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Antimicrobial use in food and companion animals

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Abstract

The vast literature on antimicrobial drug use in animals has expanded considerably recently as the antimicrobial resistance (AMR) crisis in human medicine leads to questions about all usage of antimicrobial drugs, including long-term usage in intensively managed food animals for growth promotion and disease prevention. Attention is also increasingly focusing on antimicrobial use and on bacterial resistance in companion animals, which are in intimate contact with the human population. They may share resistant bacteria with their owners, amplify resistant bacteria acquired from their owners, and act as a reservoir for human infection. Considerable effort is being made to describe the basis of AMR in bacterial pathogens of animals. Documentation of many aspects of use of antimicrobials in animals is, however, generally less developed and only a few countries can describe quantities of drugs used in animals to kg levels annually. In recent years, many national veterinary associations have produced 'prudent use guidelines' to try to improve antimicrobial drug use and decrease resistance, but the impact of guidelines is unknown. Within the evolving global movement for 'antimicrobial stewardship', there is considerable scope to improve many aspects of antimicrobial use in animals, including infection control and reduction of use, with a view to reducing resistance and its spread, and to preserving antimicrobial drugs for the future.

Keywords: Antimicrobial use, food animals, companion animals, antimicrobial stewardship

Introduction

This review can only point out some aspects of research on antimicrobial use in food and companion animals and some important issues relating to the long-term preservation of antimicrobial drugs in animals and in humans, noting that some of the issues discussed include regulatory aspects of antimicrobial use in animals. This review represents as much a critique of existing approaches as a review of research *per se*, but does highlight some directions for the research needed to preserve antimicrobial drugs for the long term.

The crisis of antimicrobial resistance (AMR) in human medicine in the last 10–15 years has led to considerable reassessment of all aspects of antimicrobial use, including further urgent questioning of long-term routine usage in intensively managed food animals for growth promotion and disease prevention. The World Health Organization (WHO) has called for an end to such practices. There was a European Union (EU)-wide ban on the use of growth promoters in 1999, engendered by Sweden's entry into the EU and by recent important findings about the link of the growth-promoter avoparcin in chickens and swine to high frequency of vancomycin-resistant enterococci (VRE) in contaminated meats at retail. The Codex Alimentarius (2007) is discussing identification of AMR in food-borne bacteria as a contaminant of food.

The crisis of resistance in medicine took many years to develop, and is the result of many influences. For many years, AMR was a problem largely of hospitalized human patients, but in recent years AMR problems have partly moved from hospitals into the community. Ultimately, the cause of the AMR crisis is the cumulative result of the widespread and extensive use of antimicrobial drugs in humans over 60–70 years, coupled with changing demographic and societal influences (for example, immunosuppressive drug treatments, day-care centers, old

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people's nursing homes, chronic care hospitals, the ease and scale of mass movement of people globally, and the rise of human immunodeficiency virus infection). Given this context, the contribution of antimicrobial use in animals to the total resistance of human pathogens is probably relatively slight (Bywater and Caswell, 2000), but it is nevertheless finite and measurable, and very well documented in specific circumstances, notably in food-borne bacteria, including some serious pathogens. The precise scale of the contribution is hard to estimate, although it may be more than generally recognized (Johnson *et al.*, 2007).

The lesson from AMR in human medicine is that extensive use of antimicrobials over time results in the emergence and spread of resistance, which can become a crisis. For decades, ready access to the 'miracle drugs' by medicine and agriculture, coupled with the ability of chemists to alter existing drugs or to develop new drugs to counter resistance, led to the expectation that the pre-antibiotic era was to become a folk memory, marked only by the tragedies recorded on old gravestones in mossy churchyards. This has been proven wrong. The crucial questions include 'Can one put the Genie back in the bottle?' and reverse (or slow) the process, and will the development of novel antimicrobials (for example, through identification of novel antimicrobial targets identified by genome sequencing and high throughput drug discovery) be hampered by bacterial pathogens that have acquired improved ways to become rapidly resistant over the last 60–70 years? The focus of so much research effort on resistance largely misses the point. Since use drives resistance, a major effort must be to reduce use of antimicrobial drugs to circumstances where the benefits are clear and substantial, as well as to optimize use of antimicrobial drugs so as to minimize development and spread of resistance.

Bacteria from animals (food, companion and wildlife) and people interconnect in numerous ways, since all live in the same world (Linton, 1977). One lesson of AMR is that all users of antimicrobial drugs have a responsibility to use them optimally and wisely. Containment of AMR will involve a coordinated and multi-dimensional global approach (WHO, 2001). One not-so-minor aspect of containment even includes the medical apparent re-discovery of the importance of the basic infection control procedure of hand-washing as one important element in preventing the spread of resistant bacteria between patients.

Classes of antimicrobial drugs used in food and companion animals

Not surprisingly, given the limited number of therapeutically useful antibiotics, the classes of antimicrobial drugs used in animals are largely those used in human medicine. One difference is that a limited number of antimicrobial drugs that are unimportant in human medicine because of toxicity problems (glycopeptides and streptogramins) were or are used as growth-promoting feed antimicrobials in food animals. The selection of VRE in chickens and swine by avoparcin, a growth-promoting glycopeptide related to vancomycin, has led to withdrawal of use of this drug from animal use in many jurisdictions. Streptogramins such as virginiamycin have also been withdrawn in some jurisdictions because of induction of resistance to pristinamycin, a streptogramin recently introduced into human medicine to treat VREs. Antimicrobial drugs such as chloramphenicol, the nitrofurans and the nitroimidazoles have been banned from use in food animals in most jurisdictions because of potential toxicity or carcinogenicity for human beings inadvertently exposed through food residues. The ionophores are a class of relatively toxic orally administered antibiotics used uniquely in food animals to control coccidiosis and improve efficiency of food use. Pleuromutilins are a unique class of antibiotics used exclusively in food animals, with activity similar to that of macrolides, with which they can induce cross-resistance.

Types of use of antimicrobial drugs in food and companion animals

In general, the types of use of antimicrobial drugs are similar in animals and humans, and in companion animals are essentially identical (Institute of Medicine, 1998) (Table 1). A practice that is far more common in food animal use than in human medicine is mass medication with therapeutic concentrations of drugs immediately before an anticipated outbreak of disease, or immediately following the onset of disease in a population ('metaphylaxis'). The greatest differences in usage are in food animals where, in some jurisdictions, antimicrobials are used for growth promotion and for disease prophylaxis (Table 1). Not only are antimicrobial drugs being used for growth promotion in many countries, but some drugs are administered in feed for prolonged periods at somewhat higher concentrations, the 'subtherapeutic levels' (defined in the United States as less than 200 g ton^{-1} of feed, lower than concentrations approved for therapeutic purposes). Drugs are administered 'subtherapeutically' for many defined, licensed, purposes at a range of concentrations varying with the drug, the food-animal species and the purpose. Such usage, which can often be prolonged, is particularly widespread in the swine industry in those countries in which the drugs are allowed for this purpose and is not under veterinary prescription.

Regulation of antimicrobial drug use in animals

In most countries, approval by the appropriate regulatory authority must be obtained before an antimicrobial drug

Table 1. Types of antimicrobial drug use in animals (adapted from Health Canada: Animal Uses of Antimicrobials and Impact on Resistance and Human Health, 2002)

Type of use	Purpose	Routes of administration	Administration to individual or groups	Diseased animals
Therapeutic	Therapy	Injection, orally (feed, water)	Individual or group	Diseased individuals or groups
'Metaphylactic'[1]	Disease prophylaxis or therapy	Injection, orally (feed, water)	Group	Some
Prophylactic	Disease prevention	Injection, orally (feed, water)	Individual or group	None evident
Growth promoter	Growth promotion (food animals)	Feed	Group	None
Growth promoter	Feed efficiency	Feed	Group	None

[1] Metaphylaxis describes mass medication of groups of food animals when some animals are diseased and others are incubating disease or at high risk.

can be legally sold, and depends on extensive testing to assure safety and efficacy, as well as, in the case of food animals, studies of safety for people consuming their products. Registration requirements for veterinary medical products have been largely harmonized internationally under the International Cooperation on Harmonization of Technical Requirements of Veterinary Medicinal products (VICH) of the World Organization for Animal Health (OIE), membership of which includes the EU and USA. A harmonized VICH guideline, GL 27, defines the data requirements for risk of transfer of resistant bacteria or resistance determinants from foods of animal origin to humans. These data are assessed in terms of exposure of food-borne pathogens and commensal bacteria, and the 'qualitative probability' that human exposure to resistant bacteria results in adverse human consequences (Tollefson *et al*., 2006; Valois *et al*., 2008). As part of this assessment, many countries are attempting to stratify the stringency of regulatory requirements by how important a drug is to public health (WHO, 2005, 2007). This is a highly contentious issue, since most antimicrobial drugs can, under various criteria, be claimed as 'critically important'. Antimicrobial drug resistance is an inevitably dynamic field. For example, for decades polymyxins were almost unused in human medicine because of their relative toxicity and would until recently be described as 'unimportant'. The rise of multi-drug resistant *Acinetobacter* spp. and *Pseudomonas aeruginosa* infections in hospitalized people means that they may be the only drug to which these infections are susceptible, and therefore become 'critically important' life-saving drugs. The drawback inherent in categorizing antimicrobial drugs into levels of importance is that the majority of antimicrobial drugs will inevitably end up on the 'critically important' list, and by implication and likely extension be unavailable for animal use. This issue is becoming a major battleground between medical and veterinary users of antimicrobials. A more useful and a more rational approach, which could be adopted in both human and veterinary medicine, is categorization into 'lines' based in part on culture and susceptibility results (Table 2) (Prescott *et al*., 2002; Weese, 2006). This approach has the advantage of simplicity of approach (for example, labels on bottles could indicate the category) and would enhance the use of laboratory diagnosis. Such an approach would reduce concern about the widespread use of third-generation cephalosporins in food animals with minimal restriction (Collignon and Aarestrup, 2007), and their more recent use in companion animals with minimal restriction. Research is needed into whether such a categorization would be accepted in the animal (and human) health world, including the barriers to acceptance and what it would take to implement such a system so that it would be widely accepted. Surprisingly, there is little or no research documenting the factors that determine how veterinarians decide what antimicrobial drugs to administer, and how readily these factors could be changed.

The regulation of antimicrobial drug use in animals is a complex process that has jurisdictional differences (Valois *et al*., 2008). Regulation is more stringent for use of these drugs in food animals, although 'off- or extra-label use' (use of the product in any manner not specified on the label) is often approved under specific circumstances and constraints. Use of antimicrobial drugs in companion animals is subject to less stringent regulation, and there is likely more 'off-label' use in companion animals (as there is in human medicine).

Although the situation is changing, there has been historically no formal interest by regulatory authorities in post-approval use (or periodic re-licensing) of antimicrobial drugs in animals. Some of the label claims for some antimicrobial drugs list approval for use in bacteria that have had their names changed several times since approval or for diseases that have subsequently been shown to be caused by other agents, so that reading labels can be like reading an outdated 1960s veterinary microbiology textbook. The post-approval monitoring of resistance in *Campylobacter jejuni* following the introduction of fluoroquinolones for use of broiler chickens in

Table 2. Suggested categorization of antimicrobial drugs for veterinary use (after Weese, 2006)

Class	Definition	Examples
First-line (primary)	Initial treatment of known or suspected bacterial infection in the absence of culture and susceptibility results. These drugs may commonly be used in human medicine but are usually considered less important for treating serious human (and animal) infections or raise less concern about development of resistance.	Penicillin, most cephalosporins, trimethoprim-sulfonamides, tetracyclines
Second-line (secondary)	Used when culture and susceptibility testing, plus patient or infection factors, indicate that no first-line drugs are reasonable choices. Drugs in this class may be more important for treatment of serious human (and animal) infections or there may be particular concern about development of infection.	Fluoroquinolones, 3rd and later generation cephalosporins
Third-line (tertiary)	Used in serious, life-threatening infections, with the support of culture and susceptibility results, when no first-line or second-line drugs are indicated.	Carbapenems
Restricted, voluntarily prohibited	Used only in life-threatening infections when culture and susceptibility testing indicates no other options. Additional requirements may be indicated, or use may be voluntarily prohibited.	Vancomycin

the USA (Food and Drug Administration, 2001), and the subsequent withdrawal of fluoroquinolones from use in poultry in the USA is, however, a well-known example of post-approval monitoring of approved use of a drug.

Monitoring antimicrobial drug usage in animals

Data on antimicrobial drug usage in animals, together with data on resistance in bacteria derived from animals, are crucially important in the development of policies to control resistance at the national and international levels (WHO, 2001, 2003, 2004; Grave *et al*., 2006). The WHO (2001, 2003) has recommended that all countries develop national monitoring programs to assess the use of antimicrobial drugs in animals. The value of development of accurate usage data is considerable, particularly when also linked to data on resistance in animal pathogens and 'indicator' bacteria. Usage data allows comparison within and between countries, interpretation of trends in development of resistance in targeted bacteria, triggering of introduction of control measures, assessment of the impact of control measures, identification of needs for further targeted research on use and resistance, and development of policies for resistance containment (WHO, 2003; Grave *et al*., 2006). There is considerable attention being paid internationally to the critical components and standardization required for useful monitoring systems (for example, the sources and reliability of the data, the antimicrobial classification systems to be used, the best units of measurement, and the purposes of monitoring), all complex issues excellently discussed by Grave *et al*. (2006).

The quality of the data on antimicrobial use in animals varies considerably between countries, because of variations in the regulations and infrastructure (Grave *et al*., 2006). Data may be accumulated from sources such as voluntary disclosure by pharmaceutical companies, importers and customs forms, pharmacies, feed mills, veterinarians or farmers. Accurate data collection is most available where all antimicrobials are obtained only by prescription and dispensed by pharmacies. In these few countries (Denmark, Norway and Sweden) the quantities used in animals are known to the kg level. Other countries such as Canada are assessing use of voluntary reporting by 'sentinel' veterinarians or farmers who are regarded as typifying usage (Canadian Integrated Program for Antimicrobial Resistance Surveillance, 2005), but such an approach is expensive and inefficient (Grave *et al*., 2006). One powerful argument for making dispensing of all antimicrobials 'prescription only' is that it would potentially allow accurate collection of data on usage. Whether drug usage is reported as total annual weight of active ingredients, doses, courses, animal daily doses (ADD) or prescribed daily doses (PDD), the amounts are useful as measures of 'selection pressure' for emergence of resistance only if they are related to total numbers of animals, and proportion of animal populations being treated. The detail available for total antimicrobial drug use in various species, age groups and types of animal, as well as resistance in bacteria obtained from these animals, in Denmark, Norway and Sweden is quite remarkable (for example, Danish Antimicrobial Resistance Monitoring and Research Program (2006); Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) (2007). The critical value of such high quality usage monitoring data has become apparent in the interpretation of AMR prevalence and changes, particularly in evaluating the usefulness of campaigns to promote prudent use and the impact of the removal of antimicrobial growth promoters on subsequent usage of antimicrobial drugs for therapy (WHO, 2002; Grave *et al.*, 2006). Precise usage data may identify surprising findings that can focus future research. For example, Heuer *et al.* (2005) reported that a comparatively small number of companion animals in Denmark annually consumed the same amount of fluoroquinolones and cephalosporins as a far larger population of food animals. In contrast to studies of use in food animals, the impact of AMR acquired by humans from companion animals as a result of use of antimicrobial drugs in these species has not been the subject of investigation, but may be seriously underestimated (Prescott *et al.*, 2002). The recent global emergence of methicillin-resistant *Staphylococcus aureus* in companion animals (Leonard and Markey, 2008) is one event focusing interest in the use of antimicrobial drugs and AMR in companion animals, including their role as reservoirs of AMR for humans.

Antimicrobial drug stewardship

Antimicrobial stewardship (also called 'prudent use' or 'judicious use') describes the process of reduction of the development, maintenance and spread of resistance through the optimal selection of drug, dosage and duration of treatment, combined with reduction of inappropriate and excessive use (Weese, 2006). Stewardship essentially means 'management of' and 'assumption of responsibility for' something of important value that one does not own, in the interests of its long-term sustainability (adapted from Allerberger and Mittermayer, 2008). The term stewardship resonates with a sense of religious obligation or of prudent preservation of wealth. The emergence and spread of resistance is a complex process that, if it is to be managed successfully, requires a multidisciplinary approach based on research, surveillance, regulation, education, clinical practice, and infection control, within the evolving conceptual framework encompassed 'antimicrobial stewardship' (Paskovaty *et al.*, 2005; Barlam and DiVall, 2006).

National veterinary professional organizations in many English-speaking countries have produced 'prudent use' guidelines within the last decade. These are readily available on the Web sites of these organizations (listed in Weese, 2006). With a few significant differences, most read almost identically, and contain rather general 'motherhood' key advice (e.g. only use when an infection is present or likely present; use as narrow a spectrum antimicrobial as possible; use culture and susceptibility testing whenever possible; use for as short a time as possible; ensure compliance by clients; use only under veterinary prescription or endorsement, etc.). One of the most comprehensive guidelines for use of antimicrobial drugs in animals was developed by the American College of Veterinary Internal Medicine (Morley *et al.*, 2005). A number of national veterinary organizations are attempting to develop 'practice- specific' guidelines (e.g. what is the drug(s) of choice with the precise dosage to be used when a cow is presented for the first time with acute pneumonia), but developing these guidelines involves intense effort and are likely to end up unread on a shelf unless they are vigorously promoted. Even if they are vigorously promoted, they may not be supported by those for whom they are intended. Some veterinarians are quite cynical about attempting to promote 'prudent use' in those countries where many antimicrobial drugs can be readily obtained by farmers as 'feed' antimicrobials for growth promotion and disease prophylaxis without prescription.

Although textbooks are written about antimicrobial use in animals (Giguère *et al.*, 2006; Aarestrup, 2006; Guardabassi *et al.*, 2008), there are numerous areas for improvement of how antimicrobial drugs are used and numerous ways in which their use can be avoided or reduced. Because 'environmental stewardship' is an area of intense current global interest, the term 'antimicrobial stewardship' may capture the imagination more than 'prudent use' or 'judicious use'. One of the mantras of the environmental movement in relation to waste is 'refuse, reduce, reuse, recycle'; in the case of antimicrobial drugs, 'refuse' (do not use) and 'reduce' will have the greatest impact on reducing resistance. However, many other approaches will reduce resistance. For example, optimal dosing is an area where resistance can be reduced. In pharmacodynamic terms, antimicrobial drug classes can be categorized into either 'concentration-dependent' or 'time-dependent' where their killing or inhibitory activity is dependent either on how much the concentration exceeds the minimum inhibitory concentration (MIC) (e.g. aminoglycosides and fluoroquinolones) or how long the drug exceeds the MIC (e.g. β-lactams). Ensuring that these features are optimal is crucial for reducing the emergence of resistance (Lees *et al.*, 2008), and should be taken into account in drug dosage, including the regulatory approval of drug dosage regimens. It seems quite pointless for veterinary diagnostic laboratories to report MIC results without reporting how these could be used to ensure optimal dosing. For example, if MIC data particularly for concentration-dependent drugs could be entered by the recipient into a calculator on a Web site (with animal species and weight), then this could help to reduce the emergence of resistance. Even laboratories determining susceptibility by disk diffusion (Kirby Bauer) could report zone sizes so that they could be used in such calculations. This is an area where veterinary diagnostic laboratories could improve their value, in collaboration with pharmacologists, pharmaceutical companies and regulators. Other approaches to prudent use include categorization as 1st to 3rd line referred to earlier, use of restriction policies and of stop orders, development of practice-based guidelines, use of immunostimulants, and vaccination (Weese, 2006). Poor infection control may be an important source of spread of multi-resistant animal pathogens (Anderson *et al.*, 2008) and there may be considerable scope to assess and if need be improve infection control procedures in veterinary practices.

Conclusions

The emergence of AMR has some similarities to the emergence of global warming associated with greenhouse gases. Both have accumulated over time and for multiple reasons, both appear to be increasing at a rapid pace, and for both there is a fear that they may become both self-sustaining and indeed catastrophic. Is the post-antibiotic era on the horizon? No one simple response, such as just removing growth promoters from food animals, will reverse these trends. The steps required to contain resistance are multiple and incremental, which cumulatively can be effective. The situation is analogous to the concept of 'stabilization wedges' in solving global climate change (Pacala and Socolow, 2004). Pacala and Socolow argue that humanity already possesses the fundamental scientific, technical and industrial know-how to solve the climate and carbon problem using a portfolio of existing and proven technologies, none of which alone will solve the problem but the cumulative effect of 15 will. The effort to develop the research that investigates many aspects of the use of antimicrobials, and which addresses the diversity of use practices encompassed by the term antimicrobial stewardship, and to put the fruits of this research into routine practices (through regulation, surveillance, clinical practice, and education) will be enormous, but is the investment required for a sustainable future for antimicrobial drugs for humanity and animals.

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