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Antimicrobial resistance, prudent use, and the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)

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The treatment of infectious disease in food-animal production is an essential component of veterinary medicine. Antimicrobial therapy is an important tool used by producers and veterinarians to ensure that animal health and welfare are maintained. In addition to therapeutic use, antimicrobials are also used non-therapeutically to aid in disease prevention, growth promotion, and production efficiency. This use of antimicrobials to prevent disease and promote growth may improve the economic and competitive viability of a producer. However, antimicrobial use in food-producing animals is under increasing scrutiny due to reports of antimicrobial resistance and emergence of multi-resistant pathogens in the scientific and lay media. This issue of *Large Animal Veterinary Rounds* discusses the use of antibiotic agents, the development of resistance, and the steps being taken to monitor and control the use and misuse of antimicrobials.

Increased antimicrobial resistance in human and animal pathogens has a substantial impact on the prevention and treatment of infectious disease.[1] Most antimicrobial resistance observed in human medicine can be related to inappropriate use in people,[2] but it is argued that antimicrobial use in veterinary medicine and food-producing animals contributes to the problem.[3-8] The magnitude of risk to human health is difficult to assess, but is a concern because of both unknown and predicted problems.[4]

To limit the dissemination of resistant bacteria and protect the efficacy of antimicrobial therapy in both humans and animals, it is necessary to identify emerging resistance and implement intervention and mitigation strategies.[1] The ultimate goal is the prevention of resistance with attention to reducing antimicrobial use. Approaches to minimizing the development of antimicrobial resistance include the use of monitoring programs, prudent-use guidelines, and educational campaigns.[9]

Antimicrobial resistance

Antimicrobial resistance is an expected form of natural selection. Resistant microorganisms existed long before the introduction of antimicrobials[1] and it is speculated that resistance was probably a defense mechanism used by antibiotic-producing organisms to protect themselves from their own antibiotic.[10,11] This phenomenon ensures that, in the presence of an antibiotic, bacteria possessing the resistance trait will survive, and those that do not, will be eliminated. If bacteria are in an environment with long-term antimicrobial exposure, over time, resistant bacteria will increase in proportion.[1]

Levy described 5 basic principles of antibiotic resistance and possible solutions:[12]

- Given sufficient time and use of an antimicrobial, resistance will develop in a susceptible organism; there is no antimicrobial to which resistance has not eventually appeared.
- Antibiotic resistance is progressive, evolving from low, through intermediate, to high levels. Increasing minimal inhibitory concentrations (MIC) are markers for future resistance.
- Bacteria with resistance to one antimicrobial are more apt to become resistant to others.
- Once resistance appears, it is likely to decline slowly, if at all.
- The use of antimicrobials in one individual affects others in the surrounding environment.

The complexity of the epidemiology associated with antimicrobial resistance is important (Figure 1). The inter-relational nature of antimicrobial resistance suggests that its development in any area can potentially result in the dissemination of resistance to a multitude of other areas. Understanding the epidemiology

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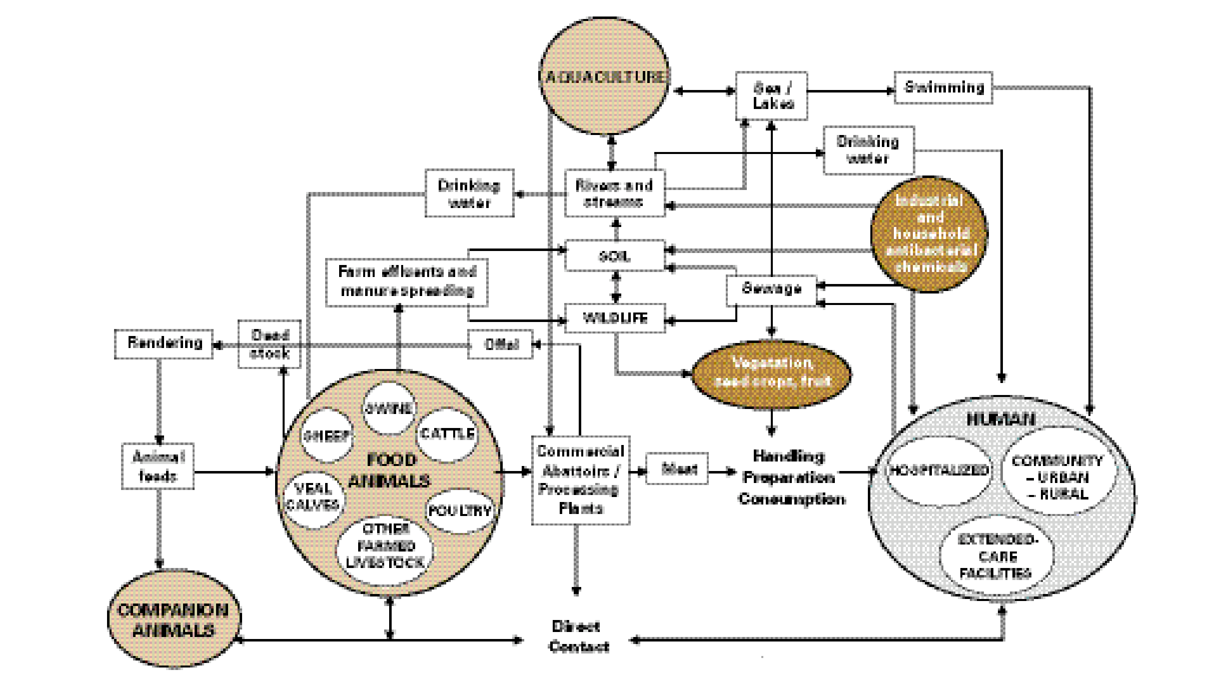
Figure 1: The epidemiology of antimicrobial resistance



Modified from Linton AH. *Vet Rec* 1977;100(17):354-360.

of antimicrobial resistance allows for the development of strategies to limit existing resistance and avoid the emergence of new strains of resistant bacteria.[13]

Mechanisms of resistance

Bacteria are very proficient at sharing the genetic information necessary to survive in the presence of antimicrobials.[1] Transfer of resistance can happen rapidly both within, and between, genera of bacteria.[1,14] Even transient passage of an ingested resistant organism through the intestinal tract can result in the transfer of resistant genes to resident microflora that can then serve as reservoirs for pathogenic bacteria.[1]

The 2 main mechanisms of resistance development are mutation and gene acquisition.[15] Mutation is a spontaneous change in the genome from susceptible to resistant, usually during replication.[15] Gene acquisition is the horizontal gene transfer of resistance from donor to recipient bacteria through conjugation, transformation, or transduction.[16]

- Conjugation is the transfer of resistance genes from a resistant organism to a sensitive organism through a protein channel.[16]
- Transformation is the uptake of naked bacterial DNA from the environment by an acceptor bacteria.[16]
- Transduction is the transfer of resistant genes via a bacterial virus or phage.[16]

Conjugation is the most important method of horizontal gene transfer[17,18] because it allows the spread of mobile genetic elements such as plasmids, transposons, or integron/gene cassettes.[16,19,20] These elements can possess multiple antimicrobial resistance genes and may be responsible for the rapid dissemination of genes among different bacteria.[14,21,22] Linked clusters of antimicrobial resistance on a single mobile element have been demonstrated to aggregate in such a way that antibiotics of a different class or even nonantibiotic substances (eg, heavy metals or disinfectants) can select for antimicrobial resistant bacteria.[22,23] Exchange of resistance genes between pathogens and nonpathogens or between Gram-positive and negative bacteria has also been documented.[24]

Antibiotic use in large animal practice

Diseases associated with the most extensive use of antimicrobials for treatment or prophylaxis are respiratory and enteric diseases of pigs and cattle, mastitis in dairy cattle, and colibacillosis in poultry.[3,4] The major licensed drug categories that have been available and used for years include beta-lactams, tetracyclines, macrolides, aminoglycosides, and sulphonamides.

Enrofloxacin, a fluoroquinolone, has only recently been approved in Canada for use in large animals. The approval is for therapeutic use against bacterial respiratory disease in beef cattle, based on a comprehensive scientific review assessing the safety, efficacy, and effectiveness of the drug, as well as an exhaustive assessment of international studies on antimicrobial resistance.[25] Upon completion of the assessment, the Veterinary Drug Directorate (VDD) concluded that if the drug is used prudently as approved, it will not pose an undue human-health risk, ie, risk associated with antimicrobial resistance in food-borne pathogens.[25] To ensure prudent use, label guidelines indicate that the drug is available by prescription only, it should not be used in an extralabel manner, and should be used only after other antimicrobials have proven ineffective.[25] It is impossible to ensure that label guidelines are followed; however, the VDD requires postmarketing surveillance for antimicrobial resistance development.[25] If surveillance indicates that there is an apparent rise in enrofloxacin resistance as a result of its use, Health Canada will ensure that appropriate interventions are taken, possibly removing the drug from market.[25] Additional measures for licensing the drug are due, in part, to the relative importance of this class of antimicrobials in human medicine and the desire to maintain their efficacy.

Role of the large animal practitioner

On a day-to-day practice basis, antimicrobial resistance is not the primary concern facing veterinarians. Treatments prescribed with traditional antimicrobials are usually successful and resistance-caused treatment failures are not the norm. To ensure that treatment failures do not increase and currently available drugs remain effective, it is necessary to prudently and judiciously use antimicrobials. The loss of efficacious drugs would be detrimental, especially if use restrictions are placed on new antimicrobials.

Veterinarians need to consider the effect of resistance on prolongation of treatment times, increased use of more expensive medications, and the implications for human health. Veterinarians play an important role in public health through the control and eradication of important zoonotic diseases.[13] A part of the Canadian Veterinary Oath is the promise to "strive to promote animal health and welfare, relieve animal suffering, protect the health of the public and environment, and advance comparative medical knowledge."[26] The International Office of Epizootics (OIE) recommends that veterinary professional associations develop species-specific clinical practice guidelines for the responsible use of antimicrobials with particular reference to the choice of product, disease prevention strategies, and treatment protocols.[27]

Prudent antimicrobial use

There is no absolute proof of a causative association between antibiotic use and resistance, but most authorities believe the association to be virtually certain.[28] Resistance mechanisms have been identified and described for all known antimicrobials currently in clinical use.[1] Research demonstrates that veterinary pathogens, such as some *Escherichia coli*, *Salmonella* spp., *Enterococcus* spp., *Staphylococcus* spp., and *Campylobacter* spp. have acquired multiple antibiotic-resistant phenotypes. Therapeutic antibiotics for these organisms could become very limited or nonexistent in the near future.[12,14,29-31]

The Canadian Veterinary Medical Association (CVMA) has taken a pro-active stance on antimicrobial resistance[26] and has made several general recommendations:

- Veterinarians, animal owners, and animal caretakers all share a responsibility for minimizing the use of antimicrobial drugs to conserve drug efficacy.[26]
- Veterinarians have a responsibility to ensure the education and training of staff, clients, and other animal handlers on the prudent use of antimicrobials.[26] They must confirm that all users are aware of the appropriate administration, handling, storage, disposal, and record keeping for antimicrobials.[26]
- Veterinarians should continually update their knowledge of disease prevention, therapeutics, and drug-resistance trends to ensure the prudent use of antimicrobials.[26]
- Implementation of preventive measures (eg, vaccination, biosecurity measures, good hygiene practices, and improved management) may prevent disease and reduce the use of antimicrobials. Additionally, if the veterinarian understands that resistance patterns are emerging on a farm, he will be better able to make recommendations for antimicrobial treatment.
- All antimicrobials (even those not purchased directly through or on prescription from a veterinarian) should be used within the confines of a valid veterinarian-client/patient relationship.[26] A veterinarian's understanding of farm management and disease status should ensure appropriate antimicrobial use and treatment design to maximize therapeutic efficacy and minimize bacterial resistance.

The structures and biochemical pathways that determine antibiotic availability within microbes and the pharmacodynamic and pharmacokinetic properties of antimicrobial drugs is complex.[32] Rational dosing of antimicrobials depends on a knowledge of physiology, anatomy, pathology, and disease conditions.[33] Resistance can result from the selection of an inappropriate antibiotic or failure to optimize the dose level (eg, for concentration-dependent antimicrobials), dose intervals (eg, for time-dependent antimicrobials), and duration of treatment.[32] Pharmacokinetic variation may result from the disease status, age, and weight of the animal, or from nonbiological factors such as route of administration, formulation, and drug interactions.[32] With an optimized dosage schedule, the beneficial effects of treatment are maximized and potential adverse effects minimized.[32] Veterinarians are trained to consider all of these factors and make recommendations for optimal antibiotic usage.

Access of producers to over-the-counter (OTC) antimicrobials often results in antimicrobial use with little or no veterinary consultation.[9] These OTC drugs are made available to producers for purely practical reasons (eg, lack of veterinarian access).[9] This practice can result in inappropriate antimicrobial choices, dosing, and treatment frequency, and may be a factor in the development of antimicrobial resistance.

The continued availability of antimicrobials in veterinary medicine depends upon the profession's ability to use these products wisely and find the balance between maximizing animal welfare and conserving antimicrobial efficacy.[34] By increasing awareness about antimicrobial resistance and implementing prudent-use recommendations, veterinarians can promote long-term efficacy and continued availability of antimicrobials. For more specific recommendations on prudent use please refer to the CVMA website (http://canadianveterinarians.net).

Initiatives in other countries

Minimizing resistance has become an international priority and many countries are implementing national surveillance systems. Properly designed surveillance systems can provide relevant, high-quality data for assessing antimicrobial resistance trends.[9] The approaches to surveillance are varied, but attempts are being made to harmonize the methodologies of antimicrobial-resistance testing and antimicrobial-use reporting between countries to facilitate more accurate international comparisons.

Regulations and restrictions concerning antimicrobial use in food-animal production are extremely variable. For example, Europe has taken a precautionary principle approach, stating that antimicrobial use must be restricted if there are potential public health risks, and consumers must be protected even if direct evidence of a problem is not available. This approach led to the European Union ban on the animal use of avoparcin in 1996, and of tylosin, zinc bacitracin, spiramycin, and virginiamycin in 1998.

Currently, the United States and Canada are not adopting the precautionary principle approach, but international policies regarding antimicrobial use may ultimately have an impact in Canada, especially in the context of international trade.

Canadian initiatives

In response to the recommendations of the 2002 Health Canada Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health (http://www. hc-sc.gc.ca/vetdrugs-medsvet/amr-final_report_june27_ tc_e.html Accessed: July 22, 2005), the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) was developed to provide a representative and unified surveillance system for antimicrobial resistance and antimicrobial use in Canada.

CIPARS is modeled after initiatives in the United States and Europe for monitoring trends in antimicrobial use and resistance development in selected bacteria from human, animal, and food sources across Canada. This is crucial information for developing and evaluating prudent-use policies and other risk-management strategies.

CIPARS is composed largely of veterinary epidemiologists who understand livestock agriculture by virtue of on-farm experience in various commodity sectors. The food-safety focus dictates that the bacteria of interest are zoonotic enteric pathogens and commensals, but where possible, animal-health pathogens important to each participating commodity group are included.

Active surveillance for the 3 major commodities – beef, poultry, and pork – is currently being conducted at the abattoir and retail levels. Abattoir surveillance involves the collection and analysis of isolates of *Escherichia coli* and *Salmonella* from the intestinal (caecal) contents of healthy animals at slaughter across Canada. Retail surveillance involves the collection and analysis of isolates of *E coli*, *Salmonella*, and *Campylobacter* from retail meat in Ontario, Quebec, and Saskatchewan. These active agri-food surveillance activities provide an indirect measure of potential human exposure to resistant organisms arising from consumption of animal products. CIPARS also includes passive surveillance of antimicrobial resistance in *Salmonella* from human and diseased-animal specimens collected from laboratories across Canada.

CIPARS is continuing to build the framework and partnerships for collecting relevant and representative antimicrobial resistance data along the food chain. Future plans include expansion of retail surveillance to other provinces and the addition of other bacterial species and food-producing animals. An on-farm component will be added to CIPARS in 2005. It will consist of a sentinel farm framework to provide data on antimicrobial use and on-farm samples for bacterial isolation and antimicrobial susceptibility testing. On-farm data collection and sampling will focus on swine initially, although there are ongoing discussions regarding the feedlot beef sector. The justifications for selecting swine as the "proof of concept" on-farm surveillance commodity included an advanced national quality-assurance program for swine called the Canadian Quality Assurance (CQA®-AQC; an auditable On-Farm Food Safety [OFFS] program), the absence of recent foreign animal-disease outbreaks in this industry, and a similar initiative for swine in the United States (Collaboration in Animal Health and Food Safety Epidemiology, CAHFSE).

The CIPARS on-farm group has been working closely with an expert review panel to develop the surveillance framework. In addition, an advisory committee of producers, veterinarians, and government representatives has been formed to consult on program implementation. The primary objective of the on-farm group is to establish an infrastructure for ongoing surveillance. Recognizing that there are gaps in knowledge regarding antimicrobial use and resistance in livestock, this surveillance framework should provide a research platform for studies to answer specific questions. The information will help refine methodologies for antimicrobial use and resistance surveillance and, ultimately, the framework may be used to examine issues beyond antimicrobial resistance that are important to the livestock industry.

CIPARS is also attempting to describe antimicrobial use in Canada. Since publicly available antimicrobial-use data are scarce and very difficult to obtain, CIPARS is trying to resolve barriers in collecting these data in food-producing animals. The gap in reliable usage data makes it difficult to state with confidence which antimicrobials are used, in what quantities, and for what purposes in the various sectors of agriculture and veterinary medicine. This slows investigations of the relationship between antimicrobial use in animals and the emergence and spread of resistant bacteria among animals, and between animals and humans.

CIPARS is committed to reporting human antimicrobial-use information. These data are more readily obtained through the Intercontinental Medical Statistics (IMS) Health database, which describes and quantifies antimicrobial use in the Canadian population.

CIPARS, at the moment, has only 2 years of information collected in a harmonized fashion to permit data comparisons. Data for 2002 and 2003 can be accessed through the CIPARS website http://www.hc-sc.gc.ca/pphb-dgsp-sp/cipars-picra/. To assess antimicrobial resistance trends in Canada, many years of data must be collected and analyzed. Collectively, these activities will elucidate factors in the development and spread of antimicrobial resistance along the food chain and inform risk-management decisions.

CIPARS results 2003

Different classes of antimicrobials are used in human and animal medicine for the treatment and prevention of bacterial diseases. Some of these antimicrobials are last-line drugs for treating life-threatening infections in humans. If these drugs become ineffective, alternative antimicrobials are unavailable. These and newer generation antimicrobials with unique mechanisms of action and/or resistance are of Very High Importance (Category I) in human medicine. Antimicrobials considered of High Importance (Category II) have limited alternatives in human medicine. First-line or second-line antimicrobials may be classified as Medium Importance (Category III) or Low Importance (Category IV) depending on their therapeutic usefulness.

In veterinary medicine, most antimicrobials used therapeutically are in Category II and III, while many feed additive antimicrobials are in Category IV. The following summary is based on the CIPARS 2003 Annual Report, Executive Summary[34] focusing on drugs classified as Category 1 by the Veterinary Drugs Directorate (VDD). Detailed information on resistance surveillance across species can be found in the full annual report.[34]

Agrifood surveillance

Generic *E coli* from abattoir samples showed resistance to ≥1 antimicrobials in 88% of swine, 84% of chickens, and 34% of cattle isolates. These results did not differ significantly from those found in 2002. No resistance was observed for fluoroquinolones, but there was resistance to ceftiofur in 26 chicken (17%) and 2 cattle (1%) *E coli* isolates. In the case of *Salmonella*, 41% of isolates from chickens and 49% from swine were resistant to ≥1 antimicrobials. One *Salmonella* isolate (0.3%) from swine and 8 (6%) from chickens were resistant to ceftiofur; one isolate from chickens (0.8%) was resistant to ceftriaxone. For the retail meat samples collected, the percentage of *E coli* isolates demonstrating resistance was lower overall than among abattoir samples. Resistance to ceftiofur in *E coli* was highest among chicken isolates (18% of Ontario and 33% of Quebec isolates). In the case of *Salmonella*, ceftiofur resistance was detected in 3 Ontario (12%) and 14 Quebec isolates (50%) from chickens. For *Campylobacter* isolates from chickens, 56 from Ontario (72%) and 74 from Quebec (79%) were resistant to ≥1 antimicrobials. In particular, 3 *Campylobacter* isolates (4%) from Ontario and 3 from Quebec (3%) were resistant to ciprofloxacin. Provincial differences in the prevalence of resistance need to be investigated through further research and continuous, expanded surveillance efforts in multiple provinces over many years.

With passive surveillance of *Salmonella* in animals, clinical isolates from cattle were more frequently resistant than those isolated from other species. This reflected an outbreak of *S Newport* in 3 Ontario dairy herds where isolates resistant to ≥9 antimicrobials were isolated. Notably, ceftiofur resistance and reduced susceptibility to ceftriaxone were observed among 100 (43%) of all *Salmonella* isolates from cattle. Ceftiofur resistance was also detected in *Salmonella* from 2 swine (2%), 3 chicken (9%) and 6 turkey (17%) clinical isolates.

Human surveillance

In 2003, a representative sample of 3056 clinical isolates from all provincial public health laboratories was collected to establish a baseline for antimicrobial resistance in human *Salmonella*. The prevalence of resistance to ≥1 of 16 antimicrobials tested varied by serovar: 315/610 isolates (52%) of *S typhimurium*, 64/127 isolates (50%) of *S typhi*, 282/613 isolates (46%) of *S Heidelberg*, 77/352 isolates (22%) of *S enteritidis*, and 28/175 isolates (16%) of *S Newport*. Resistance to ceftiofur was identified in 6% of all isolates. Resistance to ceftriaxone was identified in 3/613 *S Heidelberg* isolates (<1%), but reduced susceptibility to ceftriaxone was observed in a number of serovars. Two *S typhimurium* isolates (<1%) were resistant to ciprofloxacin. The integration of antimicrobial resistance information from retail meat and human surveillance highlighted that, for *S Heidelberg*, resistance frequencies for most cephalosporins and for amoxicillin-clavulanic acid were generally higher in chicken than in human isolates. There were also provincial differences observed at the retail level. Comparisons in resistance data for *S typhimurium* between abattoir and human samples also tended to show a higher prevalence of resistance among isolates of animal origin. Further characterizations of animal, meat, and human strains are needed to define their genetic relatedness.

Human antimicrobial use

Analysis of IMS Health data revealed that in 2003, the human systemic antibacterial classes most frequently dispensed by retail pharmacies in Canada, as a proportion of total DDDs (Defined Daily Dose), were extended-spectrum penicillins (27%), macrolides (20%), tetracyclines (14%), fluoroquinolones (12%), and first- and second-generation cephalosporins (10%). After controlling for population size, systemic antibacterial use appears to have increased between 2002 and 2003, given the higher number of DDDs, prescriptions, and dollars spent; however, use in both 2002 and 2003 was lower than observed in 2001 (with the exception of the dollars spent per inhabitant for 2003). Nevertheless, Human Health Importance Category I drugs represented an increasing proportion of the total DDDs dispensed (primarily fluoroquinolones and glycopeptides): 11.0% in 2001, 11.7% in 2002, and 12.1% in 2003. In addition to annual variations, systemic antibacterial use appeared to differ by province, season, patient sex, and patient age. Of the total number of patient visits in which the sampled physicians mentioned antimicrobial therapy between July 1, 2002 and June 30, 2003, 43% of associated diagnoses were respiratory system diseases.

Animal antimicrobial use

CIPARS is committed to the development of a national system for monitoring antimicrobial use in animals. The design is still ongoing, but will include data collected from a variety of sources. The 2004 CIPARS Annual Report will be one step closer to the eventual implementation of an operational system with the inclusion of national sales data and preliminary on-farm use data.

Conclusions

There are many gaps in our knowledge of the development and dissemination of antimicrobial resistance. Further insight into the complex ecology and molecular aspects of antimicrobial-resistant organisms is essential. Surveillance is important for supporting new treatment guidelines and interpreting the effects of current-use patterns and intervention strategies. National policies on antimicrobial use in animal husbandry and veterinary medicine will also be supported through national surveillance systems.

More prudent use of antibiotics in both human and veterinary medicine, especially as it relates to food production, is urgently needed.[29] In addition, there is a great need for continued education about bacterial antimicrobial resistance and prudent-use practices for both human and veterinary healthcare professionals.[29] The primary objectives of responsible use are to maintain efficacy of antimicrobials, avoid dissemination of resistant bacteria or resistance determinants, and avoid human exposure to antimicrobial resistance through food.[27]

It is clear that the use of antimicrobials in both humans and animals selects for resistant bacterial populations.[6,12,22,35] The question is whether the populations of resistant bacteria identified in humans and animals are independent or if they comprise a common pool, thus posing a potential threat to both human and animal health?[6,14] A concerted effort must be made by veterinarians and medical doctors to reverse the trend towards increasing antimicrobial resistance and to preserve the effectiveness of current and new antimicrobials for both their own benefit and the greater good.

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