Policy briefing

Centre for Ecology & Hydrology
NATURAL ENVIRONMENT RESEARCH COUNCIL

ANTIMICROBIAL RESISTANCE (AMR) IN THE ENVIRONMENT

Its relevance to environmental regulators and policymakers

Introduction

This policy briefing is an introduction to the "Review of Antimicrobial Resistance in the Environment and its Relevance to Environmental Regulators" (Singer *et al.*)

The increased incidence of multidrug-resistant infections in humans and animals has only recently fully engaged the global public health community. International and national antimicrobial resistance action plans [1–3] uniformly address five strategic objectives:

1. Improve awareness and understanding of AMR;
2. Improve knowledge through surveillance and research;
3. Reduce incidence of infection;
4. Optimise use of antimicrobials, and
5. Support sustainable investment in countering antimicrobial resistance.

Action plans to tackle AMR in the environment

In the **"Review of Antimicrobial Resistance in the Environment and its Relevance to Environmental Regulators"**, Singer *et al.* discuss some deficiencies of the international and national action plans. The most important of these is that they do not acknowledge the role of heavy metals and biocides in selecting and maintaining antimicrobial resistance in the environment, a phenomenon that is achieved through co-selection (see box).

Chronic use of biocides (e.g. disinfectants, antiseptics, preservatives) and heavy metals (e.g. silver, copper, zinc) across all of society (industry, hospitals, households, human and animal food, clothing, farming, transportation, recreation, furniture) has the potential to increase antimicrobial resistance in the environment [4] and in human and veterinary pathogens [5-7]. The exposure of microorganisms to chronically-low levels of antibiotics, biocides and metals in the soil, sediment, river and coastal waters, biofilms and the microbiomes of plants and animals has, arguably, led to an increased prevalence of resistance genes in the environment as well as an elevated risk of the resistance gene's transfer into human and livestock pathogens [6-8].

AMR action plans currently acknowledge four pathways for the release of antimicrobials into the environment: 1) municipal wastewater; 2) land spreading of manure and sludge; 3) pharmaceutical manufacturing and 4) hospitals.

The action plans do not offer insight into the relative contribution of each of these pathways to the overall selection, maintenance and dissemination of resistance in the environment. The Review argues that the prioritisation of different pathways for mitigating the release of resistance-driving chemicals into the environment should be based on sound evidence. For example, there is no evidence that in high income countries the antibiotic load in hospital wastewater is more important than the load of antimicrobials routinely found in a large municipal sewage plants for dissemination of antibiotics or toxicity [9]. The environmental relevance of resistance genes in hospital and municipal wastewater, however, remains an open question highlighted in the knowledge gaps.

Mechanisms of co-selection

Co-selection: an ecologically and clinically-important phenomenon for elevating resistance gene prevalence, achieved by co-resistance and cross-resistance.

Co-resistance: selection for one resistance gene allows for the retention of another resistance gene through linkages in the genomic architecture (e.g., plasmids, transposons, integrons). Co-resistance is analogous to a toolbox, whereby many tools are 'fortuitously' present even if only one tool is needed.

Cross-resistance: one resistance gene can offer protection from multiple toxic chemicals. Cross-resistance is akin to a tool that offers multiple functions. Efflux pumps, for example, provide protection from multiple chemicals by pushing the hazardous chemical out of the cell — a mechanism applicable to many hazardous chemicals.

A holistic mitigation strategy will need to start with all stakeholders critically evaluating the role they play in contributing to the composition and dissemination of resistance-driving chemicals and resistance genes.

The urgency of the AMR challenge is apparent, with increasing prevalence of drug-resistant infections worldwide. The implications of this have recently been summarised in the O'Neill AMR Reviews [5]. In the light of this increased urgency, the scientific community is faced with the challenge of prioritising and then filling the most important of the knowledge gaps.

Knowledge gaps

The urgency of the AMR challenge has recently been made apparent in a series of Reviews funded by the UK government [8], and the convening of only the fourth United Nations General Assembly dedicated towards a health topic [10]. The deficiencies in AMR action plans is arguably the result of an insufficiently robust knowledge base for informing policy. It is imperative that the research community prioritises those knowledge gaps that are best able to inform policy, now. To this end, the Review provides an initial effort to summarise these high-priority, policy relevant knowledge gaps:

1. Identify the concentration of chemicals in isolation and in mixtures that are needed to select for resistance in different environments.
2. Determine the role of co-selection in the environment and the relative role of different pathways and chemicals contributing to resistance co-selection.
3. Identify the consequences to wildlife or ecosystems from chronic exposure to resistance-driving chemicals and resistance genes.
4. Determine the risk of trophic transfer and dissemination of resistance-driving chemicals and resistance genes between animals and plants.
5. Quantify the relative importance of resistance genes, e.g. in sewage effluent, sludge and manure, on the establishment, maintenance and dissemination of resistance in the environment.

Prioritisation of knowledge gaps must be concurrent with proportional funding from national and international sources to ensure an appropriate evidence base is available to national policymakers and regulators.

Mitigation

It is argued that, at present, the evidence base for recommending *cost effective* mitigation measures does not yet exist. Implementation of the Precautionary Principle for reducing the environmental release of antibiotics, metals and biocides could potentially be achieved through extensive upgrading of all sewage works, but this would come at a high capital cost.

An interim solution could be a cross-society reduction in the use and release of antibiotics, biocides and metals, particularly when there is a risk of their release into the environment. Efforts to reduce use and emissions of resistance-driving chemicals throughout society would be implemented along-side research aimed at providing evidence for key policy-relevant knowledge gaps.

The Review concludes that:

- AMR action plans do not tackle all the potentially relevant pathways and drivers of AMR in the environment, and
- AMR action plans are deficient, in part, because the science to inform policy is lacking and this needs to be addressed.

References

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[1] NERC Centre for Ecology & Hydrology; [2] Defra, [3] Environment Agency

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