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Perspective

PERSPECTIVE

Antimicrobial resistance and the environment: assessment of advances, gaps and recommendations for agriculture, aquaculture and pharmaceutical manufacturing

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One sentence summary: Key issues are reviewed concerning the impact on the environment of antibiotic use in agriculture and aquaculture, and emissions from antibiotic manufacturing.
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ABSTRACT

A roundtable discussion held at the fourth International Symposium on the Environmental Dimension of Antibiotic Resistance (EDAR4) considered key issues concerning the impact on the environment of antibiotic use in agriculture and aquaculture, and emissions from antibiotic manufacturing. The critical control points for reducing emissions of antibiotics from agriculture are antibiotic stewardship and the pre-treatment of manure and sludge to abate antibiotic-resistant bacteria. Antibiotics are sometimes added to fish and shellfish production sites via the feed, representing a direct route of contamination of the aquatic environment. Vaccination reduces the need for antibiotic use in high value (e.g. salmon) production systems. Consumer and regulatory pressure will over time contribute to reducing the emission of very high concentrations of antibiotics from manufacturing. Research priorities include the development of technologies, practices and incentives that will allow effective reduction in antibiotic use, together with evidence-based standards for antibiotic residues in effluents. All relevant stakeholders need to be aware of the threat of antimicrobial resistance and apply best practice in agriculture, aquaculture and pharmaceutical manufacturing in order to mitigate antibiotic resistance development. Research and policy development on antimicrobial resistance mitigation must be cognizant of the varied challenges facing high and low income countries.

Keywords: antibiotic resistance; environmental dimension of antibiotic resistance; agriculture; aquaculture; antibiotic manufacturing

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The fourth International Symposium on the Environmental Dimension of Antibiotic Resistance (EDAR4) held at Michigan State University in August 2017 followed the EDAR3 symposium held in Germany in 2015 (Smalla *et al.* 2016). Key issues concerning agriculture, aquaculture and antibiotic manufacturing were deliberated in a roundtable discussion. The authors of this paper were the roundtable participants, but the approximately 100 individuals in attendance also contributed greatly to the deliberations. Informed by this discussion, this paper is intended to provide a perspective on where we have been, and where we need to go on these matters. These discussions were timely in light of the recent (December 2017) draft resolution by the United Nations Environment Assembly on Environment and Health that clearly articulates the concern for the environmental dimension of antimicrobial resistance (resolution UNEP/EA.3/L.8/REV.1; https://papersmart.unon.org/resolution/index).

AGRICULTURE

The use of antibiotics in food-animal production selects for and enriches antibiotic resistance (Hoelzer *et al.* 2017). In the past several years we have obtained a clearer understanding of the microbial composition of animal waste using molecular tools. But, in general, we do not have a clear understanding of the relationship between antibiotic use and the burden of enteric antimicrobial resistance in manures. This is further complicated by co-selection in which the development of resistance to in-feed metals (Zn, Cu) may be accompanied by the development of resistance to antibiotics. Inventories of antibiotic-resistance genes from shotgun metagenomics do not provide a genetic context, and therefore the potential for horizontal gene transfer, and do not provide insights into functional expression. Two further contextual challenges involve i) coming to terms with the abundance and diversity of 'natural' resistance in soil communities, and ii) the development of realistic target ranges for reducing resistance in agricultural environments impacted by antibiotic residues of crop and animal origin.

Recent insights into particular agroecological niches are enabling scientists to better understand environmental factors affecting horizontal gene transfer in agroecosystems. Of particular interest is the plant rhizosphere where nutrient resources and active microbial groups are in close proximity to crops used for livestock or human consumption (Kopmann *et al.* 2013). Targeting management efforts to the particular niches where horizontal gene transfer is most promiscuous and where there is the potential for microbes to easily leap into the animal or human microbiome makes good sense compared with large-scale potentially expensive whole-farm soil and manure treatment. Numerous investigations (Jia *et al.* 2017; Tien *et al.* 2017; Yoon *et al.* 2017) concerning the impact of manure treatment options typically used on commercial farms indicate that these do not always effectively reduce, and in some instances (e.g. anaerobic digestion) may increase, the abundance of some antibiotic-resistance genes. Further research into effective and economically viable treatment of agricultural waste streams is required.

Over the past decades, initiatives to streamline antibiotic use in animals have evolved in higher income countries. Sweden banned the use of antibiotic growth promoters as early as 1986, a move that was followed gradually by the whole EU implementing a total ban on antibiotic growth promoter use by 2006. In North America the use of antibiotics for growth promotion is being constrained. In some sectors (e.g. poultry) producers are reducing antimicrobial use due to consumer demand for antibiotic-free products. For more than 10 years now, stakeholder platforms such as RUMA (UK) and EPRUMA (EU) have been promoting responsible use of medicines, including antibiotics in animals. These platforms have a broad membership of farmers, veterinarians, pharmaceutical companies and feed producer associations and also include regulators such as the European Commission. Starting in 2007, the EU has built antibiotic use surveillance capacity with its ESVAC programme (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp) while some of its member states have had use monitoring in place since the 1990s. Since 2009, there has been a clear decrease in antibiotic use in animals in the EU, which is predicted to steadily continue in the years ahead. In the USA, annual sales of antibiotics are monitored and published by the Food and Drug Administration, but a decrease in use has not been observed thus far. Surveillance of antimicrobial use in animals, where available, generally follows official antibiotic sales, not actual use. It is therefore often not possible to know the antibiotic consumption by individual commodity groups. Most countries do not implement surveillance for antimicrobial resistance in animal pathogens; where resistance surveillance is in place, this mostly concerns commensal and zoonotic bacteria. However, diagnostic laboratories in, for example, Sweden, Germany and France are required to publish information on antibiotic resistance in animal pathogens, and it would greatly help global data coordination if this practice were to be adopted by other countries using a harmonised approach (Schrijver *et al.* 2018). While there clearly is a serious situation with antimicrobial resistance in human medicine, multidrug resistance in animal pathogens is far less well documented.

In lower income countries, challenges are often greater. Antibiotic use in low income settings is very poorly regulated, and there are few or no surveillance data. Consumer demand in China and India for meat protein and the adoption of commercial production practices in which antibiotics are widely employed have the potential to massively increase the global use of antibiotics in agriculture (Van Boeckel *et al.* 2015).

For antibiotic use in animals to decline, innovations are needed in technology and practice that keep farmers profitable while maintaining animal welfare and ensuring food safety (Van Boeckel *et al.* 2017). Vaccines, feed additives, improved biosecurity and barn design appropriate for each commodity may each have a role. Recent research in antimicrobial alternatives continues, but it must be paired with a thorough analysis of their effects on antimicrobial resistance. Including copper or zinc in livestock diets is often considered as an alternative to an antibiotic. Soils in Denmark showed greater concentrations of copper and zinc as antibiotic use was curtailed (Jensen, Larsen and Bak 2016), and both elements can enrich tetracycline resistance in soil (Song *et al.* 2017). As changes in food-animal production practices are implemented, potential changes in the broader agroecosystems need to be assessed. Unfortunately, to date no effective alternative to antibiotics for the treatment of diseased animals has been discovered. Since it is unlikely that any new antibiotics will be introduced for veterinary use in the future, it is essential for animal health and livestock production to maintain the efficacy of existing veterinary antibiotics through stewardship, and further research is needed into efficient and viable techniques to limit the potential spread of resistant bacteria and genes.

On the other hand, farmers and veterinarians in low income countries that face food insecurity often experience difficulties in accessing effective antibiotics to treat their livestock. The supply may not be assured and the quality of the drugs can be compromised by counterfeiting. The latter constitutes a high risk for selection and dissemination of resistant bacteria, while compromising the health of the animals, and hence increases food insecurity. Recycling wastewater for crop irrigation is commonly practiced in low income countries, and is becoming increasingly so in arid regions of middle and high income countries. The risks of soil, water and crop contamination, and how these vary with production practice, remain to be adequately characterised (Christou *et al.* 2017). Wastewater reuse and fertilization with sewage sludge have the potential to entrain antibiotic-resistant bacteria selected for in humans into agroecosystems (Lau *et al.* 2017), underscoring the complexity of the issue.

AQUACULTURE

The significance of aquaculture as a source of fish and shellfish has increased tremendously in the past 50 years (Watts *et al.* 2017). Approximately 90% of global aquaculture production is now undertaken in Norway, Chile, Egypt, and several Asian countries with China accounting for two-thirds of global production (FAO 2015; Liu *et al.* 2017). The steep increase in production has happened in the same period of time when antibiotic consumption has multiplied, but there is no clear relationship between those events. The term aquaculture refers to very different activities ranging from extensive aquaculture where the predators and competitive species are removed, to the most intensive aquaculture where all food needs are supplied. Moreover, the term covers everything from farming salmon offshore in cold Atlantic waters to tropical integrated aquaculture where livestock manure and excess animal feed are the nutrients for aquaculture ponds. Moreover, the economic conditions in the countries with substantial aquaculture vary from extremely wealthy to very poor. There is therefore tremendous diversity in antibiotic use in aquaculture with, for example, 13 different antibiotics authorised for use in aquaculture in China, compared with only five in the UK (Liu *et al.* 2017). Antibiotic residues can be detected in aquaculture products, and among these oxytetracycline and its epimers were the ones most commonly detected in a recent American study investigating aquaculture-derived products imported from a variety of countries (Done and Halden 2015). However, by analysing the data available from different aquaculture settings, some conclusions can be drawn regarding best aquaculture practice with respect to managing antibiotic resistance.

Antibiotic use in aquaculture in Europe, Northern America and Japan is strictly controlled and limited to therapeutic applications, with only a limited number of approved antibiotics. A prime example of the effect of rigorous control on antibiotic use is the Norwegian experience, where antibiotic use was reduced by 99% between 1987 and 2013, despite a more than 20-fold increase in production over this time (Norwegian Ministry of Health and Care Services 2015). The main factors behind that development were implementation of strict hygienic requirements and use of vaccines, which were at least partly the result of active scientific research in the field. Vaccination is an economically viable practice with high value species such as salmon, which, however, represent only a small fraction of global aquaculture production. In contrast, over 90% of the world aquaculture production is carried out in low- or middle-income countries where the regulation, practices and resources are much more limited (Watts *et al.* 2017). Even with the same fish species the use of antibiotics in aquaculture can vary enormously. For example, the production of 1 tonne of salmon in Norway requires 0.0008 kg of antibiotics whereas 1.4 kg of antibiotics are used per tonne of salmon produced in Chile (Cabello *et al.* 2013). The reasons behind this vast difference are not entirely clear but in the Chilean context include lack of vaccination, high animal density and sub-optimal farming practices. The latter include underdeveloped hygiene and use of feeds with unknown components that may contain unknown antibiotics at unknown dosage. Likewise, aquaculture systems that integrate the wastes from livestock production are efficient with respect to nutrient cycling, but have additional potential problems with antibiotic resistance (Cabello *et al.* 2016).

Aquaculture products are an important source of export income for many low- and middle-income countries. Products destined for export are strictly monitored for antibiotic residues, and concentrations within the product must fall below internationally accepted minimum residue limits. In contrast products containing an antibiotic above the minimum residue limit can be consumed domestically. The application of antibiotics to the aquatic environment may select for antibiotic-resistance genes not only in fish pathogens, but also in environmental bacteria (Muziasari *et al.* 2016). Some antibiotic-resistance genes conferring resistance to certain antibiotics such as quinolones, tetracyclines and β-lactams can be found in fish pathogens, human pathogens and aquatic bacteria, which are suspected of being the original hosts for these genes (Cabello *et al.* 2013). Rico *et al.* (2018) assessed the risks for development of resistance for 12 antibiotics in an intensive aquaculture production scenario using a probabilistic approach. Risks were high for all antibiotics in pond sediment and high for the majority of antibiotics in pond water. Risks were low in the effluent mixing area for most antibiotics, with the exception of rifampicin and levofloxacin. Fish farms using tetracyclines have been found to increase the diversity of tetracycline antibiotic-resistance genes in river water, while no significant differences in the abundance of antibiotic-resistant bacteria and antibiotic-resistance genes were seen between upstream, post-treatment or downstream water samples (Harnisz, Korzeniewska and Gołaś 2015). These studies suggest that the effective means of treating effluent from fish ponds is a matter for further research.

The practical reality is that fish or other aquaculture species in ponds or sea cages attract pathogens that require either prevention or treatment, and very few alternatives to antibiotics are currently available (Defoirdt, Sorgeloos and Bossier 2011). Because of the ever increasing importance of aquaculture for the global food supply, research into vaccines has stepped up in the past decades and this is encouraging. Fish DNA vaccines are very effective as demonstrated by the Norwegian experience. But they are difficult and expensive to deploy. Currently every fish must be injected so the skill level for management is very high. Further research into more practical means of vaccine administration is warranted to increase overall vaccine use in aquaculture as a valuable alternative to prevention of disease by antibiotics.

MANUFACTURING

The highest concentrations of antibiotics and the highest abundances of antibiotic-resistance genes detected in the environment are found in environments polluted by direct discharges from the manufacturing of antibiotics (Larsson 2014; Pal *et al.* 2016). Major discharges, in the mg/L range, clearly selective for resistance, have been documented from several countries and regions (Larsson 2014; Bielen *et al.* 2017). Accordingly, there is a growing consensus from major pharmaceutical companies, academia and other actors that managing and reducing such discharges is important and urgent. Compared with agricultural and human sources, industrial point sources for antibiotics and antibiotic-resistant bacteria are considerably fewer, making them a more graspable target, both economically and practically. Still, there are major knowledge gaps in how widespread inferior pollution control is, but perhaps most importantly, there are knowledge gaps with regards to how improvements are best incentivised and implemented.

Regulatory requirements for manufacturing sites and emission control worldwide vary from being non-existent to the application of high standards. Where they exist, environmental permits are provided and controlled by individual countries or states, again with vast differences in requirements and enforcement. The production and supply chain for antibiotics often involves several steps and actors in different parts of the world, providing challenges for the end producer, and to an even larger extent the consumer, to gain insight into and influence over the degree of environmental pollution control in the early, most critical steps of production of active ingredient and formulated product. Antibiotic discharges are rarely regulated directly, although discharge limits have recently been proposed (Bengtsson-Palme and Larsson 2016). India is the first country to explicitly have declared an intent to regulate antibiotic emissions nationally (Government of India 2017). Increased transparency has been stressed as a critical measure (Larsson and Fick 2009) to create pressure on manufacturers, a measure that, at least for the EU market, would be helped by making parts of the existing registration dossiers public. The strong price pressure on the generics market, together with substitution systems for generic exchange in human medicine, has not favoured investments in pollution control and has played a role in the relocation of production facilities to countries with lower production costs and also less strict environmental regulation. One possible way to incentivise 'green' investments would be to value documented pollution control, in addition to low price, when exchangeable products eligible for tax subsidy are identified (Bengtsson-Palme, Gunnarsson and Larsson 2018). Other means involve the inclusion of pollution control in procurement processes, and in public ranking/benchmarking schemes for drug companies (Access to Medicines Foundation 2017; Bengtsson-Palme, Gunnarsson and Larsson 2018).

Initiatives from industry are also critical. In 2006, the Pharmaceutical Supply Chain Initiative (PSCI; https://pscinitiative.org/home) was formed, with the broader aim of establishing and promoting responsible practices to continuously improve social, health, safety and environmentally sustainable outcomes for pharmaceutical and healthcare supply chains. Currently, 26 companies have joined the PSCI; the membership shares knowledge and expertise and this includes supplier and auditor conferences and training. Such alliances of companies are much more successful in driving change compared with individual companies alone. This initiative is fully operational and has a growing membership.

Thirteen leading pharmaceutical companies have recently signed up to the Industry Roadmap for Progress on Combating Antimicrobial Resistance (IFPMA, 2016). The roadmap includes key measures on reviewing manufacturing and supply chains, a common framework for managing antibiotic discharge, increased transparency, and the establishment of appropriate targets for discharge concentrations and methods to achieve these. An apparent challenge is how to reach companies that are not involved in these initiatives. Industries producing mainly for national markets, particularly in low and middle income countries, may be considerably more difficult to incentivise from abroad, and would be more dependent on national regulations and enforcement.

GENERAL CONCLUSIONS

Education on best practices of all parties involved in the distribution and use of antibiotics in terrestrial or aquatic food production systems is key to implementing antibiotic stewardship. Digital communication tools (e.g. mobile phones) could have an important role in providing stakeholders (e.g. veterinarians, farmers) with useful information and guidance and this needs to be developed. Consumer demand is having variable impact on the global demand for antibiotics. On the one hand the demand for antibiotic-free meats is increasing in high income countries. In some instances (e.g. Sweden) hospital organizations are increasingly including environmental contamination control during manufacturing in their procurement of antibiotics. On the other hand, rising income in lower income countries is increasing the market for animal proteins, driving the increasing implementation of production practices that rely heavily on antibiotic use. It is very important to note that good animal production practice varies tremendously across different commodities, different levels of economic development and different climates. No one set of policies or practices or any one technology will have a substantial impact on reducing antimicrobial use in every region or on every farm or aquaculture facility. Thus it is important to engage policy-makers, researchers and food-animal producers in every region to grapple with this global problem. China unveiled an antimicrobial resistance action plan in 2016, and India intends to drastically curtail antibiotic emissions from the manufacturing sector by 2020. These are very positive developments. Finally, science-based standards for acceptable antibiotic concentrations (and antibiotic-resistance genes) in terrestrial and aquatic food-animal production environments and manufacturing effluents are required to inform policy and standards. This is clearly an important research priority.

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