the potential for mixture effects. The selective potential will inevitably vary substantially between different species/chemical combinations, providing an underexplored area. Little is also known about the complex interactions between microorganisms in communities, with possible effects on the actual ability of e.g. antibiotics to select for resistance. Adequate methods and research that address selection, evolution and persistence in complex microbial communities are therefore urgently needed. This will allow us to better understand the role of different selective agents on evolution and transfer of resistance in different environments. It will also provide information on their possible role in facilitating environmental dissemination of already resistant pathogens. It is also evident that more attention should be paid to the conditions that favor rapid growth, as well as close interactions between diverse environmental bacteria and those able to colonize humans, as these pose increased risks. It is also acknowledged that antibiotics and other antimicrobials may have additional ecological effects, and thus be of concern for other reasons, in addition to their obvious role in promoting selection for resistance.

For identifying risk environments for the evolution and emergence of resistance, and hence where interventions are warranted (point 4), a global perspective is advised as bacteria do not respect national borders. Quantitative modelling could also be valuable for such purposes, although it is recognized that it is non-trivial to populate such models with relevant input data on e.g. the rate of horizontal gene transfer events and selection pressures, largely because such quantitative data are presently lacking.

A retrospective approach, aiming at understanding how the resistance factors that are clinical problems today ended up in pathogens could also be valuable. This will help elucidate further the molecular mechanisms involved in mobilization and transfer, the organisms involved in the process, and the environmental arenas for transmission - and hence determine future risks for the emergence of new forms of resistance in pathogens. Understanding the different barriers (genetic as well as ecological) that limit genetic movement from harmless environmental bacteria to pathogens would help us in stratifying risk environments and direct mitigations. To move from identification of risks factors and stratification of risks to accurately quantify risks for the *emergence* of novel forms of resistance in pathogens is probably very difficult, as these events are likely rare. In this sense, it differs from the more quantifiable risks for *transmission* of already resistant bacteria (see point 1 and 3).

Our inability to study the whole resistome deeply (including rare antibiotic resistance genes, bacterial species and strains) prevents a thorough understanding of the nature of environmental resistomes and their genetic mobility potential. Future development of both cultivation-dependent and -independent methods could expand our opportunities to identify risks.

3. How significant is the exposure of humans to antibiotic resistant bacteria via different environmental routes, and what is the impact on public health?

To date, health impacts from environmental exposure to antibiotic resistant bacteria is unclear. To be able to attribute disease burden resulting from environmental exposures and compare it to other routes, such data are essential. Without knowledge of impact, health based targets and derived operational targets will be difficult to set (under point 4). Information on how bacteria, genes and selective agents reach the environment, as well as knowledge on their evolution and other processes occurring in the environment, do not, by themselves, provide sufficient information on how important different environmental transmission routes are for human health outcomes. Quantitative human exposure assessments are also needed to comprehensively assess risks for human health. Although challenging, risks for transmission through complex routes may be assessed in a quantitative manner. There is also a need for an overarching theoretical framework on environmental transmission to drive hypothesis-driven research – expanding from current quantitative microbial risk assessment to encompass also, e.g., ecology and evolutionary aspects. One of several challenges here is to provide relevant input numbers to such models.

Often we encounter similar, or identical, genes and bacteria in both the external environment and the human/animal microbiota, indicating a flow from humans to the environment, the opposite, or both. A better understanding of the directionality behind such transfers (both at the genetic and whole bacterial dispersal levels) would help us identify what the most critical risk scenarios are. Expanded, high resolution typing efforts, expanded sampling plans and sensitive source tracking tools could be part of such an approach.

4. What are the technological, social, economic and behavioral interventions that effectively could mitigate the emergence and spread of antibiotic resistance via the environment, and which interventions would be desirable, based on cost-benefit evaluations and feasibility, in different contexts?

Intervention targets need to be established. As there may be great difficulties in evaluating an intervention all the way to reduced morbidity, mortality and social costs, surrogate measures will have to play important roles. These can, for example, include the abundances of resistant bacteria or concentrations of selective agents in various environmental matrices. Acceptable emission levels and environmental quality standards for selective agents and resistant bacteria, as well as methodology to define such levels and standards would be useful for several types of interventions, including the management of industrial discharges.

Existing practices and interventions should be evaluated to inform their efficacy and risks. A critical question is whether current interventions should be further adapted or modified? It is already clear that there is a need for cost- and energy-efficient technical solutions for waste management with respect to AMR. The most pressing needs are found in low- and middle-income regions, where waste treatment is often lacking or of limited efficacy. However, there are also initiatives to improve waste management in high income settings, including removing micro-contaminants, such as pharmaceuticals, from wastewaters or sludge. Such advanced solutions, including e.g. ozonation, activated carbon, biofilters, wetland-treatment etc., should also be evaluated for their efficiency to reduce concentrations or remove selective agents and the spread of resistant bacteria. It is acknowledged that while many advanced remediation solutions may be costly now, these costs may decrease over time (as we have seen for the development of renewable energy sources). Risk governance is an essential component in overcoming cost diversion.

Critically, interventions are not only of a technical nature, but also social. Without awareness of problems among those able to address them, problems will remain. Strategies for increasing awareness of the environmental dimensions of AMR among key actors (consumers and patients, the health-, water- and agricultural sectors, regulatory agencies, pharma companies, NGOs, media, WHO, governments etc.) therefore need to be developed and evaluated. Making all actors aware of their own

ability to make a difference is a critical step. However, even with awareness and available technological solutions, there may often be counter-incentives, typically economic, that prevent effective actions. Research is therefore needed to both reduce counter-incentives and create new economic and legal, incentives. Putting a price tag on carrying on with “business as usual” in this area, including, when possible, defining an attributable fraction of resistant infections to environmental transmission, could motivate actions. This is an area where lessons might be learned from the climate challenge.

Identifying interventions (existing and new ones) and evaluating their potential efficacy is critical, but needs to be combined with analyses of their feasibility in different contexts (geographical, social, economic, political), and balanced against their associated costs. Such costs or consequences can be both of an economic, energy or social nature, or a combination of all. Importantly, costs and benefits will not be equally shared among actors and over time, posing added ethical dilemmas. Considerations could deal with measures primarily protecting the environment from exposure to selective agents, resistant bacteria or genes, or measures that protect humans to resistant bacteria and resistance factors from environmental routes would be most efficient in a cost-benefit perspective? Would it pay off more to invest in waste management in certain sectors or certain regions of the world than in other? If so, how would benefits likely be distributed globally and over time, and how could costs be shared? Another challenge is how we move forward with policy in the face of uncertainty in the science.

Communication activities

Communications activities during and after the workshop in Gothenburg was focused on following the discussion and share on Twitter. A couple of Tweets stood out and a total reach of 61800 with 30 responses. One article on the workshop was published at the JPIAMR’s website: (<https://www.jpiamr.eu/environmental-dimensions-of-amr-in-focus/>) and another by the Gothenburg University centre for AMR, CARE (<http://care.gu.se/news-events/n//workshop-on-environmental-dimensions-of-amr.cid1519390>).

Selected participating researchers were video interviewed at the workshop. The videos will be released on the JPIAMR website at a later stage.

Contact

Joint Programming Initiative on antimicrobial resistance (JPIAMR) coordinates national funding from 26 countries (including Argentina, Canada, India, Japan, and South Africa) and supports collaborative action to fill existing knowledge gaps in AMR; A Strategic Research Agenda (SRA), which outlines key [neglected] areas to tackle, guides JPIAMR and provides framework for future investment in research priorities. The SRA also serves as a guidance documents for nations to align their AMR research agenda. JPIAMR supports projects through annual calls for proposals. /

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Appendix 1. Participant list

Namn	Surname	Country	Affiliation
Antoine	Andremont	France	INSERM - AVIESAN
Johan	Bengtsson-Palme	Sweden	Assisting discussion leader - University of Gothenburg (CARE)
Anders	Bjers	Sweden	JPIAMR - Swedish Research Council
Kristian Koefoed	Brandt	Denmark	University of Copenhagen
Ana Maria	de Roda Husman	The Netherlands	Discussion leader - RIVM/UU
Topp	Ed	Canada	Agriculture and Agri-Food Canada
Patriq	Fagerstedt	Sweden	JPIAMR - Swedish Research Council
Jerker	Fick	Sweden	Umeå University
Carl-Fredrik	Flach	Sweden	Assisting discussion leader - University of Gothenburg (CARE)
William	Gaze	UK	University of Exeter
Makoto	Kuroda	Japan	Pathogen Genomics Center, National Institute of Infectious Diseases
Kristian	Kvint	Sweden	Assisting discussion leader - University of Gothenburg (CARE)
Joakim	Larsson	Sweden	Discussion leader - University of Gothenburg (CARE)
Ramanan	Laxminarayan	India	Discussion leader - CDDEP
Celia	Manaia	Portugal	Catholic University
Kaare Magne	Nielsen	Norway	Oslo and Akershus University College
Laura	Plant	Sweden	JPIAMR - Swedish Research Council
Marie-Cécile	Ploy	France	UMR Inserm 1092
Carlos	Segovia	Spain	JPIAMR Chair - Instituto de Salud Carlos III
Pascal	Simonet	France	CNRS-ECL
Kornelia	Smalla	Germany	Julius-Kühn-Institut
Jason	Snape	United Kingdom	AstraZeneca
Arjon	van Hengel	EU	European Commission
Elizabeth	Wellington	UK	University of Warwick
David	Verner-Jeffreys	UK	Cefas
Ann-Sofie	Wernersson	Sweden	Swedish Agency for Marine and Water Management
Marko	Virta	Finland	University of Helsinki

