THE UNIQUE CONTRIBUTION OF ONE HEALTH TO COMBATING ANTIBIOTIC RESISTANCE

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One Health is the concept that the optimum health for people, animals and the environment can best be ensured through the ongoing cooperative efforts of scientists and practitioners in a variety of disciplines. Many organizations have committed to the idea that One Health can be an effective approach to addressing complex public health problems, especially antimicrobial resistance. By bringing together experts in many different fields, One Health encourages innovative problem-solving and provides opportunities to enhance the tools and processes on which public health depends for designing, implementing and evaluating disease prevention and control programmes. One Health surveillance – drawing data from multiple sources and monitoring systems, integrating that data and analyzing and interpreting it in a framework that crosses the domains of human and animal health and environmental science – serves as an example of both the potential benefits as well as the notable challenges in creating and maintaining effective One Health collaborations.

One Health is increasingly recognized as a critical framework for addressing a range of health problems, particularly antimicrobial resistance (AMR); indeed, AMR has been described as the "quintessential" One Health issue *(1)*. One Health has several related definitions, but consistently embodies the concept that optimal health for people, animals and the environment can only be obtained through close collaboration and cooperation among scientists and practitioners in many diverse disciplines *(2, 3)*. Understanding and applying a One Health approach to combating bacterial AMR is particularly important in that it offers a unique perspective to the design, implementation and evaluation of public health programmes and policies. Because One Health brings together expertise across a broad range of fields including, but not limited to, human health, animal health, and environmental science, it can also be useful in addressing rapidly evolving threats such as bacteria possessing the mcr-1 gene, the emergence of which has been ascribed to animal reservoirs in China *(4)*. This gene encodes for bacterial resistance to colistin – a drug of "last resort" for treating Gram-negative infections. The high level of concern for this evolving threat of mcr-1 mediated resistance recapitulates the alarm evoked by the emergence and transmission of bacteria producing *Klebsiella pneumoniae carbapenemase* and of highly-resistant bacteria containing the New Delhi metallo-β-lactamase (NDM-1) gene, both of which spread globally through travel and transmission within healthcare settings *(5, 6)*.

One Health is extremely broad in its scope, encompassing many zoonotic diseases and environmental health problems. Because the risks associated with the AMR crisis are so profound, many of the most prominent supporters of a One Health approach have increasingly focused on applications and approaches to addressing bacterial resistance. Global bodies such as the World Health Organization (WHO), the World Organisation for Animal Health (OIE), the United Nations Food and Agriculture Organization, along with governments, non-governmental organizations and public-private partnerships, such as the One Health Initiative, the One Health Commission and the One Health Platform, among others, have added recommendations, reports, activities, meetings and educational resources targeting AMR *(3, 7-9)*.

However, organizations and individual leaders seeking to implement and operationalize One Health to impact specific health problems such as AMR have encountered numerous challenges and obstacles. Bureaucratic divisions, publication silos, and the varied jargon and cultures of different academic and scientific disciplines all pose barriers to creating and maintaining effective One Health collaborations *(10-12)*. Human medical practitioners have generally shown less enthusiasm for One Health activities than have their veterinary colleagues *(2)*. While many US Federal departments and agencies have One Health offices and activities *(13)*, the absence of structured coordination for these activities prompted the introduction of legislation in the US Congress to create a national One Health Programme to link these efforts and promote cross-specialty public health programmes, research and training *(14)*.

These difficulties and the resulting delays in fully establishing One Health as a foundational structure in public health practice, and in implementing targeted activities in a One Health framework, pose the risk of missing opportunities to achieve both short-term and long-term successes in addressing the AMR problem. Proposals for institutionalizing One Health collaboration more centrally in public health initiatives are well-described *(15)*. The value and the challenges of putting these ideas into practice can be seen in the example of creating an integrated One Health approach to the collection, analysis, interpretation and dissemination of the data necessary for development, implementation and evaluation of AMR prevention programmes.

The One Health approach to AMR surveillance and monitoring

The Action Plans from the WHO *(7)* and the governments of the United States *(16)* and the European Union *(17)* acknowledge the importance of a One Health framework for addressing the problem of AMR and the need for public health surveillance that encompasses the human, animal and environmental domains. The European Union plan specifically calls for a "holistic approach" including "medicine, veterinary medicine, animal husbandry, agriculture, environment and trade", and states that AMR "cannot be successfully tackled through isolated, sectoral efforts." The WHO plan recommends that all member states form and participate in "multisectoral (one-health) coalitions" at the local, national, regional and global levels. Similarly, the United States National Action Plan has five goals, all of which contain objectives that span the One Health domains and one of which specifies the need to "Strengthen National One-Health Surveillance Efforts to Combat Resistance".

These recommendations principally build on and expand existing surveillance programmes. Some of these activities, as noted in the various action plans, are predicated on a One Health approach. Notable successes include, in the European Union, the collaboration of the European Food Safety Agency, the European Medicines Agency and the European Centre for Disease Control as detailed in the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report *(18)* and, in the United States, the National Antibiotic Resistance Monitoring System (NARMS) run collaboratively by the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC) and the United States Department of Agriculture (USDA) *(19)*. The NARMS system has continually improved the level of integration of its three components (human infection, retail meat, and slaughter animals/food processing plants). Other Federal programmes, such as the National Animal Health Monitoring System, National Animal Health Laboratory Network, and the Veterinary Laboratory Investigation and Response Network, offer additional valuable data which could enhance our understanding of bacterial resistance across the food supply chain *(16)*. Continuing to add laboratory capacity to increase genomic testing is a key element in programmes to enhance AMR surveillance in both the European Union and the United States. The WHO notes the value of genetic testing but as a later advancement in its proposed Global Antimicrobial Resistance Surveillance System *(20)*.

These systems with a One Health orientation were designed for and are very effective in monitoring bacterial resistance among enteric foodborne pathogens, such as *Salmonella* and *Campylobacter* in humans, and among veterinary pathogens threatening farm animals. Continued monitoring of these threats is critical for ensuring the safety of the food supply and of identifying changes in resistance patterns for these enteric microorganisms. However, the risk of a post-antibiotic world is most immediately associated with resistance in healthcare-associated pathogens and community pathogens attacking compromised hosts, as ranked in both the United States and WHO lists of priority bacterial-resistant threats *(21, 22)*. The systems described above were never intended to track resistance and identify linkages between the human, animal and environmental domains for these non-foodborne pathogens.

The recent rapid growth of knowledge about the microbiomes of humans and animals, and the rapid expansion of studies of the bacterial genome and of plasmid-mediated resistance demonstrate that the gut microbiome in all species is an extraordinary reservoir of resistance *(23, 24)*. The exchange of resistance genes can occur among bacteria in the dense populations in the gut microbiome, between pathogenic and commensal bacteria, and may include transfer among bacterial species, some of which are newly identified and may be non-culturable.

AMR prevention activities will be highly dependent on the ability to obtain and analyze public health surveillance data from ongoing monitoring of human, animal and environmental sources and from research studies, and the ability to link bacterial strains using whole genome sequencing and metagenomic analysis as well as correlations with epidemiologic information. For example, studies of extraintestinal pathogenic *E. coli* have found similarities between human-derived strains and isolates from raw retail chicken, suggesting a possible route of transmission from the farm to the human gut microbiome *(25)*. The mcr-1 gene has been isolated from several different bacterial species and from a wide range of human, animal and environmental sources, presenting a complex picture of transmission involving human travel and contact with animals and animal products *(4)*. The NDM-1 gene has been isolated from numerous species of Enterobacteriaceae, including *Salmonella*, as well as from *Pseudomonas aeruginosa* and *Vibrio cholera* and has been found in environmental samples from several countries *(6)*.

Efforts to date to produce integrated One Health monitoring data on AMR, drawing on distinct data sources, have shown both the potential benefits of these types of analyses as well as the scientific and logistical obstacles to full realization of those benefits. Both the JIACRA report and the NARMS report provide information on commensal or "indicator" *E. coli* from retail meat and/or animal sources. The JIACRA report analysis correlates antibiotic consumption in food-producing animals and the incidence of antibiotic resistance in *Salmonella* and *Campylobacter* as well as for indicator *E. coli* from human bloodstream infections *(18)*. The JIACRA data on resistance is based on determination of minimum inhibitory concentrations from traditional antimicrobial susceptibility testing but does not include the results of genomic studies on those isolates. The JIACRA report also contains a careful discussion of the logistical and analytic difficulties in relating and linking resistance across the One Health domains using disparate data sources. The NARMS report gives results for testing of genetic markers of resistance (e.g., genes encoding for the CTX-M family of enzymes) in selected isolates from retail meat samples but does not include comparable data from human-derived isolates *(19)*.

Comprehensive One Health surveillance of bacterial AMR will also need to include sources not currently part of routine data collection. The role of companion animals in the ecology of bacterial resistance and as a potential reservoir for human infection has been underappreciated and understudied. Genomic analysis has demonstrated sharing of resistant pathogens in households between humans and their pets. Dogs have been found to be carriers of hospital strains of vancomycin-resistant enterococci *(26)* and strains of *E. coli* targeting the urinary tract of both humans and canines *(27)*. Further monitoring of resistance associated with aquaculture and environmental sources including sewage, wastewater runoff and drinking water is needed to complete the picture of environmental and food-associated risks to human health *(28)*.

No single surveillance system will be able to provide this scope or breadth of data; however, greater access to genomic testing and increasing the interoperability of data systems are steps in the right direction. For example, the NARMS system need not be reconfigured to collect and analyze data on genetic resistance determinants from non-foodborne human pathogens. Such data is already being collected widely by other United States government systems, such as the National Healthcare Safety Network *(16)*. The work of combining data from different systems is complex and logistically daunting, and depends on highly sophisticated advanced computational ability, but is necessary to allow for accurate and effective analysis and interpretation and for applying these analyses to programme and policy development.

One Health perspectives can refine the interpretation of data

The complexity of the science underlying the selection, transmission and persistence of bacterial AMR in humans, animals and the environment can lead to problems in assessing information sourced from these different domains. Experts in the various One Health fields are likely to offer varying perspectives on these data and may interpret them in different ways.

While it is often correctly stated that 70–80%, by weight, of all antibiotics sold in the United States are given to animals, primarily in animal agriculture *(29)*, this statistic is sometimes misunderstood to mean that around three-quarters of clinical human AMR impact in the United States is associated with this use. This confusion occurs because these numerator data lack a denominator – that is, the size of the human and animal populations and the weight differentials between the various species.

To help clarify the relative scope of antibiotic use in humans and farm animals, the European Union now uses population correction units (PCU) adjusting total tonnage of antibiotics in milligrams per kilograms of weight in the animal species (including humans) to which those antibiotics are administered on a national scale *(18)*. The result shows considerable variability, finding that in some European Union nations animal antibiotic use is greater than human use while in others, human use exceeds animal use. No similar data is available for the United States.

Resistant bacteria and resistance genes associated with antibiotic use in animals unquestionably make their way into humans, both through the food supply and through direct contact with animals. What is not yet quantifiable is how much of the clinical impact in humans can be ascribed to animal antibiotic use. In the European Union, at least 25,000 deaths annually are attributed to antibiotic-resistant infections *(17)*. In the United States, the estimated burden from bacterial AMR is more than 23,000 deaths and over two million illnesses each year *(20)*. Knowing what proportion of these illnesses and deaths can be traced to resistance from animal or environmental sources would be very valuable in helping set public health priorities. However, estimating the proportion of disease impact, or population attributable fraction *(30)*, associated with a specific risk factor is epidemiologically complex and is dependent on having data linking risk factors to outcomes that is not currently available. There are currently no empirical data to quantitate the relationships between antibiotic use in people and animals or the presence of antibiotics in the environment as input variables, and the emergence and spread of resistance with consequential morbidity and mortality in people as the outcomes. Mathematical models showing the impact of antibiotic stewardship in hospitals on reducing infections with resistant bacteria have been developed *(31)*. Similar models for estimating the results of improved antibiotic use in animals are not available; such information would have great value but could only be achieved through highly collaborative One Health efforts.

The difficulty in accurately estimating and communicating the burden of animal antibiotic use on human illness has been a long-standing obstacle in achieving cross-sectoral cooperation for better antibiotic stewardship efforts in the United States *(32)*. While there is an urgent need to improve antibiotic use in all human and animal settings while additional research is conducted, the evaluation criteria for success in One Health antibiotic stewardship will ultimately depend on our ability to link improved antibiotic use to better clinical outcomes in people. This can only be accomplished by greatly enhanced scientific exchange between human and animal medicine and environmental science.

Conclusion

A One Health approach to controlling AMR thus requires the establishment, maintenance and expansion of collaborative scientific, programmatic and policy-making components that explicitly incorporate the expertise and activities of scientists and practitioners from across a broad range of clinical activities and academic departments, human and veterinary medicine, environmental studies, microbiology, pharmacology, and numerous other disciplines, as well as participants in healthcare, agriculture and the global food supply chain, and ultimately, consumers of healthcare and food. The discrete cultures and languages of these various scientific and programmatic fields, as well as the complexity of engaging and managing the multiple webs of relationships intrinsic to such collaborations have been significant barriers to putting the One Health approach into effective practice, despite broad acceptance of its value.

While large endeavours always require a level of funding that exceeds that available to public health enterprises, overcoming the barriers to One Health success in preventing and controlling bacterial AMR will depend on more than adequate financial support. It will require experts from multiple disciplines to engage each other at the earliest stages in the development of research and of programmatic public health activities, such as integrated disease monitoring and microbiologic surveillance. It will require broader involvement of the practice communities in human and veterinary medicine, with a significantly greater commitment to One Health on the part of professional societies representing physicians and other human health practitioners. It will require breaking down bureaucratic silos within governments and public health agencies and institutionalizing cross-organizational collaboration through management structures as durable as those within existing hierarchies. It will require publishers of quality scientific periodicals to encourage cross-disciplinary submissions and find ways to increase the availability of accurate and contextualized information to both professional and lay audiences.

Finally, achieving success in AMR prevention and control will require development of consensual long-term One Health goals. It is reasonable and necessary that short-term and medium-term goals, such as those in the United States and WHO action plans, be domain-focused – e.g., requiring that all hospitals have antibiotic stewardship programmes, ensuring veterinary oversight of animal antibiotic use through implementation of FDA guidance #213, applying research findings to technologies and practices reducing the concentrations of bacterial resistance determinants and antibiotics in soil and water *(16)*. However, unless One Health collaboration is institutionalized within governments, academic settings and industry, success in one sector will ultimately be undermined by the emergence and transmission of resistance between the human, animal and environmental domains.

There are many examples of prominent leaders promoting urgent action to combat AMR *(33)*. Translating support for the concept of One Health into targeted, effective actions focused on antibiotic resistance and closely linking the human, animal and environmental domains in science and practice, particularly for integrated, comprehensive One Health surveillance, is the next leap forward necessary to address this crisis. ■

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