ORIGINAL ARTICLE

Antimicrobials in Animal Agriculture: Parables and Policy

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Impacts

- Antimicrobial resistance among zoonotic and foodborne bacteria represents a growing threat to public health.
- Increasingly, policies implemented to control antimicrobial resistance are grounded in statements reflecting moral imperatives and ethical conduct; these policies may be unsupported by results from quantitative risk assessments.
- Barriers against, and opportunities for, implementation and adoption of risk mitigation policies differ among agricultural settings around the world; therefore, customized and optimized approaches will comprise a varying mixture of voluntary and mandatory strategies.

Keywords:
Antimicrobial resistance; policy; moral imperative; ethical practice

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Summary

In addition to the scientific, economic, regulatory and other policy factors that impact on antimicrobial decision-making in different jurisdictions around the world, there exist ethical, social and cultural bases for the contemporary use of these products in animal agriculture. Thus, the use of the word 'parable' to describe the contemporary moral stories that help to guide ethical antimicrobial use practices and broader policy decisions in animal agriculture is appropriate. Several of these stories reflect difficult decisions that arise from conflicting moral imperatives (i.e. both towards animal welfare and towards human health). Understanding the factors that combine to define the past and present paradigms of antimicrobial usage is crucial to mapping a path forward. There exist barriers, as well as opportunities, for advancing scenarios for reducing antimicrobial usage under a variety of voluntary, regulatory and legal policy frameworks. Any new approaches will ideally be structured to extend the use of present-day antimicrobials into the future, to provide novel alternatives for regulating any newly introduced antimicrobial products so as to maximize their useful life span and to ensure the optimal use of these products in animal agriculture to protect not only the health of animals and the interests of animal health/agriculture stakeholders, but also the human health and the interests of the public at large. A full range of policy approaches, which span the realm from strictly enforced regulations and laws to voluntary guidelines and compliance, should be explored with respect to their risks and benefits in a variety of worldwide settings and in full consideration of a range of stakeholder values.

Parables

There remains great controversy over the relative contribution made by antimicrobial use in animal agriculture to antimicrobial resistance (AMR) in commensal and pathogenic bacteria; and further, to negative consequences for human health (Aarestrup et al., 2001, 2010; Hurd et al., 2004; Hurd, 2006; Alali et al., 2009). Generally speaking, most concern about resistance is directed at the subset of antimicrobials known as antibiotics, and especially those designated as critically important to human medicine by the World Health Organization (WHO, 2012) and others

such as the U.S. Food and Drug Administration (FDA, 2003). Despite numerous attempts, it remains exceedingly difficult to attribute quantitative estimates of absolute or relative risk to any one particular regimen or type of antibiotic use, given the complex ecological nature of the problem. While it remains difficult to directly quantify and compare risks for the emergence, dissemination and propagation of resistance across the various antimicrobial uses and among the various livestock hosts, agricultural production systems and bacterial species, it is generally accepted that – overall – more use leads to greater selection pressure favouring resistance, and therefore, less use favours susceptible bacteria (WHO, 2000). Importantly, even among those in the agricultural sectors, decisions to use or not use antimicrobials in certain ways are strongly associated with individual decision-makers' perceptions of public health risk; these risk perceptions in turn are impacted by many other factors (Jan et al., 2012). In this example, for certain categories of antibiotic use – such as for therapy and disease control – beef feedlot veterinarian and producer practices in the present reflect a strongly held belief that these particular practices pose little present risk to public health. Thus, their current behaviours are consistent with their perceptions of risk, and future behavioural intentions do not reflect any substantive changes. The same relation was less prominent for other uses of antibiotics, such as for growth promotion, and this differed between veterinarians and their clients (McIntosh et al., 2009).

The spotlight of public concern is not equally focused on the four major labelled uses of antimicrobials in animal agriculture: therapeutic, metaphylactic (or disease control), prophylactic (or disease prevention) and growth promotion (or feed efficiency). Instead, public concerns about such uses tend to increase alongside the order in which they are listed above. Such ordered concerns about the use do not directly relate to any scientifically derived or published risk rankings; rather, they tend to derive instead from moral and ethical 'litmus tests' and as such are logically promulgated using terms such as 'prudence' or 'judiciousness'. As a recent example with significant policy implications, in June of 2010, Dr. Joshua Sharfstein (the then US FDA deputy commissioner) suggested that antibiotics should only be used to protect the health of an animal and not to help it grow faster or more efficiently. Dr. Sharfstein is quoted as having said during a conference call with reporters. 'To preserve the effectiveness, we simply must use them as judiciously as possible' (FDA, 2010).

Interestingly, the narrative that emerges concerning the continued use of antimicrobials in animal agriculture often invokes more discussion of values than science indicating that, in the absence of strong scientific evidence – or, perhaps in spite of it – the emphasis is on moral prescription. Such a values-based approach to public deliberations and policymaking is perhaps more often illustrated in the language used to enact changes in Europe when compared to North America. For example, on 30 July 2013, the European Medicines Agency issued an advisory statement suggesting that while 'colistin [a polymixin] has been used in veterinary medicine for over 50 years', and there is '. . .no available evidence on the transfer of resistance to colistin from animals to man. . .', the EMA recommends '. . . restricting its use to the treatment of infected animals and those in contact with them, and to remove all indications for preventive (or prophylactic) use' (European Medicines Agency, 2013). A prominent microbiologist in Birmingham, UK, was quoted as stating that 'The EMA recommendation is "the precautionary principle," and is laudable. . .the reality is we should question the use of any antibacterial agent outside of human medicine until there is unequivocal evidence showing no effects of animal use upon human health' (Cressey, 2013). It seems plausible that even if the scientific evidence was strong – in either direction – there would still be an emphasis on moral prescription because the purpose of science in this case is to help society decide what is right and wrong in terms of human actions; in this case, preserving efficacy for future needs of human patients stricken with multidrug-resistant Enterobacteriaceae. The fact that a lack of scientific evidence alone cannot provide policy guidance very well serves to ensure that policymakers pass very swiftly from pointing out the lack of evidence to saying society needs judicious use.

Around the globe, there exists a wide range of policies, both written and unwritten, that govern the actual use of these essential medicines. Those factors that affect agricultural usage patterns range from the glaringly obvious, such as legislative restrictions and the constraining economics of animal health and production, to the less obvious, such as social norms and a sense of moral duty and trust (McIntosh et al., 2009; Jan et al., 2010); these, in turn, can help to explain varying usage patterns within any given set of regulations or economic conditions. Adding to the complexity are the various economies (monetary, political, and moral) as well as the interests and concerns of a wide range of individuals and groups ranging from the pharmaceutical, veterinary and agricultural production side, through to the consumer and public health/healthcare advocacy sides (Dean and Scott, 2005; McIntosh et al., 2009). Setting boundaries on the limits of discussion by framing the issue either as a strictly scientific one or else as an entirely economic one will necessarily alienate and marginalize persons and groups with legitimate concerns (Ulrich, 1994; Midgley, 2000). In turn, this will work against furtherance of the objectives of reducing overall usage of antimicrobials and decreasing risks to human and animal health. Such systemic approaches as 'boundary critique' (or boundary analysis) and a plurality of other techniques should be

employed to examine the likely impacts and effects of marginalizing various stakeholder viewpoints at each step along the way (Midgley, 2000, 2006; Midgley and Pinzón, 2011, 2013). Less inclusive policy decision processes are unlikely to result in sustainable and defensible long-term solutions and to sustain conflicts far beyond their expected life span.

Policy

The process by which new animal drugs are approved, or existing drugs are re-evaluated for continued or expanded approval, is not consistent throughout the world, whether it be in the so-called 'developed world' or in the 'developing world'. Further, there are vast differences in the 'post-approval' regulatory environment the world over, leading to very real barriers to changes in marketing, prescribing, sales and use of these products. For illustrative purposes, the following discussions will be restricted to a comparison and contrast of European and the U.S. experiences over the past decade or so.

The European ban on the use of antibiotics as growth promoters (AGPs) took effect on 1 January 2006 (Aarestrup et al., 2008) and was arguably largely based on the precautionary principle. This move followed other regional country leads like Sweden (mid 1980s) and a series of somewhat voluntary bans in Denmark (from 1996 onwards). The Danes, in particular, have been vigorous in tracking the effects of the ban (preceded by profit restrictions on veterinarians) on each of sales of antibiotics, resistance among bacteria and production of pigs in particular (Aarestrup et al., 2001, 2010; Aarestrup, 2012). Results concerning the overall effects of the ban in other European countries are still being compiled; however, there is general agreement that with reductions in AGP use at least some 'substitution' of therapeutic and prophylactic products has likely taken place. Debates over any subsequent increases in the levels of critically important antimicrobials (CIAs) used as therapy, in place of AGPs or prophylaxis, are more hotly contested (Doyle et al., 2013).

In the United States, a major shift in the way that new animal antimicrobials are approved, labelled and regulated occurred in 1997 when the FDA issued prohibition orders against the extra-label use of fluoroquinolones and glycopeptides in food-producing animals (Doyle et al., 2013). At the time, the FDA was revisiting rules on the ways in which veterinarians could prescribe products in an 'extra-label' manner. One of the outcomes of this process was the identification of certain products for which prohibition orders would be issued against extra-label drug use (ELDU). For fluoroquinolones and glycopeptides, these orders were for the first time directly tied to microbial safety, in the form of resistance avoidance, as opposed to the usual (at the time) concerns over residues or toxicological endpoints. Note that no actual changes were made to the labelled (fluoroquinolone) or non-labelled (glycopeptide) products; rather, these orders focused on restricting the subset of conditions under which veterinarians were operating that allowed their prescribing practices to differ from the product label. More recently, in April of 2012, another class of antibiotics (cephalosporins) was added to the list of prohibited extra-label drugs; albeit, with some notable exemptions allowing for minor species and also the same for non-indicated dose, duration and route of administration in approved species (FDA, 2012a).

Soon after the 1997, US extra-label use, bans for fluoroquinolones and glycopeptides were put in place, a completely new approach to addressing microbial safety of new antimicrobial drugs ensued in the form of Guidance for Industry (GFI) 152 (FDA, 2003). The philosophy underlying this document will be discussed in the next section; however, perhaps of greater interest than the document itself is an intriguing process that can be found through a content and narrative analysis of the transcribed minutes of the public hearings that preceded the publication of the GFI 152 document (Dean and Scott, 2005). Chief among the deliberations was a fierce debate over the actual form that any risk assessment should take. Attention focused on the divisive interactions between agricultural, veterinary and pharmaceutical companies on one side and the U.S. FDA on the other. However, this belies the fact that what appeared on the surface to be an antagonistic public discourse was actually a process capable of simultaneously legitimizing the roles of the FDA as the official arbiter of policy on antimicrobial use in animal agriculture and as a protector of the public welfare, as well as the role of pharmaceutical companies as the producers of safe and effective products necessary for the protection of animal health and public well-being.

Implicit in the earlier statements attributed to FDA deputy commissioner Dr. Sharfstein are both ethical codes (i.e. defining appropriate professional conduct and practice) and moral duties (to preserve antibiotic effectiveness for others – be they humans or animals –who may need them in the future). It is not coincidental that GFI #209, published in 2012, which directs the pharmaceutical industry to voluntarily withdraw their growth promotion labels by December of 2016, uses much of the same language of ethical (judicious) practice to motivate its implementation (FDA, 2012b). This document leads further to document GFI #213 – which was published recently (FDA, 2013) – that allows for relabelling of some feed grade antimicrobial formulations and dosages for prevention and control purposes. The veterinarian, who is bound by codes of professional ethical conduct, has also been brought more formal into the decision-making process for all situations in which antibiotics are to be used in feedstuffs for food-producing animals.

These two documents stand in contrast to GFI #152 – discussed above – which, while motivated by many of the same moral concerns about future effectiveness, retains a modicum of scientific control and judgment over the process of new animal drug approvals by way of a qualitative risk assessment matrix (FDA, 2003; Dean and Scott, 2005; Hurd, 2006; Doyle et al., 2013). That said, prudence overrides all other factors (such as release and exposure risk, and even indication) in the GFI 152 matrix simply by way of an antibiotic being designated as 'critically important', resulting in the consequence of resistance being critically important and the risk being coded as 'high' (FDA, 2003 – page 21).

There are several good examples of where regions, countries, agricultural industries, and individual farming operations – whether via voluntary or involuntary action – have achieved measureable reductions in antimicrobial usage in veterinary medicine. As mentioned earlier, a European ban on antibiotic growth promoters (the use of antibiotics in animal feeds, often at so-called 'subtherapeutic' concentrations, to increase the growth rate and feed efficiency of animals) has been in place since January, 2006 (Aarestrup et al., 2008). At national levels, Sweden (1986) and Denmark (1999) are perhaps the longest standing where over a period of 15+ years, successively more restricted use (in volume and by class of antimicrobials) has been successfully introduced in veterinary medicine and animal agriculture. Importantly, these bans have also been suggested to have resulted in reductions in resistance, especially to glycopeptides and macrolide resistances (Aarestrup et al., 2001). Recently, in the Netherlands, a reduction of 50–70% of veterinary usage has been imposed and is expected to be achieved over the next 3- to 5-year period (Wagenaar, J., personal communication). However, the number of regions and countries where regulatory action has been introduced and deemed successful in achieving its stated goals is very limited. Worldwide, antimicrobial use in animal production is largely unregulated and unrestricted. Understanding the barriers and opportunities for change in antimicrobial use that exist worldwide, and the unique aspects of each region that could best lead to improvements in antimicrobial practices and regulations, would be useful for aiding international agencies such as WHO, the Food and Agricultural Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) to better address and achieve many of their stated development goals and health targets.

At industry and farm levels, there are instances where either 'natural experiments' have been observed (Dutil et al., 2010) or farms have elected to shift to either antibiotic-free, or certified organic (Bunner et al., 2007; Keelara et al., 2013) operations, respectively. In Dutil et al. (2010), a sharp reduction in ceftiofur resistance among *Escherichia coli* and *Salmonella* Heidelberg isolates in broilers and on broiler meat was observed following an industry-wide voluntary cessation of *in ovo* injections of ceftiofur in broiler hatcheries. Concurrently, levels of ceftiofur resistance also dropped in human cases of salmonellosis attributed to the *S.* Heidelberg serovar. It is incredibly rare that such a series of events was observed in the first place, and that an intervention could have such a dramatic result. It seems highly improbable that such a reduction in resistance would have been seen with longer-standing products such as tetracycline, streptomycin and sulphonamide resistances if those products had instead been withdrawn from use. Ceftiofur is relatively new, and coresistance in the case of *S.* Heidelberg was uncommon and therefore not coselected by tetracycline use. All of this created a 'perfect storm' of opportunity to observe a dramatic reduction in resistance following cessation of use.

In contrast, most studies of antibiotic-free versus conventional agricultural productions do not show such dramatic differences. Of course, practices vary by animal type and operation. Data from Bunner et al. (2007), conducted on *E. coli*, suggest that for long-standing drugs such as tetracyclines, there is little meaningful difference in resistance. However, for more recently reduced products, there can be substantive differences. In addition, Keelara et al. (2013) have shown that besides selecting for lower resistance among *Salmonella enterica*, there can also be a lowered overall prevalence of *Salmonella* on ABF versus conventional farms.

As has been noted by Doyle et al. (2013), the U.S. National Antimicrobial Resistance Monitoring System (NARMS) has been in place for over 15 years and holds a wealth of useful information that only increases in value over time. Several trends are apparent, including an increase in resistance to beta-lactams among *Enterobacteriaceae*. On the other hand, resistance to several antibiotic classes, including critically important classes such as fluoroquinolones, are exhibiting very low levels of resistance in *Salmonella*, suggesting that something appears to be working, policy-wise.

Major problems in scientific inquiry do not arise solely with the inappropriate choice of study design or method; instead, the points of reference of the inquirer can readily direct – or misdirect – the interpretation of results. Some say the data speak for themselves, except that they cannot; they always end up being examined and filtered through the lens of the observer (Von Foerster, 1979; Von Glasersfeld, 1985; Maturana, 1988; Hollway, 1989) – and this observer may be a scientist, journalist, advocate, policymaker or lay person. The science of antimicrobial resistance is no different than other fields of study; it is frequently possible for two scholars to examine the same data and to come to different conclusions. While the institution of science uses mechanisms such as hypothesis testing to eliminate multiple

interpretations, and research communities tend to self-select the interpretations they find most persuasive, in principle a new and compelling interpretation of any piece of evidence may be just around the corner (Popper, 1972). The reasons for this are multiple, just like the interpretations of evidence, which provides a reason for soliciting a plurality of disciplines, methods and stakeholder values in setting research agendas and regulatory frameworks, as has been consistently advocated by Midgley (2000, 2006). Acknowledging multiple interpretations does not lead to decision paralysis if systemic processes are used to engage with stakeholders to support learning, dialogue on evidence, better mutual understanding and the identification of new possibilities for action (Checkland and Poulter, 2006).

An apparent paradox is illustrated in a recent series of papers on AMR in cattle (Lowrance et al., 2007; Platt et al., 2008; Cottell et al., 2013; Kanwar et al., 2013, 2014); these point to the pitfalls inherent in interpreting data from only a single viewpoint. Traditionally, the measurable and reported endpoint of interest for monitoring and surveillance of enteric bacteria has been the prevalence of phenotypic (or genotypic) resistance traits among isolates at the bacterial population level. At rest (or equilibrium) – meaning when the bacterial ecosystem is undisturbed by antimicrobial selection pressures – prevalence alone can be a reasonable estimate of resistance load; albeit, complicated by a multivariate set of endpoints (e.g. up to 15 antimicrobials on a broth microdilution plate, with many more genetic elements to explain each resistance). However, when the system is disturbed by antimicrobial use (see Lowrance et al., 2007), the denominators of total bacteria change dramatically, sometimes giving highly biased estimates of the actual prevalence or count of resistant bacteria.

In the aforementioned series of papers, it became clear that relying solely on phenotypic or genotypic prevalence among isolates was insufficient for understanding the true bacterial dynamics and microbial ecology at play in the intestine of treated and untreated animals. As a result of using only one 'lens' to view a single endpoint (Platt et al., 2008: ceftiofur resistance among *E. coli*), it was observed that chlortetracycline in feed was associated with a reduction in ceftiofur resistance. To protect against ceftiofur resistance, it initially appeared that one could select against resistance to one antimicrobial by using another. This, despite the clear mechanistic potential for coselection given that both *tet*(A) and $bla_{\text{CMY-2}}$ genes were known to be present on the same IncA/C plasmid. In subsequent work by Cottell et al. (2012) and Kanwar et al. (2013, 2014), the authors identified additional explanations for the apparent sparing effect on ceftiofur resistance, simply by widening the view of their lens to include additional qualitative and quantitative endpoints. The take-home message should be that an imprudent choice of a single outcome measure for a scientific inquiry into AMR can serve to make interpretation of study results difficult at best, and biased at worst.

One final word of caution is in order, in fitting with the theme of paradox. Many individuals and companies are clamouring for 'alternatives' to antibiotics in the face of a changing regulatory landscape. In particular, metals such as copper (Cu) and zinc (Zn), which are known to have antibacterial properties and also to promote animal growth at higher than nutrient requirements, have been substituted for antibiotics, often in those countries where antibiotic growth promoters have been banned. It is becoming clear (see Amachawadi et al., 2011; Cavaco et al., 2011), that coselection of antibiotic resistance along with transferable metal resistance cohoused on the same plasmid(s) is making the design and selection of 'alternatives' fraught with difficulty. For copper and zinc, these have thus far been seen to play out among *Enterococcus* spp. (macrolide and tetracycline resistance) and *Staphylococcus aureus* (methicillin and tetracycline resistance), respectively.

A 2012 conference held at the headquarters of the World Organization for Animal Health (OIE) in Paris highlighted a wide range of alternatives to antibiotics, each holding some promise for success (United States Department of Agriculture, 2012). These include the metals, host antimicrobial peptides (recombinant), essential oils, immunomodulants, among others. It should be remembered that any product that disrupts bacterial populations will necessarily select for those that are able to cope. If such mechanisms can be mobilized genetically, they will be. Approaches that are holistically designed and assessed as to adverse outcomes, especially when minimizing selection pressures for bacteria resistant to critically important antimicrobials, should actively be pursued.

Regardless of the setting, it seems apparent that moving forward science will continue to play a valued and expanding role by informing debates and policy decisions over the design of the most appropriate regulations and guidance for antimicrobial use in animal agriculture. However, it is likewise apparent that such debates will be fuelled – on one side – by a sense of moral outrage over the perceived squandering of a precious resource that saves lives, and – on the other side – by a strongly felt sense of legitimacy in using products previously proven to be safe via science, regulatory approval, and ongoing scrutiny, rather than by any sense that new scientific knowledge will further enlighten stakeholders on either side of the issue. Continued vigilance is needed to ensure that multiple and varied stakeholder values are considered as much as is practicable when setting policy, and that common ground is identified wherever possible so as to avoid protracted conflicts in this area. In summary, parables can provide the moral compass to guide

ethical practice for wicked problems such as antimicrobial resistance; that is, so long as science continues to inform the most effective policy decisions.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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