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Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance

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ABSTRACT

There is growing understanding that the environment plays an important role both in the transmission of antibiotic resistant pathogens and in their evolution. Accordingly, researchers and stakeholders world-wide seek to further explore the mechanisms and drivers involved, quantify risks and identify suitable interventions. There is

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a clear value in establishing research needs and coordinating efforts within and across nations in order to best tackle this global challenge. At an international workshop in late September 2017, scientists from 14 countries with expertise on the environmental dimensions of antibiotic resistance gathered to define critical knowledge gaps. Four key areas were identified where research is urgently needed: 1) the relative contributions of different sources of antibiotics and antibiotic resistant bacteria into the environment; 2) the role of the environment, and particularly anthropogenic inputs, in the evolution of resistance; 3) the overall human and animal health impacts caused by exposure to environmental resistant bacteria; and 4) the efficacy and feasibility of different technological, social, economic and behavioral interventions to mitigate environmental antibiotic resistance.[1]

1. Introduction

Addressing the global challenge of antibiotic resistance requires a "one-health perspective" that takes into account the connections between human and animal health and the environment[2] (Robinson et al., 2016). This approach is needed because bacteria and bacterial genes often have the ability to move between all three compartments, in any direction (Forsberg et al., 2012; Martinez, 2018; Woolhouse et al., 2015). Such a strategy has been adopted not only within the Global Action Plan of the WHO (WHO, 2015), but also in regional action plans (EC, 2017), in many national action plans (e.g. (India, 2017; Sweden, 2016), by the pharmaceutical industry (IFPMA, 2016) and in the work of other organizations (Access-to-Medicine-Foundation, 2018; AMR-review, 2016). The role of the environment as a transmission route for many bacterial pathogens has long been recognized, often associated with insufficient sewage infrastructure, fecal contamination of water or organic fertilizers (Allen et al., 2010; Bengtsson-Palme et al., 2018a; Finley et al., 2013; Huijbers et al., 2015; Levin et al., 2014; Pruden et al., 2013). More recently, the understanding has developed that many of the resistance genes that we find in pathogens today originate from bacteria normally thriving in the environment (D'Costa et al., 2011; Forsberg et al., 2012; Poirel et al., 2008; Potron et al., 2011; Taylor et al., 2011; Wellington et al., 2013). Hence, the environment acts as a dispersal route and reservoir of resistant pathogens, and also as an arena for the evolution of resistance (Fig. 1; Bengtsson-Palme et al. 2018b). This paper identifies key knowledge gaps associated with both of these biological processes (transmission and evolution) and with mitigation of associated risks. Improving science related to the environmental dimension is critical in order to efficiently curb further development and spread of antibiotic resistance in pathogens (Berendonk et al., 2015; Finley et al., 2013; Gaze et al., 2013; Topp et al., 2018).

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) brings together different disciplines for collaboration on antimicrobial resistance research, harmonizes joint actions (including coordination of international research calls) and strives to reduce research overlap (www.jpiamr.eu). It currently involves 27 countries, mainly from Europe, but also from other regions of the world (e.g. Canada, India, Japan, and South Africa). The JPIAMR is organized around six priority topics, of which the Environment is one. A Strategic Research Agenda (JPIAMR, 2014) was developed in 2014, providing guidance to much of the activities. The present paper is the result of an initiative by the JPIAMR to receive expert advice on critical knowledge gaps to be considered in an upcoming revision of the Strategic Research Agenda, likely in 2018, and to identify possible areas for dedicated future research calls. However, we recognize that the value of defining such knowledge gaps extends far beyond influencing this particular, but important, policy document.

[1] The recommendations from the workshop have also been communicated in a separate report published on the website of the JPIAMR (www.jpiamr.org).

[2] There is no complete consensus on how to interpret "environment" in this context, but here we refer to environments outside the bodies of humans and domestic animals, excluding the clinical, in-door environment.

2. Structure of the workshop

A workshop was organized in Gothenburg, Sweden on the 27–28th of September 2017 by the JPIAMR, the Swedish Research Council (SRC) and the Centre for Antibiotic Resistance research at University of Gothenburg (CARe). The workshop was led by Professor Joakim Larsson with Professors Ana-Maria de Roda Husman and Ramanan Laxminarayan as additional breakout group leaders. Participants were either invited directly by the SCR or recommended by the individual member states (the majority of participants), whereas some participated in their roles in the different parts of the JPIAMR (e.g. management board, steering committee, scientific advisory board), the European Commission or the European Joint Action on Antimicrobial Resistance and Healthcare Associated Infections (JAMRAI). Prior to the workshop, a questionnaire, open to input from anyone, was launched via the websites of JPIAMR and CARe in Gothenburg, Sweden (www.care.gu.se), and was also announced in a dedicated presentation at the 4th International Symposium on the Environmental Dimension of Antibiotic Resistance held in Michigan, USA, in August 2017 (http://www.antibiotic-resistance.de). The workshop was organized into three breakout groups, each given the task to deal with knowledge gaps related to evolution, transmission or interventions. The reports of the breakout groups were then discussed among all participants to clarify and structure the areas where more research is needed. The discussions were used to describe four overarching critical knowledge gaps, and hence corresponding research needs. The core focus was on antibiotic resistance in bacteria.

3. Critical knowledge gaps

The workshop participants identified that the environmental priority topic section in the current Strategic Research Agenda should be revised to better reflect the current state of knowledge of the role of the environment in antibiotic resistance development. In particular, it should embrace the need to evaluate and develop social interventions (not just technical solutions), have a stronger emphasis of the need to understand the role of anthropogenic inputs of selective agents on evolutionary processes in the environment leading to resistance, and stress the need for quantitative risk assessment of the impacts of exposure via environmental routes on human and animal health. These and additional knowledge gaps were structured into four overarching gaps described below.

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

Although the complete picture is still unclear, there is a growing body of knowledge on the mass flows of both selective agents and resistant bacteria that reach the environment from different sources and through distinct pathways (Aubertheau et al., 2017; Bueno et al., 2017; Kummerer, 2009; SCENIHR, 2009; Wolters et al., 2016). Better quantification of the contribution from such sources, routes of propagation and exposure paths would help populate quantitative transmission and risk models and rank risks (Ashbolt et al., 2013; Pruden et al., 2013; Schijven et al., 2011). The selection pressure imposed on environmental

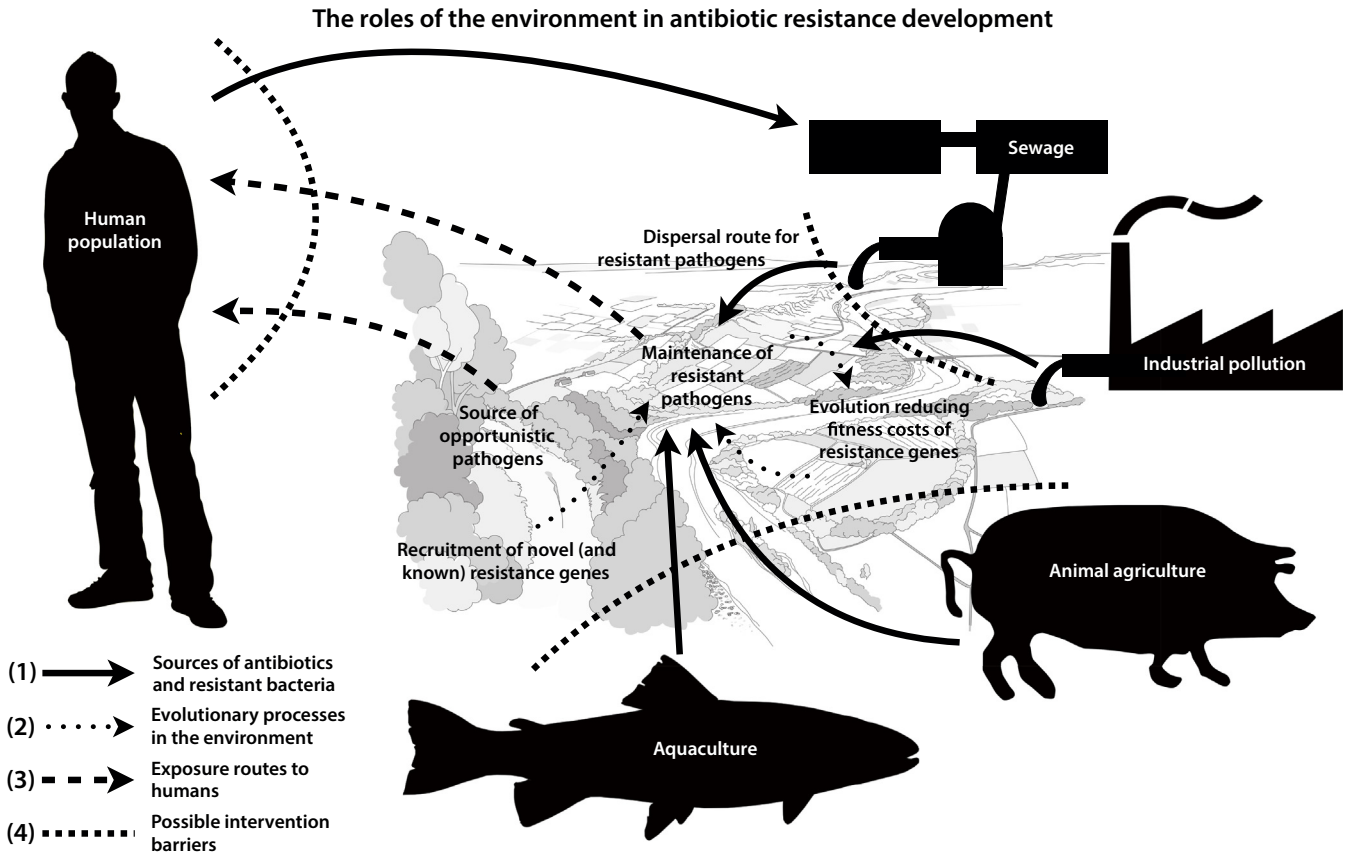

Fig. 1. Overview of the environmental processes influencing the development and spread of antibiotic resistance and how they relate to the knowledge gaps presented in this article. Silhouettes represent common sources of antibiotics and resistance genes to the environment. The human silhouette on the left also represents the human microbiome as a recipient of resistance genes and resistant bacteria from the environment. Arrows correspond to the first three broad categories of knowledge gaps, while the dashed lines show possible points of intervention (related to the fourth, broad knowledge gap). The illustration is adapted from Bengtsson-Palme et al. (2018a), FEMS Microbiol. Rev. doi: https://doi.org/10.1093/femsre/fux05, distributed under the CC-BY-NC license. (https://creativecommons.org/licenses/by-nc/4.0/).

bacteria is determined by the type of selective agent, their concentrations, their chemical speciation, co-exposure to many selective agents, the time of exposure, and to what degree the environmental conditions are permissive for bacterial growth (Baquero et al., 2009). Uncertainties in each of these aspects prevent understanding of where and to what extent selective agents promote resistance in the environment. Health risks also depend on the probability that resistant bacteria in the environment reach humans and domestic animals, covered below.

To better assess the significance of different sources of antibiotics and antibiotic resistant bacteria into the environment, knowledge of the abundance, characteristics and natural variability of resistance genes and mobile genetic elements, as well as their mobilization/transfer frequencies in different types of environments is needed (Hunter et al., 2008; McLain et al., 2016; Mirkin et al., 2003; Pal et al., 2016; Ravenhall et al., 2015; Rothrock et al., 2016; Zhu et al., 2017). Such data are also helpful when evaluating effects of interventions and intervention experiments (see below). It is important to understand that many events in microbial communities are stochastic and vary over time, resulting in quantification challenges (Nielsen et al., 2014; Pettersen et al., 2005). Standardized surveillance methods (for selective agents, bacteria, mobile genetic elements and resistance genes in matrices such as manure, wastewater and surface water) and reporting formats would be valuable in this context (Berendonk et al., 2015; Matheu et al., 2017). Surveillance of resistance in fecal bacteria in e.g. untreated sewage could potentially also serve as an indicator (or early warning) of the levels of regional clinical resistance and how they change over time (Alleweldt et al., 2017; Kwak et al., 2015).

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

The relationship between antibiotic exposure and selection for resistance in bacterial communities is poorly understood (Aminov, 2009; Bengtsson-Palme et al. 2018b; Bengtsson-Palme and Larsson, 2016; Gullberg et al., 2011; Le Page et al., 2017; Lundstrom et al., 2016). Similar gaps also exist for non-antibiotic, co-selective compounds (e.g. metals, biocides), with additional challenges involving the extent of their co-selective ability and the mechanisms involved (Ostman et al., 2017; Pal et al., 2017; Wales and Davies, 2015). Understanding of exposure-effect relationships is further complicated by the time needed for some effects to materialize (Nielsen et al., 2014) and the potential for mixture effects (Gullberg et al., 2014; Menz et al., 2017; Weinstein and Zaman, 2017). In addition, the selective potential inevitably varies substantially between different species and chemical combinations. Little is also known about the complex interactions between microorganisms in communities. For example, antibiotics and other selective agents could potentially modulate these interactions, both directly through effects on e.g. quorum sensing (Koul et al., 2016) or indirectly through the selecting for strains with intrinsic or acquired resistance (Baquero et al., 1998; Widder et al., 2016). Adequate methods and research that address selection, evolution, gene transfer and persistence in complex microbial communities are therefore urgently needed (Hiltunen et al., 2017; Jechalke et al., 2013; Klumper et al., 2017; Spencer et al., 2016). Selective agents may also, under some circumstances, play a role in facilitating environmental dissemination of

already resistant pathogens or the antibiotic resistance genes that they carry. To better understand risks, more attention should be paid to conditions that favor growth of resistant bacteria, as well as conditions that permit close interactions between diverse environmental bacteria and those able to colonize humans (Baquero et al., 2009). Antibiotics and other antimicrobials may have additional ecological impacts, such as impairing ecosystem function and services as a result of community changes, and are thus of concern for other reasons in addition to their more obvious role in promoting selection for resistance (Ashbolt et al., 2013; Brandt et al., 2015).

Bacteria do not respect national borders and resistant pathogens are often quickly disseminated around the world via travelers and the transport of goods and food (Bengtsson-Palme et al., 2015; De Valliere, 2017; Ruppe et al., 2018). Attempts to identify high risk environments for the evolution and emergence of resistance as priority targets for mitigation, should therefore not be geographically restricted but rather take on a global perspective. Quantitative modelling of evolutionary processes would clearly be valuable to understand risks for the emergence of resistance in different environments (Manaia, 2017; Martinez et al., 2015; Nielsen et al., 2014; Pettersen et al., 2005). However, we recognize that it is non-trivial to populate such models with adequate, relevant input data, such as the rate at which genes are mobilized, how often horizontal gene transfer events occur and the concentrations of antibiotics that drive resistance selection. Largely, this is because such quantitative data are mostly lacking at present (Hunter et al., 2008; Jutkina et al., 2017; Jutkina et al., 2016; Scornec et al., 2017).

A retrospective approach, aiming at understanding how the resistance determinants that are clinically problematic today ended up in pathogens could also be valuable (Davies and Davies, 2010; Forsberg et al., 2012; Ghaly et al., 2017; Jacoby et al., 2011; Poirel et al., 2008; Potron et al., 2011; Razavi et al., 2017). This will help to further elucidate the molecular mechanisms involved in mobilization and transfer, the organisms involved in the process, and the environmental arenas for transmission; and ultimately aid in estimating the risks for emergence of new forms of resistance in pathogens. Understanding the different barriers (genetic as well as ecological) that limit movement of resistance genes from harmless environmental bacteria to pathogens would help stratify/rank risk environments and direct mitigation strategies (Bengtsson-Palme et al. 2018b; Martinez, 2011; Porse et al., 2018; Waglechner and Wright, 2017). To move from identification and somewhat subjective relative ranking of risks factors to accurately quantifying risks for the emergence of novel forms of resistance in pathogens is probably very difficult, as these events are likely rare. Establishing quantitative predictions of the emergence of transferable resistance is far less tractable than estimating the more quantifiable risks for transmission of already resistant bacteria to humans (Gaze et al., 2013; Gaze et al., 2008; Huijbers et al., 2015; Pruden et al., 2013; Pruden et al., 2006; Wellington et al., 2013).

There are several technical limitations when studying environmental resistomes (Bengtsson-Palme et al., 2017). For example vast amounts of sequence data are needed to effectively allow the study of rare antibiotic resistance genes when using exploratory shotgun metagenomics. Also, challenges in cultivating many environmental bacteria limit our ability to identify the hosts carrying resistance factors, as well as their evolution. Such limitations may be overcome to some degree using technologies such as qPCR, ResCap, iChip or epicPCR (Lanza et al., 2018; Nichols et al., 2010; Spencer et al., 2016). Still, technological limitations constrain our understanding of the nature of environmental resistomes and their potential to be horizontally transferred between bacteria (Bengtsson-Palme et al. 2018b; Delmont et al., 2015). Development of methods with improved sensitivity to identify rare resistance determinants, establish their genetic context without the need for cultivation, and improved ability to culture a broader range of species could expand our opportunities to understand risks.

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

The magnitude of the health impacts, direct as well as indirect, resulting from environmental exposure to antibiotic resistant bacteria are unclear (Wuijts et al., 2017). Quantitative data on environmental exposure are essential in order to attribute an increased disease burden relative to other exposure routes, such as food consumption and community or nosocomial transmission (Franz et al., 2014; Huijbers et al., 2015; Leonard et al., 2015). Further complicating the risk assessment for environmental transmission is that an initial, rare, introduction of resistance from the environment in the longer term could have major, global consequence for health, despite that the quantitative environmental exposure is exceedingly small. On the other hand, much more common transfers from the environment of resistant bacteria and genes that are already circulating in the human population and transmitted via other routes, may only contribute marginally to the overall health effects (Bengtsson-Palme and Larsson, 2015; Bengtsson-Palme et al., 2018b). Without knowledge of the impacts, health based targets (WHO, 2010) and derived short-term goals will be difficult to set, and even more challenging to prioritize. Information on how bacteria, genes and selective agents reach the environment, as well as knowledge on the evolution and other processes occurring in the environment, does not, on its own, provide sufficient evidence to deduce 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 (de Roda Husman and Larsson, 2016). Although challenging, risks for transmission through complex routes may be assessed in a quantitative manner. There is a growing focus on relating environmental exposure to colonization of humans and animals (Dorado-Garcia et al., 2018; Leonard et al., 2018), but less so to disease. Much more research will be necessary to quantitatively attribute antibiotic resistance to specific transmission routes in different settings and regions. Furthermore, most studies of antibiotic resistance in the environment measures point prevalence, are descriptive, and limited in time and scale. Such nonsystematic “snapshots” are not sufficient to build the overarching theoretical framework of resistance dynamics that is needed to further develop hypothesis-driven research (Bengtsson-Palme et al. 2018b; Nielsen et al., 2014; Pettersen et al., 2005; Townsend et al., 2012). Some of several challenges here is to predict the relevant risk scenarios including recipient bacterial species and resistance traits and to provide relevant input numbers, e.g., transmission rates, exposure levels or infectious doses, to such models.

Similar or identical genes and bacteria are often encountered in both the environment and the human/animal microbiota. This indicates a flow between environments, but it does not necessarily ascribe the direction of transmission (Chamosa et al., 2017; Davies and Davies, 2010; Forsberg et al., 2012; Jacoby et al., 2011; Poirel et al., 2008; Potron et al., 2011). A better understanding of the directionality behind such transfers of genes and bacteria would help us identify what the most critical exposure and risk scenarios are. Expanded sampling plans spanning diverse geographical regions and integrating different environmental compartments, time points and selection pressures would contribute to understanding gene flows. Partially, this could be achieved by better sharing of data, but increased high resolution typing efforts and sensitive source tracking tools could also be part of such an approach (Berendonk et al., 2015; Harwood et al., 2014).

4. What technological, social, economic and behavioral interventions are effective to mitigate the emergence and spread of antibiotic resistance via the environment?

As there may be great difficulties in evaluating an intervention all the way to an impact on human health with respect to reduced morbidity, mortality and social costs (Ashbolt et al., 2013), surrogate

endpoints will have to play important roles. Surrogate endpoints can, for example, include the abundances of resistant bacteria or concentrations of selective agents in various environmental matrices. Currently there are essentially no standards regulating discharges of antibiotics from production facilities or other sources (Bengtsson-Palme et al., 2018a, 2018b) although a few antibiotics are included in the "watch-list" of the European Water Framework Directive (Carvalho et al., 2015). Development of 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 (Bengtsson-Palme et al., 2018a; Bengtsson-Palme and Larsson, 2018; Le Page et al., 2017; Schijven et al., 2011).

To some extent there are already practices and interventions in place that reduce risks for spreading antibiotic resistant bacteria and selective agents to the environment, or that reduce the risk for transmission back to humans and animals. Critical question are how effective those interventions are, and whether current intervention are sufficient, should be further adapted or even replaced/amended by different interventions. It is already clear that there is a need for cost- and energy-efficient technological solutions, including formal definitions of Best Available Technologies (BAT), for waste management, also with respect to AMR (Berendonk et al., 2015). However, the implementation of BAT may need to be prioritized where risks to human and environmental health are apparent and will have the greatest impact. The most pressing needs for technological interventions are found in low- and middle-income regions, where waste treatment is often lacking or of limited efficacy. In this respect, recently developed water safety plans and sanitation safety plans will play significant roles (WHO, 2009, 2016). However, there are also initiatives to improve waste management in high income settings, including removing micro-contaminants, such as pharmaceuticals, from wastewaters or sludge (Barbosa et al., 2016; Homem and Santos, 2011; Michael-Kordatou et al., 2017). Such advanced solutions, including ozonation, activated carbon, biofilters, and wetland-treatment, should also be evaluated for their efficiency to reduce concentrations of selective agents and prevent the spread of resistant bacteria. Although many advanced remediation solutions may be costly now, these costs should go down over time. How costs for such solutions can be shared is also an important aspect to consider.

Critically, interventions are not only of a technical nature, but also social. Without awareness of the challenges – and what is at stake – among those able to address them, problems will remain. Strategies therefore need to be developed and evaluated for each type of key stakeholder. These include the health-, water- and agricultural sectors, regulatory agencies, pharma companies, trade associations, NGOs, media, WHO, FAO, OIE, EU, governments, etc., but also consumers and patients (Laxminarayan et al., 2016; Laxminarayan et al., 2013). Making different stakeholders aware of their own ability to make a difference is a critical step, as well as adapting the message with the specific receiver in mind. Some stakeholders and regions have a considerably higher awareness than others. An analysis matching lack of awareness with ability to influence would therefore probably be valuable for directing communication initiatives. 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 to reduce pollution. Putting a price tag on carrying on with "business as usual", could also motivate actions (Littmann et al., 2015; Van Boeckel et al., 2017). Highlighting the accumulated economic burden of non-action is an approach where lessons might be learned from the climate challenge, where such approaches have been successful in spurring political action.

Identifying interventions (existing and new) and evaluating their potential efficacy is critical, but their feasibility in different contexts (geographical, social, economic, political) needs to be considered and their benefits must be balanced against their associated costs. Negative consequences of an intervention may be of economic, climate or social nature, or a combination of all. Importantly, costs and benefits will not be equally shared among stakeholders and over time, posing added ethical dilemmas (Anomaly, 2017; Dar et al., 2016; Degeling et al., 2018; Rogers Van Katwyk et al., 2016; Singer et al., 2016; Wilton et al., 2002). From a cost-benefit perspective, it is not clear whether measures primarily protecting the environment from exposure to selective agents, resistant bacteria and genes, or measures that protect humans from resistant bacteria and resistance determinants of environmental origin would be most efficient. It is furthermore not known if it is most beneficial to focus on one's own country or region, or certain regions of the world, even if distant (Graham et al., 2014). It could also be more effective to prioritize investments in waste management in certain sectors, such as clinical or pharmaceutical facilities (Andremont and Walsh, 2015). If so, how would benefits be distributed globally and over time, and how could costs be shared? Another challenge is how we should move forward with policy in the face of uncertainty, both with regards to the basic science, and choice of investments in interventions that are likely to be effective (Munthe et al., 2018).

4. Conclusions

There are several broad knowledge gaps that need to be filled in order to more efficiently manage the emergence and spread of antibiotic resistance in the environment. Particularly, we have identified four broad key areas where more research is urgently needed: 1) the relative contributions of different sources of antibiotics and antibiotic resistant bacteria into the environment; 2) the role of the environment, and particularly anthropogenic inputs, on the evolution of resistance; 3) the overall human and animal health impacts caused by exposure to resistant bacteria from the environment; and 4) the efficacy of technological, social, economic and behavioral interventions to mitigate environmental antibiotic resistance. Addressing all four pillars are necessary to understand the growing challenges associated with antibiotic resistance and implement effective strategies for slowing its development. We therefore encourage researchers, funding organizations, policy makers and other relevant stakeholders to take the steps needed to fill these knowledge gaps.

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Disclaimer

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