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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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Risk assessment  
Risk management  
Environmental pollution

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.<sup>1</sup>

## 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<sup>2</sup> (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.jpiaamr.eu](http://www.jpiaamr.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.

<sup>1</sup> The recommendations from the workshop have also been communicated in a separate report published on the website of the JPIAMR ([www.jpiaamr.org](http://www.jpiaamr.org)).

<sup>2</sup> 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](http://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 (Aubertreau 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

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