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COMMENTARY

Antimicrobial resistance in a One Health context: exploring complexities, seeking solutions, and communicating risks

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Four articles presented in this special issue of *Annals of the New York Academy of Sciences* stem from a meeting of experts on antimicrobial resistance (AMR) in food animal production hosted by the New York Academy of Sciences on May 8 and 9, 2018. The articles discuss (1) competing considerations of the criticality of different classes of antimicrobials used for human and animal health and how guidelines and regulations might result in more prudent patterns of use; (2) the increasingly recognized importance of the environment (i.e., soil, water, and air) as a reservoir of resistant bacteria and resistance genes as well as a pathway for the dissemination of AMR between human and animal host populations; (3) established and novel solutions for measuring and containing the AMR problem; and (4) effective strategies for communicating to consumers the risks of AMR spreading from food production and other nonhuman sources. The authors of this commentary served as the scientific advisory committee to the meeting.

Keywords: antimicrobials; antimicrobial resistance; One Health; risk communication

Introduction

Antimicrobial resistance (AMR) among commensal and pathogenic bacteria is the prototypical One Health issue of our time.[a] Bacterial resistance to all known antibiotics continues to emerge, propagate, and persist across the full spectrum of human (both community- and hospital-based) and animal health (including food animals, companion animals, and aquaculture) in a variety of environmental settings. The science of AMR is complex because of its interconnected, multilayered, and multifaceted ecological features. The consequences of AMR can be life-threatening; meanwhile, effective and readily adoptable solutions to the problem remain elusive. Individual and societal decisions that must be taken concerning the appropriateness of various uses of antimicrobial products necessarily come with conflicting moral imperatives (e.g., favor animals or humans; therapy or prevention?). To grasp this complex situation, a holistic ethical stewardship that considers the broad range of stakes and stakeholders involved seems necessary. We suggest that a One Health approach would help to achieve a more complete understanding of the AMR problem, enable efficient solutions, develop appropriate usage guidelines, and provide effective risk communications.

Initial forays in this direction were made almost two decades ago when Thomas F. O'Brien, a

[a]The One Health approach recognizes that the health of people is connected to the health of animals and the environment. The Centers for Disease Control and Prevention (CDC) describe it as "a collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment." https://www.cdc.gov/onehealth/index.html

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microbiologist at Harvard Medical School and founder of the World Health Organization's Collaborating Center for Surveillance of Antimicrobial Resistance, hypothesized that the use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else.[1] His thesis relied on the environment as facilitating the dissemination of selective effects that cross scales from local to global. For O'Brien, the technological solutions for AMR will emerge from studying the emergence, propagation, and dissemination of resistance locally and across the range of contexts where it occurs " . . . because national or global surveillance and strategy develop from local information and understanding."[2] Limiting the propagation of AMR across levels is likely to require that fewer and less antibiotics be used, so to reduce selection pressures. To mitigate dissemination, a broader explanation is needed than the simple movement of bacteria between human hosts; it must also consider animals (both domestic and wild) as well as each environmental medium in which bacteria and their resistance elements can move. Finally, the initial emergence of AMR may be targeted for intervention, although this is the least likely successful avenue, as in almost all cases the unique features of resistant microbes have existed since the origins of their species, merely requiring anthropogenic pressures to make them detectable to us. Hence, viewing AMR emergence as an event at a single point-in-time conveniently ignores both evolutionary biology and the tendency for features that benefit bacteria under selection pressures to become more efficient (or less costly) to a given host over extended periods of time.

The complexity of the issue—its scaling from local to global—and its One Health/cross-sectoral nature do not preclude the formulation of more classical, linear, and reductionist approaches to structuring the problem, quantifying the risks, and proposing critical control points at which to intervene. The late H. Scott Hurd of Iowa State University proposed such a framework for quantitatively assessing the risks (via quantitative risk assessment QRA) of AMR escaping food animal production systems.[3] A QRA typically includes several linear components including (1) hazard identification, (2) release assessment, (3) exposure assessment, and (4) consequence assessment. The aim of the QRA, as set forth by Hurd, was to avoid introducing additional quantities of resistant bacteria into the food supply above levels measured at the farm. Importantly, his framework necessarily implies that "pathways" exist for resistance to escape the farm (beyond the food supply chain), such as via spreading of manure on fields, surface and ground water contamination, and aerosol (dust) dispersion.

In his framework, Hurd explained that zeroing out the components at any of the steps along the food chain reduced the overall risk to zero; likewise, dramatic reductions in probabilistic risk at any stage would carry-through to clearly benefit consumers. Hurd and others have utilized this food–supply framework for a number of different bacteria–antibiotic combinations in different indications and settings.[4] Criticisms often leveled at such approaches include (1) temporal restrictions (i.e., the rise and fall of resistance due to treatment is on the scale of days to months), (2) employment of static baseline risks that ignore the cumulative effect of use on the farm and elsewhere, and (3) tacit ignorance of the adaptive nature of the bacterial populations under selection pressure (i.e., evolution). Nonetheless, such simplified and linear approaches do help systematically frame complex problems and explore possible solutions to mitigate and communicate remaining risks to stakeholders. Importantly, such approaches can readily be expanded to incorporate new knowledge concerning the increasingly recognized role of the environment as a major medium of dissemination, as well as the complex interplay between human and animal populations manifesting as a One Health phenomenon.

In this special issue of *Annals of the New York Academy of Sciences,*[b] four papers consider some of the complexities associated with AMR, including: (1) competing considerations of the criticality of different classes of antimicrobials used for human and animal health and how guidelines and regulations might result in more prudent patterns of use; (2) the increasingly recognized importance of the environment (i.e., soil, water, and air) as a reservoir of resistant bacteria and resistance genes, as well as a pathway for the dissemination of AMR between human and animal host populations; (3) established and novel solutions for measuring and

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containing the AMR problem that range from animal husbandry and herd management changes to technological innovations such as phage biology; and (4) effective strategies for communicating to consumers the risks of AMR spreading from food production and other nonhuman sources.

Competing lists of criticality and their impacts on use

Marketed antimicrobials begin their postapproval life span exhibiting reasonable equivalence with respect to their effectiveness against targeted bacterial pathogens; but over time, the relative importance of each drug class inversely shifts in lockstep with the inevitable rise in AMR of that pathogen. Generally speaking, the longer a drug class has been on the market, the higher the levels of resistance across the spectra of drug–bacteria combinations, and the lower the relative importance of the drug at the present time. As effective antimicrobials become scarce, and few new ones are introduced to replace them, a pressing need arises to prioritize those that remain effective as "top-shelf" drugs. As a result, various international, national, and other agencies have developed competing lists of importance for antimicrobials.[5,6] Such lists tend to prioritize the more recently introduced classes for the simple reason that resistance has had less time to emerge and propagate. These lists necessarily differ and often conflict with respect to their importance to human versus animal health needs.

In the article by Scott *et al.*, the various lists of criticality are compared and contrasted.[7] Where common ground exists, the potential for uniform guidance on prudent antimicrobial use is explored across the various indications for animals and humans, and the range of policy options from voluntary through regulatory control is examined. Approaches to measuring drug sales versus drug use and the pitfalls inherent in relying on these in the aggregate are also explored.

Dissemination of resistance across environmental systems

Over the past decade, there has been somewhat of a renaissance of scientific interest and funding opportunities for exploring the role of the environment in the ecology of AMR. Over the past 50 years, the periodic focus has been directed toward the environment, but such interest has rarely been sustained. Instead, the research agenda often returns time and again to the hospital ward or the farm. Analyses of uniquely derived and archived historical environmental samples and datasets, including by the lead author of the paper by Graham *et al.*,[9] have clearly illustrated the potential for soil, air, and water to be reservoirs and pathways for newly emergent resistance elements to emerge soon after new drug classes hit the market.[8] Graham *et al.* explore the complexities inherent in measuring bacterial resistance outside the normal selection vessel (e.g., the human or animal host) and in quantifying the presence and risk of viable bacteria versus that of their resistance determinants.[9]

Management of resistance in animal agriculture

> *Build a better mousetrap, and the world will beat a path to your door*[c]

For as long as bacterial resistance to antimicrobials has existed, solutions to this expanding problem have been proposed, researched, developed, deployed, and very often discarded. Generally speaking, useful solutions to the problem of resistance must either reduce the need for treatment, control, or prevention in the first place, or serve as viable alternatives to the anti-infective products themselves. Technological solutions abound in both categories, but few products have been a panacea for the wide range of resistance problems that exist. Substantive changes to management in modern agricultural systems are notoriously difficult to deploy; meanwhile, the current infrastructure and design of the food–animal production chain have evolved along with an increasing availability of highly effective antimicrobials during the late 20th century. Where simple technological alternatives have been proposed, such as zinc and copper feed supplements that replaced much of the Danish growth promotion and disease prevention uses of antibiotics in nursery swine in the late 1990s, well-documented bacterial resistance to these metals and coselection for the antibiotics they were meant to replace rapidly emerged.[10,11]

Kahn *et al.* describe a subset of promising solutions that span the realm from farm management strategies to bacteriophage therapy.[12] Recognized

[c] Ralph Waldo Emerson.

experts in a multitude of areas have contributed to these explorations, culminating in a broad set of approaches that can both reduce the need for antibiotics in food animal production and replace the needs that remain with alternatives to treat, control, and prevent bacterial infectious diseases of livestock, companion animals, and humans in the near future.

Communicating risks concerning AMR in the food chain

If you think you understand antimicrobial resistance, it hasn't been explained properly to you[d]

The universal problem of understanding and communicating AMR extends from the scientific community through to health professionals, food animal producers, patients, and consumers. Despite knowledge gaps, there exists a very real need to effectively communicate what is actually understood regarding the relative—if not absolute—risks associated with antimicrobial use and resistance, especially in relation to the safety of the food supply chain. The paper by Ritter *et al.* explores risk communication in this realm.[13] Further, the authors describe research on what currently drives consumers to choose "raised without antibiotics" meat and poultry products over conventionally raised products and the impacts of this niche market sector on animal health and welfare; they also explore plausible alternatives to such "never, ever" policies, relying instead on process-verified programs that blend animal welfare, environmental, and antimicrobial stewardship principles. Raising food animals in an ethical manner that ensures the health and welfare of the animal, employing sustainable environmental practices, and providing transparency regarding antimicrobial uses at an enterprise level offers the greatest opportunity for useful, open, and honest communications with consumers.

Conclusions

While AMR is among the greatest challenges to global health, there are no simple solutions. Solving this major global problem will require extensive innovation and cooperativity of interdisciplinary groups (such as the one formed to write the articles in this special issue). To preserve the utility of antibiotics in human and animal medicine, a variety of approaches to limit the spread of AMR under a One Health umbrella must be considered and implemented. This series of articles explores four of the components that comprise AMR. Beginning with consideration of the drugs themselves, their prioritization for human and animal health, and guidance for prudent use (and measurement thereof), the series closes with a discussion of effective ways to communicate with consumers and other stakeholders with the aim of adding to the ways to address consumer demands for transparency and improved antimicrobial stewardship. The overlooked—but equally important—contribution of the ambient environment expands our understanding of the ecology of resistance, along with a renewed exploration of the likely range of solutions to reduce the need for and actual use of antibiotics are offered in the two middle papers. These papers hopefully will begin to fulfill the pressing need for a wide-ranging approach to the critical issue of AMR.

[d]Guy H. Loneragan, likely adapted from Richard Feynman's famous quote: "If you think you understand quantum mechanics, you don't understand quantum mechanics."

Competing interests

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