Managing Antibiotic Resistance in Animal Agriculture amidst Conflicting Moral Beliefs and Scientific Uncertainty**

H. Morgan Scott, D.V.M., Ph.D.
Professor, Department of Diagnostic Medicine and Pathobiology,
Kansas State University, Manhattan, Kansas, United States

Summary
The moral imperative to use antibiotics for treating bacterial diseases in both humans and animals is obvious. Less obvious are the moral beliefs, social norms, and behavioral constraints (e.g., economic realities in a competitive industry) that face food animal producers and their consulting veterinarians. Anti-infective products such as antibiotics are unlike other technologies used in medicine and agriculture in that resistance — an inevitable consequence of their use — results in diminishing effectiveness over time. While such diminishing effectiveness operates on a nearly invisible scale in terms of day-to-day clinical practice and decision-making, its nonlinear decay yields an economic (or social) externality in much the same way that depletion of nonrenewable resources is seen by many to reduce natural capital.

Efforts to conserve the "resource" — in this case, the effectiveness of an antibiotic — may be thwarted by a multitude of paradoxical factors including: (i) patent laws that are inappropriate for antibiotics, since pharmaceutical company marketing efforts will necessarily aim to achieve a reasonable return on investment before cheaper generic products hit the market; (ii) the stifling of innovation if the World Health Organization (WHO) and others immediately and routinely classify newly discovered compounds as "critically important," thereby limiting their potential market; (iii) regulators removing classes of products (or certain indications) for routine use in food animals, thereby narrowing and intensifying the pressures applied on those that remain; and (iv) adopting risk assessment paradigms that misalign levels of antibiotic use with levels of antibiotic resistance, often ignoring the cumulative nature of the risk and well-documented phenomena such as co-selection by other antibiotics, and even heavy metals.

Current realities

The use of antimicrobials — especially antibiotics — in animal agriculture has been common practice for almost as long as in human medicine. Early on, the types of animal uses rapidly expanded beyond their more obvious therapeutic indications to include prevention and control of diseases, and even growth promotion. Resistance to antibiotics typically emerges soon after, and sometimes well before, the introduction of these products, and thereafter disseminates, expands, and persists as a function of readily explained, though sometimes paradoxical, selection pressures. Contrary to popular belief, most resistance factors do not develop *de novo*; rather, each tends to represent a modification or refinement of some pre-existing cell function.

The need to use antibiotics to treat acute bacterial diseases in humans is obvious. For food animals, almost all sides of the debate over the continued and future use of antibiotics in animal agriculture seem to agree that sick animals under producer and veterinary care likewise deserve to be treated. However, such agreement does not extend to the much more controversial use of subtherapeutic doses of antibiotics to enhance growth, or even to the use of timed mass treatment (or metaphylaxis) to control infectious disease in the face of an outbreak. When surveyed, both feedlot veterinarians and their feedlot producer clients placed as much emphasis on the moral duty to treat acutely ill cattle as the economics involved in such decision-making (see Figure 1). However, the attitudes and beliefs of feedlot producers and veterinarians regarding the other uses of antibiotics often differ greatly, specifically, for the treatment of chronically ill cattle, mass treatment for control of disease epidemics, and the use of subtherapeutic doses of antibiotics for growth promotion purposes (see Figure 1).

Examined more closely, these differences seem to reflect internal conflict and core differences in attitudes regarding product efficacy (e.g., sense of duty to treat chronically ill cattle despite ineffectiveness) and the expectations of clients, bankers, and others to use approved feedgrade antibiotics to improve growth. Such differences suggest opportunities to enhance communications and to explore and enact policies that recognize differences among industry stakeholder attitudes, beliefs, and their likely behaviors under a variety of future scenarios.

Scientific opportunities and challenges

Two examples of pharmaceutical products approved a long time ago are tetracycline (an antibiotic) and furosemide (a diuretic). Both furosemide and tetracycline have been surpassed in relative efficacy by newer generations of similar products. However, while the absolute effectiveness of furosemide has not meaningfully changed (i.e., patients have not evolved on a pharmaco-epidemiologic time scale), the relative effectiveness of tetracycline against many bacterial infections has diminished considerably since the product was introduced.

Because bacteria reproduce more rapidly than food animals and humans (i.e., on a scale of hours as opposed to months, years, and decades, respectively), their ability to adapt is reflected in the waning absolute clinical efficacy of the products used over periods of years to decades. Any decision by an individual to use an antimicrobial to treat an immediate problem thus has an immeasurably small but negative impact on its future effectiveness. Coast et al. (2001) describe the broad economics of such declining usefulness as a "negative externality because it has adverse consequences for society as a whole, whereby the cost borne by the individual is somewhat less than that borne by society." Recent controversy over a large Gates Foundation grant to fund research in children on what has been known about antibiotics and growth in animals (i.e., that antibiotics promote growth) arises almost entirely from the individual versus societal cost structure defined above.

It is important to note that the timescale of resistance development and expansion, and the timescale of policy development and implementation, do not coincide. In most cases (e.g., the third generation cephalosporin ceftiofur, an animal drug closely related to the human drug ceftriaxone), there is a post-introduction period of years to decades in which resistance appears to be nil, or very low, followed by expansion closely mimicking a logistic function (i.e., growing exponentially at first, then plateauing). On the other hand, when conducting *in vivo* research in animals we observe that while the prevalence of bacterial resistance (when present) rises during and immediately following treatment, it tends to fall back to baseline (or apparent zero) after a washout period. This latter phenomenon is the reason that classical quantitative risk assessment (QRA) approaches can be functionally useful for aiding in decisions about slaughter withholding times (whether using residue avoidance or microbial safety endpoints). However, these risk models are not adaptive on a microbiologically relevant evolutionary scale and thus can provide a false sense of security by relying on concurrent relations between antibiotic use and resistance in animals among enteric bacterial populations not receiving antibiotic treatment.

Policy issues

- Current patent laws are in many ways inappropriate for products whose absolute effectiveness decays with use. Novel patent laws to discourage imprudent or excessive use, and to improve the likely success of voluntary or involuntary actions such as temporary withdrawal of products from markets, will have a greater chance of success if flexible policies such as "patent holidays" (extensions of patent protection commensurate with the withdrawal period) are made available to counter the pressing short-term need for pharmaceutical company return on investment.

- Encouragement of innovation is essential. Offering extended patent protection and market exclusivity to new classes of antimicrobials could help to spur research and development in this area. Attempts to overcome an absolute reduction of efficacy through "relative" improvements are more likely to be successful when new classes of antibiotics are discovered and introduced than when copycat or "me-too" products from the same class of antibiotic are reproduced and mass-produced.

- Routinely classifying all new antimicrobial classes as "critically important" or "human-only" is likely to discourage, rather than encourage, innovation investments. Identifying novel compounds suited to other uses and separating such categories not only on the basis of "bug-drug-indication" classifications, but also on human versus food animal use, and therapeutic versus prevention/control, would create market opportunities as well as assist in prudent planning for the inevitable resistance development.

- Removing longstanding classes of antibiotics, such as tetracyclines and penicillins, from certain uses in food animals necessarily increases the need for, and narrows the selection pressure onto, other antibiotics, including those identified as critically important for human medicine. A strategy that looks beyond simple drug-bug combinations and considers impacts of such bans will help to identify many unintended consequences.

- The current paradigm of risk assessment as applied to the approval process for new and existing antimicrobials is fundamentally flawed. Holistic risk assessment approaches that consider evolutionary adaptation by bacterial populations and include factors that can co-select for resistance are needed. The development of novel surveillance approaches to detect the emergence of resistance before it becomes prevalent, as well as establishing pre-determined critical thresholds of resistance at which prescribed mitigations are deployed, should be part of the new drug approval process.

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Figure 1: Moral beliefs of feedlot operators and their veterinarians regarding four types of antibiotic use