



Forum

Critical Importance of a One Health Approach to Antimicrobial Resistance

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Antimicrobial resistance (AMR) is a complex, multifaceted problem that threatens human and animal health, the global economy, and national and global security. In the USA, an estimated 2 million drug-resistant infections occur annually, accounting for 8 million extra hospital days, 23,000 deaths, and \$20 billion in direct healthcare costs (Hughes 2011; Centers for Disease Control and Prevention 2013). Worldwide, AMR is increasing (Klein et al. 2018); if current trends continue unabated, there could be as many as 10 million annual AMR-associated deaths from a wide array of infections¹ by 2050 (Review on Antimicrobial Resistance 2016). The World Health Organization (WHO) has included AMR as one of the top ten threats to global health in 2019 (World Health Organization 2019).

Two recent examples highlight the threat of emergence and rapid geographic dissemination of antibiotic resistance genes. An enzyme that confers resistance to a wide range of antibiotics, New Delhi metallo-beta-lactamase 1 (NDM-1), has emerged in the Indian subcontinent and spread to the UK as a result of medical tourism after first being detected in 2008 (Yong et al. 2009). The NDM-1 gene was subsequently detected in surface and tap water samples in India in 2010 and in the environment in Bangladesh, indicating

the potential for environmental origin and worldwide spread of this gene and its variants (Walsh et al. 2011; Islam et al. 2017; Khan et al. 2017). The NDM-1 gene has recently been identified in nutrient-rich Arctic soil of a remote Norwegian archipelago, raising the possibility of spread by feces from migratory birds (McCann et al. 2019). The MCR-1 (mobilized colistin resistance-1) gene, a plasmid-borne gene conferring colistin resistance, was identified in pigs in China in 2014 (Liu et al. 2016) and has subsequently spread to dozens of other countries (Marston et al. 2016; Wang et al. 2018).

The purpose of this commentary is to highlight the importance of an integrated and holistic multisectoral One Health approach in combating AMR (Fig. 1) and in particular, the need for better integration of environmental, aquatic, and wildlife issues into current approaches (Andersson and Hughes 2014; Lammie and Hughes 2016; Robinson et al. 2016). Recent national and multinational strategies to address the urgency of AMR include the United States National Action Plan for combating antibiotic-resistant bacteria (White House 2015), World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance (World Health Organization 2015), Declaration from the 2016 high-level meeting on antimicrobial resistance at the United Nations General Assembly (OPGA/WHO/FAO/OIE 2016), and the FAO/OIE/WHO Tripartite Collaboration (FAO/OIE/WHO 2017)—all of which stress the importance of a multisectoral One Health response. WHO's Global Antimicrobial Resistance Surveillance

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¹Estimate based on work of two modeling groups focused on infections caused by a subset of drug-resistant bacteria including *M. tuberculosis*, drug-resistant HIV infection, and drug-resistant malaria infections.

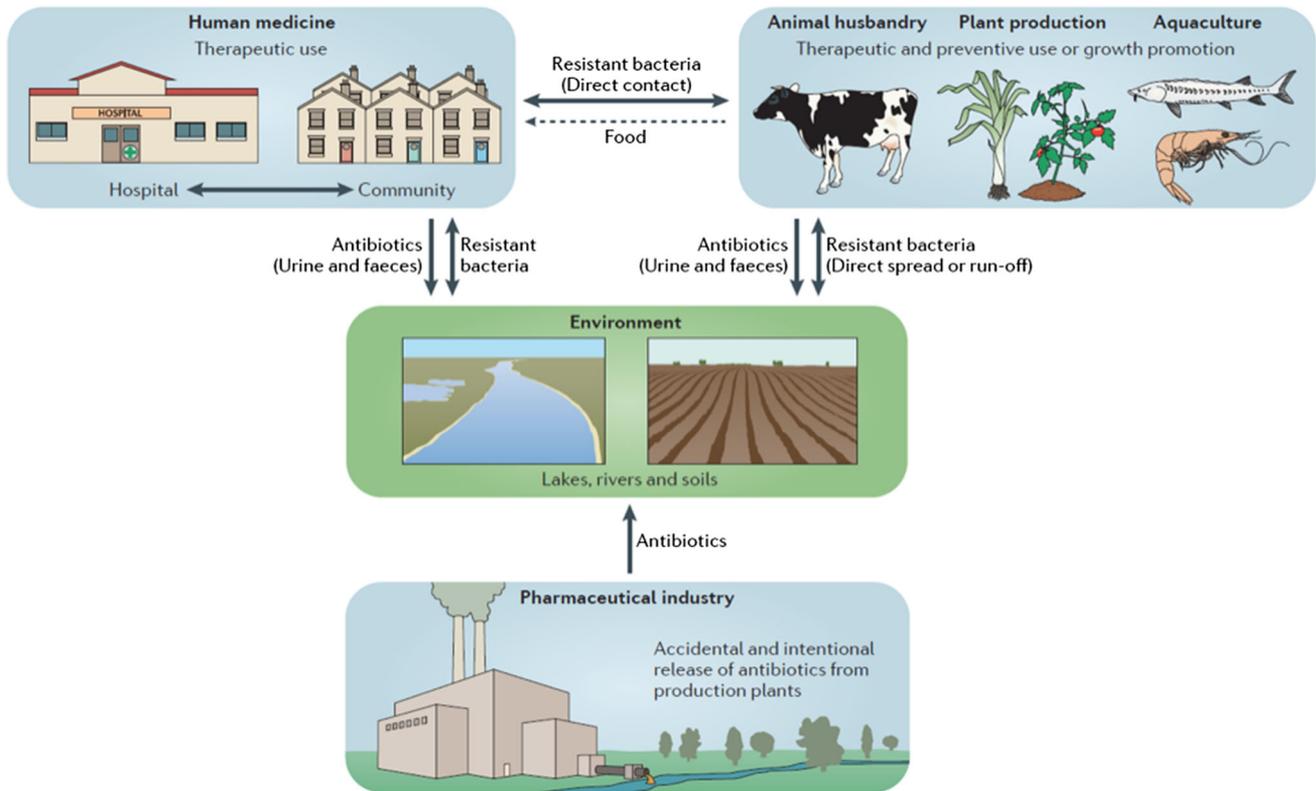


Fig. 1. Integrated ecosystem of the transfer and spread of antimicrobial resistance illustrates the critical importance of a One Health approach to the problem (Andersson and Hughes 2014)

System (GLASS), established in 2015, is helping countries strengthen national surveillance systems and provides more comprehensive standardized AMR surveillance data (Tornimbene et al. 2018). AMR is included as a priority in the World Bank’s recent One Health operational framework (World Bank Group 2018). Recently, AMR has been the focus of several multisectoral meetings and conferences, including an AMR workshop at the recent Prince Mahidol Annual Conference in Bangkok, Thailand, a Forum on Microbial Threats of the U.S. National Academies of Sciences, Engineering and Medicine workshop (2017, 2018d), Ogawa et al. 2018), and the International One Health Congress in Saskatoon, Canada in 2018 (2018a).

Current One Health approaches to AMR focus primarily on reduction in antibiotic use in food animals. Recent systematic reviews and meta-analyses found associations between reduction in antibiotic use in food animals and a decrease in AMR in animals and limited evidence of some reduction in humans, recognizing that the complexity of the system prevents demonstration of a clear causal pathway and highlighting research gaps

(Hoelzer et al. 2017; Tang et al. 2017; Scott et al. 2018). This complexity was highlighted in the 2014 Report to the President on Combating Antibiotic Resistance (President’s Council of Advisors on Science and Technology 2014; World Health Organization 2017).

WHO recently published new guidelines to limit antibiotic use in healthy food animals (World Health Organization 2017). While guidelines on antibiotic use in humans and food animals are important components of a One Health approach to AMR, a more comprehensive approach, which addresses wildlife, aquaculture, and especially the environment, is needed (2018c; Thakur and Gray 2019). Wildlife ecosystems are a potentially important reservoir of resistant organisms (AROs) and resistance genes (ARGs); drug-resistant *E. coli* have been found in multiple wildlife species as have isolates with plasmid-mediated resistance, which could be a result of environmental spread of human and livestock antibiotics (Carroll et al. 2015; Furness et al. 2017; Dolejska and Papagiannitsis 2018; Weiss et al. 2018). Wildlife may also be impacted by increasing antibiotic resistance; one study found human

strains of drug-resistant *Staphylococcus aureus* in chimpanzees in sanctuaries, indicating that antimicrobial use and resistance in humans may impact nonhuman primates (Schaumburg et al. 2012). Wildlife populations have the potential to serve as sentinels for resistance resulting from environmental contamination, human use, and livestock use. Engaging wildlife and conservation colleagues in development and implementation of AMR surveillance and prevention strategies should be a priority.

While limited data on the public health impact of antibiotic use in aquaculture exist, it has been suggested that administration of antibiotics in aquatic systems can promote the development of resistance (Cabello et al. 2016). Studies have found ARGs in aquatic systems and evidence of horizontal gene transfer from aquatic bacteria to human pathogens (Jiang et al. 2012; Tomova et al. 2015). Such use involves potentially large amounts of antibiotics that are widely dispersed in the aquatic environment providing containment challenges (Heuer et al. 2009).

Finally, this approach must address the roles that environmental contamination with AROs, ARGs, and antibiotic residues plays in AMR. Environmental contamination related to antibiotic administration in both humans and in food production (livestock, aquaculture, and cropland) through runoff has been identified in several studies (Kumar et al. 2005; Boxall 2012) and, as mentioned, has the potential to impact wildlife and other populations. However, a recent review of One Health networks concluded that environmental health expertise was underrepresented (Essack 2018; Khan et al. 2018), and there has been a recent call for inclusion of environmental issues in national action plans for AMR (Iossa and White 2018). Environmental pollution from antibiotic production facilities has been linked to contamination of the surrounding environment (Fick et al. 2009; Khan et al. 2013; Larsson 2014). A 2017 UN report highlighted AMR as an “emerging issue of environmental concern,” focusing on the potential risk of contamination from agriculture (including aquaculture), improper disposal of antibiotics for human use, challenges in removing antibiotics by traditional water treatment measures, and pollution from pharmaceutical production (UNEP 2017). A 2015 review on AMR recommended environmental waste management as a key measure in combating resistance (Review on Antimicrobial Resistance 2015). A recent white paper from the Wellcome Trust focuses on the issue of AMR in the environment with action items including manufacturing waste, crop production, as well as use in humans and animals, highlighting the

importance of the environment and the One Health nature of this challenge (2018c). Comprehensive AMR research, surveillance, and control efforts must incorporate an environmental assessment and monitoring component.

Given this complexity and the multiple routes of exposure, it is difficult to determine the relative contribution of different sectors to AMR in humans. The 2014 Report to the President’s Council of Advisors on Science and Technology on combating antibiotic resistance concluded that while it appears clear that both human and animal use contribute to AMR, it is challenging to quantify the relative importance of each system to resistance development (President’s Council of Advisors on Science and Technology 2014). This conclusion reinforces the importance of examining AMR through a One Health lens—as an issue impacting humans, livestock, wildlife, and the environment. While additional research on the mechanisms and pathways of AMR is urgently needed, enough is known now to focus research and control efforts on developing and evaluating methods to combat resistance as well as on the development of new drugs, alternative therapeutic approaches, treatments, vaccines, and rapid diagnostic tests.

There is a need for a comprehensive One Health research agenda to address AMR that incorporates human, animal, environmental, ecosystem, and wildlife perspectives and identifies key priorities for this research. Communication, collaboration, and public engagement are necessary for engaging partners and developing strategies to prevent the emergence and spread of resistance, recognizing the gaps that have existed and working to fill them. Strategies should be developed by representatives from these fields working together to ensure an integrative approach, leveraging the resources of current systems and networks and engaging persons with expertise from the environmental and wildlife sectors which have often been overlooked. A global AMR governance structure to guide these efforts has recently been proposed (Padiyara et al. 2018; Rochford et al. 2018).

We encourage EcoHealth readers to actively approach any AMR issue through a One Health lens and engage scientists, policy makers, industry leaders, and other professionals in AMR forums, meetings, or research groups, ensuring that environment and wildlife sectors are included in development and implementation of country AMR national action plans. USAID’s IDEEAL and DEAL projects in Southeast Asia utilize this approach on the issue of land use change and health, incorporating human health and eco-

nomics into development analyses and including public and private stakeholders—expanding the scope and highlighting additional perspectives in land use planning and management (Zambrana-Torellio et al. 2015, 2018b). We encourage research groups and funders to require plans for One Health integration of AMR and include representatives of all of these sectors in monitoring and evaluation efforts.

This One Health research agenda should acknowledge that multiple sectors play a role in the development and spread of AMR and focus efforts on actionable, impact driven research. We urge countries and networks at the forefront of AMR efforts to engage these additional stakeholders in developing such an agenda, recognizing that an effective strategy will have far-reaching benefits in minimizing the impact of this urgent problem on human and animal health, the environment, the global economy, and national and global security.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST Dr. Hughes is a former president of the Infectious Diseases Society of America and currently serves on the Board of Directors of the EcoHealth Alliance and of the One Health Commission.

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