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Uses of Antimicrobials in Food Animals in Canada: Impact on Resistance and Human Health

Report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health

Prepared for:
Veterinary Drugs Directorate, Health Canada

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Canada

UNIVERSITY of GUELPH

ONTARIO VETERINARY COLLEGE
Department of Population Medicine

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Diane Kirkpatrick
Director General,
Veterinary Drugs Directorate,
Health Products and Food Branch,
Health Canada

Dear Ms. Kirkpatrick:

The Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health has completed the tasks assigned to it and is pleased to submit its report. The committee encourages Health Canada to make the report publicly available as soon as possible.

As described in its terms of reference, the committee focused on providing information relevant to reducing the potential resistance and human health and safety impacts associated with animal uses of antimicrobial agents. This included the identification and prioritization of relevant issues surrounding antimicrobial uses and their contribution to resistance. The committee determined that actions should be taken to better protect the health and interests of Canadians. Accordingly, it made 38 recommendations for Health Canada, or in some cases (especially recommendations 20-24), for Health Canada's partners in provincial governments, veterinary professional organizations or industry.

Committee members represented a broad range of expertise and stakeholders. The report is a consensus opinion that may not always represent the position of every member's organization or affiliation.

The committee is grateful to Health Canada for providing financial, logistical and secretarial support for its meetings and report preparations. Able secretariat assistance was provided by a number of Health Canada and CFIA scientists, in particular, Drs. Lateef Adewoye, Rebecca Irwin and William Yan. We thank Drs. Paula Fedorka-Cray and Stephen Sundlof from the U.S. and Dr. John Turnidge from Australia for their presentations and discussions with the committee. The editorial services of Dr. Jane Sadler Richards are gratefully acknowledged. Special thanks to Drs. André Broes, Robert Higgins, Serge Larivière, and Serge Messier for their collaboration on chapter 7. Thanks also to Dr. Jane Gates for reviewing the final draft and making many helpful suggestions on style.

On behalf of the committee, thank you for the opportunity to address this part of the complex problem of antimicrobial resistance in Canada.

Sincerely,

Scott McEwen D.V.M., D.V.Sc. Diplomate ACVP
Professor and Committee Chair

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Executive Summary

Resistance to the effects of antimicrobial drugs is a serious problem in Canada and the world. The problem, often referred to as antimicrobial resistance or AMR, costs lives and money and threatens our ability to treat infections in humans and animals. Our traditional response to the development of antimicrobial resistance has been to use different, often new, drugs to treat the disease. This approach is no longer tenable because the supply of new, effective, safe and affordable products is expected to diminish in the future.

The medical community in Canada recognizes that the most serious resistance problems in people are attributable to overuse in human medicine. Nevertheless, large quantities of antimicrobial drugs are used in food-animal production, many of which are the same, or close relatives of drugs used in humans. Although antimicrobials are very beneficial in modern livestock production, many wonder what, if any, impacts such use has on human health, and what, if anything, should be done about it?

In 1999, Health Canada established the group responsible for this report, the "Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health." Its role was to provide advice and assistance to Health Canada in the development of policy options related to the animal uses of antimicrobial agents. The committee members are based in academia, animal welfare, consumer interest groups, the feed industry, the food-animal industry, human medicine, the pharmaceutical industry, public health, and veterinary medicine. The committee was assisted by a secretariat consisting of Health Canada and Canadian Food Inspection Agency (CFIA) scientists. During its deliberations, the committee reviewed and discussed relevant scientific literature and consulted with experts from abroad.

Over time, the complexity and sometimes-contentious nature of the issues facing the committee became evident. Although mindful of the many detailed reviews and sets of recommendations available in the public domain and reluctant to "reinvent the wheel," the committee decided it was important to present the Canadian perspective in their recommendations along with a fairly detailed discussion of the scientific evidence of human and animal health impacts, the international response to the problem, stakeholder perspectives on the benefits of antimicrobials in animals, and the options for managing resistance risks. In the interests of openness and the need for a broad consultation on the problem of antimicrobial resistance, the committee believes that Health Canada should make this report public and seek comment from Canadians.

As the federal agency primarily responsible for the health of Canadians, Health Canada must make some difficult decisions concerning management of the risks associated with antimicrobial resistance. The committee trusts that its recommendations will continue to be helpful to the decision-making process. Although the committee's mandate is to provide advice to Health Canada, it suggests

that provincial agencies and other groups in Canada should also consider the recommendations that affect them. Health Canada is responsible for regulating the safety and efficacy evaluation, sale, and labelling of veterinary drugs, but provinces are responsible for regulating the practice of veterinary medicine, and many further regulate the sale and distribution of antimicrobials. Also, there are relevant self-regulatory responsibilities that fall on the food-animal and pharmaceutical industries, and on veterinary medical organizations.

Altogether, the deliberations led to 38 recommendations. These are listed in full at the end of this summary, and at the ends of chapters of the accompanying report. Six of these, deemed by the committee to be most important, are featured within this summary.

Adverse effects of antimicrobial resistance from food animals on human health

The committee began by defining the nature of the problem. A bacterium can acquire resistance to an antimicrobial when a genetic mutation occurs within the organism or when it acquires existing resistance genes from another organism. Genes encoding resistance to multiple drugs are often linked together, therefore use of one drug can select for resistance to a completely unrelated drug (co-selection). Resistance among bacteria in animals can adversely affect human health directly or indirectly. Direct effects are the result of resistance among zoonotic infections (zoonoses are diseases transmitted from animals to humans). Indirect effects occur when resistance genes from animal bacteria are transferred to human pathogens.

Resistance in bacteria is observed most where antibiotics are in wide use and where bacteria can readily be passed between individuals. It is well established that the longer an antimicrobial drug is used, the more likely it is that resistance will emerge (*e.g.* resistance to older drugs, including sulfonamides and tetracyclines). This is the major reason that microbiologists question the prolonged administration of important antimicrobial drugs in the feed of animals. Antimicrobial selection pressure is cumulative in a population.

Direct effects

Food animals are important reservoirs of many bacterial infections of humans. In Canada, the most prominent include *Salmonella enterica* and *Campylobacter jejuni*. Thousands of cases of these infections occur annually, and most are transmitted through contaminated food or water, although contact with animals and person-to-person spread are sometimes responsible. Many, but not all of these infections are resistant to antimicrobials, and there is considerable evidence that resistance does make matters worse. Although scientists often do not know the precise origin of resistance in these bacteria, antimicrobial use in animals is probably the major contributing factor.

There are several ways that resistance may directly increase the burden of human illness due to these pathogens. First, resistant zoonotic infections can be more difficult or expensive to treat than susceptible infections. Second, some resistant pathogens may be more virulent or pathogenic to humans than susceptible pathogens,

thereby causing more severe or longer-lasting disease. Third, the presence of antimicrobial resistance in zoonotic pathogens can increase the number of cases of illness, because prior antimicrobial therapy (*e.g.* treatment for another reason, before the onset of salmonellosis) can increase the risk of disease. Finally, resistance in bacteria may enhance the spread of infection or the duration of fecal shedding in animal populations that are undergoing antimicrobial therapy, making these pathogens more available for infection of humans.

Special recent concerns focus on resistance to drugs of critical importance to human therapy, for example, the fluoroquinolones. Studies in Europe and the United States indicate that use of these drugs in animals can select for resistance (or reduced susceptibility) in human pathogens, in particular *Campylobacter jejuni* and *Salmonella enterica*. The incidence of fluoroquinolone-resistant human *Campylobacter* infections increased after these drugs were licensed for use in food animals. Some pathogens, for example *Salmonella* Typhimurium DT104, are resistant to multiple antimicrobials. Multiple antimicrobial resistance is a highly complex phenomenon. It may reflect years of antimicrobial selection pressures from many different farms, different animal species (including humans) and perhaps even different countries. This makes it very difficult to trace the origins of resistance. The best way to prevent this type of complex resistance development is to reduce selection pressure, *i.e.* reduce antimicrobial use in all areas as much as possible.

Indirect effects

Even resistance in animal bacteria that are harmless to humans is important to public health because these bacteria are a pool of resistance genes available to be transferred from animal bacteria to human pathogens. This can involve any of the hundreds of species of bacteria that inhabit the gut of animals and humans, but is best studied in *Escherichia coli* and *Enterococcus spp*. A good example of the importance of resistance in these organisms is the case of vancomycin-resistant enterococci (VRE). Enterococci are part of normal human and animal microbial flora, and are opportunitic pathogens of humans, especially in hospitals. In northern Europe and some other regions (but not Canada or the United States), avoparcin, an antibiotic related to vancomycin, was used in animal feed until 1997. Genetic typing studies showed that strains of VRE from animals, meat and humans were related, and provided evidence of an animal source of resistance genes.

Control of antimicrobial resistance in the human health sector

The most important issue in community infections of humans is the increase in prevalence of antimicrobial resistance in respiratory, enteric, and sexually transmitted disease pathogens, most of which do not originate in animals. There are a number of programs and initiatives underway in Canada to prevent and control the emergence and dissemination of antimicrobial resistance in the human health sector, including surveillance, education, infection control and reductions in the consumption of antibiotics.

Within the last five years there has been a decrease, overall, in the use of antibiotics in the outpatient setting. This may be, in part, a result of the education of physicians regarding the threat of antimicrobial resistance and/or the increased awareness of the

public due to extensive and sustained media interest in this issue. In the hospital setting, major improvements include an appreciation of the importance and adoption of infection control practices to limit the spread of resistant pathogens, and improvements in laboratory recognition and reporting of resistance.

Lessons learned from the human sector could well be applied to the animal field. These include recognition of problems through surveillance, education regarding the consequences of inappropriate use, greater control of antimicrobial use, guidelines for best practices, and improvements in private and public laboratories' abilities to recognize and report on emerging drug resistance problems.

Regulation and distribution of antimicrobials for use in food animals

In general, the committee is concerned that Health Canada lacks specific plans to manage the risks associated with antimicrobial resistance transmitted from food animals and lacks credible, scientifically valid methods and criteria to assess the safety of veterinary drugs with respect to antimicrobial resistance and human health. Canadian regulatory authorities are not as active and effective as they should be in addressing these deficiencies.

Regulation

Health Canada regulates the sale of drugs in Canada through the *Food and Drugs Act* and *Regulations*, and the *Controlled Drug and Substance Act*. For human drugs, these legislations are administered primarily through the Therapeutic Products Directorate (TDD). For veterinary drugs, including antimicrobials for food animals, these legislations are administered primarily through the Veterinary Drugs Directorate (VDD), formerly Bureau of Veterinary Drugs (BVD). The VDD is responsible for human food safety issues pertaining to veterinary drugs.

Before issuing a license to market a drug in Canada, Health Canada evaluates information provided by sponsor companies concerning product quality, animal safety, toxicology, efficacy, and human safety. Presently, there are no specific methods and criteria available in Health Canada for human health safety assessment of veterinary drugs with respect to antimicrobial resistance. Without scientifically sound methods for safety assessment, it is impossible for Health Canada to completely and objectively analyze the health risks associated with antimicrobial resistance, and thus, whether any current or future use of antimicrobials in animals warrants regulatory action. Without sound methods and criteria, it is impossible for the informed public (including drug sponsors) to know "what the rules are." On the other hand, it is important that Health Canada provide timely approvals of new antimicrobials that can be used legitimately and safely in animals. This is in the public's interest because the lack of safe and effective drugs is a prime motivator for extra-label use, a use pattern where there is much less assurance of safety.

It would be wrong to suggest that these are simple issues to address. There is no international consensus on safety standards for antimicrobial resistant pathogens in foods or in the environment. However, progress is being made internationally, and Canada's participation needs to be more effective.

The committee believes that regulation of antimicrobials for veterinary use in Canada is not well coordinated. Health Canada regulates the sale of antimicrobials, but the use of drugs is considered veterinary medicine, which is a provincial responsibility. Licensed veterinarians must meet standards of professional conduct in serving the public and maintain competency in the diagnosis and treatment of disease. Nevertheless, the committee is concerned that some important responsibilities (*e.g.* enforcement) fall between the cracks of federal-provincial jurisdiction. The committee found no evidence that these groups have met to coordinate antimicrobial distribution and use matters.

Availability and sale of antimicrobials

We do not have an ideal system for distribution of food-animal antimicrobials in Canada. In an ideal system, only drugs manufactured to Good Manufacturing Practices (GMP) standard and evaluated and approved for safety and efficacy by Canadian regulatory authorities would be administered to animals. A licensed veterinarian who is not in a conflict of interest with respect to antimicrobial sales would make treatment decisions. Antimicrobials would be available only under prescription, and would be readily available to farmers and economically priced. Several gaps between the ideal and reality exist in this country. Some should be remedied soon to protect public health.

Federal regulations divide veterinary antimicrobials into those that can be sold only under prescription and those that can be sold without a prescription (over-the-counter, OTC). Pharmacists, veterinarians and approved layperson outlets may sell antimicrobials. Non-prescription antimicrobials for feed use are approved by Health Canada and listed in the Canadian Compendium of Medicated Ingredients Brochure (CMIB). Only drugs and drug combinations that are specifically listed in the CMIB may be used in feed unless accompanied by a veterinary prescription. A drug that has only therapeutic approval cannot be used as a growth promoter, even under a veterinary prescription.

Each province in Canada has its own regulatory body and has the right to regulate more stringently, but not more leniently, the sale of drugs once they are approved at the federal level. Several provinces enable licensed veterinarians to buy and sell veterinary drugs if they have a veterinarian-client-patient relationship. Most provinces also license lay premises to sell veterinary antimicrobials. These premises include feed mills or dealers and retail outlets.

Quebec has more stringent regulations than other provinces. The sale of veterinary drugs is restricted to pharmacists and veterinary surgeons. Some drugs may only be sold under veterinary prescription, while others may be sold in a veterinary office. Permits are required to manufacture, distribute and sell medicated premixes or medicated feeds.

Canada is one of the few industrialized countries that allows OTC sale of antimicrobials for food animals. On first glance, movement to a prescription-only system would appear to be a logical step towards more responsible use of antimicrobials. On purely scientific or public health grounds, there is little argument

against a prescription-only system. The committee was made well aware, however, that things are not quite so simple or straightforward, and that there are socio-economic arguments (*e.g.* costs and convenience) against such a system.

OTC availability of antimicrobials may contribute to the risks associated with antimicrobial resistance because there is no direct professional oversight of the use of these products. Without veterinary input, OTC use is largely incompatible with many of the principles of prudent use of antimicrobial drugs for disease treatment and control. Treatments may be administered inappropriately, for the wrong diseases, in insufficient doses, or for incorrect periods of time or routes of administration. A substantial proportion of producers rarely, if ever, seek the professional advice of a veterinarian concerning antimicrobial treatments.

The committee was advised of concerns that prescription-only access will drive up the cost of animal health care. To some extent, calls for prescription-only availability are linked, in the minds of producers, to self-interest by the veterinary profession. Producers are concerned that there will be insufficient competition in the marketplace, leading to higher drug costs and therefore higher costs of production. Quebec successfully implemented a retail network for pharmaceuticals to the food-animal industry through licensed veterinary practitioners by means of price ceilings. While the committee did not extensively investigate the Quebec model for distribution, it believes that careful consideration of Quebec's drug policy and its applicability to the rest of the country is warranted.

The committee believes that movement to a prescription-only system need not require a veterinarian to visit the farm each and every time an animal requires treatment. This would be both very expensive to the producer and impractical on many farms. Rather, prescriptions could be provided for specific conditions over a finite period of time and with regular re-evaluations of the need for treatment by their veterinarian.

Recommendation

Make all antimicrobials used for disease treatment and control available by prescription only.

Antimicrobial sale by veterinarians

Most, but not all veterinarians in food-animal practice obtain a portion of their income from the sale of antimicrobial drugs. As the diagnostician, the prescriber of treatment, and the owner of a drug inventory, veterinarians are in a position of conflict of interest with respect to prescription-only drugs. If those antimicrobial drugs that are currently available for OTC sale are limited to sale by prescription only, then veterinarians will be placed even further in a position of conflict of interest. The committee agreed that it is appropriate for veterinarians to dispense antimicrobials and that they should be appropriately compensated for their services. The committee also agreed that the dispensing of antimicrobials should not lead to

any incentive to veterinarians to dispense antimicrobials, or to recommend any specific antimicrobial. Prescribing and pricing mechanisms such as those used in Quebec should be studied as a potential national model.

Extra-label use

In general, federal law is designed to protect the health of Canadians, and provincial law is designed to deliver health services and license practitioners. Accordingly, Health Canada does not regulate veterinary medicine — it is under provincial jurisdiction; therefore, federal regulation does not prevent veterinarians from using their discretion when prescribing drugs. In some cases, veterinarians use this discretion to prescribe use of an antimicrobial drug that is not indicated on the product label (often called “extra-label or off-label use”). Typically, these treatments are prescribed when no approved drugs or dosages are effective for given species or conditions, and because of the limited availability of approved drugs for minor species (*e.g.*, fish, goats, llamas, sheep).

There are legitimate reasons for extra-label prescribing by veterinarians, however the practice raises concerns. Current professional education emphasizes the need when prescribing extra-label to ensure that illegal residues do not occur in foods from treated animals. Very little attention, however, is given to the possible resistance risks from such use. Prominent among these is the extra-label use of antimicrobials that are very important in human medicine but unapproved in food animals.

The committee is concerned about the lack of a clear and comprehensive policy on extra-label use in Canada, especially as it pertains to antimicrobial resistance. The committee believes that Health Canada should use its authority to define the acceptable limits of this practice with respect to impact on antimicrobial resistance. A sensible approach is to limit extra-label use as much as possible, especially for those drugs considered to be critical for therapy in humans or animals. If appropriate, regulatory authorities should prohibit extra-label use of certain drugs.

Recommendation

Develop an extra-label use policy, which ensures that this practice does not endanger human health. Such a policy should include the ability to prohibit the extra-label use of specific drugs of critical importance to human health.

Direct importation and use of active ingredients

The committee was informed that some farmers are legally importing from retailers overseas (sometimes via the Internet) antimicrobials for use in their own animals. Under current law, antimicrobials may be imported for the treatment of a person's own animals, if they are not to be re-sold, if the drug is not listed prescription-only, and if it is clearly marked "for veterinary use only."

The committee was also informed that some active pharmaceutical ingredients (APIs) are being illegally offered for sale and administered as drugs directly to food animals in Canada. APIs are defined as bulk, pharmaceutically active substances that are used in the formulation of drugs in dosage form. There are few restrictions or controls in place regarding the importation and sale of APIs in Canada.

The committee is very concerned about the loopholes in Canadian law allowing importation and use in food animals of antimicrobials under "own-use" provisions, or direct use of APIs, because they bypass the pre-market approval process, and because they raise questions about Health Canada's capacity to enforce its legislation. There can be no assurance, therefore, that products used under these circumstances are safe. Their continued use undermines the credibility of national and international strategies to control antimicrobial resistance and acts a deterrent to the sale of antimicrobials by legitimate means in Canada.

Recommendations

Evaluate, register and assign a DIN to all antimicrobials used in food animals, whether manufactured domestically or imported. This includes antimicrobials imported in bulk (API), which should be allowed into Canada only under permit. The intent of this recommendation is to stop the direct use of APIs in food animals.

Stop the importation, sale and use of antimicrobials not evaluated and registered by Health Canada. The intent of this recommendation is to stop the "own use" loophole.

Uses of antimicrobial drugs in food animals

Antimicrobials are used in food animals for therapy to treat disease, to control or prevent infection and for growth promotion and production efficiency. Therapeutic treatments may be administered to individual animals; however, it is often more feasible and efficient to treat entire groups by medicating feed or water. Prophylactic treatments are typically used during high-risk periods for disease (*i.e.* after weaning or transport). Most controversially, food animals (except farmed fish) may also be administered antimicrobials for growth promotion or performance enhancement purposes.

Benefits of antimicrobials are clearest in treatment of animals sick with bacterial infection. In the case of growth promoters, reports in the scientific literature suggest that under experimental conditions, improvements of 1–15% in weight gain or feed efficiency may be realized; but no one really knows how beneficial they actually are. It appears that benefits are greatest under conditions of poor hygiene and management, and although benefits may be small on a per-animal basis, the net effect across an entire industry may be substantial.

Examining the range of drugs registered for animals in Canada, their indications for use and relatedness to drugs used in humans raises several points relevant to

resistance risks to humans and animals. On the positive side for resistance, some drugs used in animals currently have no drug class counterpart in humans. Second, some important drugs in humans, such as glycopeptides, have no drug class counterpart registered for use in animals. Third, some drugs used in animals are not used in humans, although there are human drugs in the same class. Fourth, some classes important in humans have few related drugs registered for use in animals.

There are, however, several points of concern with regard to resistance. First, most of the classes of drugs used in animals are also used in humans. Second, some of these are registered for use in feed as growth promoters or prophylactics. Third, some antimicrobials used in humans are administered routinely to large numbers of animals for treatment, prophylaxis or growth promotion. Such routine use is of special resistance concern because of the numbers of animals involved. Fourth, modern production methods dictate that even therapeutic treatments in some types of animals necessarily involve treatment of entire groups of animals through feed or water. This effectively increases the potential exposure to resistance selection pressure. Fifth, some drugs are registered for two or more of the following categories: growth promoters/improved feed efficiency; disease control/prophylaxis, or therapy. This could increase resistance selection pressure, eventually compromising efficacy in one or another category.

Managing antimicrobial resistance risks

Health Canada's mission is to protect the health of Canadians, and this should be reflected in its policy decisions concerning management of resistance risks. These decisions should always be science-based, which entails careful weighing of the available scientific information. Health Canada should consult with Canadians and effectively communicate the resistance risk issues, its process for assessing and exploring risk management options, and the rationale for its decisions. These would be consistent with Canadian regulatory policy.

Before implementing new regulatory action, Health Canada should consider the magnitude of the resistance problem, the risks and benefits associated with antimicrobial use in Canada, the impact of any interventions on society, and the best use of the resources it has available. Restrictions on antimicrobial use intended to protect public health could have adverse economic consequences, including decreased incentive for pharmaceutical companies to develop new animal drugs, poorer animal production efficiency, and increases in the incidence of infectious disease in animals. Alternatively, restrictions could result in little or no change in animal health or production efficiency. Other considations include which sectors of society benefit from the use of antimicrobials, and which sectors bear the risks. Concerns have also been expressed that antimicrobials may compromise animal welfare by enabling closely confined, intensive rearing, or that they may be used to compensate for poor management.

Unfortunately, there are resistance risks associated with all uses of antimicrobials, and Health Canada must decide which risks are acceptable for the benefits gained. Health Canada cannot simply arbitrarily stop approving new antimicrobial applications on the grounds that resistance risks exist. Animals will continue to become sick and need treatment to protect animal welfare and the financial

investment of producers. The lack of approved, efficacious antimicrobials is a prime motive for extra-label use of drugs. The committee agrees with Australia's Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), which concluded that antimicrobial uses in animals should be reserved for situations where benefits are clear and substantial.

The committee believes that benefits are most clear and substantial when antimicrobials are used for therapy under the conditions of prudent use and under veterinary prescription. Benefits are less clear and substantial when these drugs are used for prophylaxis (especially when such use becomes routine) or growth promotion, where benefits are almost entirely economic.

In formulating its recommendations throughout this report, the committee tried to apply good risk analysis principles. However, the committee was neither prepared nor able to conduct thorough risk analyses of all antimicrobial uses in animals. It was prepared, however, to use its expertise to show the type of information required to qualitatively analyze risks of specific drugs. Properly analyzing resistance risks is a daunting task; Health Canada will need to prioritize its efforts in this area as it builds capacity. The committee believes that highest priority should be placed on assessing risks of new drug applications. Re-evaluation of existing drug claims should focus on drugs of substantial importance to human health and drugs used in a manner that enhances the selection and spread of resistance, especially for long-term, in-feed uses.

The committee had special concerns about growth promoters. Several growth promoters used in Canada are the same drugs or are related to drugs used in humans, or can select for resistance to drugs used in humans. Growth promoters account for a considerable amount of the total antimicrobial exposure. In addition, they are not used under veterinary prescription, nor to treat infections in animals. Some members believed that growth promoters facilitate animal husbandry practices that are unhealthy and therefore questionable on welfare grounds. Still others were concerned about the economic impact on producers and international trade implications of changes in growth promoter policy. Thus, the committee felt it should consider risks and benefits associated with this practice and make a special recommendation.

Recommendation

Evaluate antimicrobials for growth promotion or feed efficiency using sound risk analysis principles and rapidly phase out antimicrobial claims not fulfilling the following criteria: demonstrably effective; involving products rarely, if ever used in human therapy; and not likely to impair the efficacy of any other prescribed antimicrobial for human infections through the development of resistant strains.

Impacts of antimicrobial resistance on animal health

The committee's principal mandate was to examine the human health impacts of resistance. It assumed the additional task of examining animal health impacts because it is part of the larger problem of resistance, and because human health is affected when resistance in animal pathogens leads to use of newer antimicrobials that are important to humans.

It is clear that the development of antimicrobial resistance is a growing concern in both animal and zoonotic bacterial pathogens, especially when multiple-drug resistance is present. This resistance endangers our ability to control certain bacterial infections in animals.

In Canada, resistance has been studied in some of the more important bacterial pathogens of animals. Available information suggests that resistance is a problem in some, but not all, bacterial pathogens of domestic animals. However, the lack of coordinated systems to monitor antimicrobial resistance among animal pathogens in Canada makes it difficult to assess patterns of antimicrobial resistance in these pathogens at a regional, provincial or national scale. There should be a Canadian surveillance network to ensure the management and sharing of data from the various laboratories and the rapid dissemination of information to veterinarians in the event of the emergence of multidrug-resistant bacteria.

Strategies to ensure prudent use of antimicrobial drugs

Prudent use of antimicrobials is central to preserving their long-term effectiveness in animals and humans. It involves optimal therapeutic effect and control of antimicrobial resistance in animals. The Canadian Veterinary Medical Association (CVMA) has issued general and specific prudent-use principles. These principles are very sound, and, if achieved in practice, should help to reduce resistance risks. However, the committee believes there are substantial gaps between the ideal and the current reality of antimicrobial use in Canadian farming and veterinary practice.

There are currently insufficient incentives and many barriers to aggressive implementation of these prudent-use principles. Probably most important, there is insufficient awareness among veterinarians and food-animal producers about resistance issues in their industry. It is probable that due to heightened concerns in human medicine about antimicrobial resistance, the flow of new veterinary antimicrobials onto the market in Canada and most other industrialized countries will not return to its late twentieth-century level. The committee believes this is not sufficiently appreciated within the Canadian veterinary and agricultural communities.

Food safety programs used in food-animal production

To maintain the public's confidence, many national commodity groups are promoting on-farm food safety or quality assurance programs. These programs are designed to manage biosecurity, disease, and biological, chemical and physical safety hazards that may occur on the farm. Although none specifically targets antimicrobial resistance, a direct goal of all programs is to promote and implement prudent-use

practices for antimicrobial use on farms. This should reduce the amount of antimicrobials used and as a consequence reduce selective pressure favouring antimicrobial resistance. There are currently 14 programs in various stages of development within the food-animal production sector. These include programs for beef cattle, dairy cattle, hogs, honey bees, sheep, cervids (deer and elk), bison, chickens, turkeys, hatcheries, hatching eggs, table eggs, shellfish and salmon.

Monitoring of antimicrobial drugs used in food animals

Publicly available antimicrobial use data are scarce in Canada and indeed most countries in the world. We have no mechanism by which antimicrobial consumption data for food-producing animals is collected, analyzed, and reported. We don't know the quantities of various antimicrobials used in animals, and we do not collect use data in a manner that helps to further our understanding of resistance and its impact on human health.

Health Canada should monitor antimicrobial use in Canada in order to aid interpretation of antimicrobial resistance surveillance data from human, animal, food and environmental sourcess, to evaluate effectiveness of prudent-use programs, and for use in risk analyses relating to the use of antimicrobials in food-animal production and the protection of human health. Confidentiality agreements and laws should be respected, but barriers to reporting use data must be resolved.

Surveillance of antimicrobial resistance in food animals

Assessment of the full impact on human health of antimicrobial drug use in food animals has also been hampered by the relative lack of reliable resistance data. In Canada, as in most countries, these data are fragmentary, often biased, focused on a narrow and variable range of bacterial pathogens, collected in an unsystematic way, and not generally comparable between laboratories and/or countries because methods used for testing resistance have not been standardized.

Surveillance of resistance in selected animal pathogens, particularly those that reach people through the food chain, has proven useful in other countries in assessing where interventions are needed and supporting removal or proposed removal of certain antimicrobial drugs from use in food animals. Bacteria isolated from healthy animals are more representative of the population than those isolated from treated animals. Bacteria selected for surveillance are foodborne pathogens (*Campylobacter, Salmonella*); commensal, Gram-negative, enteric pathogens (*Escherichia coli*); and commensal, Gram-positive bacteria (*Enterococcus* species).

The methods used within a surveillance program must meet international standards. They should be compatible with, if not identical to, those used by NARMS in the U.S. A program of active collection of animal-derived bacteria followed by testing for antimicrobial resistance is more valid than a passive system for determining the broad range of resistance in clinically normal animals and in animal-derived food products. Development of the infrastructure for an active surveillance system would mean that additional microorganisms could be added on an occasional, as-needed basis, and also that the system could be fine tuned over time. The surveillance system

should be integrated with activities underway in both the human and agri-food sectors.

Recommendation

In consultation with the provinces, other federal agencies and industry groups, design and implement an ongoing, permanent, national surveillance system for antimicrobial resistance arising from food-animal production. Surveillance should include indicator and pathogenic bacteria isolated from animals, foods, and imported animal products.

Alternatives to antimicrobial drugs in food animals, research and education needs

Calls to reduce antimicrobial use in animals provide incentives to search for alternatives that may achieve similar goals, *i.e.* prevent or control infectious disease and promote growth and increase feed efficiency. Furthermore, there are important educational and research efforts required to effectively implement many of the recommendations made in this report.

Alternatives to antimicrobials

There are many approaches that can potentially be used to promote the health and productivity of food animals without the use of antimicrobial drugs, especially for disease prophylaxis and growth promotion. In general, these include management practices that reduce the likelihood and impact of infectious diseases (biosecurity), probiotics, enzymes, oligosaccharides, minerals, herbs, acidification, vaccines, novel peptides, novel antibodies, immune potentiators, selective breeding, and improved management and housing. Many of these alternatives will be subject to efficacy studies and human safety risk assessment before they can be used commercially.

Currently, some of these alternatives are not perceived to be as economical, convenient, or as effective for their intended purposes as antimicrobials. In Canada, more studies are needed to complement the research in these areas coming from other countries. The experiences of countries such as Sweden and Denmark, which have had considerable success with the husbandry of animals after the market withdrawal of antimicrobial drugs used for growth promotion, need to be carefully analyzed by producers and veterinarians here. Research is also needed to identify the design, construction and husbandry system(s) in livestock buildings that minimize disease transmission while maximizing livestock health and performance without the routine use of antimicrobial drugs for growth promotion or disease prophylaxis.

Education

Some governments, veterinarians and producer organizations have assumed leadership roles in enhancing efforts to evaluate the use of antimicrobial drugs in animals. While such activities could be regarded as exploratory, they illustrate the

impact that criticism of agriculture's use of antimicrobial drugs has had on the industry. Also, they illustrate that these groups are open to change or to promote change.

The Canadian Committee on Antibiotic Resistance (CCAR) has a mandate to facilitate the implementation of an Integrated Action Plan for Canadians on Controlling Antimicrobial Resistance. The plan promotes control strategies across all sectors, including antimicrobial use in agricultural production. This is an important multidisciplinary group, which collates and coordinates national activities to address the issue of antimicrobial resistance. CCAR has provided funds for initiatives such as that of the Canadian Veterinary Medical Association to educate its members about prudent use of antimicrobial drugs. The CVMA identified antimicrobial resistance as a national priority in 1999 and has an ongoing Antimicrobial Resistance Committee that promotes prudent-use guidelines, among other activities.

Conclusions

The committee believes that antimicrobial resistance is an important problem for both human and animal health. The problem approaches crisis proportions in human medicine, where efforts are being made to curtail unnecessary antimicrobial use in people, and to control infection in hospitals and in the community. In animals, resistance occurs whenever antimicrobials are used, whether for therapy, disease prophylaxis, or growth promotion. This is a problem in veterinary medicine, because it reduces the effectiveness of available antimicrobials in treating infections and leads to use of more expensive drugs of importance to human health. It is also important because resistant bacteria spread from animals to humans. Some of these bacteria make people sick or transfer their resistance genes to human bacteria. While the precise magnitude of the public health impact is unknown, it is known that resistance is a serious problem in bacterial infections of humans that originate in animals.

The committee believes that these problems warrant changes to the ways that antimicrobials are regulated, distributed and used in animals. These changes include: consideration of resistance risks as part of the regulatory review process for new and existing antimicrobials, adoption of prescription-only availability, closure of own-use and API loopholes, development of an improved extra-label use policy, rapid phasing out of growth promoters that select for resistance in humans, and development of surveillance systems for antimicrobial use and resistance. Recommendations are listed in full at the end of this summary, and by relevant chapters in the accompanying report.

List of Recommendations

Chapter 3. Control of antimicrobial resistance in the human health sector.

1. Continue support for integrated approaches to address the issue of antimicrobial resistance in humans and animals through Health Canada and organizations such as CCAR.

Chapter 4. Regulation and distribution of antimicrobial drugs for use in food animals.

2. Ensure that regulation of antimicrobials (including licensing, sale, distribution, use, and regulatory compliance) includes consideration of the human health impact of antimicrobial resistance.
3. Develop specific methods and criteria for human and animal health safety assessment of veterinary drugs with respect to antimicrobial resistance as soon as possible.
4. Define threshold levels of resistance for post-approval surveillance and provide for appropriate remedial action if thresholds are surpassed, up to and including modification of approval or suspension of marketing.
5. Wherever possible and appropriate in the interest of Canadian citizens, strive to harmonize veterinary drug regulatory approaches and standards with those used in other countries, especially the U.S.
6. Regularly seek independent, expert advice on antimicrobial resistance and related matters. Health Canada must, however, retain decision-making responsibilities with respect to regulation.
7. Ensure adequate coordination of federal and provincial policies concerning antimicrobial use and resistance management, and ensure the strict enforcement of all relevant regulations.
8. Evaluate, register and assign a DIN to all antimicrobials used in food animals, whether manufactured domestically or imported. This includes antimicrobials imported in bulk (API), which should be allowed into Canada only under permit. The intent of this recommendation is to stop the direct use of APIs in food animals.
9. Stop the importation, sale, and use of antimicrobials not evaluated and registered by Health Canada. The intent of this recommendation is to stop the “own-use” loophole.
10. The prescribing and pricing of antimicrobials should not result in any incentives to dispense antimicrobials. Study the Quebec approach as a potential national model.

11. Give due consideration to claims made in pharmaceutical advertisements and promotion practices that may concern antimicrobial resistance, to ensure claims or statements can be substantiated.
12. Make all antimicrobials used for disease treatment and control available by prescription only.
13. Develop an extra-label use policy, which ensures that this practice does not endanger human health. Such a policy should include the ability to prohibit the extra-label use of specific drugs of critical importance to human health.

Chapter 6. Managing antimicrobial resistance risks

14. Employ sound risk analysis methods to manage the risks associated with antimicrobial resistance.
15. Improve the transparency of risk assessment and management related to antimicrobial resistance. Explain what is known about the risks, the extent and limits of scientific knowledge, how uncertainty is taken into account, and how human health is to be protected.
16. Conduct risk-based evaluations of the potential human health effects of all uses of antimicrobial drugs in food-producing animals, including currently approved products. In the evaluation of currently approved products, give priority to those products considered most important in human medicine (*e.g.*, third generation cephalosporins, streptogramins and macrolides). Characterization of the risk should include consideration of the importance of the drug or members of the same class of drug to human medicine, the potential exposure to humans from antimicrobial resistant bacteria and their resistance genes from food animals, as well as other appropriate scientific factors. Those antimicrobials judged to be essential for human medicine should be restricted and their use in food animals should be justified by culture and susceptibility testing.
17. Evaluate antimicrobials for growth promotion or feed efficiency using sound risk analysis principles and rapidly phase out antimicrobial claims not fulfilling the following criteria: demonstrably effective; involving products rarely, if ever used in human therapy; and not likely to impair the efficacy of any other prescribed antimicrobial for human infections through the development of resistant strains.

Chapter 7. Impacts of antimicrobial resistance on animal health

18. Develop a coordinated, ongoing, national surveillance system for antimicrobial resistance in the major pathogens affecting food animals.
19. Ensure the appropriate dissemination of food-animal pathogen resistance surveillance data to concerned parties, *e.g.*, veterinary practitioners and governments. These data should be available in a form that supports prudent use of antimicrobials in food animals.

Chapter 8. Strategies to ensure prudent use of antimicrobial drugs

20. Veterinarians and veterinary medical organizations should effectively implement the prudent-use principles developed by the Canadian Veterinary Medical Association (CVMA), and periodically review the principles and their implementation.
21. Provincial licensing bodies and veterinary medical associations should endorse and promote the CVMA's prudent-use principles.
22. Only under exceptional circumstances should antimicrobials with unique mechanisms of action or novel resistance patterns in human medicine be used in veterinary medicine.

Chapter 9. Food safety programs used in food-animal production.

23. Food-animal industries should develop on-farm food safety programs (OFFSPs) that address antimicrobial resistance issues, subscribe to CVMA prudent-use principles, and be audited. Programs that successfully address these matters should be acknowledged (and ideally, accredited) by appropriate government agencies.
24. Encourage food-animal industries to develop OFFSPs that are audited, maintain a national registry of participating farms, and provide accurate information on antimicrobial use. Use this drug use information to assist national surveillance.
25. Encourage measures to reduce transmission of zoonotic infections from animals to humans throughout the food production and processing system.

Chapter 10. Monitoring of antimicrobial drugs used in food animals

26. Design and implement a national monitoring program of antimicrobial use in food animals that provides valid data in a timely and methodologically transparent fashion. Design the program to support risk analysis related to human health and policy development related to antimicrobial use. The data should be publicly available.
27. Provide an annual report of antimicrobial use monitoring by appropriate means (*e.g.*, website, paper report).

Chapter 11. Surveillance of antimicrobial resistance in food animals

28. In consultation with the provinces, other federal agencies and industry groups, design and implement an ongoing, permanent, national surveillance system for antimicrobial resistance arising from food-animal production. Surveillance should include indicator and pathogenic bacteria isolated from animals, foods, and imported animal products.
29. Collect, interpret, and publish resistance surveillance data, ideally in partnership with other groups. Approach the food-animal and pharmaceutical industries to provide support for pilot or special studies.
30. Design the program to support human health risk analysis and policy development on antimicrobial use.
31. The bacteria chosen for active surveillance and the laboratory methods used within the surveillance program should be comparable to those of NARMS, so that Canada

can participate in a global system of surveillance of antimicrobial resistance in bacteria of food-animal origin.

32. Integrate the surveillance system with the national surveillance of antimicrobial resistance in human enteric bacterial pathogens conducted by Health Canada.

Chapter 12. Alternatives to antimicrobial drugs in food animals, research and education needs

33. Assume a leadership role in encouraging agriculture-related research on antimicrobial resistance, particularly on alternatives to antimicrobial drug use, including management systems that reduce dependence on antimicrobials. Governments, producer associations, research foundations, and national funding agencies should give high priority to supporting research in these areas.
34. Support demonstration projects to evaluate programs that use multiple interventions to promote prudent use of antimicrobial drugs and reduce infection rates.
35. Give priority in the regulatory assessment process to antimicrobial drugs and related products that are unlikely to result in antimicrobial resistance in human pathogens, and to products that will reduce the use of antimicrobial drugs in animals.
36. Encourage partners (including Agriculture and Agri-Food Canada, CFIA, commodity organizations and provincial authorities) to improve education strategies to provide veterinarians and producers with information about the roles and benefits of prudent use of antimicrobial drugs and the risks of inappropriate use. Evaluate the effectiveness of educational programs on prudent use so they may continually be improved.
37. Enhance funding to CCAR to support its mission in promoting strategies aimed at preventing antimicrobial resistance. CCAR should also educate consumer groups about the human health aspects of antimicrobial use in food animals and efforts underway to reduce adverse effects.
38. Encourage Canadian veterinary colleges and veterinary associations to ensure that preventive medicine, prudent use, and antimicrobial resistance are given high priority in veterinary undergraduate, postgraduate, and continuing education programs.

CHAPTER

1

Introduction

Resistance to the effects of antimicrobial drugs is a serious problem in Canada and the world. The problem, often referred to as antimicrobial resistance or AMR, costs lives and money, and threatens our ability to treat infections in humans and animals. The World Health Organization (WHO) estimates that 85% of human mortality due to infectious disease is attributable to diarrhoeal diseases, measles, acquired immunodeficiency syndrome (AIDS), malaria, and tuberculosis (TB). There are serious problems with microbial resistance to front-line drugs used to combat many of these pathogens, which comprise bacteria, viruses and parasites (1). The resistance problem is most acute in the case of bacterial infection; consequently the focus of this report is exclusively antimicrobial resistance in bacteria. Our traditional response to the development of antimicrobial resistance is to use different, often new, drugs to treat the disease. This approach is no longer tenable because the supply of new, effective, safe, and affordable products is expected to diminish in the future. Thus, we must protect the antimicrobial drugs now available to minimize resistance impacts on our health and economies. Although emergence of resistance is virtually inevitable whenever these drugs are used, evidence indicates it can be slowed by prudent use of antimicrobials and better infection control.

In fact, expert panels around the world have recently examined the ways antimicrobial drugs (often referred to as simply “antimicrobials”) are used in human medicine, with a view to recommending improvements in the use (often referred to as “prudent use”) of antimicrobials (Table 1.1). Prudent antimicrobial use maximizes therapeutic effect while minimizing resistance. With respect to clinically important infections in humans, most resistance problems probably arise from use of antimicrobials in humans. Serious questions have been raised about the inappropriate use of antimicrobials for treatment of viral infections of people, non-prescription use in some countries, and incomplete treatment courses (1,2,3,4). Clearly, improvements can be made in how antimicrobials are used in human medicine.

Inevitably, however, when considering the use of antimicrobials in Canada and the world, attention turns to the use of antimicrobials in agriculture. In countries where reliable data are available, as much as 50% or greater of the total volume of antimicrobials produced or imported in these countries is administered to animals. Of this volume, a significant proportion is used in food animals to increase growth rate and/or weight gain (called “growth promotion”) and to prevent disease (called “disease prophylaxis”). Antimicrobials are not used for growth promotion in humans, and mass medication for disease prophylaxis is more

limited in human medicine. This begs the questions, "If countries, including Canada, must restrain antimicrobial use in humans to control the impacts of antimicrobial resistance, then shouldn't they examine how antimicrobials are used in agriculture too? If necessary, shouldn't agriculture also change the way these drugs are used in food animals, especially for growth promotion and disease prophylaxis?"

The answer to these questions depends, in part, on the degree to which antimicrobial use in animals impacts human health. However, this is one of the most controversial dimensions of the resistance problem, and has been debated since resistance was first encountered during the middle of the last century. In recent years, numerous panels have been charged with examining the evidence and with providing appropriate guidance. Although the details differ, consistent themes have emerged from the reports prepared by these panels:

- Antimicrobial resistance eventually develops in bacteria hosted by animals when antimicrobials are administered to animals;
- Bacteria, including those resistant to the effects of antimicrobial drugs, spread from animals to humans;
- Some of these bacteria make humans sick;
- The overall magnitude of the impacts of antimicrobial resistance on human health is unknown;
- The relative contributions of antimicrobial use in humans and animals to the development of antimicrobial resistance is unknown;
- Changes to antimicrobial use policies are expected to have negative economic consequences for agriculture; and
- The issues are complex.

The opinions of scientists, government authorities and stakeholders around the world are divided on which antimicrobial resistance control actions are warranted by the scientific evidence and are in the best interests of the public.

It is clear that antimicrobial resistance is an international problem; resistant bacteria are carried easily between countries by travellers, animals, food, and other carriers. Most solutions to the problem, however, are necessarily national or local in scope because they involve government regulation or changes in prevailing farming practices. The European Community (E.C.), for example, banned four drugs for use as growth promoters because they are also used for therapy in humans and animals and recently announced plans to eliminate remaining growth promoters by 2006 (see Chapter 6). However, antimicrobials of critical importance to human medicine (e.g., fluoroquinolones, cephalosporins) are still used in the E.C. for the treatment of sick animals (5,6). The United States (U.S.) is taking a somewhat different tack by focusing its regulatory efforts on reshaping the approval process for new drug applications. Recently, the U.S. used quantitative risk assessment to guide its decision to seek revocation of approval of a fluoroquinolone for therapy in poultry (7). Australia recently examined its antimicrobial programs and policies and made recommendations aimed at improving regulatory controls, surveillance, infection prevention, education and research (8).

Table 1.1: Recent expert reports on antimicrobial resistance in humans and animals.

Year	Country or Organization	Title	Source
2001	World Health Organization	WHO Global Strategy for Containment of Antimicrobial Resistance	WHO http://www.who.int/emc/amr.html
2001	Office International Des Epizooties	Antimicrobial Resistance: Reports Prepared by the OIE Ad Hoc Group of Experts on Antimicrobial Resistance	OIE http://www.oie.int/eng/publicat/ouvrages/a_106.htm
2001	World Health Organization/Alliance for the Prudent Use of Antimicrobials	Antibiotic Resistance: Synthesis Of Recommendations by Expert Policy Groups	WHO http://www.who.int/emc/amr.html
2000	British Columbia, Canada	Antimicrobial Resistance: A Recommended Action Plan for British Columbia	Office of the Provincial Health Officer, British Columbia
2000	World Health Organization	WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food	WHO http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm
2000	United States	Antimicrobial Resistance: An Ecological Perspective	American Academy of Microbiology http://www.asmusa.org/acasrc/aca1.htm
1999	Australia	Antibiotics in Food-Producing Animals: Antibiotic-Resistant Bacteria in Animals and Humans	Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR)
1999	United Kingdom	Report on Microbial Antibiotic Resistance in Relation to Food Safety	Advisory Committee on the Microbiological Safety of Food. London: The Stationery Office
1998	United States	Antimicrobial Resistance: Issues and Options, Workshop Report	Institute of Medicine http://www.nap.edu/
1998	United Kingdom	Resistance to Antimicrobials and Other Antimicrobial Agents	House of Lords, Select Committee on Science and Technology
1998	United Kingdom	The Path of Least Resistance	Department of Health http://www.open.gov.uk/doh/smac
1997	Canada	Controlling Antimicrobial Resistance: An Integrated Action Plan for Canadians	Health Canada http://www.hc-sc.gc.ca
1997	World Health Organization	The Medical Impact of the Use of Antimicrobials in Food Animals	WHO http://www.who.int/emc/diseases/zoo/antimicrobial.html

What about Canada? In 1997, Health Canada convened a national consensus conference on antimicrobial resistance at which agricultural uses of antimicrobials were discussed. From this conference it was recommended that Canada "establish a national surveillance system to monitor antimicrobial resistance and use in the agri-food and aquaculture sectors. The exact modalities of this system, the target microorganisms, the methods to be used, and the involvement of stakeholders in promoting the judicious use of antimicrobials should be determined by an expert working group" (9). Recently, British Columbia and Ontario produced antimicrobial resistance reports (10,11). In 1999, Health Canada provided financial support to the Canadian Committee on Antimicrobial Resistance (CCAR). CCAR "advocates

for, facilitates and promotes programs related to surveillance, optimal antimicrobial use and infection prevention and control to limit antimicrobial resistance," and includes input from the agri-food sector. Also in 1999, Health Canada established the group responsible for this report, the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health.

Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health

The advisory committee held its inaugural meeting in December 1999 and its tenth meeting in April 2002. As described in its Terms of Reference (Appendix 1), the role of the committee is to provide advice and assistance to Health Canada in the development of policy options related to the animal uses of antimicrobials. The committee members work in a variety of fields, including academia, animal welfare, consumer interest groups, the feed industry, the food animal industry, human medicine, the pharmaceutical industry, public health, and veterinary medicine (Appendix 2). The committee was assisted by a secretariat consisting of scientists from Health Canada and the Canadian Food Inspection Agency (CFIA).

The committee reviewed and discussed relevant scientific literature and various national and international reports, most of which are referenced in this report. It also reviewed the recommendations of these reports and in some cases adapted them to the Canadian situation. Reports of WHO consultations and Australia's JETACAR were especially helpful in this regard (1,8,12). The committee received oral presentations from members of the committee and the secretariat who had special expertise, from officials within various Health Canada branches with responsibilities pertaining to the regulation of veterinary drugs in Canada, and from experts from the U.S. (Drs. Stephen Sundlof and Paula Cray) and Australia (Dr. John Turnidge). See Appendix 4 for a complete listing of oral evidence.

In time, the complexity and sometimes-contentious nature of the issues facing the committee became evident. The committee agreed that there are no simple solutions to microbial resistance problems, especially resistance arising from antimicrobial use in food animals. Although mindful of the many detailed reviews available in the public domain (Table 1.1) and reluctant to "reinvent the wheel," the committee eventually resolved to present the Canadian perspective in their recommendations, along with a fairly detailed discussion of the scientific evidence of human and animal health impacts, the international response to the problem, stakeholder perspectives on benefits of antimicrobials in animals, and the options for managing resistance risks. In the interests of openness and the need for a broad consultation on the problem of antimicrobial resistance, the committee believes that Health Canada should make this report public and seek comment from all Canadians.

Health Canada did not remain static while the committee deliberated on antimicrobial resistance issues. The Veterinary Drugs Directorate (VDD) was formed from the Bureau of Veterinary Drugs (BVD) in this interval and acquired an increase in budget and staff. Health Canada's policies on veterinary drugs also evolved in parallel with the committee's work. The committee believes that some of these changes (*e.g.*, enhancements in surveillance and microbiological expertise) were influenced directly by interim recommendations and indirectly by participation of the Health Canada secretariat in the committee's deliberations.

As the federal agency primarily responsible for the health of Canadians, Health Canada must make some difficult decisions concerning management of the risks associated with antimicrobial resistance. The committee trusts that its recommendations will continue to be helpful to the decision-making process. Although the committee's mandate is to provide advice to Health Canada, it suggests that provincial agencies and other groups in Canada should also consider the recommendations that affect them. Health Canada is responsible for regulating the safety and efficacy evaluation, sale, and labelling of veterinary drugs, but the provinces are responsible for regulating the practice of veterinary medicine, and many further regulate the sale and distribution of antimicrobials. Also, there are relevant self-regulatory responsibilities that fall on the food-animal and pharmaceutical industries, and on veterinary medical organizations. All stakeholders who have the ability to bring about changes that will help to control the impacts of antimicrobial resistance in the agriculture and aquaculture sectors should consider the findings of this report.

Scope of the report

The committee focused on issues associated with bacterial resistance arising from the use of antimicrobials in food animals because the members believe these resistance issues are of greatest concern to human health. The committee also considered the impacts of antimicrobial resistance on animal health; an issue it felt was important but missing in many other reports. The committee did not address resistance in other pathogens (*e.g.*, parasites, viruses) or address the use of antimicrobials in companion animals or plants, the use of other antibacterials, sanitizers, or disinfectants (*e.g.* teat dips for mastitis prevention in dairy cows), as important as these issues may be. Therefore, the committee's recommendations specifically address the use of antimicrobials in animals raised for human food.

Among concerns about human safety arising from the use of antimicrobials in food animals, issues related to antimicrobial resistance must be clearly distinguished from issues related to residues. Antimicrobials are natural or synthetic substances that kill or inhibit growth of microorganisms but cause little or no toxicity when administered to the host. Antimicrobial resistance is the inherent or acquired ability of bacteria to resist the inhibitory effects of antimicrobial drugs. Residues are remnants of antimicrobial chemicals or their break-down products (called metabolites) that are present within meat, milk, or eggs produced from treated animals. While both conditions are caused by the use of antimicrobials in food animals, their biology and methods of control are almost entirely different. In general, awareness of residue issues is higher than that of resistance issues within the agri-food community. Residue prevention programs are well developed within the food industry, but resistance prevention programs are not.

Organization of the report

The report begins with a discussion of real and potential human health impacts from antimicrobial use in animals. For perspective, efforts to control resistance arising from human uses of antimicrobials are discussed. Next, the regulation and methods of distribution of antimicrobials in Canada are addressed. Antimicrobial uses for therapy, prophylaxis and growth promotion in food animals are then described, followed by a discussion of methods used to measure risks and benefits of antimicrobials, the animal health impacts of resistance, prudent-use practices, and food animal quality assurance programs that may have a bearing on resistance management. Finally, the report addresses needs for surveillance of antibiotic

use and resistance, alternatives to antimicrobials, and research and education. Recommendations are listed at the end of appropriate chapters.

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CHAPTER

2

Adverse effects of antimicrobial resistance from food animals on human health

Key Points

- **Antimicrobial use in any setting (*e.g.*, farm, hospital) leads to resistance**
- **Spread of resistance can occur between and among bacteria and is enhanced by antimicrobial selection pressure**
- **Resistance in bacteria of food animals can spread to humans through the food chain, or through water or contact with animals**
- **Food and waterborne bacteria, many resistant to antimicrobials, are important causes of illness in Canadians**
- **Resistance in these bacteria can affect public health by limiting the effectiveness of antimicrobial treatments and by increasing the number, severity, and duration of infections**

Food animals are important reservoirs of many bacteria that cause infections in humans. In Canada, the most important of these bacteria are *Salmonella enterica*, *Campylobacter jejuni*, and verotoxin-producing *Escherichia coli* (especially serotype O157:H7). These infections often are transmitted through contaminated food (*e.g.*, meat, poultry, eggs, fruit, vegetables, seafood) or water, although contact with animals (including farm animals, pets, birds, and turtles) and with people is sometimes responsible. Most cases of infection occur sporadically in humans; however, outbreaks are also reported, some of which are large and devastating (but many are not associated with resistance). Examples include the outbreak of *Salmonella* Typhimurium in eastern Canada in 1984, during which 1,500 cases (no deaths) were confirmed. The source of the infection was contaminated cheddar cheese. In 2000, an outbreak of waterborne illness in Walkerton, Ontario, due to *E. coli* O157:H7 and *Campylobacter*, caused approximately 2,300 cases of illness and 7 deaths.

In Canada, many people suffer from these infections every year (1). In 1998, the last year for which official data are available, 7,040 cases of salmonellosis, 14,236 cases of campylobacteriosis, and 1,484 cases of verotoxin-producing *E. coli* infection were officially reported in Canada (2). It is believed, however, that for a variety of reasons, most cases of infection are not officially reported. This suggests the problem is larger than the records indicate. In the U.S., where the conditions for animal production, food processing and

distribution are broadly similar to Canada, public health authorities have accounted for under-reporting, and estimate that approximately 1.4 million cases of salmonellosis, 2.4 million cases of campylobacteriosis, and 73,480 cases of *E. coli* O157:H7 occur in the U.S. annually (3). It is reasonable to assume that Canadian figures are similar when adjusted for population size.

Not all bacteria that cause disease (often called "pathogens") are resistant to antimicrobial drugs, nor is this an essential element of their ability to cause disease (often called "pathogenicity") in humans. Nevertheless, there is considerable evidence, particularly for *Salmonella* and *Campylobacter,* that resistant infections have a greater negative impact on human health than antimicrobial susceptible infections. While antimicrobial resistance does occur in *Escherichia coli* O157:H7, this has not been shown, thus far, to increase the impact of this pathogen on human health (4). Therefore, the committee decided to focus its attention on other enteric pathogens (i.e., bacteria causing intestinal infections) and on non-verotoxin producing *E. coli*.

While all bacteria have the capacity to develop resistance, some species or strains, such as *Salmonella enterica* serovar Typhimurium (hereafter called *Salmonella* Typhimurium) and *Campylobacter jejuni*, seem inclined to do so. Of 1,286 strains of *S.* Typhimurium examined in a Canadian study in the 1980s, 866 (67%) were resistant to one or more antimicrobials (5). Poppe et al. (6) examined *Salmonella* collected from animals, animal food products, and animal environments from 1994 to 1997 and observed that among *S.* Typhimurium, resistance to ampicillin, chloramphenicol, kanamycin, neomycin, streptomycin, sulfisoxazole, and tetracycline persistently increased. Similar findings have been reported from other countries. In 1999, 179 of 362 (50%) *S.* Typhimurium examined in the U.S. were resistant to at least one antimicrobial drug (7).

Few Canadian studies have assessed resistance among *C. jejuni* infections in humans or animals. One recent study of 144 clinical isolates (*i.e.*, 144 individual strains of bacteria) from humans and 39 food isolates found fluoroquinolone resistance in 14% and 2.6% of isolates, respectively (8). Resistance among *Campylobacter* infections from countries other than Canada is discussed later in this chapter.

How common are these resistant infections in humans, and what is the extra burden of illness attributable to resistance? Unfortunately, there are no precise answers to these questions. Canada, like many other developed countries, lacks a fully integrated surveillance system of resistance to antimicrobial drugs in animals and humans. Because of this, we do not completely understand the extent of the resistance problem in the important pathogens, where resistance emerges and how it transmits from animals to humans or vice versa. Nevertheless, information is available from some Canadian studies and, since science is not limited by international boundaries, it is appropriate to consider information from studies conducted abroad, after the necessary allowances for geographical differences in animal husbandry practices and antimicrobial use are made. However, before reviewing the scientific evidence on the impacts of antimicrobial resistance from food animals on human health it is helpful to understand some of the basic principles regarding the acquisition and transfer of antimicrobial resistance in bacteria.

Antimicrobial resistance in bacteria

In the 50 years since antimicrobial drugs were introduced, many species of bacteria have evolved and developed mechanisms that allow them to resist the negative effects of these drugs. This acquired resistance has become a major problem for human and animal health care. The development of resistance to antimicrobial drugs in bacteria illustrates the complexity of genetic change and the response of bacteria to selection pressures; it superbly exemplifies the principle of natural, Darwinian selection (*i.e.*, survival of the fittest). The speed with which resistance has developed, however, has surprised many. The development of acquired resistance in bacteria lies at the heart of the issue of antimicrobial resistance.

A bacterium can acquire resistance when a genetic mutation occurs within the organism or when it acquires existing resistance genes from another organism. Often a combination of the two processes occurs. Essentially all genes have the potential to change and move to other, often totally unrelated bacteria. *De novo* synthesis and/or acquisition of resistance genes happen(s) continuously in bacterial populations. However, bacteria that have recently become resistant will only emerge from the general population when a selection pressure occurs, such as the presence of an antimicrobial drug. Although there is a causal relation between drug use and the selection of resistance, the development of resistance in all bacteria to all drugs is not inevitable. Some bacteria do not have the mechanisms to readily develop or acquire resistance.

De novo development of acquired resistance through genetic mutation in bacteria is a characteristic effect of certain drugs. Spontaneous mutations in bacterial genes occur continuously, resulting in a characteristic, expected frequency for emergence of resistance to these drugs. Such mutations may cause immediate, high-level resistance to one or a group of drugs, or they may have a cumulative effect leading to progressive loss of susceptibility (which eventually makes the organism resistant) through repeated different mutations in a gene, as observed in the fluoroquinolones (in most bacteria). An example of genetic mutation to resistance is mutation in the *mar* gene involved in regulating a bacterial efflux pump, which can result in resistance to a wide variety of antimicrobial drugs and antiseptic agents (9).

Transferable or infectious drug resistance, which involves the acquisition of existing, mobile genetic elements that contain the coding for antimicrobial resistance, is the most important form of acquired resistance because the spread of antimicrobial resistance occurs in an epidemic manner. It is also the way in which newly synthesized genes can sometimes move through bacterial populations. Resistance genes can be spread to susceptible bacteria by several mechanisms:

a. Transduction. Viruses can transfer resistance genes from one bacterium to another; this mechanism is probably underestimated in importance.

b. Conjugation. Resistance genes are often present in bacteria as a plasmid, a piece of circular, self-replicating deoxyribonucleic acid (DNA) that is maintained in the cell separate from the chromosomes. These resistance plasmids (often called “R factors” or “R plasmids”) frequently contain a region for transfer that allows for mating (conjugation) between a donor and a recipient cell. A donor containing the R plasmid conjugates with a recipient that does not have an R plasmid. The donor transfers the R plasmid to the recipient while retaining a copy for itself. Since R plasmids commonly contain genes for resistance to unrelated antimicrobial drugs, their acquisition can lead to resistance to multiple antimicrobial drugs. Because of the existence of plasmids encoding multiple antimicrobial resistance genes,

exposure to any one of several antimicrobial drugs for which the plasmid carries resistance genes can provide the selection pressure needed to maintain resistance to the suite of totally unrelated antimicrobial drugs for which the plasmid is also carrying resistance genes. This principle of co-selection is important, and can extend beyond just antimicrobial resistance genes. For example, reacting to the antimicrobial resistance crisis by an obsession with disinfection and antisepsis may be problematic. Bacterial resistance genes to some products may also be linked to antimicrobial resistance genes, so that use of some antiseptics may maintain antimicrobial resistance (10).

c. Transposition. Transposons are genetic elements (often called "jumping genes") that can insert (transpose) into DNA independent of the usually required recombination process, since they require no relationship (homology) with the DNA strand into which they insert. The nature of transposable genetic elements means there is no part of the bacterial genome that cannot be moved into other bacteria. Transposons are thus the key elements in the formation of R plasmids and the reason that plasmids of very diverse origins often possess identical genes. Transposons bearing resistance genes can transpose from one plasmid to another, explaining the progressive development on plasmids of multiple antimicrobial resistance. They can transpose from a plasmid to the chromosome, and some transposons can even cause bacteria to conjugate, like plasmids. Molecular analysis of plasmids and transposons has repeatedly shown that identical resistance elements are found in diverse bacteria isolated from animals and from humans, emphasizing the interrelatedness of resistance genes in bacteria isolated from humans and animals.

The principle of co-selection is important not only for plasmids but also for transposons. For example, the unexpected persistence of vancomycin resistance in enterococci in pigs in Denmark following the withdrawal of avoparcin as a growth promoter was attributed to the continued use of a second antimicrobial drug, tylosin. This occurred because the tylosin resistance gene was found on the same transposon as the vancomycin resistance gene (11).

d. Integrons. An integron is generally a non-mobile DNA element with two conserved segments flanking a central region into which a gene “cassette” encoding resistance or other functions can be inserted, like tape cassettes into a tape recorder. One or many gene cassettes can be integrated into the central region, which occurs by homologous recombination, (it can contain 8–10 different gene cassettes encoding 8-10 different resistance genes). For example, the multi-resistant *Salmonella* Typhimurium definitive phage type 104 (DT 104) contains a class I integron, which contains most or all of the resistance genes that it carries. Integrons are an extraordinary, even bizarre, class of transposable elements of great significance in the spread of antimicrobial resistance.

Mechanisms of resistance

Table 2.1 summarizes some of the mechanisms of resistance to common antimicrobial drugs and whether or not this resistance is usually transferable. The table differentiates mechanisms of resistance through antimicrobial efflux mechanisms, alteration to bacterial permeability through changes in porins, destruction of antimicrobials by enzymes, or changes in the target molecules.

A more detailed discussion of antimicrobial resistance in animal pathogens is available elsewhere (12).

Table 2.1: Selected examples of bacterial resistance mechanisms and mobility of resistance genes to different classes of antimicrobial drugs

Drug	Class	*De novo* resistance	Transferable resistance	Efflux[a]	Permeability[a]	Inactivation[a]	Target alteration[a]
Ampicillin	Beta-lactam	Yes	Yes	Yes	Yes	Yes	Yes
Ceftiofur	Beta-lactam	Yes	Yes	Yes	Yes	Yes	Yes
Gentamicin	Aminoglycoside	Yes	Yes	Yes	No	Yes	Yes
Erythromycin	Macrolide	Yes	Yes	Yes	No	Yes	Yes
Tetracycline	Tetracycline	Yes	Yes	Yes	No	?	Yes
Enrofloxacin	Fluoroquinolone	Yes	(Rare)	Yes	No	No	Yes
Sulfamethoxazole	Sulfonamide	Yes	Yes	Yes	Yes	Yes	No

[a]Mechanism of resistance

Some factors affecting development and spread of resistance

Resistance in bacteria is observed most where antimicrobials are in wide use and where bacteria can readily be passed between individuals. A hospital or an intensive livestock operation are thus excellent settings. It is well established that the longer an antimicrobial drug is used, the more likely it is that microbial resistance to the drug will emerge (as seen with resistance to older drugs, including sulfonamides and tetracyclines). This is the major reason that microbiologists question the prolonged administration of important antimicrobial drugs in the feed of food animals. In comparison, most human medical practice limits the administration of a drug to short courses of treatment only in people suffering from bacterial infections. As a generalization, it is probable that antimicrobial resistance will develop in bacteria whether a small or a large quantity of a drug is present to provide the selection pressure. It may even develop more readily when the quantity is small. As a result, when developing resistance bacteria may not distinguish between growth promotional (low) and therapeutic (high) quantities of a drug. This understanding leads to the important conclusion that, to counteract the problem of antimicrobial resistance, the exposure of bacteria to important drugs must be reduced, so that the evolution of bacteria to resistant forms is slowed or stopped.

Origin and spread of resistance genes

Some resistance genes originate from soil microorganisms. These organisms have evolved to resist the antimicrobial agents naturally produced by bacteria and fungi and from which man-made antimicrobial drugs were originally derived. Nevertheless, blaming nature as the cause of resistance suggests a total misunderstanding of the fundamental processes by which some of these genes have since evolved. Many have become established on promiscuous genetic elements because of the widescale use of antimicrobial drugs. Others have developed *de novo* and have then been mobilized. However, bacteria in the natural environment may harbour resistance genes derived from human and animal use of these drugs. For example, indigenous soil inhabitants of a wide variety of bacterial species acquired tetracycline resistance genes from the groundwater near sewage lagoons from two pig farms (13). Such resistance genes could, in turn, be acquired by human and animal bacterial pathogens, and would be expected to emerge if people or animals were exposed to tetracycline. The complex ways in which resistant bacteria can flow between humans and animals and be “expanded” by antimicrobial drug use in different settings are illustrated in Figure 2.1. This figure depicts how resistant

organisms or genetic elements can be spread among populations of bacteria, animals or humans by direct contact, or via secondary sources such as water, food, or fomites.

Figure 2.1: Epidemiology of antimicrobial resistance (after Linton (14)).

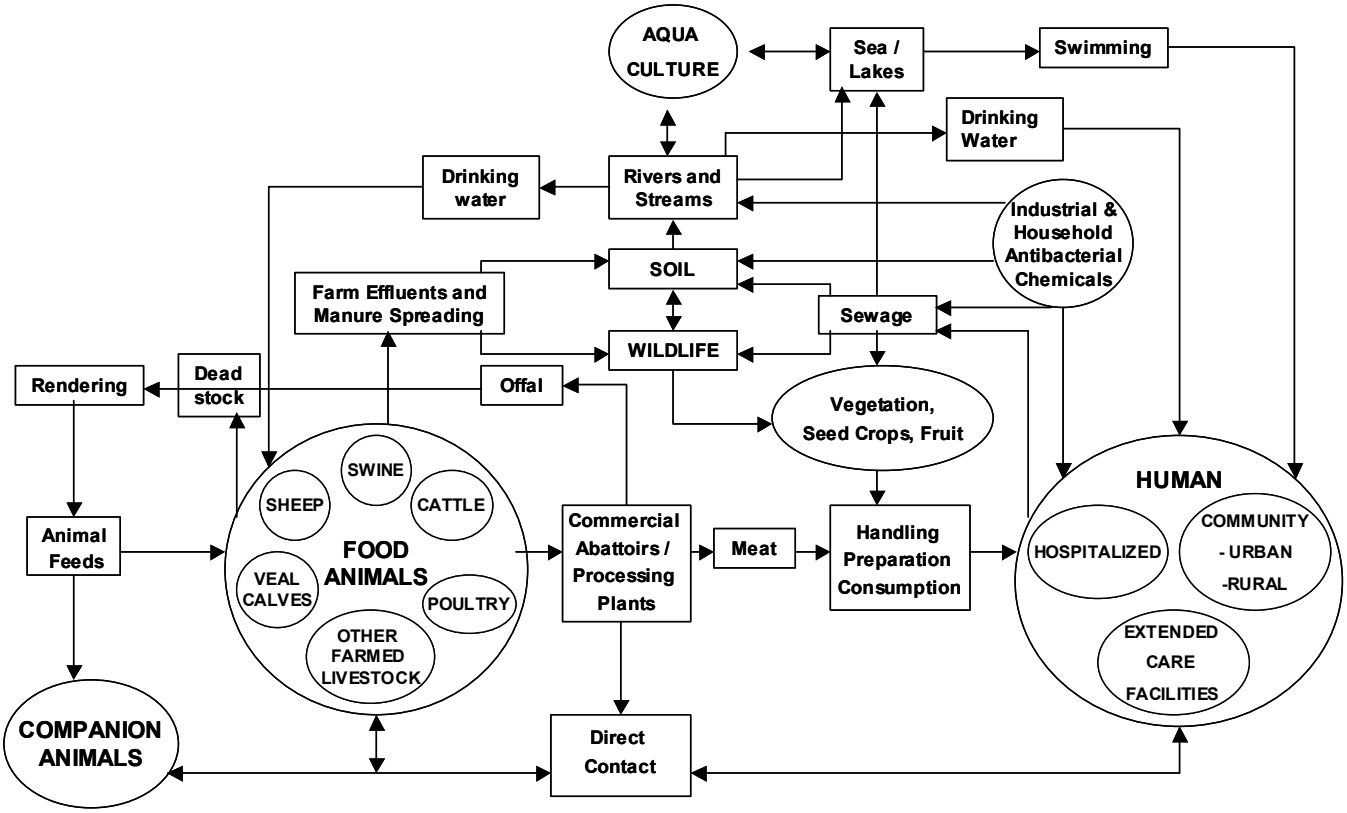


Figure 2.1 describes potential pathways by which resistant organisms may be introduced or transferred between populations of humans, animals, fish, water sources, and plants, and demonstrates the complexity of this ecosystem. The major risk factor for the emergence of resistance among bacterial populations is the use of antimicrobials. Areas where antimicrobials are used are indicated by circles and include human medicine, food animals, companion animals, aquaculture, horticulture, and disinfectants used in consumer products. The size of the circles or their position in the figure is not intended to reflect their relative impact on the spread or emergence of resistance.

Effects on human health

Once established in bacterial populations, antimicrobial resistance originating from agricultural sources can adversely affect human health either directly or indirectly. Direct effects are the result of resistance among zoonotic infections (zoonoses are diseases transmitted from animals to humans). Indirect effects occur when resistance genes from bacteria in animals are transferred to human pathogens. These will be explained with three example scenarios, hypothetical but supported by scientific study, that depict direct and indirect mechanisms by which the use of antimicrobials in animals can select for resistance in

human pathogens. It should be emphasized, however, that treating animals with antimicrobial drugs is not always a necessary or sufficient cause for resistant infections to occur in these situations. For example, once resistance is acquired by some pathogens (*e.g.*, *Salmonella* Typhimurium DT 104), they appear quite able to spread among animals and to humans, even in the absence of antimicrobial selection pressure, provided the resistance genes do not impair their fitness as pathogens. Additionally, factors other than antimicrobial use facilitate spread, including intensity of animal husbandry and mixing of animals from different sources.

Direct transmission

As described above, bacterial enteric pathogens are important causes of disease in Canada, and they are also among the most common causes of infectious disease worldwide. There are several ways that resistance may directly increase the burden of illness due to these pathogens (15). First, resistant zoonotic infections can be more difficult or expensive to treat than susceptible infections. Although antimicrobial therapy in bacterial diarrhoeas is controversial and generally not warranted in mild or resolving disease, it should be considered in patients with shigellosis, some traveler's diarrhoea, cholera, and some patients with *Campylobacter* enteritis (16). It is also recommended in patients with *Salmonella* infections in their bloodstream (bacteremia or septicemia).

Second, some resistant pathogens may be more virulent or pathogenic to humans than susceptible pathogens, thereby causing more severe or longer-lasting disease. In both nosocomial (hospital-acquired) and community-based outbreaks of disease in the U.S., the death rate attributable to resistant strains was higher than that attributable to susceptible strains. The highest mortality rate was observed with multi-resistant strains (17,18). In a recent study of salmonellosis in the U.S., Lee et al. (19) found that people with infections resistant to antimicrobial drugs were more likely to be hospitalized than those with susceptible infections, even after correction for the underlying illness. These individuals also tended to be sick longer (two extra days on average) and hospitalized longer (one extra day on average).

Third, the presence of antimicrobial resistance in zoonotic pathogens can increase the number of cases of illness (20,21). A number of studies of resistant *Salmonella*, and more recently, of *Campylobacter* infections in humans, showed that prior therapy (*i.e.*, treatment for another reason, before the onset of salmonellosis) using antimicrobials increased the risk of disease. It is believed that the prior treatment with antimicrobials disrupts the normal microflora of the intestine, making the victim more susceptible to the resistant *Salmonella* infection.

Finally, resistance in bacteria may enhance the spread of infection or the duration of faecal shedding (when bacteria exit the host animal in its faeces) in animal populations that are undergoing antimicrobial therapy, making these infections more available for infection of humans by contamination of the food chain or environment. For example, a recent study of Canadian pig farms showed that antimicrobial use, especially in feed, was associated with increased risk of resistance among faecal *Escherichia coli* (22).

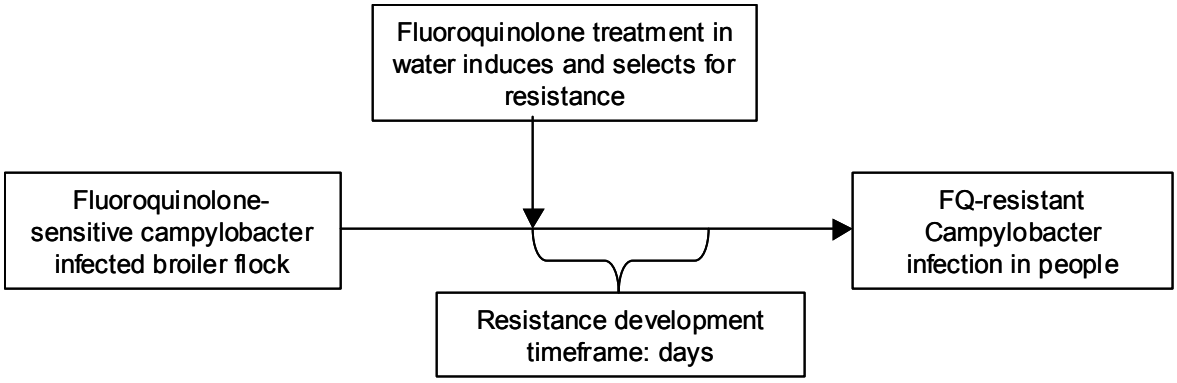
Consequently, antimicrobial resistance in zoonotic enteropathogens is a human health problem because necessary treatments may fail, be delayed or made more expensive, and because resistant infections may be more numerous, severe, and long-lasting than those infections that are more sensitive to the effects of antimicrobials. While resistance to many different classes of antimicrobials in these enteropathogens has emerged, it is useful to focus

on two examples to illustrate how resistance threatens human health. The first example involves resistance to the fluoroquinolones, a family of drugs of great importance to human health, and the second example involves multidrug-resistant (MDR) *Salmonella enterica*, an important infection in Canada and abroad.

Fluoroquinolone resistance in Campylobacter jejuni

The fluoroquinolones are valuable first-line antimicrobials used for the treatment of salmonellosis and campylobacteriosis in humans. Currently, they are not approved for use in food animals in Canada. Antimicrobial resistance to this family of drugs is of serious concern (23). Smith et al. (24) reported an increase in domestically acquired infections involving quinolone-resistant *Campylobacter jejuni* (*i.e.*, those acquired in the U.S.) in Minnesota, from 1992 through 1998. The increase in infections was linked to the licensing of fluoroquinolones for use in poultry production in the U.S. in 1995. The investigators detected a high prevalence of quinolone-resistant *Campylobacter* in retail chicken products produced domestically. They documented DNA fingerprints in quinolone-resistant *C. jejuni* from domestically produced poultry that were identical to those in the resistant *C. jejuni* from domestically acquired infections in humans. Patients infected with resistant *C. jejuni* who were treated with fluoroquinolones were found to have a longer duration of diarrhoea than patients with fluoroquinolone-sensitive infections (an average of 10 days vs. 7 days). Thus, a human health effect due to the use of quinolones in animals was identified.

Figure 2.2: Direct effect: resistance arising *de novo* on-farm in a zoonotic enteropathogen with transfer to humans through food or water, *e.g.*, fluoroquinolone-resistant *Campylobacter jejuni* in broilers



Recent research shows that resistance to fluoroquinolones may develop in *C. jejuni* and be selected during the course of treatment of chickens (25). This can occur because *C. jejuni* easily and quickly acquires resistance to fluoroquinolones through a single-step mutation (26). This is an example of *de novo* development and selection of resistance, the simplest type of direct effect on human health. In the hypothetical scenario depicted in Figure 2.2, susceptible *C. jejuni* infects broiler chickens on a farm (bacteria can be easily introduced to farms by infected animals, wildlife, environmental contamination, or by other means). The flock is treated with a fluoroquinolone drug because some of the birds have an *E. coli* infection. Resistant strains are then selected and available for transmission to humans through

contamination of chickens at slaughter and at other points prior to consumption. This drug is not approved for such use in Canada, but it is in some other countries.

Multidrug-resistant Salmonella enterica

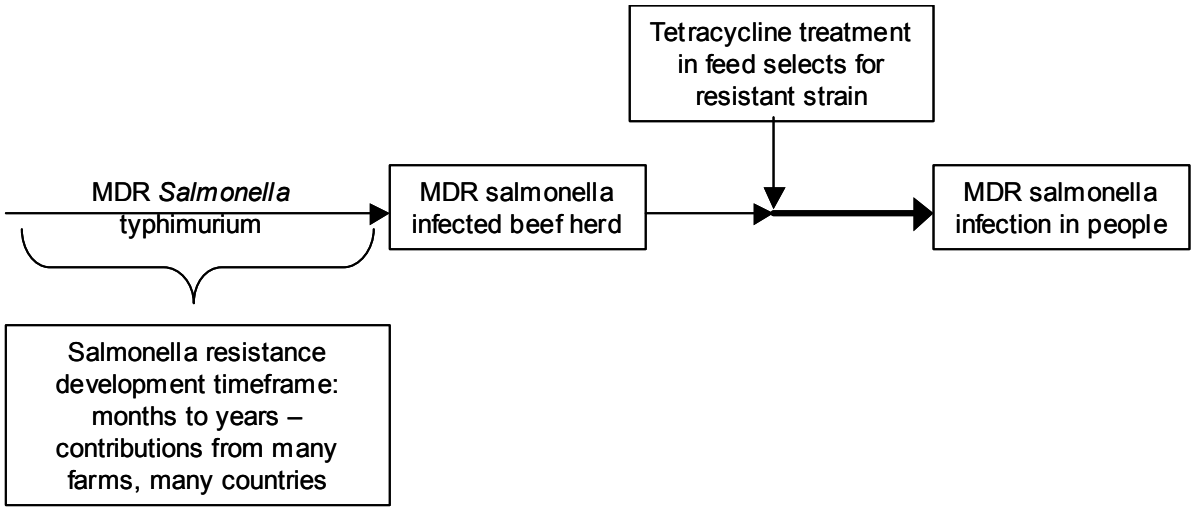
Multidrug-resistant (MDR) strains of *Salmonella enterica* have been a problem in Canada and many other countries for decades (27). A variety of studies have attempted to document the role of antimicrobial use in animals in the development and selection of these organisms (28). Many scientists believe that these and similar studies provide conclusive evidence of the link between such use and resistance in important enteropathogens (29). Other scientists contend that the evidence is not conclusive, either because of insufficient information, study design limitations, or differences in interpretation of scientific data (30). Much of this uncertainty can be attributed to the complexity of resistance genetics in pathogenic bacteria, technological limitations in tracing the lineage of these genes, and difficulties in linking resistance to antimicrobial use or other causes, which may have occurred over many years in widely disparate locations around the globe (31).

As previously mentioned, *Salmonella* Typhimurium is a pathogen that appears to develop resistance to one or more antimicrobials with relative ease. It also causes severe disease in animals and humans. In past years, a variety of different subtypes of MDR *S.* Typhimurium (e.g. DT 204 and DT 193) have swept across many countries, infecting cattle and humans in particular.

In the 1990s, a new MDR strain of *Salmonella* Typhimurium, strain DT 104, emerged and was first recognized in the United Kingdom. In the following years, the strain was isolated in other countries, including Germany, the U.S., Canada, Italy, Belgium, Israel, and Denmark. This strain was initially characterized as having chromosomal genes for resistance to the antimicrobial drugs ampicillin, chloramphenicol, streptomycin, the sulfonamides, and tetracycline (resistance type, ACSSuT). In recent years, strains with additional resistance or decreased susceptibility to gentamicin, trimethoprim, and/or fluoroquinolones have been observed. MDR strain DT 104 has been isolated from a wide range of host animal species, and the organism has become the second most common cause of human salmonellosis, after *Salmonella enteritidis* phage type 4 (PT4), in the U.K. and Germany.

Figure 2.3 shows a hypothetical example of the direct effect of resistance on human health due to *Salmonella*. In this scenario a strain of *Salmonella* Typhimurium resistant to multiple drugs (including tetracycline) arrives on a beef farm, the strain already in possession of resistance genes. Treatment of cattle on this farm with tetracycline can select for the resistant strain and facilitate its spread among animals. In this example, the selective pressure of drug treatment has increased the prevalence of infection in the herd, and thus the potential for spread to humans through contaminated food, water, or other means. The role of antimicrobial use in animals (and perhaps humans) is much more complex in this example than the fluoroquinolone-resistant *Campylobacter* example shown in Figure 2.2. Here, the *Salmonella* arrived on the farm already resistant to a host of drugs; therefore, its genetic lineage and history of prior exposure to antimicrobial drugs must be considered in the overall assessment of selection pressure. Unfortunately, the means by which bacteria acquire resistance in such circumstances is almost never known. Probably, it arises from the cumulative effect of antimicrobial use in many species of animals (or humans) on many different farms over many years, perhaps involving many species of bacteria that exchange genetic information when it is to their advantage.

Figure 2.3: Direct effect: a resistant zoonotic enteropathogen introduced to a farm and selected by antimicrobial use, with transfer to humans through food, water, or animal contact, *e.g.*, multidrug-resistant (MDR) *Salmonella* Typhimurium in cattle



Zoonotic enteropathogens such as *Salmonella* and *Campylobacter*, which spread readily within and between farms, probably acquire most of their resistance on farms because animals are the predominant reservoirs of these organisms. In developed countries, food animals are the principal source of these infections for humans, and when people do become infected, person-to-person spread is uncommon. Therefore, selection pressure from antimicrobial use in humans probably plays only a minor role in the epidemiology of resistance in zoonotic enteropathogens. Antimicrobial use in animals probably plays the predominant role. Many of the phenomena concerning resistance development, selection, and spread discussed earlier in this chapter are almost certainly involved in this example. The complexity of this scenario illustrates the difficulties in fully understanding the role of antimicrobial use in animals and its impact on resistance problems in humans.

Indirect transmission

Indirect effects of antimicrobial resistance from animals on human health occur when resistance genes are transferred from animal bacteria to human pathogens. For some drugs, it is difficult to determine the direction of gene flow, *i.e.*, animal to human or vice-versa. However, when unique classes of drugs are introduced into animals, it is possible to follow the movement of resistance genes from animals to humans. It is apparent that a pool of resistance genes exists for currently used antimicrobials and for those antimicrobials used in animals but not yet used in human medicine. The principles of indirect transmission of resistance from animals to humans (often called "gene flow") can be illustrated by three examples: nourseothricin use only in animals, avoparcin use in animals and VRE in humans, and virginiamicin use in animals and resistance to quinupristin/dalfopristin in bacteria from humans.

Nourseothricin resistance in Escherichia coli

Witte (32) was able to demonstrate, in the former East Germany, how resistance to nourseothricin, a drug used only in animals, moved from animals to humans. Nourseothricin was used as a growth promoter from 1983 to 1990, replacing the similar use of oxytetracycline. Resistance to nourseothricin in Enterobacteriaceae from humans and animals was negligible in 1983. Two years later, resistance (by means of the transposon-encoded streptothricin acetyltransferase gene) was found in *E. coli* from the gut of pigs and from meat products. By 1990, resistance to nourseothricin had spread to *E. coli* from the gut of pig farmers, their families, citizens from municipal communities, and patients suffering from urinary tract infections. The spread among humans occurred without apparent selective pressure. In 1987, the same resistance determinant was detected in other enteric pathogens, including *Shigella*, an organism found only in humans.

There are other examples where resistance genes have evolved in bacteria of animal origin and been directly transferred to humans, colonizing them and/or causing disease. Once such resistant organisms have been introduced into the human environment, they have the potential to transfer their resistance mechanisms to other human strains. VRE are the quintessential examples of this type of event, and streptogramin-resistant enterococci represent another, more recent example of this problem.

Vancomycin-resistant enterococci (VRE)

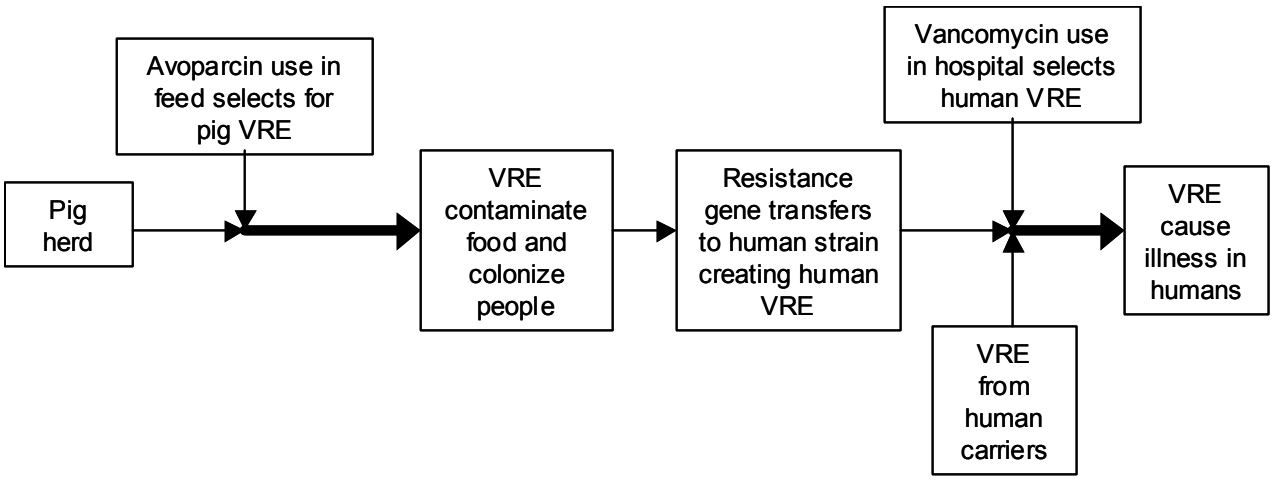
Enterococci are normally found in humans, with the highest concentration in the large intestine (33). They are also found in water, soil, food, a variety of other animals, and the inanimate environment of hospitals. Enterococci are opportunistic pathogens best known for their resistance to antimicrobial drugs, and are commonly recovered from patients who have received multiple courses of antimicrobials and who have been hospitalized for prolonged periods of time. Vancomycin resistance in enterococci was first documented in 1969, but did not emerge as a problem until the 1990s (34–37). Since then, this type of resistance has spread to many countries (38–50).

VRE of humans are linked to food-animal production through the use of avoparcin as a growth promoter in swine and poultry. Avoparcin is a glycopeptide antimicrobial related to vancomycin and was used in animal feed from 1974 until 1997 (51) in Europe and some other regions, but not in North America. Epidemiological studies in animals showed that avoparcin use selected for VRE (52).

VRE from animals can colonize humans, at least briefly (53). Although it is possible that some animal strains are pathogenic in humans, it is more likely that resistance impacts from animals are indirect. This indirect effect is depicted in Figure 2.4. In this hypothetical scenario, vancomycin-resistant enterococci (VRE) are introduced to a pig herd. The animals are fed an antimicrobial growth promoter, avoparcin (a glycopeptide drug related to vancomycin), that selects for the resistant strain. As mentioned, avoparcin was never approved for use in Canada, but was widely used in Europe and elsewhere. The human health effect is indirect in this case, because the VRE from pigs are not themselves pathogens for humans. Rather, they can act as donors of the vancomycin resistance gene to human strains of enterococci, which can be pathogenic to humans under the selection pressure of vancomycin treatment of humans. As shown, VRE may also be introducd by human carriers.

The epidemiology of VRE in humans varies, depending on the geographic area, including Canada (54-56), and for this reason some questions remain about the role of avoparcin use in animals and VRE problems in humans. For example, in Europe, where avoparcin was widely used, asymptomatic human carriage is common in the community, but hospital outbreaks of VRE are uncommon (57). In North America, however, where vancomycin was not used, VRE are found almost exclusively in hospital settings, where they are a serious problem. The spread of VRE occurs within and between hospitals (58). More than 25% of enterococci isolated from intensive care units in the National Nosocomial Infections Surveillance (NNIS) system are resistant to vancomycin. In two recent case series, VRE comprised 40% of all enterococcal bacteremias, and 67% of all *Enterococcus faecium* bacteremias (59-61.

Figure 2.4: Indirect effect: resistant commensal bacteria selected by antimicrobial use with transfer of a resistance gene to a human pathogen, *e.g.*, vancomycin-resistant enterococci in pigs



There is good evidence that avoparcin use in animals played an important role in the VRE problems in Europe. In the 1990s, after VRE were recognized to be a problem, European researchers isolated them from farm animals and meat, and from adults living in communities (62–64). In the early 1990s, glycopeptide use in animals exceeded use in humans 500 to 1000 fold (65). After the European avoparcin ban in 1997, the prevalence of vancomycin resistance declined substantially among enterococci of pigs, poultry, meat and humans (51,66). Results of molecular typing studies are consistent with an animal contribution to human VRE (67).

What about North America? Here, the role of antimicrobial use in animals is less clear. The VRE problem in North American hospitals occurred at a time when conditions were ripe for the dissemination of a hearty faecal multidrug-resistant pathogen. Vancomycin was used much more extensively than in Europe (65). Multiple case-control and cohort studies have demonstrated that risk factors for colonization and infection with VRE include increasing severity of the underlying illness, presence of invasive devices, antibiotic use and hospital length of stay, and prior colonization with VRE (38,49,64,57-61). Renal dialysis, transplant, and oncology patients are commonly those affected. Recently, studies have also shown that

"colonization pressure," that is, the number of other colonized patients to which each patient is exposed, is also a powerful predictor of colonization (58).

Did avoparcin use in other parts of the world contribute to the VRE problems in North America? Quite possibly it did, although we may never know for sure. VRE can easily spread through international travel or imported food products. Once introduced to North America, intensive vancomycin use in hospitals and the other risk factors mentioned above could quickly select for those strains. Clearly, the VRE problem in human medicine is attributable to a wide variety of factors, and there is good evidence that avoparcin use in food animals in a number of countries around the world is one of those factors (68). VRE is a good example of the global dimensions of the antimicrobial resistance problem.

Quinupristin/dalfopristin Resistance

Quinupristin/dalfopristin is a new combination, streptogramin-type antimicrobial that will be useful to inpatients with vancomycin-resistant *Enterococcus faecium* bacteremia. Although streptogramins have not been used in the hospital setting previously, a related, mixed compound, virginiamycin, has been used in Europe and North America for many years as a feed additive to enhance growth in food animals, or to prevent disease. High numbers of virginiamycin-resistant *E. faecium* have been isolated from the faeces of food animals. These were also resistant to quinupristin-dalfopristin, indicating cross-resistance between virginiamycin and quinupristin-dalfopristin. Jensen et al. (69) provided evidence of the occurrence of the same resistance genes in streptogramin-resistant *E. faecium* isolates of animal and human origins.

Conclusions

Food animals are important reservoirs of food and waterborne disease due to *Salmonella enterica*, *Campylobacter jejuni*, *Escherichia coli*, and other bacteria. Thousands of human cases of these infections occur annually in Canada. Antimicrobial resistance occurs in many of these infections and is a human health problem when antimicrobial treatments fail, are delayed, or are made more expensive. Also, the presence of antimicrobial resistance may increase the number, duration, and severity of these infections, when compared with their sensitive counterparts. There are good examples of direct (*e.g.*, resistant *Salmonella*, *Campylobacter*) and indirect (e.g., *Enterococcus*, *E. coli*) effects of resistance on human health. These examples demonstrate the nature of the resistance problem as it pertains to antimicrobial use in food animals. The magnitude of the problem is the subject of Chapter 6, in which quality of evidence and methods used to estimate the magnitude of the human health risk are discussed in more detail.

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CHAPTER

3

Control of antimicrobial resistance in the human health sector

Key Points

- **Among community-based infections, resistance is most important in respiratory (*e.g. Streptococcus pneumoniae*), enteric and sexually transmitted diseases (*e.g. Niesseria gonorrhoeae*).**
- **In hospitals, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant Gram-negative bacteria are serious problems**
- **Resistance contributes to increased morbidity and mortality, higher health care costs, and increased use of new drugs**
- **In humans, access to antimicrobial drugs is controlled by prescription; physicians in Canada do not profit from antimicrobial sales**
- **Canadian initiatives to control resistance include surveillance, education, infection control, and reductions in the consumption of antimicrobials**

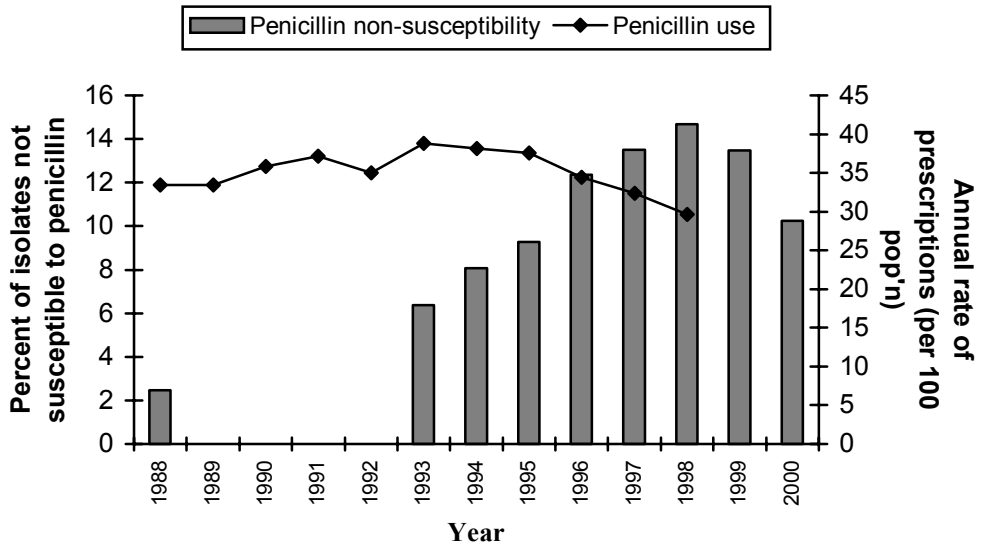
Unlike resistance in the zoonotic enteropathogens, resistance in most non-enteric (*e.g.*, respiratory, skin, genitourinary) bacterial infections of humans is almost entirely attributable to antimicrobial use in humans. These infections are major human health problems in Canada and abroad. The purpose of this chapter is to briefly review the major issues and efforts to control antimicrobial resistance in the human health sector, in order to complement the focus on food-animal production that occurs elsewhere in the report. It also provides an opportunity to identify lessons from human medicine that may be applicable to the use of antimicrobial drugs in food animals.

In the last decade, there has been an unprecedented increase in the rate of evolution and dissemination of antimicrobial resistance in pathogens found in the community and the hospital setting. In the United States, approximately 75% of prescriptions for antimicrobial drugs are for the treatment of five acute respiratory infections: otitis media, sinusitis, pharyngitis, bronchitis, and upper respiratory tract infections (1). Prescriptions for colds, upper respiratory tract infections and bronchitis account for a large portion of the "unnecessary" use of antimicrobial drugs. These conditions have a predominantly viral etiology, and treating them with antimicrobials does not have a major clinical impact (2). In the hospital setting, the emergence and spread of multidrug-resistant (MDR) pathogens is a serious problem.

Major issues

The most important issue in the community has been the increase in prevalence of antimicrobial resistance in respiratory, enteric (discussed in Chapter 2), and sexually transmitted disease pathogens, most of which are unrelated to animals. *Streptococcus pneumoniae* is the most important cause of bacterial meningitis, otitis media, sinusitis, and community-acquired pneumonia. Although the threat of MDR *S. pneumoniae* (MDRP) was first identified in the 1970s, in the late 1990s resistance in this respiratory pathogen increased sharply. In Canada, the rates have increased from <2% in the 1980s to >12% in the late 1990s (Figure 3.1).

Figure 3.1: The prevalence in pneumococcal resistance to penicillin in Canada and its association with the use of penicillin (Data from the Canadian Bacterial Surveillance Network and IMS HEALTH, Canada)

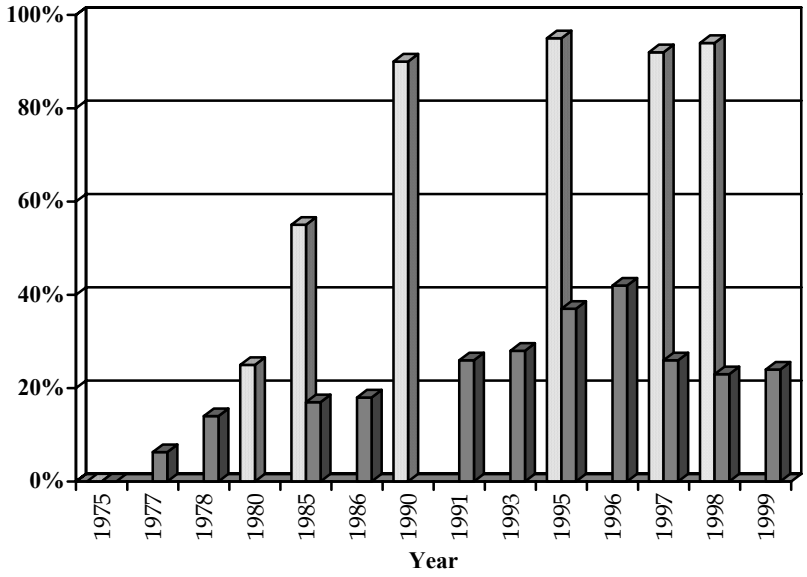


Disturbing information arose from a surveillance study from the U.S. where it was found that strains of *S. pneumoniae* that are highly resistant to the effects of penicillin now occur with greater frequency than intermediately resistant strains (32.5% versus 18%) (3). Resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* to the aminopenicillins, as the result of β-lactamase production, increased from 0% in the 1970s to >30% and >90% for *H. influenzae* and *M. catarrhalis*, respectively, in the 1990s (Figure 3.2) (4).

Fluoroquinolones and cephalosporins became the recommended therapies for gonorrhoea following the appearance of penicillin- and tetracycline-resistant *Niesseria gonorrhoeae* during the 1980s and early 1990s (6). Fluoroquinolone-resistant *N. gonorrhoeae* (ciprofloxacin maximum inhibitory concentration (MIC) greater than or equal to 1.0 μg/mL) emerged during the 1990s and became well established in several areas (*e.g.*, Hong Kong, Japan and the Philippines) (7). During the same period of time in the U.S. and Canada, *N. gonorrhoeae* with decreased susceptibility to ciprofloxacin were identified (7).

In the hospital setting, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and MDR Gram-negative bacteria have been observed. In the past few decades, MRSA has been recognized worldwide as an important nosocomial pathogen. The emergence and rapid spread of this organism has created important new challenges for infection prevention and control services in hospitals and other health care facilities. MRSA was first reported in Canada in 1981 (8). Since then, the organism has been identified in many Canadian health care facilities. One report has documented rapid, interprovincial spread of a single clone of MRSA (9). In Ontario, the Quality Management Program-Laboratory Services has documented the emergence of MRSA in hospitalized patients. Also, community-acquired MRSA has been described. Simor et al. (10) reported the results of surveillance carried out in Canadian hospitals. A total of 4,507 patients infected or colonized with MRSA were identified between January 1995 and December 1999. The rate of MRSA increased each year from a mean of 0.95 per 100 *S. aureus* isolates in 1995, to 5.97 per 100 isolates in 1999.

Figure 3.2: Frequency of β-lactamase positive *Haemophilus influenzae* and *Moraxella catarrhalis* in Canada. The dark columns represent *H. influenzae* and the light columns represent *M. catarrhalis* (Data from the Canadian Bacterial Surveillance Network)



Medical outcomes

There are several consequences arising from the development of antimicrobial resistance in bacterial pathogens (many of these also apply to zoonotic enteropathogens, discussed in the previous chapter). First, treatment of resistant infections is more likely to fail. Affected patients have an increased morbidity and mortality in association with their infections. For example, four children infected with MRSA in their community were inappropriately treated with an oral cephalosporin and, as a result, failed therapy and died (11). Second, the development of resistance to first-line antimicrobials often means that more expensive, and

sometimes less effective, drugs must be used. In the worst situation, with some resistant pathogens, there are no effective alternatives. This was initially the case with the appearance of VRE. Third, for hospitalized patients, infection with a resistant pathogen is associated with increased length of stay, increased costs related to infection control, and increased laboratory costs. Kim et al. (12) projected, assuming an infection rate of 10% to 20% of MRSA in hospitalized patients, that the costs associated with MRSA in Canadian hospitals would be $42 to $59 million annually. Finally, the presence of resistance to one antimicrobial drug may increase the use of another antimicrobial drug, which will further drive resistance to the latter compound. For example, treatment options for the management of serious MRSA infections are limited. The current medication of choice is vancomycin. Higher rates of MRSA in Canadian health care facilities could lead to increased use of vancomycin, which is in turn associated with the emergence of vancomycin resistance in enterococci and MRSA. Although *Staphylococcus aureus* with reduced susceptibility to vancomycin has not yet been identified in Canada, it is probably just a matter of time before this occurs.

There is no doubt that patients with VRE bacteremia are more likely to die than those with vancomycin-susceptible enterococcal bacteremia. However, it is also true that patients with enterococcal bacteremia have chronic underlying illness that is more serious. To a large extent, assessing whether death is due to the bacteremia itself or some other cause is subjective. Studies suggest that VRE bacteremia is associated with higher mortality than non-VRE enterococcal bacteraemia (13).

Efforts to control resistance in human pathogens

Canada

In Canada, patient access (>99%) to antimicrobial drugs is controlled by prescription, which is received from a physician and taken to a pharmacist, where the drug is dispensed. Individuals may also legally import medications for their own use. Physicians in Canada do not profit from antimicrobial sales. In Canada, it is illegal to advertise antimicrobials to the public, although advertising antimicrobials is legal in the U.S., and many Canadians are exposed to these advertisements via access to U.S. networks.

There are a number of programs and initiatives underway in Canada to prevent and control the emergence and dissemination of antimicrobial resistance in the human health sector, including surveillance, education, infection control, and reductions in the consumption of antimicrobials (14,15). In-facility surveillance has been bolstered through the establishment of the Canadian Nosocomial Infection Surveillance Program (CNISP), which tracks antibiotic-resistant organisms (ARO) in most major sentinel facilities in the country. The Canadian Committee on Antibiotic Resistance (CCAR) coordinates activities and information on antimicrobial resistance matters, including surveillance, infection prevention and control, and optimal antimicrobial use (16). The National Information Program on Antibiotics (NIPA) is a group of health organizations in Canada that promotes the appropriate use of antimicrobials and provides information for health care workers and patients (17).

World Health Organization

The World Health Organization (WHO) places major emphasis on antimicrobial resistance. In 2001, it published the "WHO Global Strategy for Containment of Antimicrobial Resistance" (18). The intent of the strategy is to promote wiser use of antimicrobials and to

emphasize the global nature of the resistance problem. WHO recommends improved education of prescribers and dispensers, patients and the general community; improved use of treatment guidelines and formularies; better hospital management of infection; and greater access to diagnostic laboratories. Other areas of focus include better regulation, surveillance, drug and vaccine development, and better international collaboration to contain the spread of resistance.

Europe

Recent major reports and initiatives on antimicrobial resistance have emerged in Europe and its member states, including the 1998 House of Lords Report of the Standing Medical Advisory Committee from the United Kingdom and the 1999 report of the European Commission (19–21). These reports drew attention to the need for more prudent use of antimicrobials in medical practice and made several recommendations for tighter controls on the sale, supply and distribution of antimicrobials, improved prescription practice, better use of sensitivity testing, and enhanced surveillance and infection control. Some European countries have taken action to slow the development of resistance in medicine. For example, in 1999 Denmark altered its drug subsidization policy to reduce the use of fluoroquinolones because of resistance concerns (22). Recently, British public health officials launched a patient education program entitled "Antibiotics: Don't Wear Me Out," which asked the public not to expect their doctor to prescribe antibiotics for colds, or for most coughs and sore throats (23).

United States

A number of public health agencies in the U.S., including the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), recently released "A Public Health Action Plan to Combat Antimicrobial Resistance" (24). It is a consensus of federal agencies on actions to address resistance, focusing on surveillance, prevention and control, research and product development. Top priority actions include development and implementation of a coordinated, national plan for resistance and drug-use surveillance; extension of the useful life of antimicrobial drugs through appropriate use policies; and prevention of infection transmission.

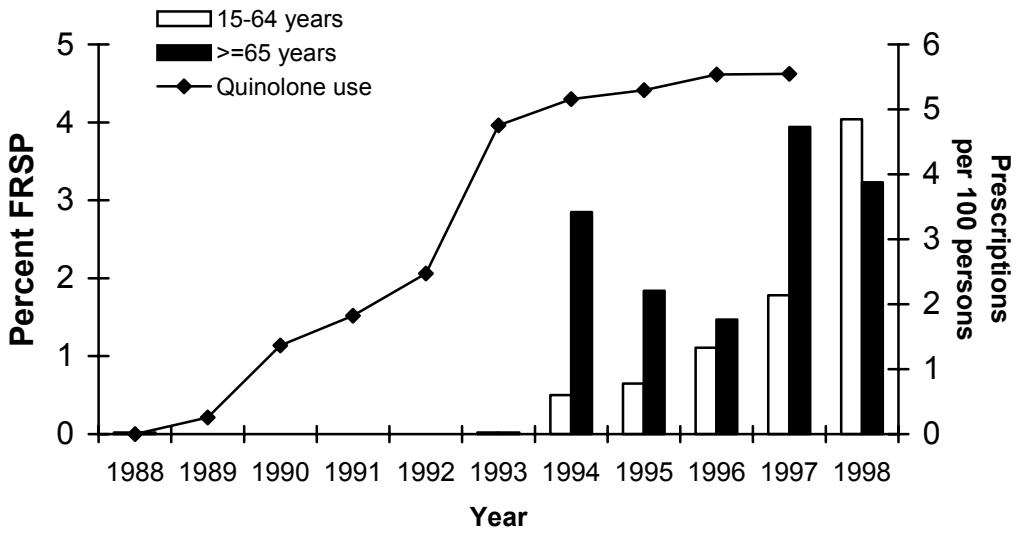
Analysis: impact of efforts to control antimicrobial resistance in the human health sector

Globally, resistance surveillance in the human health sector is fragmented and generally inadequate (25). In Canada, the situation is somewhat better; directed surveillance and investigation programs have enhanced the understanding of resistance selection and spread. But gaps exist in the data systems. Most professional education in the medical field has been accomplished through the leadership of infectious disease specialists and infection control practitioners. These services are available in major centers in Canada but are sporadically available in other health care facilities. Management of antimicrobial use in hospitals is facility specific. Guidelines are often available, but compliance with such guidelines to physicians is inconsistently measured and rarely enforced. Evidence suggests that simple dissemination of guidelines is usually ineffective, but combined strategies using worksite training, use of opinion leaders and ongoing supervision and monitoring of practices can improve antimicrobial use (25). Infection control practices remain the responsibility of the

governance organization and are not linked. The degree of implementation of nationally recommended procedures and practices to prevent the spread of resistant pathogens has not been determined. Control has been incorporated into facility accreditation procedures.

Data on gross volumes of antimicrobial use are available at the national and, occasionally, at the provincial level. For example, IMS HEALTH, Canada, provided an estimate of the total number of antibiotic prescriptions dispensed in Canadian retail pharmacies, based on a representative sample of 2,000 pharmacies, stratified by province, store type, and size. These data allowed researchers to show how increased use of the fluoroquinolones was associated with increased resistance of *Streptococcus pneumoniae* to these agents (Figure 3.3) (26).

Figure 3.3: The prevalence of fluoroquinolone resistance in *Streptococcus pneumoniae* in Canada and its association with fluoroquinolone use in humans (Data from the Canadian Bacterial Surveillance Network)



Also, researchers have demonstrated that a decrease in the use of one class of antibiotics is associated with a decrease in bacterial resistance to that same class of antibiotics (D.E. Low, unpublished data) (Figure 3.1).

Laboratory reports of resistance levels are not coordinated, although some local information may be available to practitioners in certain geographic areas. The push for more professional education has been spurred on by the pharmaceutical sector and through the leadership of the academic infectious disease community. A few pilot sites, with intensive support systems available to professionals, have demonstrated success, but widespread initiatives have not been forthcoming in most jurisdictions. Leadership in public education has not fallen to any specific group, and there are federal, provincial, and local issues of jurisdiction. A national coalition of agencies, supported in part by pharmaceutical resources, has provided some awareness of the issue. Specific professional groups have also aided in increasing awareness about the issue of antimicrobial resistant organisms (often called “superbugs”). Demonstration projects have tended to combine professional and public education as the basis for reduced use of antimicrobials in the community.

Within the last five years there has been a decrease by 11%, overall, in the use of antimicrobials in the out-patient setting (http://www.ccar-ccra.org/). This may be, in part, a result of the education of physicians regarding the threat of antimicrobial resistance and/or the increased awareness of the public due to extensive and sustained media interest in this issue. In the hospital setting, health practitioners and patients continue to be faced with an increasing prevalence of MDR pathogens. Major improvements include an appreciation of the importance of and adoption of infection control practices to limit the spread of resistant pathogens, and improvements in laboratory recognition and reporting of resistance.

Conclusions

Major problems related to antimicrobial resistance exist in the human health sector. Control efforts emphasize surveillance, education, infection control, and reductions in the consumption of antimicrobials, both in the community and in hospital settings. Some success has been achieved, but many improvements are needed. Lessons learned from the human sector could well be applied to the food-animal sector. These include recognition of problems through surveillance, education of veterinarians and producers regarding the consequences of inappropriate use, greater control of antimicrobial use, guidelines for best practices and improvements in private and public laboratories' abilities to recognize and report on emerging problems regarding resistance.

Recommendation

1. Continue support for integrated approaches to address the issue of antimicrobial resistance in humans and animals through Health Canada and organizations such as CCAR.

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CHAPTER

4

Regulation and distribution of antimicrobial drugs for use in food animals

Key Points

- **Before marketing is permitted, Health Canada evaluates antimicrobials for quality, efficacy, animal safety and human safety**
- **Some antimicrobials are available only by prescription; others may be sold over the counter (except in Quebec)**
- **Provinces have the right to regulate more stringently, but not more leniently, the sale of drugs once they are approved at the federal level**
- **Antimicrobials are distributed through veterinarians, pharmacists, feed companies, and lay retail outlets**
- **Issues to address include:**
    - **The need for valid methods and criteria to assess the safety of veterinary drugs with respect to antimicrobial resistance**
    - **Coordination of antimicrobial use regulation by federal and provincial governments, and veterinary licensing bodies**
    - **Use of antimicrobials without prescription**
    - **The importation of antimicrobials by producers for their "own use," *i.e.*, treatment of their own animals**
    - **Potential for illegal direct use in animals of imported bulk pharmaceutical ingredients**
    - **Veterinary prescription for extra-label use**
    - **The potential for profit motives to negatively influence prescribing practices**

This chapter presents a brief overview of the regulation, distribution, and sale of antimicrobials used in food-animal production in Canada. Practices used or proposed in other countries that are relevant to the management of antimicrobial resistance are also discussed.

Regulatory role of the federal government

Health Canada regulates the sale of drugs in Canada through the *Food and Drugs Act* and *Regulations*, and the *Controlled Drug and Substance Act*. For human drugs, these legislations are administered primarily through the Therapeutic Products Directorate (TDD). For veterinary drugs, including antimicrobials for food animals, the legislation is administered primarily through the Veterinary Drugs Directorate (VDD), formerly the Bureau of Veterinary Drugs (BVD). The VDD is responsible for human food safety issues pertaining to veterinary drugs.

The Veterinary Drugs Directorate

This program administers the pre-market evaluation of drugs, establishes drug quality standards, establishes control regulations, restricts drug availability, manages emergency drug release, evaluates new drugs for use in animals, may authorize manufacturers to sell Investigational New Drugs to qualified investigators for the purpose of conducting clinical evaluations, and may issue Experimental Studies Certificates to researchers to carry out experimental projects for drugs used in animals.

To obtain a Notice of Compliance, which is essentially a license to market a drug in Canada, the VDD requires that manufacturers submit data and information about the following properties of the drug:

1. Product quality, including manufacturing process, chemistry, purity, stability, and other similar information;
2. Animal safety, toxicology, and efficacy in each intended species, including food and companion animals; and
3. Human safety, toxicology, residues and any other residual outcomes, such as antimicrobial resistance, via the treated animals.

Presently within VDD, there are no specific methods and criteria available for human health safety assessment of veterinary drugs with respect to antimicrobial resistance. This also applies to animal safety.

Canadian Food Inspection Agency

The Canadian Food Inspection Agency (CFIA), which is responsible to the Minister of Agriculture and Agri-Food Canada (AAFC), regulates veterinary biologics and medicated feeds. Under the authority of the federal *Feeds Act* and *Regulations*, CFIA administers a national feed program to verify that livestock feeds manufactured and sold in Canada or imported into Canada, are safe, effective and labelled properly. The CFIA evaluates and approves ingredients for use in livestock feeds, with the exception of veterinary drugs, which are Health Canada's responsibility.

Drug classification at the federal level

Veterinary drugs are classified into groups based on a risk management approach (Figure 4.1):

1. Controlled Drugs are used for specific therapy under strict control by the veterinarian. This group of drugs includes products such as stimulants, anaesthetics, and sedatives.

2. Non-scheduled veterinary drugs are those sold without a prescription, such as aspirin.
3. Schedule F Drugs are classified into two parts:
    i. Part I includes drugs intended for human or veterinary use that require a prescription through a pharmacist, practitioner (*i.e.*, veterinarian) or licensed manufacturer.
    ii. Part II includes drugs that may be sold without a prescription when intended for veterinary use and are so labelled. These drugs, such as vitamins or cough syrup, are often sold over the counter (OTC). When sold for human use, these drugs require a prescription.
4. Medicated Feeds. The Canadian Compendium of Medicated Ingredients Brochure (CMIB or MIB) lists medicated ingredients (including antimicrobials) that are approved by Health Canada for feed use.

Only drugs and drug combinations that are specifically listed in the CMIB are allowed in feed unless accompanied by a veterinary prescription. Any medication for use in feed must be of an approved "feed grade" designation, and must carry a Drug Identification Number (DIN), assigned by the VDD. Any drug product having only therapeutic claims cannot be used as a growth promoter, even by veterinary prescription. However, several of the growth promotion claim levels also overlap therapeutic claims (*e.g.*, CMIB #34 - chlortetracycline HCl: Claim 22 for turkeys "As an aid in stimulating appetite and maintaining weight gains…" at 110 mg/kg, versus Claim 33 "As an aid in the prevention of synovitis and infectious sinusitis in turkeys," also at 110 mg/kg). Medications, including growth promoters, are approved for use in feed and included in the CMIB on the basis of specific claims made by the manufacturer of the drug. A claim represents a specific use, use rate, and product formulation for a particular medicating ingredient. A complete claim specifies the reasons for use, feeding directions, warnings, and cautions. This information is required to appear on the label, which, by federal regulation (*The Feeds Act* and *Regulations*), must appear on every package or bulk shipment of final feed product. In general, "warnings" refer to human health and safety issues (*e.g.*, withdrawal times for residue avoidance) while "cautions" refer to non-target animal species (*e.g.*, toxicities, interactions).

Since the *Feeds Act* and *Regulations* cover feed use of antimicrobials, such use is monitored by the CFIA. Feed manufacturers (commercial and on-farm) are subject to inspection by the agency. Under specific regulatory programs (*e.g.*, Program 60), feed samples are taken and assayed on a periodic basis to ensure that properly approved levels are met and that labelling is in accordance with the regulations.

Regulatory role of the provincial governments

Each province in Canada has its own control body and has the right to regulate more stringently, but not more leniently, the sale of drugs once they are approved at the federal level. Certain provinces have enacted their own legislation (Table 4.1).

British Columbia

Drugs are regulated through the *Pharmacists Act* of British Columbia. The Chief Veterinarian with the Animal Health Branch of British Columbia's Minister of Agriculture, Fisheries and Food (BCMAFF) administers these regulations on behalf on the BCMAFF. Under the regulation, the Chief Veterinarian licenses lay premises to sell veterinary drugs and/or biologics. The license may be for a feed mill to mix and sell medicated feed, for a feed dealer

to mix and sell medicated feed, or for a retail outlet to sell veterinary drugs or biologics. The licensed dispenser is the only person who can sell the drugs. This act regulates the sale of antimicrobials and enables licensed veterinarians to buy and sell veterinary drugs if they have a veterinarian-client-patient relationship (VCPR). This act also makes provisions for licensing layperson outlets to sell certain veterinary drugs to food animal producers and feed manufacturers for medicating rations.

Alberta

Drugs are regulated by the *Alberta Livestock Disease Act* and administered by the Alberta Department of Agriculture. Permits may be issued not only to veterinarians, but also to licensees under the *Veterinary Profession Act* to sell medicine OTC only. Sale of veterinary drugs is restricted to veterinarians, permit holders operating at OTC retail outlets, and through medicated feeds prepared according to the Feeds Act.

Saskatchewan

There are no provincial legislations. Apart from the licensing body for veterinarians, the province relies on regulations imposed federally by the *Food and Drugs Act* and *Regulations*.

Manitoba

Veterinarians are empowered by the *Veterinary Medical Act* of Manitoba. The *Pharmaceutical Act of Manitoba* gives veterinarians the power to prescribe medicines. No other provincial legislation is in place.

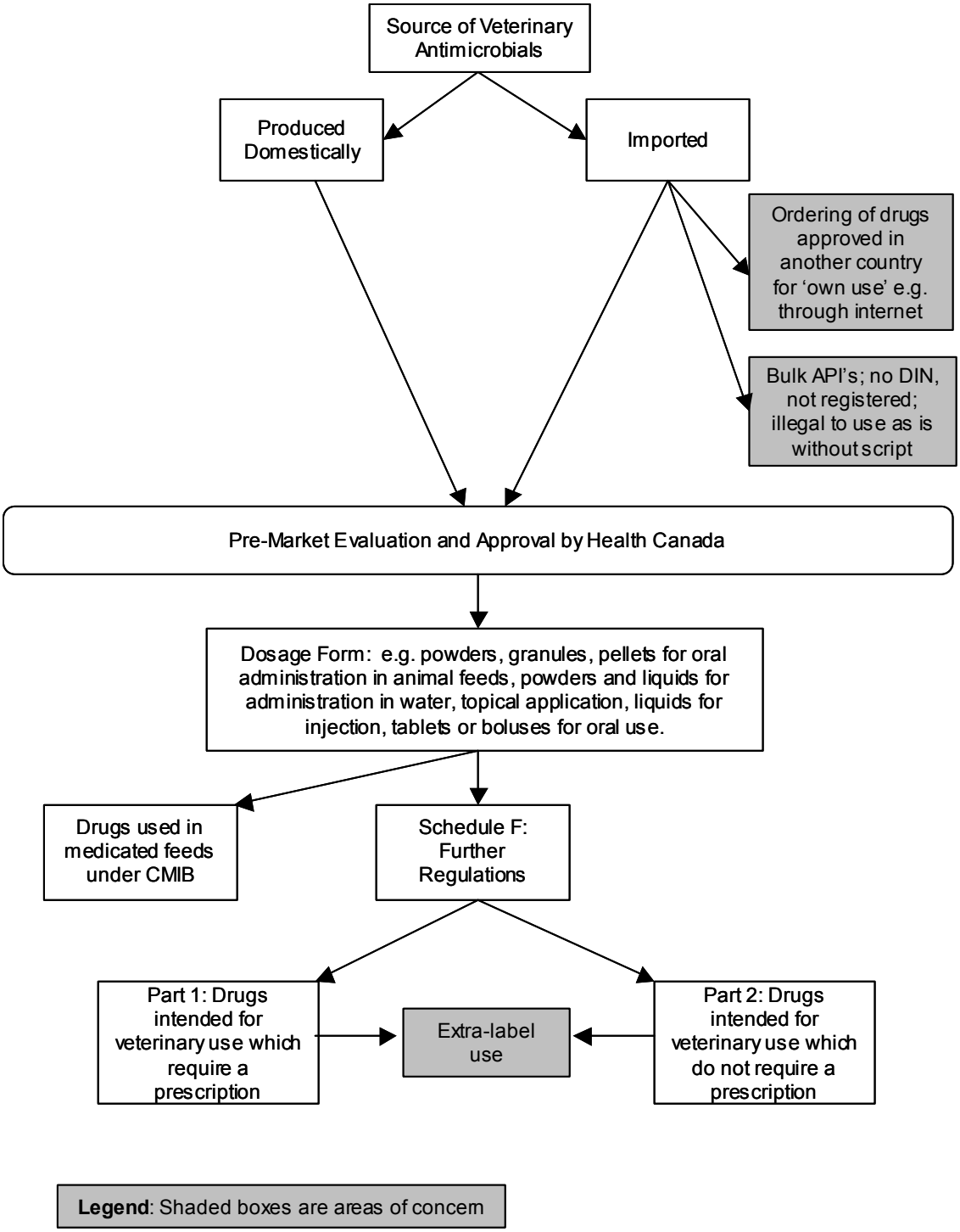
Ontario

OTC drugs are regulated through the *Livestock Medicines Act* and administered by the Livestock Technology Branch, Agriculture and Rural Division, Ontario Ministry of Agriculture and Food (OMAF). The *Livestock Medicines Act* governs provincial drug sales of scheduled products through licensed retail sales outlets. Its objective is to control distribution of drugs by people other than veterinarians or pharmacists.

Quebec

Veterinary drugs are regulated through the *Pharmacy Act*, the *Veterinary Surgeons Act* and the *Animal Health Protection Act*. In Quebec, the sale of veterinary drugs is restricted to pharmacists and veterinary surgeons. The regulation respecting the terms and conditions for the sale of medications contains five annexes; the first three list drugs for humans and the other two list those for animals. Annexe IV determines which drugs must be sold only under veterinary prescription and Annexe V determines which must be sold in a veterinary office. Permits may be issued to persons manufacturing, distributing, and selling medicated premixes or medicated feeds. A permit holder must obtain and keep a veterinary prescription to sell medicated feed. Any person may prepare medicated feed for his own animals without holding a permit as long as he prepares no more that one kilogram or one litre of medicated feed.

Figure 4.1: How antimicrobials reach food-producing animals in Canada



Maritime Provinces

Aside from acts governing veterinarians, Prince Edward Island, New Brunswick, and Nova Scotia have no further controls beyond federal regulations.

Newfoundland and Labrador

The veterinary association and licensing board are currently rewriting legislation and, during the process, are considering an increase in the control of veterinary pharmaceuticals. The actual types of products under consideration are all products listed under Schedule F, Part II of the *Food and Drugs Act* and *Regulations* with the exception of anthelmintic preparations, all vaccines for use in animals, and all products for use in animals that are administered by injection.

Table 4.1: Provincial legislation concerning veterinary antimicrobials

Province	Provincial Legislation	Drugs Regulated	Additional Measures
Alberta	*Alberta Livestock Disease Act* and *Veterinary Profession Act*	Prescription and OTC[a] (permit holders)	
British Columbia	*Pharmacists Act*	Prescription and OTC (layperson outlets and feed mills or dealers)	
Manitoba	*Pharmaceutical Act*	Prescriptions by veterinarians	
Newfoundland and Labrador	Current legislation under review		
New Brunswick	*An Act Respecting the New Brunswick Veterinary Medical Association*		VCPR[b] needed for prescription drug dispensing
Nova Scotia	*Veterinary Medical Act Pharmacy Act*		VCPR needed for prescription drug dispensing
Ontario	*Livestock Medicines Act*	OTC (licensed retail sales outlets)	
Prince Edward Island	*Veterinary Medical Act Pharmacy Act*		VCPR needed for prescription drug dispensing
Quebec	*Veterinary Surgeons Act, Pharmacy Act* and the *Animal Health Protection Act*	Prescription and OTC	Permits for manufacturing and selling medicated feeds

[a] Over-the-counter
[b] Veterinarian-client-patient relationship

Distribution

Drugs in dosage form

Antimicrobial drugs in dosage form include those that have been evaluated by Health Canada, granted a DIN, and are available in a form for use in food animals. They may be distributed in several ways.

By prescription through licensed veterinary practitioners

Under the *Food and Drugs Act* and *Regulations*, licensed veterinarians have the right to prescribe antimicrobials within the framework of valid VCPR. Antimicrobials listed under *Food and Drug Regulations* Schedule F, Part II, are only available by prescription and include, with few exceptions, all antimicrobials first registered for use in food animals in the past two decades. These drugs may be sold by veterinarians or licensed pharmacists when a prescription is provided.

Provincial boards confer licenses upon veterinarians. Provincial statutes define the practice of veterinary medicine and impose professional standards of conduct in day-to-day practice. A complaint that a veterinarian's prescribing practices may, in any way, jeopardize food safety potentially brings the practitioner before a disciplinary board of peers, which has the authority to limit the veterinarian's practice.

In general, federal law in this area is designed to protect the health of Canadians, and provincial law is designed to deliver health services and to license practitioners (1). Accordingly, Health Canada does not regulate veterinary medicine; it is under provincial jurisdiction. Therefore, federal regulation does not prevent veterinarians from using their discretion when prescribing drugs (2). In some cases, veterinarians use this discretion to prescribe a use of an antimicrobial drug that is not indicated on the product label (often called "extra-label use"), *e.g.*, an increased dose or duration of treatment, or use for a different disease or animal species. Typically, these treatments are prescribed when no approved drugs or dosages are effective for given species or conditions, and because of the limited availability of approved drugs for minor species (*e.g.*, sheep, goats, llamas). This practice has also filled a need for the aquaculture industry, where very few drugs are licensed. In the past, Health Canada has exercised its authority under the *Food and Drugs Act* to narrow the veterinarian's discretion to prescribe by prohibiting use of certain drugs in food animals under any conditions (*e.g.*, chloramphenicol, 5-nitrofurans, diethylstilbestrol). These actions were taken to ensure that residues of these drugs do not occur in foods produced from animals. Furthermore, food-animal producers are not allowed to initiate extra-label treatments; this can be done only on veterinary prescription. Veterinarians assume responsibility for any adverse reactions or illegal residues in edible tissues of treated animals.

A 1990 survey by Rescan Consultants, conducted on behalf of BVD, found that 76% of veterinary practitioners believe extra-label use, as practised in Canada, is helpful (3). Eighty-four percent of veterinarians reported that they have administered drugs extra-label, most commonly antimicrobials. Sixty-five percent of veterinarians reported they were concerned about residues when drugs were used in an extra-label fashion. Questions about antimicrobial resistance were not included in the survey. The AMR committee was advised that some veterinary practitioners, especially those in large consulting practices, are now reluctant to

prescribe extra-label uses of drugs because of liability concerns. However, many other veterinarians extensively prescribe extra-label uses of antimicrobial drugs.

Emergency drug release

Unregistered products cannot be sold in Canada except through an Emergency Drug Release (EDR), or by special authorization for investigational studies in the form of Experimental Studies Certificates. The EDR Program allows veterinary practitioners to obtain limited quantities of unapproved drugs for treatment of a medical emergency of patients under their direct supervision. The committee was advised that the total volume of drugs, especially antimicrobials, entering food animal production via EDRs is small, governed in part by the need for applicants to provide credible residue, human safety, and pharmacological data when seeking an EDR.

Non-prescription antimicrobials

Some antimicrobials used for food animals are sold to the purchaser in a retail setting (often called OTC sales) under Part II of Schedule F of the *Food and Drug Regulations*. This practice, however, may be prohibited by provincial regulation (*e.g.*, Quebec, where antimicrobials are only available under prescription). These products have a DIN and must be clearly labeled. Vendors may draw attention to label statements but cannot prescribe use. OTC status applies when drugs can be safely used in food animals without the supervision of a licensed veterinarian. If they choose, manufacturers may allow the sale of these drugs only through veterinarians. Antimicrobials listed under the CMIB are available in feeds without veterinary prescription.

OTC antimicrobials available in Canada include: injectable antibiotics (*e.g.*, oxytetracycline, penicillin, tylosin), antimicrobials used in feed and water (*e.g.*, neomycin, spectinomycin, lincomycin, oxytetracycline, chlortetracycline, sulphonamides), anti-mastitis preparations, scour boluses and wound dressings. The committee was advised that this route of distribution of antimicrobials is perceived by the food-animal industry to be important for the convenient and economical supply of medicines for animals.

Drugs imported for "own use"

Under current law, antimicrobials may be imported for the treatment of a person's own animals if:

- the drug is not offered for re-sale;
- the drug is not a prescription pharmaceutical (Schedule F, Part I); and
- the drug is clearly marked "for veterinary use only."

The committee was advised that the total volume of antimicrobials imported under this loophole is unknown. It is thought, however, that most antimicrobials imported in this way are already available in Canada

Drugs not in dosage form (Active Pharmaceutical Ingredients)

Active Pharmaceutical Ingredients (APIs) are defined as bulk, pharmaceutically active substances that are used in the formulation of drugs in dosage form (Figure 4.1). There are few restrictions or controls regarding the importation and sale of APIs in Canada. This has

led to the illegal promotion, sale and representation for use as veterinary drugs of bulk APIs. Good Manufacturing Practices (GMPs), *i.e.*, government-approved standards that guide the manufacture of products, are in place for drugs sold in dosage form as a product. Generally, however, GMPs are not in place for the manufacture of APIs. Bulk APIs that are administered directly to animals bypass the drug pre-market approval system in Canada, as mandated by the *Food and Drugs Act* and *Regulations*. APIs are, therefore, not registered, have no DIN and are potentially used with or without further processing or re-formulating. An enforcement directive from the Therapeutic Products Directorate, dated February 22, 1999, states that, as a temporary solution, APIs should be imported only to designated sites of the licensed manufacturer (4). In addition, unless imported or sold to a licensed establishment, pharmacist or veterinarian for modification (e.g. compounding) prior to use, bulk APIs will be considered drugs in dosage form, and GMP, DIN, labelling, and other provisions will be enforced. Who actually enforces the provisions for APIs and the efficiency of this enforcement is unclear. However, at this time, APIs can still be ordered by anyone in Canada.

Advertising

Advertising for OTC antimicrobial drugs can be directed to all interested parties including the public and lay user. However, advertising for prescription antimicrobial drugs is closely monitored. A Pharmaceutical Advertising Board (PAAB) scrutinizes all advertising in medical journals. The VDD acts as an advisor and resource body to the PAAB and can request suspension of advertising material that, in its view, contravenes the *Food and Drugs Act* and *Regulations*. Pharmaceutical companies may present information on products and extra-label use to veterinarians. The information must be presented within the context of scientific exchange as defined by Canadian law, be non-promotional in nature and include data originating from valid scientific studies.

Enforcement

Enforcement of laws and regulations related to drug use in the food-animal industry is a significant problem due, in part, to the diversity of Canadian agriculture and the large number of individual farms.

Existing enforcement measures (some of which have already been mentioned) include border controls, TPD enforcement of the *Food and Drugs Act* and *Regulations*, CFIA enforcement of the *Feeds Act* and *Regulations*, provincial enforcement of legislation governing antimicrobial sales and the practice of veterinary medicine, veterinary professional licensing body oversight, and voluntary food-animal industry codes of practice or quality assurance programs.

Regulation and distribution in other countries

In recent years, a few countries have adopted or are in the process of developing specific regulatory measures to deal with issues related to antimicrobial resistance and animals. Regulatory developments in Australia, the European Union and the United States are most relevant to Canada.

Australia

Australia recently reviewed its capacity and needs related to risk management of antimicrobial resistance. The Australian Commonwealth Government formed a Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) in May 1998, to evaluate scientific evidence on the transmission of antibiotic resistance from food animals to humans and to make recommendations to control the spread of resistance (5). In September 2000, the Australian government accepted the recommendations from JETACAR and is now implementing them.

JETACAR concluded that there is strong evidence of the transmission of antimicrobial resistance from animals to humans. It also concluded that the principles used to manage antimicrobial resistance should be the same for humans and animals. In the committee's view, the most important objective is to reduce the use of antimicrobials to areas/indications where the benefits are clear and substantial. Several recommendations pertained to regulation and are relevant to the Canadian situation:

1. Australia should adapt a conservative approach and not permit the use of in-feed antibiotics (low-dose, long-term use) unless:
   - there is demonstrable efficacy in livestock production;
   - the drugs are rarely or never used as systemic, therapeutic agents in humans or animals, or are not considered critical therapy for human use, and;
   - the drugs are not likely to impair the efficacy of any other prescribed antibiotic(s) for animal or human infections through the development of resistant strains.
2. Review current drugs that possibly are not fulfilling the conditions of Recommendation 1 (*e.g.*, glycopeptides (avoparcin), streptogramins (virginiamycin), macrolides (tylosin)).
3. License all antibiotic importers (almost all antibiotics are imported into Australia).
4. Define thresholds of antibiotic resistance in pathogens.
5. Designate all antibiotics in humans and animals as prescription only.
6. Harmonize state controls on veterinary chemicals.
7. Make it an offence to prescribe a veterinary chemical contrary to a label constraint.
8. Include microbial resistance safety in new drug applications.
9. Establish an Expert Advisory Group on Antibiotic Resistance (EAGAR) with responsibilities for risk analyses for new and extended uses of antibiotics and advice for regulatory and other pertinent national authorities.

European Community

Within the European Community, there are "centralized" and "decentralized" or "mutual recognition" routes for authorization of veterinary drugs, including antimicrobials, which apply throughout the E.C. and within specific member states, respectively. The European Medicines Evaluation Agency (EMEA) deals with centralized authorizations (which are valid in all member states), while member states have their own authorities. For example, the Veterinary Medicines Directorate (VMD) deals with authorizations within the U.K.. Recently, EMEA published for discussion guidelines for pre-authorization studies to assess the potential for resistance (6).

Therapeutic use of antimicrobials is subject to either E.C. or member state authorizations; however, "feed additives" are subject only to E.C.-wide authorization (7). E.C. regulations

authorize antimicrobials as feed additives only if treatment or prevention of animal disease is excluded at permitted levels (7). Growth promoters are regulated separately from veterinary drugs used for therapy, including those administered through feed. Regulatory directives indicate three important criteria that must be met before authorization (approval for use) can be granted:

1. Approval may be granted only if the substance does not adversely affect human or animal health or the environment;
2. There are no serious reasons to restrict the use to human or veterinary medical uses; and
3. The permitted levels have no therapeutic or prophylactic effects.

In addition, there is a "safe-guard clause," which allows any member state to temporarily suspend or restrict the authorization of a product if there is any new evidence to suggest that any of the above conditions have been breached. Subsequent to the E.U. implementation, Sweden, Finland, and Denmark made applications for adjustment based on the above safe-guard clause. By the end of 1998, as a precautionary measure designed to protect human health, the E.C. suspended growth promotion use of bacitracin, tylosin, spiramycin, and virginiamycin. In March 2002, the E.C. presented proposals to prohibit the use of the remaining authorized antimicrobial growth promoters and dictated that they would have to be phased out as of January 2006 (E.C. press release, March 25, 2002).

United States

The Center for Veterinary Medicine (CVM), Food and Drug Administration (FDA), is responsible for regulation of antimicrobials used in veterinary medicine in the U.S. Until recently, pre-approval evaluations of the safety of an antimicrobial in relationship to human health focused on drug residues in foods of animal origin and on microbial safety studies for antimicrobial products used for more than 14 days in animal feed. The CVM now recognizes, however, the need to assess the human health impact of microbial effects from all uses of antimicrobial drugs in food animals. The CVM has published and discussed publicly a number of relevant documents (8). The key components of its regulatory approach centre on categorization of drugs, establishment of resistance thresholds, monitoring resistance to foodborne pathogens in both humans and animals, and drug-use information.

The CVM proposed to categorize new antimicrobial drugs based on their importance in human medical therapy (9). Category I drugs (or members of a class of drugs) are essential for treatment of life-threatening diseases of humans, or are important for treatment of foodborne diseases of humans, or are members of a unique class of drugs used in humans (*e.g.*, fluoroquinolones, glycopeptides). Category II drugs are important for treatment of human diseases that are potentially serious, but for which suitable alternatives exist (*e.g.*, ampicillin, erythromycin). Category III drugs have little or no use in human medicine, or are not the drug of first choice for human infections (*e.g.*, ionophores).

Drugs would also be placed into high, medium, and low categories based on the likelihood of human exposure to resistant human pathogens arising from the use of drugs in food animals. Categorization would include consideration of drug attributes (*e.g.*, mechanism of resistance and rate of acquisition and expression, or cross-resistance induction), the expected product use patterns (*e.g.*, duration of treatment, species of food animal, number, type of animals treated), and potential human contact (*e.g.*, bacteria of concern, environmental and food contamination, food processing effects).

The CVM is also attempting to establish "Human Health Impact Thresholds" for antimicrobial resistance (10). The threshold for a given drug is the maximum allowable prevalence of resistant infections in humans. Exceeding the threshold would trigger a regulatory response that could include one or more regulatory actions, including restrictions on use in certain species of animals, restrictions on routes of administration, or complete withdrawal of drug approval. The CVM has not yet published specific methods and criteria for human health or animal health safety assessment of veterinary drugs with respect to antimicrobial resistance; however, the measures described above are important steps in this direction.

The distribution of antimicrobials to food animals in the U.S. is broadly similar to that in Canadian practice, but there are notable differences. In the U.S., for example, new drugs for use in animals are assigned to one of three categories: prescription, OTC, or veterinary feed directive. A drug for use in animals may be classified as a prescription drug if it is not considered safe for animal use except under the professional supervision of a licensed veterinarian.

Under provisions of the *Animal Medicinal Drug Use Clarification Act* of 1994 (AMDUCA), veterinarians were given the authority to use approved animal drugs in an extra-label manner and to prescribe approved human drugs for use in animals under certain conditions. Extra-label use of an approved animal or human drug in animal feed is not permitted. Extra-label use of an approved human drug is only permitted when no animal drug can be used in an extra-label manner. The following drugs are prohibited for extra-label use: fluoroquinolones, glycopeptides, chloramphenicol, dimetridazole, ipronidazole, nitroimidazoles, furazolidone, and some sulfonamides in lactating dairy cows. The FDA introduced professional, flexible labelling in 1995. It provides for treatment of a wider range of clinical conditions.

Feed manufacturers handling medications in the U.S. are required to hold a license (although currently not required, similar regulations are anticipated in the near future in Canada). The nature of the license is dependent upon the concentration and type of drugs employed in feed manufacture. More concentrated drug products, and those carrying a withdrawal requirement, are deemed more difficult to handle.

International Organizations

A variety of international organizations are active in promoting communication, consensus, and harmonization with respect to regulation of antimicrobials used in veterinary medicine. For example, the World Health Organization (WHO) sponsored several expert consultations in recent years on the impacts on human health of antimicrobial resistance transmitted from animals (11–13). Several recommendations from the consultations dealt with regulation of antimicrobials.

The Office International des Epizooties (OIE) is an intergovernmental organization based in Paris, with 158 member countries (14). Its main objectives are to inform governmental veterinary services of the occurrence and course of animal diseases, to safeguard animal and human health in world trade, and to promote and coordinate research into surveillance and control of animal diseases throughout the world. The OIE recently published guidelines on risk analysis, prudent-use, antimicrobial quantities used, resistance surveillance and laboratory methodology.

International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medical Products (VICH) is a trilateral (E.U., Japan and U.S.) program aimed at harmonizing technical requirements for veterinary product registration. It operates under the auspices of the OIE (15). Australia, New Zealand, and recently, Canada have observer status, and other countries are kept informed of VICH agreements. In June 2001, VICH released a draft document titled, "Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance" (16). The draft describes the types of data and information that regulatory authorities may request from drug sponsors to help them assess antimicrobial resistance risks. This information falls into two categories: "basic" (*i.e.*, required) and "optional." Basic information includes antimicrobial class, mechanism and type of action, antimicrobial spectrum of activity (including minimum inhibitory concentrations of target pathogens, foodborne pathogens and commensal organisms), resistance mechanisms and genetics, occurrence and rate of transfer of resistance genes, occurrence of cross-resistance, and pharmacokinetic data. Optional information includes *in vitro* mutation frequency studies, occurrence of co-resistance (with other antimicrobial agents), antimicrobial drug activity in the gut, and other animal studies.

The Codex Alimentarius, or the food code, is an international set of standards, codes of practice, guidelines, and recommendations that relate to national food control agencies and the international food trade (17). It operates under the WHO and the Food and Agriculture Organization (FAO). The Codex Committees on Food Hygiene and Residues of Veterinary Drugs in Foods are currently deliberating on antimicrobial resistance standards for foods. In July, 2001, Codex published a discussion paper on antimicrobial resistance and a draft code of practice to minimize antimicrobial resistance (ftp://ftp.fao.org/codex/ccrvdf13/rv01_10e.pdf).

Analysis: regulatory gaps and related issues

Safety standards, criteria and assessment methods

The lack of specific plans to manage the risks associated with antimicrobial resistance transmitted from food animals and the lack of credible, scientifically valid methods and criteria to assess the safety of veterinary drugs with respect to antimicrobial resistance and human health are serious deficiencies within Health Canada assessments. Canadian regulatory authorities are not as active and effective as they should be in addressing these deficiencies, either nationally or internationally.

Without scientifically sound methods for safety assessment, it is impossible for Health Canada to completely and objectively analyze the health risks associated with antimicrobial resistance. Without a safety standard (*i.e.*, important or "acceptable" level of risk) that equates specifically to antimicrobial resistance, it is impossible to objectively judge whether any current or future use of antimicrobials in animals warrants regulatory action. Without sound methods and criteria, it is impossible for the informed public (including drug sponsors) to know what the rules are. It is also important that Health Canada provide timely approvals of new antimicrobials that can be used legitimately and safely in animals. This is in the public's interest because the lack of safe and effective drugs is a prime motivator for extra-label use, a use pattern for which there is much less assurance of safety.

It would be wrong to suggest that these are simple issues to address. There is a degree of international consensus concerning safety standards for chemical residues in foods and the environment (*e.g.*, methods to establish residue tolerances and standards for risk due to carcinogens). Unfortunately, no such consensus exists for bacteria resistant to the antimicrobial drugs that are found in foods or in the environment. Progress is being made internationally, however, and Canada's participation needs to be more effective.

External expertise and advice

Antimicrobial resistance is a complex issue, and many countries are grappling with ways to control it. The VDD should have its own scientists and managers with expertise in resistance; but it should also, from time to time, seek the advice of external experts. The decision-making responsibility, however, should remain with the Directorate. There is precedent for this within Health Canada and abroad. The Therapeutic Products Directorate (TPD) has several advisory committees composed of external experts (18). In the U.S., the CVM, FDA, has a Veterinary Medical Advisory Committee (VMAC) that "advises the Commissioner in discharging her responsibilities as they relate to assuring safe and effective drugs, feeds and feed additives, and devices for animal use, and, as required, any other product for which the FDA has regulatory responsibility" (19).

Jurisdictional and enforcement issues

Regulation of antimicrobials for veterinary use in Canada is not well coordinated. Health Canada regulates the sale of antimicrobials through the *Food and Drugs Act*, but not their use. The CFIA regulates antimicrobial use in feed, but otherwise the use of drugs is considered veterinary medicine, which is a provincial responsibility. Some provinces have ancillary legislation, mainly to regulate OTC sales. Legislation in all provinces directly empowers professional associations, or creates appointed boards of licensure with the responsibility to license and regulate practicing veterinarians. Licensed veterinarians must meet standards of professional conduct in serving the public and maintain competency in the diagnosis and treatment of disease. Nevertheless, there is the potential that some important responsibilities (*e.g.*, enforcement) will fall between the cracks of federal-provincial jurisdiction. The committee found no evidence that these groups have met in the context of antimicrobial resistance to coordinate matters related to the distribution and use of antimicrobial drugs.

The VDD has no enforcement capabilities of its own, but relies on those of the TPD of Health Canada. The committee is concerned that insufficient resources are available for vigorous enforcement of veterinary controls.

Analysis: distribution issues

Canada does not have an ideal system for distributing the antimicrobial drugs used in food animals. An ideal system, as laid out by the World Health Organization (12), would have the following characteristics:

- antimicrobials manufactured to GMP or another clear, transparent standard;
- antimicrobials evaluated by regulatory authorities for safety (including resistance) and efficacy;

- the person deciding when and how to use the antimicrobial would be trained, licensed, held to professional standards and not in a conflict of interest (*i.e.* veterinarian);
- the person distributing the antimicrobial would be trained, licensed, held to professional standards and not in a conflict of interest (*e.g.* pharmacist or veterinarian);
- a strong system to ensure compliance and traceability;
- antimicrobials available only under prescription; and
- antimicrobials readily available to producers at an economical price

The current system, is complicated and neither uniformly regulated nor administered across the country. In Table 4.2, the above characteristics are cross-tabulated with some of the current controls on use, and areas where there are deficiencies or gaps. The committee is concerned that, at the very least, the present system creates the potential for risk arising from antimicrobial resistance. In particular, the committee is concerned about the own-use loophole; the potential for use of unregulated, unapproved, bulk APIs; the extensive use of antimicrobials without prescription; the extensive extra-label use practised by veterinarians; and the potential for profit motive to negatively influence prescribing practices. The committee was not able to determine whether these concerns currently compromise human health, but it believes there are insufficient control measures in place to adequately protect the public.

Active pharmaceutical ingredients and drugs imported for "own use"

The apparent loopholes in Canadian law that allow the importation and use in food animals of antimicrobials under "own use", or the direct use of APIs are of concern because they bypass the regulatory approval process, and there is no way to track their use. There can be no assurance, therefore, that products used under these circumstances are safe. Their continued use undermines the credibility of national and international strategies to control antimicrobial resistance. Also, their continued use acts a deterrent to the sale of antimicrobials by legitimate means in Canada. Serious consideration should be given to a system of licensure or permits for importers of APIs, so that control over these products is maintained. Alternatively, it is possible that adoption of GMP standards throughout the antimicrobial production system (including both raw ingredients, compounded products and finished products) could achieve this goal.

Non-Prescription Antimicrobials

Canada (along with the U.S.) is one of the few industrialized countries that allows OTC sale of antimicrobials for food animals. In contrast, OTC antimicrobials have not been available in human medicine in Canada for many years (with the exception of minor topical uses). At first glance, movement to a prescription-only system would appear to be a logical step towards a more responsible policy of antimicrobial use. On purely scientific or human health grounds, there is little argument against a prescription-only system. The committee is well aware, however, that the situation is not quite so simple or straightforward in practice, and that there are arguments against such a shift in the system. Therefore, to arrive at a conclusion on whether the OTC sale of antimicrobials should be allowed to continue, the committee considered the advantages and disadvantages of a prescription-only system (Table 4.4).

Table 4.2: Routes of entry of antimicrobials into food-animal production systems

Desirable Characteristics	Route Of Entry To Food Animal Production Systems					
	Prescribed by Veterinarian			Not prescribed		
	On label	Off label	OTC sale	Medicated feed	Imported for "own use"	Purchase as API
Manufactured to regulated, GMP standards	Yes	Yes	Yes	Yes	Unknown, probable registration somewhere	Unknown
Product and use approved by regulators	Yes	Approved for label use in at least one species	Yes	Yes	Unknown, probable registration somewhere	Unknown
Veterinarian makes decision to use product[a]	Yes	Yes	Maybe	Maybe	Maybe	Maybe
Product distributor is trained and licenced	Yes	Yes	Some training of OTC	Yes	Unknown	Unknown
Regulations in place to enforce product use	*Food & Drugs Act* *Feeds Act* *Veterinarians Act*	*Food & Drugs Act* *Veterinarians Act*	*Food & Drugs Act* Provincial acts	CMIB	No	No
Tracking of product use	Veterinary medical records, feed mill records of prescriptions	Veterinary medical records, feed mill records of prescriptions	Records of sale	Records of sale	Possible record of treatment on farm	Possible record of treatment on farm

[a] current systems create a conflict of interest for veterinarians between prescription and sale of drugs

Table 4.4: Advantages and disadvantages of prescription-only system

Prescription-Only System	
Advantages	**Disadvantages**
More prudent use (including use of culture and sensitivity)	Disruption of current system
Track quantities used (increases, reductions)	Availability of drugs (pharmacy service in rural areas and possible veterinary monopoly)
Controls, oversight	Practicality of repeated prescriptions, especially for feed medications
Reduced resistance selection and co-selection	Veterinary oversight may not decrease use

OTC availability of antimicrobials may contribute to the risks associated with antimicrobial resistance because there is no direct professional oversight of the use of these products. Without veterinary input, OTC use is largely incompatible with many of the principles of prudent use of antimicrobial drugs for disease treatment and control. Treatments may be administered inappropriately, for the wrong diseases, in insufficient doses, or for incorrect periods of time or routes of administration. A substantial proportion of producers rarely, if ever, seek the professional advice of a veterinarian. For example, in a 1991 survey of 639 Ontario swine producers, only 50% stated that they obtained information about in-feed antimicrobials from veterinarians (20). Without adequate veterinary input, the committee believes there is greater potential for the inappropriate use and, possibly, the abuse of antimicrobial drugs.

The committee was advised of concerns that prescription-only access will drive up the cost of animal health care. Most producers believe they have two supply options when purchasing antimicrobials: their veterinarian or the local retail outlet. Few producers purchase from pharmacies, although there are exceptions in some areas. To some extent, calls for prescription-only availability are linked, in the minds of producers, to self-interest by the veterinary profession. Producers are concerned that there will be insufficient competition in the marketplace, leading to higher drug costs and therefore higher costs of production. The committee was further advised that eliminating direct access to antimicrobials for treatment of individual animals, *e.g.*, penicillin and tetracyclines, which are presently sold through OTC outlets in most provinces, could create uproar among producers. Quebec successfully implemented a retail network for pharmaceuticals to the food-animal industry through licensed veterinary practitioners by means of price ceilings. While the committee did not extensively investigate the Quebec model for distribution, it believes that careful consideration of Quebec's drug policy and its applicability to the rest of the country is warranted.

The committee believes that movement to a prescription-only system need not require a veterinarian to visit the farm each and every time an animal requires treatment. This would be both very expensive for the producer and impractical on many farms. Rather, prescriptions could be provided for specific conditions over a finite period of time, within the limits of a

valid VCPR, and with regular re-evaluations of the need for treatment by their veterinarian. Also, there are substantial implications arising from a system of prescription-only feed medications. Many veterinarians in Canada currently have had little to do with feed medication, and significant adaptations among veterinarians, feed manufacturers, and farmers would be needed to make the system work.

In view of the considerations for and against OTC antimicrobials, and the possible implications of change, it was difficult for the committee to agree on appropriate recommendations. Various options were explored, and all things considered, the majority of committee members believed that antimicrobials for disease treatment and control in Canada (including feed medication) should be available by prescription only. A minority believed that decisions to change a drug claim from OTC to prescription only should be conducted on a claim-by-claim basis during a regular re-evaluation for efficacy and risk of the development of antimicrobial resistance.

Not all antimicrobials, however, are used for disease treatment and control. Many are used for growth promotion and feed efficiency (see Chapter 5). Antimicrobials used purely for these purposes are a special case with respect to prescriptions because:

- They are not intended to treat, control or otherwise manage disease;
- Most Canadian Veterinary Medical Association prudent-use principles (see Chapter 8) are focused on disease management and therefore do not clearly apply; and
- They are available without prescription in nearly all jurisdictions (*e.g.* Europe, United States, Australia), although Quebec requires prescriptions.

In Canada, this situation is complicated by several factors:

- Some growth promoters (*e.g.* penicillins, tetracyclines, sulfonamides) are also used in human medicine;
- Few growth promoters are in fact used purely for growth promotion and feed efficiency. Many also have feed label claims for disease prophylaxis, control and even therapy;
- Some disease control claims are at doses equivalent to their growth promotion counterparts (*e.g.* chlortetracycline in turkeys);
- Feed drugs are sometimes used in combination; one drug may be used for growth promotion while the other may be used to control disease; and
- Growth promoters are believed to have disease prophylaxis benefits, notwithstanding label claims for growth promotion or feed efficiency only.

The committee discussed the matter of prescriptions for growth promoters in light of these factors. It considered whether growth promoters should be available by prescription only, or whether there should be interim use of prescriptions for growth promoters until such time as risk-based evaluations were conducted on existing growth promoters. The committee decided, in light of recommendation 17 (Chapter 6), not to recommend prescriptions for growth promoters. It acknowledged the merits in completely separating drugs or even classes of drugs into those for veterinary use (*i.e.* treatment and control of disease) and those for growth promotion and feed efficiency, as is the case in Europe. It would be simpler, clearer and more rational in such a system to require prescriptions for veterinary use while not requiring them for growth promotion. The committee believes that recommendations made in this and other chapters will help Health Canada move in that direction.

Growth promoters are discussed further in Chapters 5 (uses and benefits) and 6 (risk management and review of resistance risk).

Veterinary prescriptions and profit

Most, but not all, veterinarians in food-animal practice obtain a portion of their income from the sale of antimicrobial drugs. As the diagnostician, the prescriber of treatment, and the owner of a drug inventory, veterinarians are in a position of conflict of interest with respect to prescription-only drugs. If those antimicrobial drugs that are currently available for OTC sale are limited to sale by prescription only, then veterinarians will be placed even further in a position of conflict of interest. The possibility that profit motive could affect prescription practice is discussed at greater length in Chapter 8 on prudent use. The committee was advised, however, that many veterinarians recover a portion of the cost of their professional services from the sale of antimicrobial drugs, and that producers are accustomed to this cost-recovery practice. It was suggested, however, that this practice contributes to the perceived high cost of medications, and that, in such circumstances, veterinarians would be better to charge directly for professional services. The committee recognized that the issue of antimicrobial dispensing is associated with a perceived conflict of interest. The committee agrees that it is appropriate for veterinarians to dispense antimicrobials and that they should be appropriately compensated for their services. The committee also agreed that the dispensing of antimicrobials should not lead to any incentive to veterinarians to dispense antimicrobials, or to recommend any specific antimicrobial. Prescribing and pricing mechanisms such as those used in Quebec should be studied as a potential national model.

Extra-label use

Although there are legitimate reasons why veterinarians prescribe the extra-label use of antimicrobial drugs, the practice does raise concerns (advantages and disadvantages are listed in Table 4.5).

Table 4.5: Advantages and disadvantages of extra-label use of antimicrobials

Extra-Label Use of Antimicrobials	
Advantages	**Disadvantages**
Treatment of sick animals when no drug approved in that species is effective for the condition	By-passes legitimate approval process
Treatment of sick animals where no drug is approved for the species	Reduced incentive for industry and government to approve drugs through legitimate channels
Useful when drug is effective at doses higher than originally approved, but there is insufficient incentive for pharmaceutical companies to renew the claim (*e.g.*, off patent)	Can displace an approved product for a given species and condition (*e.g.*, if cheaper)
	Effects of altered dose/treatment regime/dosage form on resistance are unknown
	Legal liability of veterinarian
	Difficult to enforce

Veterinary school curricula and the veterinary literature (1,2) emphasise the need, when prescribing extra-label, to ensure that illegal residues do not occur in foods produced from treated animals. Very little attention, however, is given to the potential risk of antimicrobial resistance arising from such use. Prominent among these concerns is the extra-label use of antimicrobials that are very important in human medicine but not approved for use in food animals, for example, the extra-label treatment of a group of animals with a fluoroquinolone. Furthermore, even when drugs important to human medicine are approved for use in food animals, they may be used more extensively than the label recommends. One example of this is the routine treatment of all animals in a pen or flock with a third generation cephalosporin because they are at risk of disease. Both examples are perhaps extreme, but possible under current regulation. The mass medication of animals with drugs of critical importance to humans without a prior evaluation of safety relative to antimicrobial resistance is highly questionable. Another concern is compounding of extra-label medications (*e.g.*, one dosage form made into another by pharmacies, veterinarians, or others). All of these situations bypass the regulatory approval process for antimicrobial drugs.

The committee is concerned about the lack of a clear and comprehensive policy on extra-label use in Canada, especially as it pertains to antimicrobial resistance. Does extra-label use fall within the domain of veterinary medicine and outside of the legal authority of Health Canada? In the past Health Canada has used its authority under the *Food and Drugs Act* to prohibit the use of certain drugs (*e.g.* chloramphenicol, diethylstilbestrol) in food animals. The committee believes that Health Canada should now use its authority to define, with greater clarity, the acceptable limits of this practice with respect to its impact on antimicrobial resistance. A sensible approach is to limit extra-label use as much as possible, especially for those drugs considered to be critical for therapy in humans or animals. If appropriate, regulatory authorities should prohibit extra-label use of certain drugs. The policy should address the following issues:

- legal authority
- limits of legitimate and safe prescription (*i.e.*, defining and prohibiting unsafe extra-label uses)
- the need for adequate records and trace-back system
- guidelines for minor species (*e.g.*, goats, fish)
- role of intermediate licensing measures (*e.g.*, EDR)
- limits of legitimate compounding

In devising such a policy, careful review should be made of the U.S. policies and legislation on extra-label use. AMDUCA established provisions for veterinarians to prescribe extra-label. It requires veterinarians to keep records of these prescriptions and grants FDA access to these records. AMDUCA also stipulates labelling requirements for safe and proper use. In the U.S., extra-label use of a human drug is not permitted if a drug approved for use in food animals is available. AMDUCA gives FDA the authority to prohibit extra-label uses under specific circumstances (21. These provisions should be adopted in Canada.

Conclusions

The essential elements of a good regulatory and distribution system for veterinary drugs are in place, however there are some areas to address. There is a need to develop valid methods and criteria to assess the safety of veterinary drugs with respect to antimicrobial resistance.

Regulatory responsibilities for antimicrobials are shared by the federal and provincial governments, and to some extent by the veterinary licensing bodies. These groups should better coordinate their activities to ensure that adequate regulatory controls are in place. With regard to the distribution of antimicrobials in Canada, there are several areas of concern. These include the use of antimicrobials without prescription, importation of antimicrobials by producers for their "own use," the potential for illegal direct use in animals of imported bulk pharmaceutical ingredients, the potential for profit motive to negatively influence prescribing practices, and veterinary prescription for extra-label use.

Recommendations

2. Ensure that regulation of antimicrobials (including licensing, sale, distribution, use, and regulatory compliance) includes consideration of the human health impact of antimicrobial resistance.
3. Develop specific methods and criteria for human and animal health safety assessment of veterinary drugs with respect to antimicrobial resistance as soon as possible.
4. Define threshold levels of resistance for post-approval surveillance and provide for appropriate remedial action if thresholds are surpassed, up to and including modification of approval or suspension of marketing.
5. Wherever possible and appropriate in the interest of Canadian citizens, strive to harmonize veterinary drug regulatory approaches and standards with those used in other countries, especially the U.S.
6. Regularly seek independent, expert advice on antimicrobial resistance and related matters. Health Canada must, however, retain decision-making responsibilities with respect to regulation.
7. Ensure adequate coordination of federal and provincial policies concerning antimicrobial use and resistance management, and ensure the strict enforcement of all relevant regulations.
8. Evaluate, register and assign a DIN to all antimicrobials used in food animals, whether manufactured domestically or imported. This includes antimicrobials imported in bulk (API), which should be allowed into Canada only under permit. The intent of this recommendation is to stop the direct use of APIs in food animals.
9. Stop the importation, sale and use of antimicrobials not evaluated and registered by Health Canada. The intent of this recommendation is to stop the "own-use" loophole.
10. The prescribing and pricing of antimicrobials should not result in any incentives to dispense antimicrobials. Study the Quebec approach as a potential national model.
11. Give due consideration to claims made in pharmaceutical advertisements and promotion practices that may concern antimicrobial resistance to ensure claims or statements can be substantiated.
12. Make all antimicrobials used for disease treatment and control available by prescription only.

13. Develop an extra-label use policy, which ensures that this practice does not endanger human health. Such a policy should include the ability to prohibit the extra-label use of specific drugs of critical importance to human health.

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CHAPTER

5

Uses of antimicrobial drugs in food animals

Key Points

- **Antimicrobials are very beneficial in reducing morbidity and mortality due to bacterial diseases**
- **These drugs are administered therapeutically to individual sick animals, or to entire groups where some animals are sick and additional cases are expected**
- **They are also administered prophylactically in feed, water, or by injection, to prevent disease in animals at high risk of disease (*e.g.* after transport or mixing)**
- **In cattle, poultry and swine, antimicrobials are also administered in feed for growth promotion and increased feed efficiency**
- **Some antimicrobial classes are unique to veterinary medicine or human medicine; however, most classes are used in both fields**
- **Some antimicrobials used in humans are administered routinely to large numbers of animals, either for control/prophylaxis, or for growth promotion**

Antimicrobials are used in food animals for therapy to treat disease, to control and prevent infection and for growth promotion and production efficiency (Table 5.1). Therapeutic treatments may be administered to individual animals; however, it is often more feasible and efficient to treat entire groups of animals by putting the medication in the feed or drinking water. In some cases (*e.g.*, poultry, fish), this may be the only practical method. Mass medication of groups of animals with therapeutic levels of drugs is sometimes called "metaphylaxis," when some animals are clinically diseased while others may be subclinically affected (incubating disease) or at high risk. All the animals are therefore treated with the intention of preventing further disease. Prophylactic treatments are typically used during high-risk periods for disease (*i.e.*, after weaning or transport of animals).

The most controversial use of antimicrobial drugs in food animals (except farmed fish) involves the administration of antimicrobials for growth promotion or performance enhancement purposes, *e.g.*, feed efficiency, digestive enhancers. The matter is complicated by the fact that some drugs are approved for both growth promotion and disease prophylaxis. Even those drugs approved only for growth promotion are believed by many users to be beneficial in disease prophylaxis (1).

For the purposes of this report, growth promoters are defined as antimicrobials used in low concentrations in feed to stimulate an animal's growth, resulting in increased daily live-weight gain and/or feed conversion efficiency (2). The terms "growth promotion" and "subtherapeutic use" are often used interchangeably. However, subtherapeutic use extends to include disease prevention, or prophylactic use, as well as growth promotion. Some agencies have attempted to define subtherapeutic use in measurable terms. In the U.S., concentrations below 220 mg/kg of feed were defined as subtherapeutic, but in light of the varying doses typically applied in Canada, this term has little meaning (3).

Table 5.1: Types of antimicrobial use in food animals

Type of Antimicrobial Use	Purpose	Route or Vehicle of Administration	Administration to Individuals or Groups	Diseased Animals
Therapeutic	Therapy	Injection, feed, water	Individual or group	Diseased individuals or some of the individuals in groups.
"Metaphylactic"	Disease Prophylaxis/therapy	Injection (feedlot calves), feed, water	Group	Some
Prophylactic	Disease Prevention	Feed	Group	None evident although some infections may be subclinical
Growth Promoter	Growth Promotion	Feed	Group	None
	Feed efficiency	Feed	Group	None

Finally, some antimicrobials are used as coccidiostats to prevent the parasitic disease coccidiosis. Coccidiostats are typically administered in feed at strategic intervals during the life of the animals, especially poultry. Some coccidiostats (*i.e.*, ionophores, sulfonamides) also have antibacterial properties and, in the case of ionophores, may be used for growth promotion and the prevention of other diseases, such as ketosis in cattle.

Food animal production and antimicrobial use

To understand the rationale for using antimicrobials in food animals in Canada, it is helpful to consider some basic information on animal production and the most common infectious diseases that require treatment. Food-animal production in Canada is a large, diverse and dynamic industry. Since World War II, the scale and intensity of farming has increased, with more animals being raised on fewer farms. Improvements in infectious disease control (antimicrobial use, vaccines) and better management and nutrition in animal production have facilitated these changes. Few surveys of treatment practices involving antimicrobial drugs have been conducted in Canada (4), however, more information is available from the United

States (U.S.), where animal production and treatment practices are somewhat similar. A list of antimicrobials registered for use in animals in Canada for treatment and prevention of disease, and/or growth promotion, along with those registered for humans, is shown in Table 5.2.

Table 5.2: Antimicrobials registered for use in animals and humans in Canada

Antimicrobial Class and Drug	Registered in Animal Species[a]			Drugs in Same Class Registered for Human Therapy
	Therapy	Growth Promotion, Weight Gain and/or Feed Efficiency	Disease Prevention, Prophylaxis and/or Control	
Aminoglycosides				Amikacin, Gentamicin, Neomycin, Streptomycin
Amikacin	H			
Apramycin	Sw			
Gentamicin	Pi, Ca,D,C,T,Ch,H		Ch, T (day-olds)	
Neomycin	Br,Brl, L, C,D,H,Sh,Sw,T	C	Br,Brl, L, C,D,H,Sh,Sw,T,M	
Spectinomycin	C,Br,T,Sw		Sw,Brl,Br	
Streptomycin	C,Pi,		Pi,	
Cephalosporins				
Cefadroxil	Ca,D			Ceftriaxone, Cefadroxil, Cefaclor, Cefepime, Cefixime, Cefotaxime, Cefotetan, Cefoxitin, Cefprozil, Ceftazidime, Ceftizoxime, Ceftriaxone, Cefuroxime, Cephalexin, Cephalothin
Ceftiofur	Sw, C, H, Sh, T, D		T (day-old poults)	
Cephapirin	C			
Chloramphenicol and Congeners				
Chloramphenicol	Ca,D,H			Chloramphenicol
Florfenicol	Fi,C			

[a] C = cattle, Sw = swine, Ch = chicken, T = turkey, D = dog, Ca = cat, Bi = bird, Fi = fish, H = horse, Sh = sheep, R = rabbit, M = mink, G = goat, Br = breeder, Brl = broiler, L=layer, Pi = piglets, Du = duck, G = geese, Lo=lobster

Antimicrobial Class and Drug	Registered in Animal Species[a]			Drugs in Same Class Registered for Human Therapy
	Therapy	Growth Promotion, Weight Gain and/or Feed Efficiency	Disease Prevention, Prophylaxis and/or Control	
Fluoroquinolones				
Enrofloxacin	D,Ca[a]			Ciprofloxacin, Difloxacin Gatifloxacin, Levofloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Trovafloacin Nalidixic Acid
Marbofloxacin	D			
Orbifloxacin	D,Ca			
Glycopeptides				
	None			Vancomycin
Lincosamides				
Clindamycin	D, Ca			Clindamycin Lincomycin hydrochloride
Lincomycin hydrochloride	S, Ch, Br, Du, G, T, D, Ca	Br	Br,Du,G,T,Sw	
Pirlimycin	C			
Macrolides				
Erythromycin	C,Pi,Sh,Sw,Br,Brl,T	Br,Brl	Ch, T (control); Sh (prevention); Sw, Pi (MMA, scours management aid)	Erythromycin, Azithromycin
Tilmicosin	C,Sh,Sw			
Tylosin	C,Sw, Ch, T, D,Ca,	Sw	C, Sw, Ch	
Nitrofurans				
Furazolidone	D,H			Nitrofurantoin
Nitrofurantoin	Ca,D,H			
Nitrofurazone	Ca,D,H,C,G,Ch,Sh,Sw,Ex		C,G,H,Ch,Sh,Sw	
Penicillins				
Amoxicillin	D,Ca			Amoxicillin, Clavulanic acid, Ampicillin, Pivampicillin
Amoxicillin, Clavulanic acid	D, Ca			
Ampicillin	C, Sw, D, Ca			

[a] C = cattle, Sw = swine, Ch = chicken, T = turkey, D = dog, Ca = cat, Bi = bird, Fi = fish, H = horse, Sh = sheep, R = rabbit, M = mink, G = goat, Br = breeder, Brl = broiler, Pi = piglets, Du = duck, G = geese, Lo=lobster

Antimicrobial Class and Drug	Registered in Animal Species[a]			Drugs in Same Class Registered for Human Therapy
	Therapy	Growth Promotion, Weight Gain and/or Feed Efficiency	Disease Prevention, Prophylaxis and/or Control	
Ampicillin, Sulbactam	C			Ampicillin, Sulbactam, Cloxacillin sodium, Penicillin G benzathine Penicillin G potassium Piperacillin, Ticarcillin
Cloxacillin	C			
Penicillin G benzathine	C,Ca,D,H,Sh,Sw			
Penicillin G potassium	T,Sw	Ch (Br, Brl), T	T	
Penicillin G procaine	Ca,D,C,H,Sh,Sw,F,M,R[a]	Ch, T, Sw	T, Sw, C, Sh	
Polymixin				
Polymixin B	C, D, Ca			Polymixin B
Streptogramins				
Virginiamycin	Sw		Brl, Sw	Quinupristin, Dalfopristin
Tetracyclines				
Chlortetracycline	Ch, T, Sw, C, Sh, Mi	Ch (Br, L), T, Sw, C, Sh	Sw, Ch, T, C, Sh	Tetracycline hydrochloride Doxycycline
Oxytetracycline	C, Ch, T, Sw, Sh, Bees, Fi, Lo	Sw, Ch, T, C, Sh	T, Ch, C, Sw, Bees	
Tetracycline hydrochloride	Ch, T, Sw, C, Sh, H, D, Ca		Ch, T	
Doxycycline	Ca, Bi			
Pleuromutilins				
Tiamulin	Sw		Sw	
Sulfonamides				
Sulfadiazine	C,H,Sh,Pi,Ca,D,Fi,Sw			Sulfamethoxazole
Sulfadimethoxine	C,Pi,Ca,D,H, Fi,			
Sulfaguanidine	C,D,H,Sh,Sw,Ca		C,H,Sh,Sw (oral)	
Sulfamethazine	C,H, T,Br,Brl,Sh,Sw,Du,G,Ca,D	Sw,C	C,Sh,Sw,H (oral)	

[a] C = cattle, Sw = swine, Ch = chicken, T = turkey, D = dog, Ca = cat, Bi = bird, L=layer, Fi = fish, H = horse, Sh = sheep, R = rabbit, M = mink, G = goat, Br = breeder, Brl = broiler, Pi = piglets, Du = duck, G = geese, Lo=lobster

Antimicrobial Class and Drug	Registered in Animal Species[a]			Drugs in Same Class Registered for Human Therapy
	Therapy	Growth Promotion, Weight Gain and/or Feed Efficiency	Disease Prevention, Prophylaxis and/or Control	
Diaminopyrimidines				
Trimethoprim	C, Sw, Pi, H, Fi, D, Ca			Trimethoprim
Ormetoprim	Fi			
Ionophores				
Lasolocid sodium		C	Ch (coccidiosis)	
Maduramicin			Ch, T (coccidiosis)	
Monensin		C	Ch, T, C (coccidiosis); C (bloat and ketosis)	
Narasin		Sw	Ch (coccidiosis)	
Salinomycin sodium		Sw, C	Ch (coccidiosis)	
Miscellaneous Drugs				
Arsanilic acid		Brl, T, Sw		
Bacitracin				
Bacitracin	D,Ca	Ch,Sw,T,C	Br,Sw	Bacitracin
Bambermycins				
Bambermycin		Br,T		
Quinoxalines				
Carbadox	Pi	Sw	Sw	

[a] C = cattle, Sw = swine, Ch = chicken, T = turkey, D = dog, Ca = cat, Bi = bird, L=layer, Fi = fish, H = horse, Sh = sheep, R = rabbit, M = mink, G = goat, Br = breeder, Brl = broiler, Pi = piglets, Du = duck, G = geese, Lo=lobster

Beef

At about seven months of age, beef calves raised on pasture are typically weaned, shipped to backgrounder farms, and eventually to feedlots where they are confined in large groups and fed high-energy rations. Pneumonia and diarrhoea are major infectious diseases, and cattle are often individually or mass medicated (5).

In general, feedlot beef cattle are routinely fed rations medicated with an ionophore to promote growth, and some are fed tylosin (a macrolide) or oxytetracycline to control liver abscesses. Individual animal injections with therapeutic levels of penicillin, tetracycline, ceftiofur (third generation cephalosporin), tilmicosin (a macrolide), florfenicol (a derivative of chloramphenicol), or trimethoprim/sulfadoxine are occasionally administered on beef cow-calf operations and, more frequently, in feedlots. In western Canada, many calves are mass medicated with oxytetracycline,

trimethoprim/sulfadoxine, or tilmicosin upon arrival at feedlots for treatment or prevention of respiratory disease. This metaphylactic treatment has been shown to reduce losses due to clinical disease and mortality (6,7). Comparatively fewer antimicrobials are used in cow-calf production systems where the animals are raised extensively (outside on pasture).

Veal

Typically, bull calves, culled shortly after birth from dairy herds, are used to produce red or white veal (1). Respiratory and enteric diseases are important causes of illness in veal calves due to their young age, diverse origins, and the stress of transport and confinement rearing. Although a number of antimicrobials are available for use, few data concerning the relative frequency of treatment with these antimicrobials in the veal industry are available. Many feed products used to replace milk for calves contain antimicrobials.

Poultry

Broilers and turkeys are typically raised in barns containing several thousand birds. The poultry industry has controlled many infectious diseases through vaccines, biosecurity, and good management; however, other diseases are still a problem and are prevented, controlled, and treated with antimicrobials (Table 5.2). Many broiler rations contain antimicrobial drugs, including ionophores and sulfonamides, to prevent coccidiosis. Several antimicrobials are approved for growth promotion and feed efficiency in broilers, turkeys, and layers (*e.g.*, bacitracin, bambermycin, chlortetracycline, penicillin, virginiamycin, arsenical compounds). However, few data concerning the frequency and average duration of use of these drugs are available.

Chicks and poults may be injected prophylactically with gentamicin or ceftiofur (poults only) to prevent yolk-sac infections (omphalitis) and vaccine injection-site abscesses. Treatment of individual sick birds is not generally practical, and nearly all medications are administered to entire flocks through feed or water. *Escherichia coli* infections, leading to cellulitis and septicemia, are major disease problems in poultry, but other diseases caused by bacteria and mycoplasma are prevented, treated, and controlled with antimicrobials.

Swine

Swine are usually raised in pens, either on farrow-to-finish operations, which house the animals from birth to market, or in segregated management systems, where pigs are moved to different farms at various stages of growth (*i.e.*, farrowing, nursery, and grower/finisher). To help control the spread of infectious disease, many farmers practise “all-in-all-out” management, where all livestock in a barn are sent to market and the barn is emptied, cleaned, and prepared for the next group of animals. The average size of operation is increasing in the swine industry, with many barns housing greater than 1,000 head. Antimicrobial use for growth promotion or disease prophylaxis is probably more prevalent in the swine industry than in the other commodities: 20–90% of rations are medicated with an antimicrobial, depending on the age group (4,8). Therapeutic treatments may be administered to groups or individual animals. After weaning, most pigs receive antimicrobials in “starter rations” or water when they are most vulnerable to infectious disease caused by viruses, mycoplasma, and bacteria. This may be related to the stress of weaning or movement within the production unit. Antimicrobials in greatest use include tetracyclines, tylosin, and sulfamethazine or other sulfas.

Pneumonia is an important problem in swine production, and antimicrobials are used to treat and prevent clinical cases and outbreaks (*i.e.*, ceftiofur, sulfonamides, tetracyclines, tiamulin) (9). Bacterial diarrhoea caused by *Escherichia coli* may be treated with gentamicin, apramycin, and neomycin. Swine dysentery, caused by *Brachyspira hyodysenteriae,* and ileitis, caused by *Lawsonia intracellularis,* may be treated with lincomycin, tiamulin, or macrolides (10).

Dairy

Most calves are separated from their dams at birth and housed separately in hutches or pens to control infection. Diarrhoea and pneumonia are important diseases of dairy calves. Antimicrobials may be administered orally (*i.e.*, tetracyclines, penicillins, sulfonamides) or by injection (*i.e.*, ceftiofur) for treatment or prophylaxis. Lactating dairy cows receive few if any antimicrobials in their feed because of the need to avoid drug residues in the milk. However, mastitis caused by a variety of bacteria is an important problem in the industry and is responsible for most antimicrobial use. Clinical cases in individual lactating cows may be treated by intra-mammary infusion (administered directly into the udder). To prevent and treat mastitis, antimicrobials may be routinely infused into the udder at the start of the non-lactating period ("drying-off" period), often to the entire herd. Most mastitis pathogens are Gram-positives (*e.g.*, *Streptococcus*) and are treated with penicillins, cephalosporins, erythromycin, and oxytetracyclines.

Aquaculture

Salmonids (salmon and trout) are the predominant aquaculture species in Canada, although some shellfish and other species are also produced (11,12). No antimicrobials are registered for growth-promotion purposes, and only four are licensed for therapy. Treatments are administered in the feed to the entire group of fish in the tank or pen. Brood stock, however, may be treated on an individual basis by injection. Oxytetracycline is used most frequently, but potentiated sulfonamides (sulfadiazine/trimethoprim, sulfadimethoxine/ormetoprim) and florfenicol are also administered (13).

The primary bacterial diseases of concern in salmon and trout culture are septicemias caused by various bacterial pathogens, namely *Aeromonas salmonicida*, several marine *Vibrio* species and *Renibacteriam salmoninarum*, amongst others. However, there are now licensed vaccines for all of these and many other common bacterial pathogens of fish, all of which are highly efficacious and have resulted in a significant decrease in antimicrobial use in aquaculture (see Chapter 12). Most antimicrobial treatments are administered to juveniles (Sheppard, 2000).

Sheep

In Canada, the majority of sheep operations raise lambs for meat purposes. Sheep may be raised under a number of systems, including total or partial confinement in pens, and pasture. Because few drugs are approved for sheep, much antimicrobial use is extra-label. In mature ewes in western Canada, mastitis is one of the most important and frequent diseases requiring antimicrobial treatment. In lambs, pneumonia and coccidiosis are common indications for treatment. The use of antimicrobial drugs in feed is not common. Some sheep receive

prophylactic injections (*e.g.* post-lambing) with oxytetracycline or other drugs. For treatment of infections such as mastitis and pneumonia, ceftiofur, florfenicol or tilmicosin may be used.

Other species

Other livestock commodities, including goats, farmed deer and rabbits, are not further addressed within this report. In general, there are only a few drugs approved for these species.

Antimicrobials used in feeds

Several antimicrobial drugs are approved for use in feeds in Canada, either by themselves or in combination with other agents (Table 5.3). Although the ionophores are excluded from the table they have antimicrobial activity.

Table 5.3: Antimicrobials used in feeds in Canada

Name of Antibiotic Compound	Applicable CMIB Numbers
Chlortetracycline	10.1; 34; 38; 49
Bacitracin	10.2; 10.14; 37, 37A; 48
Lincomycin	10.5; 62; 68
Novobiocin	40
Spectinomycin	62
Penicillin	10.7; 10.14; 37; 38
Tylosin phosphate	10.10; 43
Virginiamicin	10.11; 63
Erythromycin	41
Bambermycins	10.12
Oxytetracycline	35, 35A; 55
Neomycin	55
Tiamulin	74
Tilmicosin	80
Sulfamethazine	38; 49; 67

International concerns and controversies surrounding the use of growth promoters in food-animal production warrant a more detailed discussion of this practice.

Benefits of growth promoters

Livestock and poultry producers are interested in any practice that promotes animal growth or an increase in productive efficiency. The following benefits are claimed:

1. Increased productive and feed efficiency, thereby improving producer margins and yielding cheaper foods for consumers. A shortened days-to-market interval, thus lowering interest costs and allowing more productive cycles per unit of time;
2. Increased efficiency of feed yields less waste and potentially reduces the environmental impact; and,

3. Reduced incidence of disease (even though this is not an explicit claim for growth promotion or feed efficiency, therefore it is an indirect benefit – see Chapter 4).

It is not precisely known how antimicrobials facilitate growth when fed at low concentrations to animals. Effects may be physiologic, nutritional, or metabolic in nature. However, they probably involve the intestinal bacterial flora, because animals reared "germ-free" (gnotobiotic), when given antimicrobials, show no further increase in growth (14). Improvement in growth performance is probably due to one or more of a variety of mechanisms (13,15,16), including reduction of "detrimental species" of bacteria, reduction in absolute numbers of microbial organisms (thereby exerting a "nutrient sparing effect"), and reduction in overall infectious disease challenge to the animal.

Reports in the scientific literature suggest that under experimental conditions, improvements of 1–15% in weight gain or feed efficiency may be realized (17). Although gains in weight and feed efficiency may be small on a per-animal basis, the net effect across an entire industry may be quite large (14). The response may be dependent on a number of additional variables such as animal age, sex, diet, health status and vaccination regime.

The benefits of growth promoters are reportedly greater under poor hygiene conditions (18), and questions have been raised about their current efficacy as disease prophylactics now that other means of controlling disease (*e.g.*, biosecurity, vaccination, and improved management) have been introduced widely into intensive animal husbandry. Nevertheless, some growth promoters are still believed to prevent certain diseases, *e.g.*, necrotic enteritis (*Clostridium perfringens* infection in poultry) (19). On the other hand, the committee was advised that sometimes production animals grow too fast (especially broilers), lessening the need for growth promoters. The committee was advised, however, that the food-animal industry (particularly poultry) regularly assesses the benefits of antimicrobials in feed and believes them to be profitable. Shryock (14) provides the following data:

Table 5.4: Percentage improvement in performance of pigs fed antimicrobials 1950–1985

Years	Improvement, %		
	Periods[a]	Daily Weight Gain	Feed efficiency
1950–1977	Starter	16.1	6.9
	Grow-finish	4	2.1
1978–1985	Starter	15	6.5
	Grow-finish	3.6	2.4

[a] Starter period from about 8–26 kg and grow-finish period from 27–92 kg body weight. Source: Zimmerman, 1986, adapted from Shryock, 2000.

Approved products

There are nineteen products listed in the CMIB (20) that carry specific claims for growth promotion in various species of animals, except fish (Table A.3.1, Appendix 3). Note that growth promotion and/or feed efficiency is a specific claim; it should not be confused with claims for the control of specific disease entities, *e.g.*, necrotic enteritis or mycoplasma

infection. It is sometimes difficult and subjective to categorize a claim as either growth promotion or disease prophylaxis. For example, many claims, especially for the tetracyclines, refer to growth promoter characteristics, *e.g.*, maintenance of appetite, and to "stress" conditions, which, arguably, could involve disease prophylaxis. For the purposes of this report, any product that carries a growth promoter reference in its claim, and in the absence of any mention of a recognized or specific disease entity, *e.g.*, chronic respiratory disease, synovitis, atrophic rhinitis, is considered to fit the definition of a growth promoter.

Three other products/combinations deserve special mention because of their large number of claims and the fact that they are clinically important antimicrobials in human medicine. These are chlortetracycline, oxytetracycline, and the combination product of chlortetracycline/sulfamethazine/penicillin (Tables A.3.2-A.3.4 are in Appendix 3).

Antimicrobial treatment practices and policies of other countries

Therapeutic treatment practices vary among countries, mainly with respect to the specific drugs that are approved and to the prevailing farming conditions and diseases encountered. For the purposes of this chapter, the main international issue of interest is growth-promoter policy in Australia and Europe (the situation in the United States is broadly similar to that in Canada).

Australia

Prior to 2000, a number of antimicrobials, including arsenicals, glycopeptides (avoparcin), macrolides, ionophores, polypeptides, quinoxalines, streptogramins (virginiamycin), and others, were registered as growth promoters and made available for over-the-counter (OTC) sale to livestock owners, feed millers, and feed mixers (21). In 2000, the Australian government accepted the Joint Expert Technical Advisory Committee on Antibiotic Resistance (21) recommendations to review the use of these growth promoters, with priority on glycopeptides (which were ultimately withdrawn voluntarily from the market in June 2000), streptogramins, and macrolides. It was recognized that curtailment of antimicrobial use in domestic agriculture could have economic consequences and international trade implications.

Sweden

Antimicrobial growth promoters were banned completely in 1986. Further, antimicrobials were made available only under the auspices of a veterinary prescription. Subsequent to the ban, total antimicrobial use initially increased, presumably due to an increase in therapeutic application, but later declined to a level approximately 55% of the use rates documented prior to the legislation (as measured by absolute kilograms of active drug). Although some animal health problems were encountered in broiler and weaner pig production facilities, there were no reported problems with beef, turkey, egg, or finishing pig production. Dietary modifications, changes in production practices and changes in facility management are all cited as being instrumental in helping to overcome the immediate negative production impacts experienced by some sectors (22). Swedish farming is somewhat different than Canadian farming, so it is not absolutely clear whether the same effects would be observed here under similar restrictions.

Denmark

In the late 1990s, the Danish authorities issued bans on a number of antimicrobials, *i.e.*, avoparcin, virginiamycin, bacitracin, spiramycin, and tylosin, for use in animals. In early 1998, various food-animal industries in Denmark agreed to voluntarily discontinue the use of all antimicrobial growth promoters by the end of 1999. Concurrent with these changes, regulations were implemented to the effect that veterinarians could not profit from the sale of therapeutic antimicrobials to livestock and poultry producers. Also, a comprehensive surveillance program for antimicrobial resistance was initiated (23).

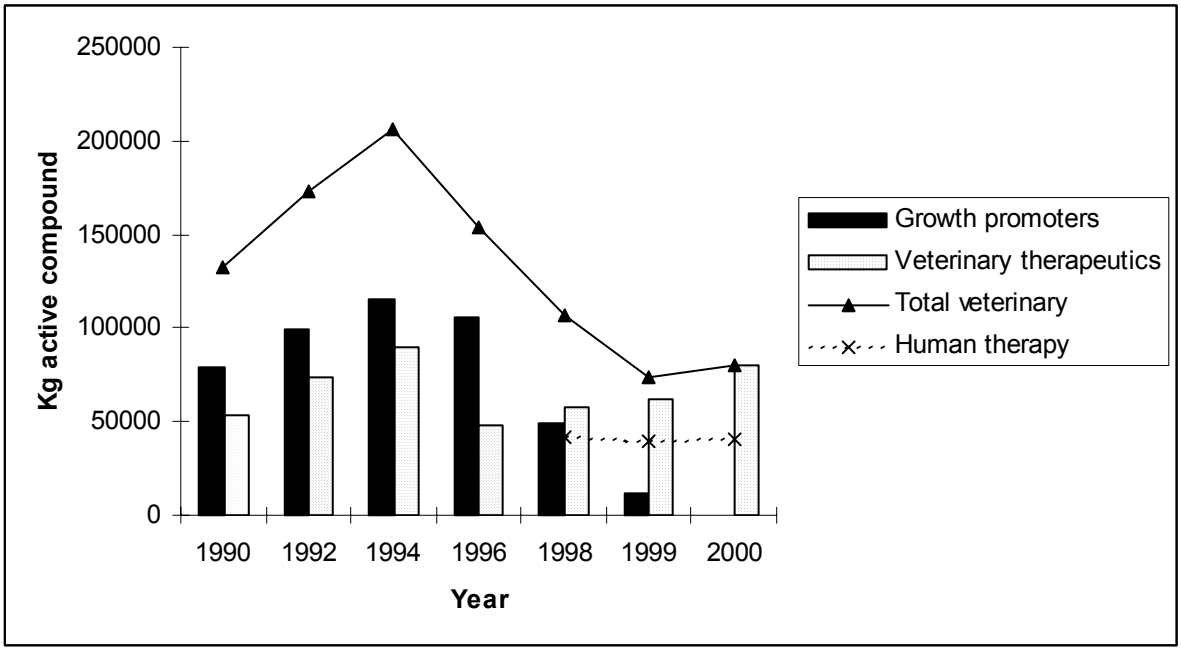
Although the bans were quite recent, some follow-up data are emerging. Total antimicrobial use in Denmark declined steadily from 1994–2000 along with declines in growth promoter use. Quantities of therapeutic antimicrobials increased modestly since 1996; however, total therapeutic quantities remained lower in 2000 than in 1994 (Figure 5.1) (24). For comparison purposes, this figure also shows total antimicrobial use for therapy in humans. Recent increases in therapeutic use are relative to previous years. In absolute terms, Danish farmers still use relatively small quantities of antimicrobials to treat individual animals; an estimated 3.3 g/pig slaughtered compared with >20g/pig in the U.K (Flemming Bager, personal communication).

According to a recent study, removal of growth promoters reduced broiler chicken feed efficiency by less than 1% without affecting other measures of production efficiency. There was some increase in the rate of necrotic enteritis infections, however death rates did not change and there was no loss in kilogram of broilers produced per square meter (25). Furthermore, recent follow-up data on antimicrobial resistance show striking changes in antimicrobial use patterns, as well as in the occurrence of resistant isolates (Table 5.5) (26). Additional details on trends in antimicrobial use and temporal relations with resistance in monitored bacteria are available in the annual report of the Danish resistance monitoring program, DANMAP (24).

Table 5.5: Change in rates of resistance in specific organisms isolated from broilers and pigs in Denmark subsequent to a decrease in antimicrobial use (adapted from (26).

Type	Isolate	Peak Rate, % (year)	Rate, % (2000)
Broiler	glycopeptide res. *E. faecium*	73% (1995)	6%
Pig	glycopeptide res. *E. faecium*	20% (1997)	6%
Broiler	erythromycin res. *E. faecium*	76% (1997)	13%
Pig	erythromycin res. *E. faecium*	90% (1997)	47%
Pig	erythromycin res. *E. faecalis*	90% (1997)	28%
Broiler	virginiamycin res. *E. faecium*	66% (1997)	34%
Broiler	avilamycin res. *E. faecium*	77% (1996)	5%

Figure 5.1: Trend in use of antimicrobials for growth promotion and therapy in food animals and use for therapy in humans in Denmark (reprinted with permission)(24).



Analysis: antimicrobials used in food animals

An examination of the range of drugs registered for use in food animals in Canada, their indications for use, and their relatedness to drugs used in humans, raises several points relevant to the risk of antimicrobial resistance in humans and animals.

On the positive side:

1. Some drugs used in animals currently have no drug class counterpart in humans (*i.e.*, tiamulin and the ionophores salinomycin, monensin sodium, lasalocid sodium, narasin);
2. Some important drugs in humans, such as glycopeptides, have no drug class counterpart registered for use in animals (avoparcin, a glycopeptide, was never registered for use in Canada);
3. Some drugs used in animals are not used in humans, although there are human drugs in the same class. Examples include apramycin (an aminoglycoside), florfenicol (a fluorinated derivative of chloramphenicol), and tylosin (a macrolide); and
4. Some classes important in humans have few related drugs registered for use in animals i.e., third generation cephalosporins, fluoroquinolones.

On the negative side:

1. Most of the classes of drugs used in animals are also used in humans;
2. Some of these are registered for use in feed as growth promoters or prophylactics, including several aminoglycosides, erythromycin, penicillins, and tetracyclines;

3. Some antimicrobials used in humans are administered routinely to large numbers of animals, either for control/prophylaxis using penicillin, gentamicin, or ceftiofur; treatment of subclinical diseases such as routine dry-cow treatment; or for metaphylaxis, the therapeutic treatment of entire groups of feedlot calves. Such routine use is of special resistance concern because of the numbers of animals involved;
4. Modern production methods dictate that even therapeutic treatments in some types of animals necessarily involve treatment of entire groups of animals through feed or water. This effectively increases the potential exposure to resistance selection pressure; and
5. Some drugs are registered for two or more of the following categories: growth promotion/improved feed efficiency; disease control/prophylaxis; therapy. This could increase resistance selection pressure, eventually compromising efficacy in one or another category.

Further analysis and recommendations concerning these matters are included in Chapter 6.

Conclusions

Antimicrobials are very beneficial in reducing sickness and death in animals due to bacterial diseases. Most animals receive antimicrobials at some stage in their lives, either for therapy, disease prophylaxis or for growth promotion. In some species (*e.g.* dairy cattle), individual animal treatment is feasible, however for others (*e.g.* poultry, fish), treatment of entire groups of animals is the only practical way of administering drugs. Some antimicrobial classes are unique to veterinary medicine or human medicine; however, most classes are used in both fields. Some antimicrobials used in humans are administered routinely to large numbers of animals, either for control/prophylaxis, or for growth promotion.

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CHAPTER

6

Managing antimicrobial resistance risks

Key Points

- **Risk is the probability that an adverse event will occur, along with its impact or consequences**
- **Scientists generally agree that antimicrobial drug use in food animals can select for resistant bacteria, and that some of these resistant bacteria can be transferred to humans and cause illness. However, the magnitude of the impact has been difficult to fully assess**
- **Resistance risk to human health increases when:**
    - **drugs are important to human health, or they select for resistance to drugs important to human health**
    - **treatment is administered to entire groups of animals**
    - **treatment is long in duration or low in dose**
    - **treatment is widely used in the industry and in multiple species**
    - **resistant infections spread among animal and human populations**
- **Resistance risks can be at least partially controlled or managed, and a variety of management strategies are available**
- **Choosing the optimal strategy to manage resistance risk (including no action if appropriate) requires careful assessment of the nature of risk, the cost and effectiveness of the management options available, consideration of socio-economic issues, and effective communication**
- **Socio-economic considerations include:**
    - **cost of pharmaceuticals**
    - **international trade**
    - **effects of reduced sales on the pharmaceutical industry**
    - **disease and production losses**
    - **animal welfare considerations**
    - **consumer preferences**
- **There are resistance risks associated with all uses of antimicrobials, and Health Canada must decide which risks are acceptable for the benefits gained**
- **Antimicrobial uses in animals should be reserved for situations where benefits are clear and substantial**

When protecting the health of Canadians from risks associated with antimicrobial resistance, Health Canada should make policy decisions that are science-based. However, scientific information is often lacking and these decisions are made even more difficult by the need to consider the benefits from antimicrobial use in addition to the risks, and the trade-offs associated with different risk management options. Risk analysis is a systematic approach to evaluating risk that was developed to assist decision-making in difficult and complex fields such as antimicrobial resistance. This chapter briefly describes the general principles of risk analysis that relate to antimicrobial resistance and reviews the practices employed in Canada and other countries. Next, examples demonstrate the information that should be used in assessing risks and the difficulties encountered when weighing evidence. The chapter concludes with recommendations on the process of managing risk and antimicrobial resistance in Canada, and in particular, on managing the risk associated with using antimicrobials as growth promoters.

General principles

Risk is the probability that an adverse event will occur, along with its impact or consequences (1,2). We cannot eliminate all risks from society. An important role of government is to decide which risks should be publicly managed and how best to accomplish this using legislation and resources. These decisions are often difficult to make and sometimes very controversial. This is especially true in situations involving new, potentially serious risks, and where a simple, widely accepted remedy is unavailable. Under these conditions, there are advantages to a regulatory decision-making process that is open, clearly communicated, based on scientific evidence, and consistent with societal values.

The Society of Risk Analysis (SRA) describes risk analysis as "a fundamentally science-based process that strives to reflect the realities of Nature in order to provide useful information for decisions about managing risks" (3). SRA guiding principles include the view that risk analysis "seeks to integrate knowledge about the fundamental physical, biological, social, cultural, and economic processes that determine human, environmental, and technological responses to a diverse set of circumstances (3,4). Because decisions about risks are usually needed when knowledge is incomplete, risk analysts rely on informed judgment and on models reflecting plausible interpretations of the realities of Nature."

In the context of human health, risk management is the process of choosing, implementing, and evaluating the optimal set of actions for the alleviation or mitigation of health risk from among the range of options available. Consideration should be given to societal benefits and costs of the available management options, relevant laws, public values, and results of consultation with interested parties in industry, government, academia, and the general public. Thus, in the case of regulatory matters, risk management necessarily and properly involves "political" considerations. Risk management and analysis are thoroughly discussed in the literature (1,2,5).

Risk assessment is the process of estimating the probability and impact of adverse health effects attributable to resistance arising from using antimicrobials, for example, on farms. These estimates may be expressed in qualitative terms (*e.g.*, low, medium, or high); however, quantitative expression of risk is preferred whenever possible (*e.g.*, expected number of human infections, illnesses, or fatalities per year). Some examples (mainly qualitative) are provided later in this chapter.

Risk communication is the process of consultation, discussion and review that seeks to enhance the validity, effectiveness, and general acceptance of risk assessment and risk management. Good risk management decisions emerge when the views of those affected by the decision are elicited and when incentives for research, innovation and risk prevention are included.

Human health risks from residues and resistance

Assessment of human health risk from antimicrobial residues in food is the current focus of safety evaluations of veterinary antimicrobials in Canada and most other countries. Assessments of risk from residues in food and from resistance in bacteria of animal origin differ in at least two important ways:

1. Drug residues are chemicals, and their post-harvest concentrations in edible animal products do not change very much with processing and temperature changes. Bacteria, however, are very dynamic; they can die, grow, and interact with other organisms between harvest and eventual consumption. This has important implications for exposure assessment; and
2. Drugs are approved for intentional administration to animals and treatments can be scheduled to minimize exposure to residues. Conversely, microbial contaminants are naturally occurring, and exposure cannot be so readily manipulated.

Socio- economic considerations and impacts on trade and the pharmaceutical industry

Wise management of resistance risks occurs at many levels (international, national, farm operation, individual animal) and may involve many stakeholders. For example, at the national level, Health Canada must decide whether to register a drug for use in an animal species for a specific indication. In part, this includes deciding whether any resistance risk from such use is reasonable or acceptable given the benefits that accrue from treatment of animals, the value placed on these benefits by Canadians, and their willingness to tolerate risk. As an example at the local level, veterinarians must decide when it is appropriate to prescribe an antimicrobial to an animal. If the drug is being used prudently, this includes consideration of the possibility of selecting for resistance, but also the label indication for the drug, the pharmacological properties of the drug, its cost, the animal's health and welfare, the economic value of the animal, and the production goals of the farmer.

Socio-economics

In general, once the resistance risks have been assessed scientifically, it is appropriate to consider socio-economic issues before deciding which strategy is the best for managing the risks. These issues may include communications, benefit-cost analysis, the legal or government jurisdictional framework, societal values, and political consequences. The assessment of risk and the selection of the optimum management strategy should be an open and transparent process. It should include consultation with the public, pharmaceutical companies, producers, scientists, and other affected parties.

Economic analyses (or benefit/cost analyses) should be incorporated within the risk analysis framework to assist in making and communicating wise decisions. There are however, many barriers to including this type of analysis, including cost and technical demands, lack of data or understanding of the financial elements involved, and difficulty in ascribing dollar values

to components such as human lives, lost days at work, and quality adjusted life-years. In addition to health care costs attributable to resistance, there is a need to consider animal health care and production costs associated with restrictions on antimicrobial use. Such restrictions could have adverse economic consequences, including decreased incentive for pharmaceutical companies to develop new animal drugs, poorer animal production efficiency, and increases in the incidence of infectious disease in animals. Alternatively, restrictions could result in little or no change in animal health or production efficiency.

Few formal analyses of the economic impacts of antimicrobial use and their withdrawal from animal production have been conducted. The ban on growth promoters in Europe and some early data on the effects on animal production, as discussed previously, provide some insight into the impacts. The potential economic effects of restrictions on subtherapeutic antimicrobial use in the United States (U.S.) were recently assessed (6). One report by the National Academy of Sciences (NAS) stated that producers using good management practices would be affected less than producers using poor management practices. The report suggested this was because antimicrobial drugs are most effective in animals living in poor conditions, *e.g.*, stress due to crowding and sub-optimal sanitation. Based on assumed 4–5% feed efficiency/growth promotion, estimated average annual per capita costs of a hypothetical ban on subtherapeutic antimicrobial use were U.S.$ 4.84 to $9.72 (U.S.$ 1.2 to 2.5 billion over the U.S. population). Estimated increases in cost per pound were lowest for chicken (U.S.$ 0.013 to 0.026) and highest for beef and pork (U.S.$ 0.03 to 0.06). The committee believes that these findings represent relatively minor economic impacts.

International trade

Profit margins in farming are, in most cases, so narrow that it is difficult to concede any advantage to a competitor. If Canadian farmers are asked to limit the use of antimicrobials, *e.g.*, growth promoters, and if this limitation causes a decline in efficiency, then Canadian farmers could become less competitive with imports from countries where drug use is less restrictive. On the other hand, the issue of antimicrobial resistance could become a basis for international trade restrictions, which could create a competitive advantage for Canadian farmers if a more limited-use policy was in place. For example, if a country can demonstrate, through science-based risk assessment, that use of a certain antimicrobial in food animals selects for resistance in a human pathogen, that country could make a case for excluding products from other countries with less restrictive use policies. The European Union bars the importation of Canadian- and American-produced beef because of the potential presence of growth promoting hormones. It is conceivable that similar action could be placed on other animal products because of differences in antimicrobial use policies.

Pharmaceutical industry

There is little doubt that antimicrobial resistance issues and the risk reduction steps that have been taken or proposed, such as bans on growth promoters, new regulation, and calls for reduced antimicrobial use, are threats to the financial future of the pharmaceutical industry. Around the world, many fear that these threats may result in limited or no new drug approvals because of the altered regulatory climate and the decreased incentive to develop new drugs for use in food animals. It is important that legitimate, registered antimicrobials are available for use in animals; otherwise, sick animals could go untreated (with negative effects on animal welfare) and problems with excessive extra-label use or black marketing could arise.

Who benefits and who bears the risk

It is important to understand which sectors of society benefit from the use of antimicrobials in animals, which sectors bear the risks associated with antimicrobial use, and which sectors are affected by measures used to mitigate the risks associated with antimicrobial resistance. This is particularly difficult when the benefits (*e.g.*, reduced incidence of drug-resistant salmonellosis in humans, or increased drug sales) and the costs, (*e.g.*, reduced profitability of pig farming because of lack of approved drugs to treat pneumonia, or increased resistance in foodborne pathogens) are not borne by the same sectors of society. Consideration of who benefits and who bears the risks starts at the farm, where treatment decisions are made. Antimicrobials will be used to save the life of an animal, return it to health, reduce its susceptibility to disease, or increase its rate of growth. From a production standpoint, economics are a prime motivator when deciding to treat an animal or herd. Thus, the benefits accrue to the farmer. Also, treatment financially benefits the drug manufacturers and distributors, including pharmaceutical companies, wholesalers, retail outlets, veterinarians, and feed companies.

In a free-market system, more efficient production on the farm and more competition in the distribution of drugs should eventually benefit the consumer by reducing the cost of food. The effectiveness of the marketplace, however, in fairly apportioning benefits and costs of resistance mitigation is not as clear. The principal beneficiary of resistance mitigation should be society as a whole, and in particular, consumers. Therefore, consumers should be expected to pay an appropriate portion of the cost of mitigation measures. At present in Canada, this seems not to be flowing back to the farm in the form of higher prices. Consequently, there is little direct financial incentive for a farmer to attempt to reduce resistance in his animals. There should, indeed, already be some incentive for producers to reduce resistance in animal pathogens, so that important clinical infections in their animals will respond to treatment. The situation is different, however, for foodborne infectious agents (*e.g.*, *Salmonella*, *Campylobacter*, most *Escherichia coli*, *Enterococcus*), which are usually subclinical infections in animals and are therefore of little consequence to the productivity of the farm in terms of illness and disability (morbidity) and death (mortality) in animals. *Salmonella* is sometimes an exception because it is the zoonotic enteropathogen most likely to cause illness in animals, *e.g.*, calf diarrhoea or septicemia. However, most *Salmonella* infections in animals are subclinical, and the other organisms, *e.g.*, *Campylobacter jejuni*, important to human health are essentially non-pathogenic in animals. Some farm programs are starting to address this deficiency by focusing on improved product quality. At present, however, these programs do not focus on resistance hazards.

If it is fair to ask those who contribute to the risk of antimicrobial resistance to pay for its mitigation, then we will have difficulty being entirely fair, because, for most types of resistance, we will not be able to identify all the contributors. As discussed previously, resistance in a population of bacteria often emerges gradually, sometimes over many years, and may involve assembly of complex arrays of genes that have their origin in other species of bacteria, animals, or people. The existence of a resistant pathogen in a treated animal or group of animals is usually not a consequence of *de novo* generation and selection due to that treatment in those specific animals (fluoroquinolone resistance in *Campylobacter jejuni* is an exception). Rather, the existence of a resistant pathogen in a treated animal or group of animals is usually the product of a very complicated series of events, of which the latest treatment of the animal may be only one step. In contrast, antimicrobial residues in foods of animal origin are, in most cases, clearly attributable to a treatment event on a single farm.

Therefore, responsibility (and liability) are more easily attributed. Although drug residues are prone to degradation, unlike bacteria, they are not prone to multiplication, evolution, perpetuation, or spread among species of animals.

Antimicrobials that are active against *Salmonella* or other enteropathogens would be expected, under some circumstances, to reduce infection and/or faecal shedding of the bacteria in animals. This occurs in some animal species with some antimicrobials, *e.g.*, apramycin and oxytetracycline in pigs, oxytetracycline in calves , and oxytetracycline in poultry, and is a basis for the claim that antimicrobial use in animals can benefit human health by reducing the load of pathogens flowing through the food chain to humans. In general, however, because of resistance concerns, food animals are not treated with antimicrobials specifically to reduce or eliminate faecal carriage and shedding of enteropathogens, although they may be used to treat clinical cases of salmonellosis. Any human health benefits of this type would accrue indirectly, from antimicrobial use for therapy and prophylaxis of infectious diseases of animals, or for growth promotion.

Notion of acceptable levels of risk

It is generally agreed that some level of risk associated with treating animals with antimicrobial drugs is acceptable in exchange for the benefits gained from alleviating animal suffering or reducing losses due to disease. However, difficulties arise when identifying the line of demarcation between acceptable and unacceptable risk. A quantitative threshold of acceptable risk is often useful during the development of standards. In theory, risk estimates surpassing the threshold would trigger appropriate regulatory action. There is experience with this approach within the area of chemical residues in food. The concept of maximum residue levels (MRLs) or "tolerance levels" of residues in foods has a quantitative relationship to an extremely low or negligible level of risk for disease in humans (within the limits of science to detect hazards). In the case of carcinogens in foods, some jurisdictions use an acceptable level of cancer risk of one chance in a million (often referred to as 10^{-6}) over a lifetime of exposure. This is also considered equivalent to negligible risk, which is practically zero. It is also important to consider the range of susceptibilities in the population, the severity of the outcome, and the availability of alternative ways to mitigate risk.

In the microbial field, there is little experience with defining acceptable levels of risk for regulatory purposes. One example, however, is the area of microbiological standards for water. The U.S. Environmental Protection Agency (EPA) uses an acceptable risk of 1 in 10,000 over a year of exposure for enteric disease from water. This factor is used in risk analysis to determine safe levels of bacteria in drinking water. In Canada, how could we start to define an acceptable level of resistance risk? What would the final level be: a 10^{-6} risk of mortality due to resistance over lifetime exposure? Any resistance in an enteric pathogen? A 1% increase in the prevalence of *Salmonella* in slaughter animals? Any resistance genes reaching humans in pathogens or commensals? No country in the world has published precisely defined standards that have been agreed to by stakeholders.

Another approach is to define, based on surveillance data, background or baseline levels of risk, and use them to discourage or prohibit practices that lead to an increase relative to the baseline, or to require interventions that ensure a reduction in baseline risk. This is the principle employed in some food safety regulations, *e.g.*, canning requirements for low-acid foods and pathogen reduction standards in fermented meat products. Defining resistance thresholds, as proposed by the U.S. FDA, would involve a similar concept.

One of the great difficulties with determining acceptable risk is addressing the idea of what risk is acceptable to whom. Other questions arise around whether the risk is assumed voluntarily or involuntarily, whether there is potential for catastrophic outcome, whether children are involved and the implications of this, and whether there are clear benefits to assuming the risk. Few, if any, countries have come to grips with these matters when addressing food safety issues involving microbes, including antimicrobial resistance.

Consumer perspectives

On the one hand, antimicrobials have been important for the control of animal infections that could be spread to humans. They have allowed the consumer a safer, more abundant and more affordable food supply than in previous decades, which ought to contribute to a healthier population. However, it is argued that the misuse/overuse of antimicrobials in food animals is compromising our ability to fight certain human diseases because of the development of antimicrobial resistant pathogens in animals that are transferred to humans. From the consumer's perspective, which of the current options poses the greatest risk to one's health: eating food that may carry drug-resistant pathogens; eating food that is "drug free" but may be diseased; or eating no food animals? Are fruits and vegetables any safer with respect to antimicrobial resistance? What level of risk are consumers willing to tolerate? Can regulatory policy-makers give the consumer improved options by, for example, banning the use of antimicrobials as growth promoters?

The consumers of food animals face financial risks if public policies are drafted with the intention of reducing the use of antimicrobials in food animals. As mentioned previously, it is argued that reduction in the use of antimicrobials as growth promoters will increase the cost of production and thus the cost, to the consumer, of animal food. Clearly, some consumers are ready to bear the cost for what they consider to be "healthier" food. This is indicated by the number of consumers who pay more for "drug free," organic, or "free range" food.

Antimicrobial growth promoters are not used in certified “organic” animal production. The National Standard of Canada for Organic Agriculture specifies that under no circumstances should feed medications, including all hormones and antibiotics used to promote growth, be added to livestock diets (7). Organic foods currently represent a small, but growing, segment of Canadian food production, estimated to be a 1.5% market share (*Globe and Mail*, August 20, 2001). Loblaws, Canada’s largest grocery chain, in May 2001, announced plans to carry 200 organic products at competitive prices by the fall of 2001 (*Ontario Farmer*, May 8, 2001). Organic farming movements are also active in other countries. In Sweden, for example, consumers are making "increasing demands for more openness, transparency, and accountability in foodstuff production. The consumer cooperatives believe that the use of antibiotics as growth promoters, together with intensive and industrialized production systems, does not address consumer expectations on food safety.” (8).

Animal welfare perspectives

Antimicrobials used for therapy improve animal welfare. However, concerns have been expressed that some antimicrobial uses may compromise animal welfare by enabling closely confined, intensive rearing, or that they may be used to compensate for poor management. Europeans appear to be more aggressive about animal welfare standards than North Americans. Along with ending the use of animal growth promoters in 1986, Sweden passed

animal welfare legislation that granted increased space to farm animals. Sweden placed emphasis on improving animal environments, good animal management and care. It was thought that antimicrobials should never be used as a substitute for adequate hygiene, rather that animals should be kept healthy through improved management and hygiene and through disease control programs.

Compassion In World Farming is a farm-animal advocacy organization in the United Kingdom that successfully lobbied for the legislated phase-out of sow crates, battery cages, and veal crates in the U.K. and the E.U. The agency has conducted field trials with focus groups that have said they would like to see antibiotics removed from the food chain.

Specially branded products, claiming to be derived from animals raised under more humane conditions, are being developed. Freedom Foods in the U.K. were developed seven years ago by the Royal Society for the Prevention of Cruely to Animals (RSPCA), and now represent nearly 25% of Britain's animal-based food products. The U.S. has its first such product line, Free Farmed, introduced last year, and includes du Bré pork products from Quebec. In Canada, Manitobans have Winnipeg Humane Society Certified products on their grocery shelves. Though still a small, North American niche market at this point, these product lines may grow if consumers become more concerned about animal welfare issues. The fast-food giants, McDonald's, Burger King, and Wendy's, recently announced policies that, if implemented, will specify how the animals from which company food products are made are reared and slaughtered. McDonald's Corporation, headquartered in Illinois, told American pork producers it expects within five years to buy only meat raised without hormones and antibiotics (*Western Producer*, February 15, 2001).

Legal/statutory issues

Any regulatory actions related to risk management and antimicrobial resistance that are considered by Health Canada must be consistent with Canadian laws and regulations. The objective of the regulatory policy of the Government of Canada is, "To ensure that use of the Government's regulatory powers results in the greatest net benefit to Canadian Society"(9). It states that "Canadians view health, safety, the quality of the environment, and economic and social well-being as important concerns. The Government's regulatory activity in these areas is part of its responsibility to serve the public interest."

The policy requires that federal regulatory authorities ensure that:

1. Canadians are consulted, and that they have an opportunity to participate in developing or modifying regulations and regulatory programs;
2. they can demonstrate that a problem or risk exists, federal government intervention is justified, and regulation is the best alternative;
3. the benefits outweigh the costs to Canadians, their governments, and to businesses. In particular, when managing risks on behalf of Canadians, regulatory authorities must ensure that the limited resources available to government are used where they do the most good;
4. adverse impacts on the capacity of the economy to generate wealth and employment are minimized and no unnecessary regulatory burden is imposed. In particular, regulatory authorities must ensure that:
    a. information and administrative requirements are limited to what is absolutely necessary and that they impose the least possible cost;
    b. the special circumstances of small businesses are addressed; and

    c. parties proposing equivalent means to conform with regulatory requirements are given positive consideration.
5. international and intergovernmental agreements are respected and that full advantage is taken of opportunities for coordination with other governments and agencies; and
6. systems are in place to manage regulatory resources effectively. In particular, regulatory authorities must ensure that:
    a. the Regulatory Process Management Standards are followed;
    b. compliance and enforcement policies are articulated, as appropriate; and
    c. resources have been approved and are adequate to discharge enforcement responsibilities effectively and to ensure compliance where the regulation binds the government.

Federal regulatory authorities are required to meet Regulatory Process Management Standards (10). These standards require that authorities identify the problem that requires government intervention; that alternative regulatory solutions are analyzed; that the benefits of the regulatory requirements are greater than the costs; that no unnecessary regulatory burden, *i.e.*, red tape, is imposed; and that there is intergovernmental coordination, an implementation plan, timely and thorough consultation with interested parties, and that there are methods to communicate the new regulations to stakeholders.

The federal government is faced with many issues requiring international collaboration, either because of restrictions involving international trade agreements, *e.g.*, the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Agreement (NAFTA), or because collaboration with regulatory authorities in other countries may be advantageous (11). Regulators are urged to be proactive in international harmonization in the interests of reducing non-tariff trade barriers, the costs of gathering test data, and the advantage of the spin-off benefit of improving domestic regulation. In Canada, the efficiency and effectiveness of regulation can be increased if there is appropriate mutual recognition, especially when consumer perception of risk is low or there is confidence in international standards; if we are selective in defining partners, *e.g.*, countries with standards at least as high as Canada's; if we agree to test protocols; if we make an active contribution to the knowledge pool; and if we share databases (11).

Risk analysis practices

Health Canada scientists and others have conducted assessments of a variety of human health risks related to food and water safety (12-14). To the knowledge of this committee, a risk assessment on antimicrobial resistance in Canada has not been done. Health Canada first published a framework for risk assessment and risk management in 1993 and revised it in 2000 (15). This initiative occurred in response to criticisms arising from the Krever Commission of Inquiry on the Blood System in Canada, directed towards the decision-making process employed by Health Canada. The "Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks," articulates several major underlying principles, (15):

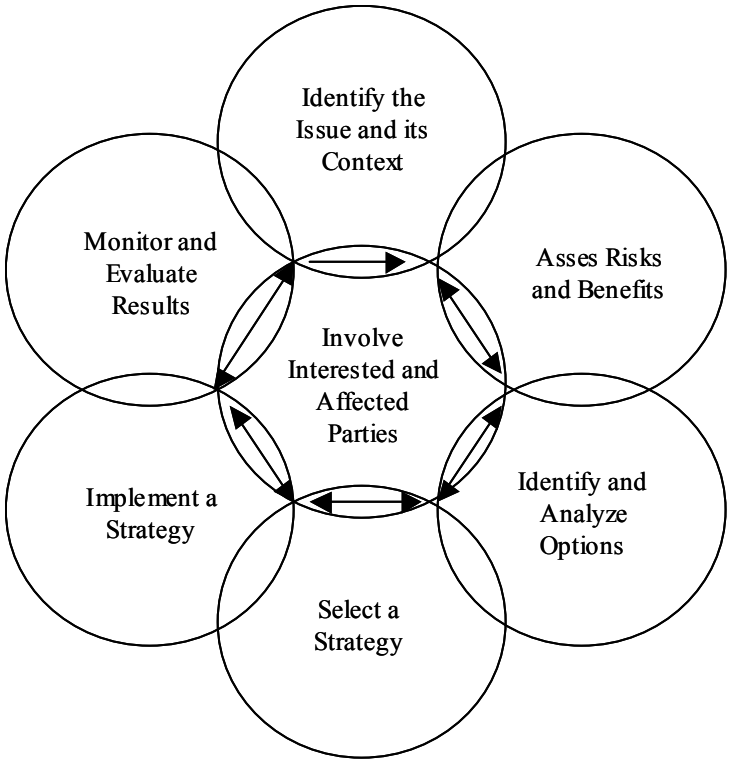
- maintain and improve health as the primary objective;
- involve interested and affected parties;
- communicate in an effective way;
- use a broad perspective;
- use a collaborative and innovative approach;
- make effective use of sound, scientific advice;

- use a “precautionary” approach;
- tailor the process to the issue and its context;
- clearly define roles, responsibilities, and accountabilities; and
- strive to make the process transparent.

The framework lays out the necessary steps in the decision-making process, including issue or hazard identification, risk/benefit assessment, identification and analysis of management options, strategy adoptions, implementation and follow-up. Figure 6.1 illustrates the essential components of the decision-making framework and emphasizes the interconnectedness of all stages of the risk analysis process. The figure also emphasizes the need for these analyses to be iterative; as new information is obtained there should be enough flexibility to re-conduct risk analyses and reconsider risk management options. The framework also includes comprehensive discussion of the need for socio-economic analysis, public involvement, and development of health-based outcomes measures. The approach outlined in this document is similar, conceptually, with approaches used in other countries, including that described in the “United States Presidential Commission/Congressional Commission on Risk Assessment and Risk Management,” although there are some important differences (1).

The recent “Report of the Committee on the Drug Review Process of the Science Advisory Board to Health Canada” also contains information and recommendations relevant to effective risk analysis of veterinary drugs (16). Although focused on human drugs, the report emphasizes the need for transparency throughout the approval process and the desirability of harmonization with other countries, as long as the health and safety of Canadians are not compromised.

Figure 6.1: Decision-making framework (15)



Excellent and comprehensive reviews of risk analysis in Canada and expert advice on government science and technology issues are available in "Managing Health Risks from Drinking Water: A Background Paper for the Walkerton Enquiry," (17) and "Science Advice for Government Effectiveness (SAGE)," (18) respectively.

Risk analysis practices in other countries

United States

Many of the principles and practices of risk analysis were developed in the U.S. A number of documents have been published describing applications to the environmental, chemical, and food safety fields (1,5). The FDA "Framework Document" was published in 1998 and includes the essential components of a qualitative risk assessment process (19). It provides for categorization of drugs based on their importance to human health and potential for human exposure to any resistant bacteria that may develop from the use of antimicrobials in animals.

In 1999, the FDA prepared and publicly presented a "Draft Risk Assessment on the Human Health Impact of Fluoroquinolone Resistant *Campylobacter* Associated with the Consumption of Chicken" (20). It is an attempt to estimate, in quantitative terms, the public health risk in one year from resistant foodborne pathogens due the use of antimicrobials in food-producing animals. Within the assessment, a mathematical model was developed that related the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* infections in humans to the prevalence of fluoroquinolone-resistant *C. jejuni* in chickens, which is a major source of *C. jejuni* infection in the U.S. Using data from epidemiological studies and the FOODNET surveillance system in the U.S., the model estimated the most likely number of people sick with resistant *Campylobacter* infections, and estimated the possible range of fluoroquinolone-resistant *C. jejuni* infections that occur in one year in the U.S., as well as which are treated with fluoroquinolones by physicians.

In 2000, the FDA extended its risk assessment to risk management with publication of "An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-Producing Animals" (21). It identifies the concept of a resistance threshold in humans beyond which the risk of illness in people is no longer acceptable, and describes in detail a proposed methology for determining such thresholds. These concepts have been discussed and critiqued at public meetings. The FDA, however, has not yet published its final guidelines on the use of thresholds.

In 1989, the National Research Council (NRC) Institute of Medicine published a risk assessment entitled "Human Health Risks with the Subtherapeutic Use of Penicillin and Tetracyclines in Animal Feed" (22). This assessment used methods similar, conceptually, to the more recent FDA assessment. The former assessment focused on the annual number of human fatalities attributable to resistance in *Salmonella* infections from in-feed medications.

Europe

In July 1999, the European Medicines Evaluation Agency (EMEA) Committee for Veterinary Medicinal Products published a qualitative risk assessment of *Salmonella* Typhimurium and the quinolone/fluoroquinolone class of antimicrobials in the E.U. (23). Specifically, the

assessment addressed the following question: "What is the risk of adverse human health effects consequent upon the development of antibiotic resistance to (fluoro)quinolones in *S.* Typhimurium which is due specifically to the use of (fluoro)quinolones as veterinary medicines in farm livestock?" A number of potential risk pathways were examined, with the result that the probability of adverse health effects was considered low, but with a high degree of uncertainty overall.

United Kingdom

The U.K. has had more than its share of food safety crises. It has recently reviewed its risk procedures and use of expert advisory groups (24, 25). In essence, these reviews highlight the varied approaches that exist in risk practices associated with food safety and the need to closely link the essential stages of risk analysis (communication, management, and assessment). The reviews noted improvements in the openness and accessibility of U.K. risk procedures, but stated that communications could be better. It was emphasized that distinctions between voluntary and involuntary risks and the needs of vulnerable groups required greater recognition. A number of best practices for committees advising the government on risk were also laid out.

Office International des Epizooties

The Office International des Epizooties (OIE) ad hoc group on antimicrobial resistance published a draft set of guidelines entitled "Risk Analysis Methodology For The Potential Impact On Public Health Of Antimicrobial Resistant Bacteria Of Animal Origin" (26). It contains detailed descriptions of the principles of risk analysis, and a general description of good risk analysis practices related to antimicrobial resistance.

The "precautionary principle"

The precautionary principle stipulates that risk reduction actions should not await scientific certainty (18). The E.U. interpretation of the precationary principle presupposes there could be negative effects from a process or practice. If, after scientific assessment, there remains sufficient uncertainty of the risk, it warrants precautionary action (27). The decision to act or not *i.e.*, take risk management action, often weighs the political consequences of each option. In theory, the precautionary principle is consistent with qualitative risk analysis, however other countries outside of the E.U. are suspicious that the precautionary principle could be used in ways that are inconsistent with existing trade agreements. Further information on the Government of Canada's principles for precautionary measures can be found in a discussion document published in Septmeber, 2001 (28).

Science-based policy development: weighing the evidence

Scientists who have studied the question generally agree that antimicrobial drug use in food animals can select for resistant bacteria, and that some of these resistant bacteria can be transferred to humans. However, the scale or extent of this process, and its full impact, have been difficult to assess. The committee was impressed, however, by the evidence-based approach taken by the Australian Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) in its literature review (29). As a result, it decided to borrow extensively from the JETACAR approach and information. The AMR committee frequently referred to

JETACAR documents when weighing the evidence on the effect of antimicrobial drug use in food animals on antimicrobial resistance in human bacterial pathogens in Canada (29,30).

Assumptions

Based on the evidence available, the committee agrees with the following assumptions made by JETACAR:

1. Epidemiological assumptions
The major food-producing animals are the greatest source of non-typhoidal *Salmonella*, *Campylobacter jejuni*, and shiga-toxin producing *Escherichia coli*. The main route for transmission of these serious, enteric pathogenic bacteria is through the food chain. Other less virulent enteric commensal bacteria of animals, including various *Enterococcus* species, also reach people through the food chain. Intensive farming promotes transfer and re-infection of enteric bacteria among animals and their environment. There are other routes besides the food chain by which resistant bacteria can reach humans from animals (*e.g.*, direct contact with infected animals, water, environmental contamination), but these are probably less important than the food chain.

2. Bacterial resistance assumptions
Bacteria have mechanisms for mutational genetic change to antimicrobial resistance, as well as ways to transfer this resistance among unrelated bacteria. There is a vast reservoir of genetic bacterial resistance factors in animal-associated bacterial populations and the environment of these animals, and a great capacity for transfer of resistance. Exposure of animals to antimicrobial drugs selects for the emergence of resistant bacteria and for their subsequent amplification. Once acquired, antimicrobial resistance may only slowly be lost. Efficient mechanisms exist in bacteria for the accumulation of multidrug resistance over time.

Weight of evidence approach

In the complex world of medicine, it may be hard to demonstrate a cause-and-effect relationship between events. For example, demonstration of the link between cigarette smoking and lung cancer has been documented by well-designed case-control studies from many centres rather than by more direct studies. In a more direct study, for example, randomly selected people might be made to smoke 40 cigarettes a day for 30 years, while a randomly selected control group would be denied access to cigarettes. Since such studies are totally unethical, medicine has developed different criteria to assess the quality of evidence for the association between events. One such system, the Australian National Health and Medical Research Council Quality of Evidence Rating System, is shown in Table 6.1.

On this scale, Rating I represents the highest possible level of evidence. For antimicrobial resistance, the highest level of evidence cannot be expected to exceed Rating III, because of the near impossibility of performing randomized, controlled studies that examine horizontal resistance transfer. For perspective, the current evidence for the association between smoking and lung cancer is rated as III-2.

The committee adopted the Australian National Health and Medical Research Council Quality of Evidence Criteria (Tables 6.1 and 6.2), and the modifications by the JETACAR literature review panel when assessing the evidence during the preparation of answers to the following four critical questions:

1. *Does administration of antimicrobial drugs to animals result in the emergence of antimicrobial-resistant bacteria?*
2. *Do these resistant bacteria spread from animals to humans?*
3. *Do these resistant bacteria cause disease in humans?*
4. *Do the resistance genes in these bacteria spread to human pathogens?*

Table 6.1: Australian National Health and Medical Research Council Quality of Evidence Rating System and modification by JETACAR to review evidence of the adverse impact of antimicrobial drug use in food animals on resistance in human bacterial pathogens (reprinted from 29).

NHMRC rating	Source of evidence	Modification for JETACAR review
I	Systematic review of all relevant randomized control trials	Not applicable
II	At least one properly designed randomized controlled trial	Experimental controlled studies of *in vivo* exposure to antimicrobial drugs
III-1	Evidence obtained from well-designed, non-randomized controlled trials	Broad-range studies showing strain concordance of resistance determinants or clonality among animal, food, and human isolates (Some experimental studies and controlled studies also in this category)
III-2	Evidence from well-designed cohort or case-control analytic studies, ideally from more than one research centre	Cohort evidence of resistance development in defined populations with different exposure characteristics (*e.g.*, comparisons of country-wide data or farm cohort comparisons
III-3	Evidence obtained from multiple time series with/without the intervention. Dramatic results in uncontrolled experiments	Development of resistance over time in the same population after change in exposure conditions or introduction of a new agent
IV	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	As described

The committee added to the JETACAR "quality of evidence for human health effects" by attempting to assess, qualitatively, the magnitude of such effects. The committee also used (and in some cases adapted) the FDA "Framework Document" qualitative classification system of drug importance to human health and potential for spread of resistance to humans (20).

Risk assessment — classification of human health risk of antimicrobials used in food animals

A variety of methods may be used to assess resistance risk, including description and enumeration of documented cases of human illness, analysis of disease data from resistance surveillance programs, extrapolation from animal experiments, or use of models of human exposure and disease (31). Careful study of naturally occurring illness in humans is the traditional, and perhaps most reliable method; however, it is severely constrained in many situations by the limits of our technical ability to correctly correlate illness with exposure to hazards, *e.g.*, resistant bacteria arising from antimicrobial treatment of food animals. Scientific data for risk assessments may be assembled from a variety of sources, including published scientific literature, government reports, or from industry.

Committee analysis of resistance risks

Using committee expert opinion and JETACAR literature review information, the committee made qualitative estimates of factors important to estimating human health resistance risks for a few selected drugs representing classes of importance to human and/or veterinary medicine. These examples are intended to show the types of information that should be used in analyzing risk, to give an indication of gaps in knowledge and uncertainties that must be contended with and to show the difficulties encountered in balancing risks and benefits.

Table 6.3 shows the committee's assessment of the importance of each selected drug class to human health, the degree to which resistance occurs in zoonotic enteropathogens or commensal bacteria, and evidence of resistance impact on human health. By summing the semi-quantitative information in each column, the committee arrived at a total subjective "score" for resistance impact in humans. It should be emphasized that this subjective score is relative, not absolute. In classical risk assessment terms, this information relates to the hazard assessment and hazard characterization steps.

Table 6.4 summarizes the committee's assessment of the potential for spread of resistance to these same classes of antimicrobials. This contributes to the exposure assessment step in the classical model. The aim was to subjectively categorize the potential for spread into high (H), medium (M), and low (L), based on the FDA Framework Document system (31). To accomplish this, the committee assessed the spectrum of drug class activity, doses used (therapeutic or subtherapeutic), the usual routes of administration, range of species for which drugs are licensed in Canada (with the exception of fluoroquinolones and glycopeptides), whether the drugs are administered to individual animals or groups, and the committee's estimate (in the absence of national drug-use surveillance data) of the likely proportion of animals or herds/flocks treated with these drugs in Canada.

In Table 6.5, the committee presents some of the socio-economic information that regulatory authorities could use in decision-making, specifically subjective estimates of the potential beneficial effects of antimicrobials. For the purposes of this exercise, the committee did not attempt to summarize some of the other socio-economic information that could be used in decision-making, including, but not limited to, animal welfare considerations and quantitative economic impacts.

Table 6.2: Quality of evidence rating using Australian National Health and Medical Research Council scale for evidence (from 29).

Bacterial pathogen	Animal drug(s) of concern (drug class)	Human drug(s) of concern	Q1. Development of resistance after exposure?	Q2. Spread from animals to humans?	Q3. Resistant animal clones cause disease in humans?	Q4. Horizontal transfer of resistance into human pathogens?
			Quality of evidence rating			
Enterococcus spp.	Avoparcin (Glycopeptide)	Vancomycin	Yes (III-2)	Yes (III-2)	Yes (IV)	Yes (III-1)
	Tylosin, Spiramycin, Kitasamycin, Oleandomycin (Macrolide)	Erythromycin, lincosamides	Yes (II) (tylosin)	Yes (III-2)	Unknown	Yes (III-1)
	Virginiamycin (Streptogramin)	Pristinamycin Quinipristin/ dalfopristin	Yes (III-2)	Yes (IV)	Unknown	Unknown
Escherichia coli	Noursethricin	No drug of this class	Yes (III-2)	Yes (III-3)	Unknown	Yes (IV)
	Apramycin (Aminoglycoside)	Gentamicin, Tobramycin	Yes (III-2)	Yes (IV)	Unknown	Yes (IV)
Campylobacter jejuni	Oxolinic acid, Fluoroquinolone	Ciprofloxacin, nalidixic acid, norfloxacin	Yes (II)	Yes (III-2)	Yes (III-2)	Rare (?)
Salmonella serovars (multi-resistant)	Multiple drug classes	Multiple drug classes	Yes (III-3)	Yes (III-3)	Yes (III-3)	Yes (IV)

Finally, Table 6.6 summarizes information from previous tables, including scores for human health impact, potential for spread of resistance, and total benefits of antimicrobial use. This is the sort of information that can be used to qualitatively weigh benefits and risks as an aid in decision making. For example, in the committee's judgement, glycopeptide use would have high potential for human health impact, high potential for spread of resistance, and moderate potential for benefit. The committee does not believe that the benefits outweigh the risks for the glycopeptide class of growth promoter. Conversely, the committee believes that ionophores have low potential impact on human health (none are used in humans and cross-resistance selection has not been shown), high potential for spread of resistance, and high potential benefit (as both growth promoters and coccidiostats). Therefore, the committee believes that in this case the benefits outweigh the risks. The situation for the other drug classes listed in the tables (aminoglycosides and fluoroquinolones), and drugs not listed, is more complex and merits more detailed analysis.

The information presented in Tables 6.3 to 6.6 is necessarily a simplification of complex phenomena; the committee made no attempt to explicitly account for all of the factors that affect resistance, nor the innumerable uncertainties that exist in these data. The data presented should not be viewed as fact, but as the committee's best estimates based on their collective knowledge of the scientific literature and experience in the field. The committee trusts this information is useful for communication purposes, but in practice, regulatory decision-making should involve more thorough review of the scientific literature, consultation with affected groups, more detailed analysis of the risks posed, and weighing of the scientific and non-scientific factors on a drug-by-drug basis. Nevertheless, the scientific evidence will probably never be entirely complete, and decisions will have to be made on the basis of imperfect information and updated as new information becomes available.

Analysis: managing resistance risks

The responsibility of managing the risks associated with antimicrobial resistance in Canada does not rest solely with Health Canada; provincial governments, veterinarians, food-animal producers and pharmaceutical companies have roles to play. However, Health Canada has special regulatory responsibilities that are particularly important in managing risks from antimicrobial uses in animals. The committee believes that sound regulatory policy is the most important mechanism for protecting public health in this area. In formulating such policy, Health Canada must make some difficult and contentious decisions, for example, whether to permit the sale, for use in animals, of certain new or existing antimicrobials of critical importance to humans; the use of antimicrobial growth promoters; the sale of non-prescription antimicrobials; and the extra-label use of antimicrobials by veterinarians.

The principles of wise decision-making in the public health sector are not new to Health Canada. The "Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks" (15) is an excellent generic vision for risk analysis and decision-making. It is designed to protect Canadians and is consistent with risk analysis principles adopted in other countries. There is no evidence, however, that this framework is being applied as it should be to the risk of antimicrobial resistance in human pathogens that may stem from the use of antimicrobials in animals. Health Canada should explore and adopt a variety of methods for identifying, analyzing, and managing resistance risks.

Table 6.3: Committee assessment of weight of scientific evidence of resistance impact on human health for selected drugs.

Antimicrobial drug class (example drugs used in food animals)	Evidence of resistance impact on human health (quality of evidence using Australian National Health and Medical Research Council scale)				Impact on Human Health			
	A	**B**	**C**	**D**	**E**	**F**	**G**	**Sum(A–G)**
	Development of resistance after exposure to drug [a]	Spread from animals to humans	Resistant animal clones cause disease in humans	Horizontal transfer of resistance into human pathogens	Importance of drug class in human medicine (example drugs used in humans)	Degree of resistance in zoonotic Gram-negative enteric pathogens	Degree of resistance in commensal or non-enteric bacteria	Combined impact and evidence score (subjective)
Aminoglycoside (gentamicin, neomycin)	+++ (*Salmonella, E. coli*) III-2	++ (IV)	++ (IV)	?	++ (Gentamicin) (IV)	++ (*Salmonella*) (IV)	++ (*E. coli*) (IV)	M
Fluoroquinolone [b] (enrofloxacin)	+++ (*Campylobacter)* (II)	+++ (III-2)	+++ (III-2)	?	+++ (Ciprofoxicin) (IV)	+ (*Campylobacter*, *Salmonella*) (IV)	+ (*E. coli*) (IV)	H
Glycopeptide [b] (avoparcin)	+++ (*Enterococcus*) III-2	+++ III-2	+++ IV	+++ III-1	+++ (Vancomycin) (IV)	-	+++ VRE (IV)	H
Ionophore (monensin)	+	?	?	?	-	-	?	- or L

[a] Columns A-G: +++= high; ++ = medium; ++ = low; - none

[b] No fluoroquinolones or glycopeptides are currently licensed for use in food animals in Canada, but they are important internationally

Table 6.4: Committee assessment of potential for spread of resistance (quality of evidence = IV using ANHMRC scale)

Antimicrobial drug	Spectrum (narrow or broad)	Dose	Route of administration	Average duration of treatment	Approved for use in animal species in Canada[a]	Growth promotion (GP), group (GT) or individual (IT) treatment	Proportion of animals / herds treated	Combined potential for spread score (subjective sum of other columns) (H, M, L)[b]
Aminoglycoside (gentamicin, neomycin)	Broad	Therapy	Parenteral	<1 week	Pi, Ca,T,Ch,H	IT, GT	<1%	L (M for group tx (GT))
Fluoroquinolone (enrofloxacin)[c]	Broad	Therapy	Parenteral, oral	<1 week	None in Canada	IT, GT	<1%	L (M for GT)
Glycopeptide (avoparcin)[c]	Narrow	Growth promotion	Oral	<4 weeks	None in Canada	GP	None in Canada	H (when used)
Ionophore (*e.g.* monensin, salinomycin and others)	Narrow	Growth promotion, coccidiostat	Oral	<8 weeks	Ch, T, C, Sw	GP, GT	<80%	H

[a] C = cattle, Sw = swine, Ch = chicken, T = turkey, Bi = bird, Fi = fish, H = horse, Sh = sheep, G = goat, Br = breeder, Brl = broiler, Pi = piglets, Du = duck, G = geese

[b] Adapted from the FDA "Framework Document" (31) classification for potential for spread: H= high; M = medium; L = low

[c] No fluoroquinolones or glycopeptides are currently licensed for use in food animals in Canada, but they are important internationally

Table 6.5: Subjective estimation of antimicrobial benefits for antimicrobial resistance regulatory decision-making

Antimicrobial drug	Beneficial effects			
	A	B	C	(Sum A–C)
	Feed or growth efficiency [a]	Disease prophylaxis or control	Therapy	Total benefits (subjective combined score) [b]
Aminoglycoside (Gentamicin, neomycin)	-	++	++	M
Fluoroquinolone [c] (enrofloxicin)	-	-	+++	H
Glycopeptide (avoparcin)	+++	-	-	M
Ionophore (monensin, salinomycin and others)	+++	+++ (coccidiostat)	-	H

[a] Columns A-C: +++= high; ++ = medium; + = low; - none
[b] Classification for potential for benefits: H= high; M = medium; L = low
[c] No fluoroquinolones or glycopeptides are currently licensed for use in food animals in Canada, but they are important internationally

Table 6.6: Summary of estimates of impact on human health, potential for spread and benefits

Antimicrobial drug	Impact on human health (combined impact and evidence score from Table 6.3)	Potential for spread (combined score from Table 6.4)	Total benefits (combined score from Table 6.5)
Aminoglycoside (Gentamicin, neomycin)	M	L (M for group tx (GT))	M
Fluoroquinolone (enrofloxicin)	H	L (M for GT)	H
Glycopeptide (avoparcin)	H	H (when used)	M
Ionophore (monensin, salinomycin and others)	- or L	H	H

[a] H= high; M = medium; L = low

Some methods may be quite simple and employ traditional methods (*e.g.*, use of expert scientific opinion); some may be qualitative, others quantitative; some may involve modeling the farm-to-fork continuum; others may be based on resistance and drug use surveillance. A scan of the scientific literature and practices in other countries reveals that there is no "right" method or set of methods for assessing resistance risks. Health Canada should collaborate with sister agencies in other countries and the scientific community to develop better risk analysis methods.

Before implementing new regulatory action, Health Canada should consider the magnitude of the resistance problem, the risks and benefits associated with antimicrobial use in Canada, the impact of any interventions on society, and the best use of the resources it has available. It should also consult with Canadians and effectively communicate the resistance risk issues, its process for assessing and exploring risk management options, and the rationale for its decisions. These would be consistent with Canadian regulatory policy.

Unfortunately, there are resistance risks associated with all uses of antimicrobials, and Health Canada must decide which risks are acceptable for the benefits gained. Health Canada cannot simply arbitrarily stop approving new antimicrobial applications on the grounds that resistance risks exist. Animals will continue to become sick, and with this the need for effective treatment to protect animal welfare and the financial investment of producers also will continue. The lack of approved, efficacious antimicrobials is a prime motive for extra-label use of drugs, a practice the committee believes should be applied more sparingly. The committee agrees with the Australian JETACAR, which concluded that antimicrobial uses in animals should be reserved to situations where benefits are clear and substantial.

The committee believes that benefits are most clear and substantial when antimicrobials are used for therapy under the conditions of prudent use and under veterinary prescription. Benefits are less clear and substantial when these drugs are used for prophylaxis (especially when such use becomes routine) or growth promotion, where benefits are almost entirely economic. To justify continued use, these benefits must outweigh resistance risks plus associated costs (*e.g.*, veterinary input, drug costs, residue prevention). Considering the information described in this and previous chapters, the committee believes that resistance risk to human health increases when drugs are important to human health or when they select for resistance to drugs important to human health; when treatment is administered to entire groups of animals; when treatment is long in duration or low in dose; and when treatment is widely used in the industry and in multiple species. Non-treatment factors also affect risk, for example, the intensity of animal rearing, mixing of animals from multiple sources, and use of other means to prevent disease (*e.g.*, vaccines, biosecurity).

In formulating its recommendations throughout this report, the committee tried to apply good risk analysis principles. However, the committee was neither prepared nor able to conduct thorough risk analyses of all antimicrobial uses in animals. It was prepared, however, to use its expertise to show the type of information required to qualitatively assess risks of specific drugs (as described earlier). Properly analyzing resistance risks is a daunting task; Health Canada will need to prioritize its efforts in

this area as it builds capacity. The committee believes that highest priority should be placed on assessing risks of new drug applications. Re-evaluating existing drug claims should focus on drugs of substantial importance to human health and drugs used in a manner that enhances the selection and spread of resistance, especially long-term, in-feed uses.

The committee had special concerns about growth promoters. Several growth promoters used in Canada are the same drugs or are related to drugs used in humans, or can select for resistance to drugs used in humans. Growth promoters account for a considerable amount of the total antimicrobial exposure. They are used for long periods of time, given to entire groups of animals, often given in low doses, and are potentially given to large numbers of herds or flocks. In addition, they are not used under veterinary prescription or to treat infections in animals. Some members believed that growth promoters facilitate animal husbandry practices that are unhealthy and therefore questionable on welfare grounds. Still others were concerned about the economic impact on producers and international trade implications of changes in growth promoter policy. Thus, the committee felt it should consider risks and benefits associated with this practice and make a special recommendation.

Various options were identified and discussed. The committee reached consensus but not unanimity. A majority favoured a recommendation modified from other reports (JETACAR, WHO):

> "Evaluate antimicrobials for growth promotion or feed efficiency using sound risk analysis principles and rapidly phase out antimicrobial claims not fulfilling the following criteria: demonstrably effective; involving products rarely, if ever, used in human therapy; and not likely to impair the efficacy of any other prescribed antimicrobial for human infections through the development of resistant strains."

Other options discussed and favoured by a minority were:

> "Antimicrobials should not be used for growth promotion."; and
> "Antimicrobials to promote growth and feed efficiency should not be used unless they are demonstrably effective; they involve products rarely, if ever, used in humans; and they are not likely to impair the efficacy of any other prescribed antimicrobial for animal or human infections through the development of resistant strains. Products not fulfilling these criteria should be rapidly phased out, by legislation if necessary."

The committee discussed whether to include a timetable for implementing this recommendation, but decided against it because the time needed to undertake appropriate risk analyses is unknown. The committee also discussed whether the importance of drugs to animal health should also be included as a criterion for continued use and considered pros and cons (Table 6.7). The decision was taken to not recommend inclusion of this criterion.

Table 6.7: Pros and cons for including importance to animal health as a criterion in evaluating resistance risks from growth promoters.

Importance to Animal Health	
Pros	**Cons**
Use of the same drugs for growth promotion and therapy may lead to high resistance (*e.g.*, tetracyclines, penicillins) and loss of therapeutic efficacy for some drugs in some species	Beyond the committee's mandate
Forces the use in animals of more expensive, newer drugs of greater importance to human health	Not considered an important issue by some
Fewer new drugs are expected on the market, therefore we need more prudent use of the ones we have	Would effectively remove most or all claims

Conclusions

Some degree of resistance risk exists whenever antimicrobials are used, because antimicrobials can select for resistant bacteria and some of these resistant bacteria can be transferred to humans and cause illness. However, this does not always, or even usually, occur. Resistance risk (the probability and impact of antimicrobial resistance on human health) increases when the drugs used in animals are important to human health, or they select for resistance to drugs important to human health, when treatment is administered to entire groups of animals, when treatment is long in duration or low in dose, when treatment is widely used in the industry and in multiple species, and when conditions are favourable for resistant infections to spread among animal and human populations.

Resistance risks can be at least partially controlled or managed, and a variety of management strategies are available. Choosing the optimal strategy to manage resistance risk (including no action if appropriate) requires careful assessment of the nature of risk, the cost and effectiveness of the management options available, consideration of socio-economic issues, and effective communication.

Antimicrobial uses in animals should be reserved for situations where benefits are clear and substantial.

Recommendations

14. Employ sound risk analysis methods to manage the risks associated with antimicrobial resistance.
15. Improve the transparency of risk assessment and management related to antimicrobial resistance. Explain what is known about the risks, the extent and limits of scientific knowledge, how uncertainty is taken into account, and how human health is to be protected.
16. Conduct risk-based evaluations of the potential human health effects of all uses of antimicrobial drugs in food-producing animals, including currently approved products. In the evaluation of currently approved products, give priority to those products considered most important in human medicine (*e.g.*, third generation cephalosporins, streptogramins, macrolides). Characterization of the risk should include consideration of the importance of the drug or members of the same class of drug to human medicine, the potential exposure to humans from antimicrobial resistant bacteria and their resistance genes from food animals, as well as other appropriate scientific factors. Those antimicrobials judged to be essential for human medicine should be restricted, and their use in food animals should be justified by culture and susceptibility results.
17. Evaluate antimicrobials for growth promotion or feed efficiency using sound risk analysis principles and rapidly phase out antimicrobial claims not fulfilling the following criteria: demonstrably effective; involving products rarely, if ever, used in human therapy; and not likely to impair the efficacy of any other prescribed antimicrobial for human infections through the development of resistant strains.

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CHAPTER

7

Impacts of antimicrobial resistance on animal health[a]

Key Points

- **Antimicrobial resistance is regularly observed in bacteria that cause disease in animals (animal pathogens)**
- **Some bacteria (*e.g. Salmonella* Typhimurium DT 104), are important pathogens of both animals and humans (zoonoses) and are resistant to multiple antimicrobials**
- **Resistance in animal pathogens may lead to increased morbidity and mortality in animals, to use of more expensive drugs, to use of drugs important in human medicine, or to extra-label use of drugs**
- **Resistance in important animal pathogens (*e.g. Pasteurella, Actinobacillus, Escherichia coli, Aeromonas*) varies widely from near 0% to 90%, depending on the antimicrobial tested, host species of animal, and geographical location**
- **Ideally, the decision to administer antimicrobial therapy should be supported by the appropriate diagnosis and the choice of antimicrobial drugs should be validated by laboratory analysis**
- **Canada lacks a coordinated system to monitor antimicrobial resistance among animal pathogens**

Other chapters in this report emphasize human health impacts of resistance. This chapter departs from that theme to discuss animal health impacts. This is an important topic in its own right, but it also affects human health because resistance in animal pathogens leads to use in animals of newer antimicrobials that frequently are important to humans. The development of antimicrobial resistance is a growing concern with regard to both animal and zoonotic bacterial pathogens, especially when multidrug resistance is present. This resistance could drastically reduce our capacity to control certain microbial infections.

Antimicrobial resistance in veterinary medicine

General principles of antimicrobial resistance were presented in Chapter 2. The focus here is on clinical aspects in veterinary medicine. Antimicrobial resistance refers to

[a] With contributions from André Broes, Robert Higgins, Serge Lariviere and Serge Messier

the loss of susceptibility by a pathogen to the effect of an antimicrobial to the point where cure or *in vivo* control, *i.e.*, control in the living animal, can no longer be obtained with the drug. Laboratory tests of susceptibility to an antimicrobial, *i.e.*, *in vitro* determination of susceptibility, should reflect the actual, or *in vivo*, situation in the animal population. In veterinary medicine, the correlation between the two situations has not been established for most antimicrobials. Interpretation of test results generally is based on data obtained for humans and susceptibility panels ofter contain drugs used in human medicine (e.g. ampicillin). However, the declaration that a strain of bacteria is resistant to a given antimicrobial using *in vitro* testing means that the strain has generally lost "considerable" susceptibility to the drug, often to the point where treatment with the antimicrobial is ineffective.

Bacteria of concern

Three categories of animal bacteria are monitored in veterinary medicine:

1. pathogens specific for animals
2. pathogens for both animals and humans (zoonotic pathogens)
3. harmless bacteria (commensals) that are normally found in animals and that can be used as indicator bacteria. These bacteria also form a pool of resistance genes for pathogens.

A relatively limited number of pathogenic bacteria can cause severe and contagious diseases in animals if no treatments are administered, *e.g.*, *Actinobacillus pleuropneumoniae* in pigs (Table 7.1). Most other bacteria that cause disease are "opportunistic" pathogens that affect only one or a few animals at a time. These bacteria require the presence of certain contributing factors to cause disease *e.g.*, inadequate ventilation in housing, viral infections in the host animal.

Certain pathogens are transferred from animals to humans (zoonoses) or vice versa (Table 7.1). Some, such as *Salmonella* and *Leptospira,* are frequently associated with disease in animals. Others, such as *Campylobacter*, *Listeria monocytogenes*, and *Yersinia enterocolitica*, rarely cause disease in domestic animals.

Indicator bacteria are increasingly being monitored for antimicrobial resistance. *Escherichia coli* and *Enterococcus*, which are normal inhabitants of the gastrointestinal tract of humans, mammals, and birds, are the most frequently studied indicators. Only bacteria that are significantly pathogenic for the animal species cited will be further discussed in this chapter.

Table 7.1: Recognized bacterial pathogens in food-animal species

Bacterial Pathogen	Food Animal Species				Zoonosis
	Fish	Cattle	Poultry	Swine	
Actinobacillus lignieresii		C[a], D			No
Actinobacillus pleuropneumoniae				C, D	No
Actinobacillus equuli		C, D		C, D	No
Actinobacillus suis				C, D	No
Actinobaculum suis				C, D	No
Actinomyces bovis		C, D		C	No
Aeromonas hydrophila	C, D	C, D	C, D	C,D	Yes
Aeromonas salmonicida ssp. salmonicida	D				No
Arcanobacterium pyogenes		C, D		C, D	No
Bacillus anthracis		D		D	Yes
Bacteroides spp.		C, D?		C, D?	No
Bordetella avium			C, D		No
Bordetella bronchiseptica				C, D	Suspected
Brachyspira hyodysenteriae				D	No
Brachyspira pilosicoli				C, D	Suspected
Campylobacter coli			C	C	Yes
Campylobacter fetus ssp. fetus		C, D			Yes
Campylobacter fetus ssp. venerealis		D			No
Campylobacter jejuni		C, D	C, D	C	Yes
Clostridium chauvei		C, D			No
Chlamydia spp., *Chlamydophila* spp.		C,D	C,D	C,D	Yes
Clostridium difficile				C, D	Suspected
Clostridium novyi		C, D			No
Clostridium perfringens type A		C, D	C, D	C, D	Suspected
Clostridium perfringens type C		D		C?, D	No
Clostridium septicum		C, D			No
Corynebacterium renale		C, D			No
Coxiella spp.		C,D			Yes
Dermatophilus congolensis		D			Yes
Enterococcus durans				C, D	No
Enterococcus faecalis		C	C	C	No
Enterococcus hirae				C, D	No
Edwarsiella tarda	C, D				Yes
Erysipelothrix rhusiopathiae			D	C, D	Yes
Escherichia coli		C, D	C, D	C, D	Suspected
Escherichia coli (ETEC)		D		D	No
Escherichia coli (STEC)		C, D	C, D	C, D	No
Escherichia coli (VTEC)		C, D		C, D	Yes
Escherichia coli O157 :H7		C, D			Yes

[a] C: normal flora commensals and/or opportunistic bacteria; D: disease; ?: seldom reported under certain conditions; empty cell: not usually reported

Bacterial Pathogen	Food Animal Species				Zoonosis
	Fish	Cattle	Poultry	Swine	
Flavobacterium columnaris	C, D[a]				No
Flavobacterium psychrophilum	C, D				No
Flexibacter maritimus	C, D				No
Fusobacterium necrophorum		C, D		C, D	No
Haemophilus parasuis				C, D	No
Haemophilus somnus		C, D			No
Klebsiella pneumoniae		C, D			No
Lawsonia intracellularis				D	Suspected
Leptospira spp.		C, D		C, D	Yes
Listeria monocytogenes		C, D	C, D	C, D	Yes
Mannheimia haemolytica		C, D	C, D		Suspected
Moraxella bovis		D			No
Mycobacterium avium group		C		C?, D	Suspected
Mycobacterium avium ssp. paratuberculosis		D			Suspected
Mycobacterium marinum	C, D				Yes
Mycoplasma bovis		C, D			No
Mycoplasma gallisepticum			C?, D		No
Mycoplasma hyopneumoniae				D	No
Mycoplasma hyorhinis				C, D	No
Mycoplasma hyosynoviae				C, D	No
Mycoplasma synoviae			C?, D		No
Nocardia spp.	C, D	C, D			No
Pasteurella multocida		C, D	C, D	C, D	Yes
Pasteurella piscida	D				No
Piscirickettsia salmonis	D				No
Pseudomonas spp.		C, D	C, D		No
Pseudomonas fluorescens	C, D				No
Reimerella anatipestifer			D		No
Renibacterium salmoninarum	D				No
Rhodococcus equi				C,D	Suspected
Salmonella spp	C	D	C, D	D	Yes
Staphylococcus aureus		C, D	C, D	C	Yes
Staphylococcus hyicus		C, D	C, D	C, D	No
Streptococcus agalactiae		D			No
Streptococcus dysgalactiae ssp. dysgalactiae		C, D			No
Streptococcus dysgalactiae ssp. equisimilis		C, D		C, D	No
Streptococcus iniae	D				Yes
Streptococcus suis				C, D	Yes
Streptococcus equi ssp. zooepidemicus		C, D		C, D	No
Streptococcus porcinus				C,D	Suspected
Streptococcus uberis		C, D			No
Ureaplasma spp.		C, D			No

[a] C: normal flora commensals and/or opportunistic bacteria; D: disease; ?: seldom reported under certain conditions; empty cell: not usually reported

Bacterial Pathogen	Food Animal Species				Zoonosis
	Fish	Cattle	Poultry	Swine	
Vibrio anguillarum	C, D				No
Vibrio ordalii	C, D				No
Vibrio salmonicida	C, D				No
Vibrio vulnificus	C, D				Yes
Vibrio woodanis	C, D				No
Yersinia enterocolitica		C		C	Yes
Yersinia pseudotuberculosis				C,D	Yes
Yersinia ruckeri	C, D				No

C: normal flora commensals and/or opportunistic bacteria; D: disease; ?: seldom reported under certain conditions; empty cell: not usually reported

Summary of evidence of resistance problems in animals

Antimicrobial resistance is regularly observed in bacteria from a variety of animal species. Emphasis here is placed on the most important food animals, *i.e.,* cattle, poultry, swine, and fish; however, antimicrobial resistance is also a growing concern in other food-animal species such as sheep and rabbits, and in companion animals such as horses, dogs, and cats.

The significance of acquired resistance depends on the type of antimicrobial and the bacterial species involved (Tables 7.2, 7.3, 7.4 and 7.5). Resistance is an even greater problem in those major pathogens where a certain percentage of isolates show multidrug resistance. Such is the case with *Salmonella* Typhimurium definitive phage type 104 (DT 104), an important pathogen of both animals and humans, and for which animals are the principal reservoir (1).

To control infections in animals caused by multidrug-resistant bacteria, the newest, often more expensive, antimicrobials are needed. This is a cause of great concern, since these costly antimicrobials are often very valuable drugs for treating humans (2).

Evidence from Canada and other countries

Data on antimicrobial resistance in bacteria of animal origin come from either case studies of bacterial infections mainly associated with acute diseases and/or antibiotic therapy problems, or from targeted studies analyzing the susceptibility profiles of a number of isolates of specific bacterial species. This latter category of studies is increasingly being integrated into antibiotic resistance surveillance programs. These programs usually target bacterial pathogens of the respiratory system, digestive system, and mammary gland of dairy cows (3,4).

Pasteurella

In Canada, findings for *Pasteurella multocida* and *Mannheimia haemolytica* (formerly known as *Pasteurella haemolytica*) isolated from the respiratory tract of cattle and/or swine reveal resistance in less than 7% of the isolates to many newer antimicrobials tested, such as ampicillin (*P. multocida*, 0%), ceftiofur (<1%), and the trimethoprim/sulfamethoxazole (TMP/SXT) combination (1–6%) (5,6). On the other hand, resistance to tetracycline is greater than 15% for *P. multocida* (1996–1999) and higher than 50% (1984–1996) for *M. haemolytica*. In the early 1980s, an Ontario study revealed that bovine and porcine *P. multocida* were susceptible to a wide variety of antimicrobials, except sulfas (7).

Regarding European data and considering the technical differences between studies, antimicrobial resistance by bacteria is variable. A study of cattle *Pasteurella* in France found 11% of *Pasteurella multocida* isolates resistant to ampicillin, and 48% resistant to TMP/SXT, while 61% of the *Mannheimia haemolytica* isolates were resistant to ampicillin and 71% resistant to TMP/SXT (8). By contrast, in Sweden, a study found 100% susceptibility to these same antibiotics in *Pasteurella* from calves (4).

Actinobacillus pleuropneumoniae

Several studies have reported antibiotic resistance in *Actinobacillus pleuropneumoniae*, a specific porcine bacterium that causes pleuropneumonia. The resistance observed in the past 20 years has varied from country to country. In many countries, resistance to erythromycin, oxytetracycline, and spectinomycin has been reported (9). In the 1980s, a study of 726 *A. pleuropneumoniae* isolates from Quebec found more than 20% resistance to ampicillin and penicillin and over 40% resistance to tetracycline (10). Less than 4% of the isolates were resistant to TMP/SXT. This study showed that antimicrobial resistance could vary from one serotype to another. From 1993 to 1999, an upward trend in resistance by *A. pleuropneumoniae* isolates to ampicillin/penicillin, tetracycline, and tiamulin was observed in Quebec (6). By 1994 to 1999, resistance to tetracycline had risen above 70%. By contrast, Denmark reported the absence of resistance to all these drugs except tetracycline (11).

Salmonella

The phenomenon of antibiotic resistance by *Salmonella* is being studied in many countries (impacts on human health are discussed in Chapter 2). The findings are usually presented either according to the most commonly found serotypes for a given animal species in the region, or without animal species and/or serotype distinction. In Canada, a retrospective analysis of 1997 data (12), with no distinction of isolate origin, revealed resistance to antimicrobials used by veterinarians: ampicillin (16% of isolates), neomycin (8%), sulfas (22%), and tetracycline (26%). Similarly, an exhaustive study of isolates from turkeys demonstrated significant resistance to gentamicin (26%), neomycin (14%), sulfas (58%), and tetracycline (38%), but only 2% resistance to TMP/SXT (13). In a Prince Edward Island study, *S. heidelberg* isolates of chicken source had predominant resistance to gentamicin, streptomycin, and sulfisoxazole (14).

Table 7.2: Major cattle pathogens and antimicrobial resistance characteristics in Canada

Bacterial Pathogens	Infections	Reported resistance to antimicrobials used for treatments	Level of resistance (estimation)[a]
Clostridium perfringens type B and C	Enterotoxemia		+
Corynebacterium renale	Cystitis, pyelonephritis		-
Escherichia coli (ETEC)	Neonatal colibacillosis	Ampicillin, gentamicin, neomycin, sulfas, tetracycline, trimethoprim-sulfamethoxazole	++
Haemophilus somnus	Infectious thromboembolic meningoencephalitis, hemophilosis, myocarditis, pneumonia, polyarthritis		±
Leptospira	Leptospirosis		-
Mannheimia haemolytica	Pneumonic pasteurellosis	Gentamicin, neomycin, penicillin, sulfas, tetracycline, trimethoprim-sulfa	++
Moraxella bovis	Infectious bovine keratoconjunctivitis		++
Mycobacterium avium ssp paratuberculosis	Paratuberculosis		-
Mycoplasma bovis	Mastitis, pneumonia, polyarthritis	Lincomycin, tetracycline	±
Pasteurella multocida	Pneumonic pasteurellosis	Gentamicin, neomycin, penicillin tetracycline, trimethoprim- sulfa	+
Salmonella	Salmonellosis, septicemia	Ampicillin, gentamicin, neomycin, tetracycline, trimethoprim-sulfa sulfa	++
Staphylococcus aureus	Mastitis	Erythromycin, penicillin, pirlimycin, tetracycline	+
Streptococcus agalactiae	Mastitis	Erythromycin, penicillin, spectinomycin, tetracycline	+
Ureaplasma	Granular vulvitis		±

[a] Legend: +++, >50% resistant isolates; ++, 10–50%; +, <10%; ±, uncertain; -, resistance absent; based on the literature, clinical observations following treatment, and laboratory observations

Table 7.3: Major fish pathogens and antimicrobial resistance characteristics in Canada

Bacterial Pathogens	Infections	Reported resistance to antimicrobials used for treatments	Level of resistance (estimation) [a]
Aeromonas salmonicida ssp salmonicida	Furunculosis	Ormetoprim-sulfadimethoxine, sulfas, tetracycline	++
Flavobacterium columnaris	Columnaris Disease		-
Flavobacterium psychrophilum	Cold Water Disease		-
Renibacterium salmoninarum	Salmonid bacterial kidney disease (BKD)		-
Vibrio anguillarum	Vibriosis	Tetracycline	+
Vibrio ordalii	Vibriosis	Tetracycline	+
Vibrio salmonicida	Cold water vibriosis	Tetracycline	+
Yersinia ruckeri	Enteric red mouth disease		-

[a] Legend: +++, >50% resistant isolates; ++, 10–50%; +, <10%; ±, uncertain; -, resistance absent; based on the literature, clinical observations following treatment, and laboratory observations

Table 7.4: Major poultry pathogens and antimicrobial resistance characteristics in Canada (4)

Bacterial Pathogens	Infections	Reported resistance to antimicrobials used for treatments	Level of resistance (estimation) [a]
Campylobacter spp.	Vibrionic hepatitis	Erythromycin, tetracycline	+ to ++
Clostridium perfringens	Necrotic enteritis		+
Erysipelothrix rhusiopathiae	Erysipelas		-
Escherichia coli	Airsacculitis, colibacillosis,	Ampicillin, ceftiofur, gentamicin, neomycin, tetracycline, trimeth- sulfa	+++
Mycoplasma gallisepticum	Chronic respiratory disease		±
Mycoplasma synoviae	Airsacculitis, infectious synovitis		±
Pasteurella multocida	Fowl cholera		
Reimerella anatipestifer	Infectious serositis		±
Salmonella spp.	Salmonellosis	Ampicillin, ceftiofur, gentamicin, neomycin, sulfas, tetracycline, trimethoprim- sulfa	++
Staphylococcus aureus	Arthritis, septicemia	Penicillin, tetracycline, trimethoprim- sulfa	+

[a] Legend: +++, >50% resistant isolates; ++, 10–50%; +, <10%; ±, uncertain; -, resistance absent; based on the literature, clinical observations following treatment, and laboratory observations

Table 7.5: Major swine pathogens and antimicrobial resistance characteristics in Canada

Bacterial Pathogens	Infections	Reported resistance to antimicrobials used for treatments	Level of resistance (estimation) [a]
Actinobacillus pleuropneumoniae	Pleuropneumonia	Penicillin, spectinomycin, tetracycline, tiamulin, trimethoprim- sulfa, tylosin,	++
Actinobacillus suis	Diarrhea, pneumonia, septicemia	Amoxicillin, penicillin, tetracycline, trimethoprim- sulfa	++
Brachyspira hyodysenteriae	Dysentery	Carbadox, dimetridazole, lincomycin, tiamulin? tylosin	+
Clostridium perfringens type A	Neonatal diarrhea		±
Clostridium perfringens type C	Clostridial enteritis		-
Erysipelothrix rhusiopathiae			-
Escherichia coli (ETEC)	Neonatal and post-weaning diarrhea	Amoxicillin, apramycin, gentamicin, neomycin, trimethoprim- sulfa	+++
Haemophilus parasuis	Arthritis, meningitis, polyserositis, septicemia	Lincomycin, penicillin, tetracycline	+
Lawsonia intracellularis	Proliferative enteropathy		-
Mycoplasma hyopneumoniae	Enzootic pneumonia		+
Mycoplasma hyosynoviae	Polyserositis		±
Pasteurella multocida	Pneumonia, progressive atrophic rhinitis	Penicillin, spectinomycin, sulfas, tiamulin, tetracycline, tylosin, trimethoprim- sulfa	±
Salmonella spp	Salmonellosis	Amoxicillin, apramycin, neomycin, tetracycline, trimethoprim- sulfa	++
Staphylococcus hyicus	Exudative epidermitis	Neomycin, penicillin, tetracycline	++
Streptococcus suis	Meningitis	Penicillin	+

[a] Legend: +++, >50% resistant isolates; ++, 10–50%; +, <10%; ±, uncertain; -, resistance absent; based on the literature, clinical observations following treatment, and laboratory observations

Passive surveillance of *Salmonella* in Quebec has revealed more than 40% resistance to tetracycline by isolates from birds and 80% in 1999 by isolates of porcine origin (6). In the U.S., the National Antimicrobial Resistance Monitoring System (NARMS) tracks enteric bacteria from animals. The 1998 data for *Salmonella* from different animal species show that resistance was more common to tetracycline (38% of isolates), sulfas (32%), and ampicillin (18%). It was less than 5% for apramycin, ceftiofur, and TMP/SXT (15). In Denmark, the DANMAP 2000 report presents findings for three major farm-animal species. The resistance of bovine and porcine

Salmonella to tetracycline, sulfas, and streptomycin was above 20%. In poultry, resistance was below 5%. By contrast, in Sweden, the resistance of animal *Salmonella* was reported to be less than 3% for all the antimicrobial drugs studied (4). The majority of these studies identified the typical multidrug resistance (ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline) of *Salmonella* Typhimurium DT 104 (3, 4, 12, 14, 15).

Escherichia coli

Resistance among pathogenic *Escherichia coli* is reported either according to the serotypes associated with disease in the various animal species or with no distinction of the serotypes involved. Resistance problems in pathogenic *E. coli* from poultry and pigs have been observed. From 1994 to 1998, an increase in resistance of porcine *E. coli* associated with postweaning diarrhoea was noted in Quebec (16). The antimicrobials involved were ampicillin, apramycin, gentamicin, neomycin, and TMP/SXT. In Prince Edward Island, most *E. coli* isolated from calves and pigs with diarrhoea and resistant to TMP/SXT (42%) were also resistant to ampicillin (74%), neomycin (80%), and tetracycline (98%) (17). A significant number of these *E. coli* isolates are now resistant to all antimicrobials approved for the treatment of pigs. This situation is responsible for the increasing number of treatment failures and increased extra-label use of unapproved antimicrobials such as the fluoroquinolone enrofloxacin (18). In Spain, a study of avian septicemic *E. coli* revealed significant resistance to ampicillin (35%), tetracycline (94%), and TMP/SXT (63%) (19). The resistance was 14% for gentamicin and neomycin. The fluoroquinolones tested revealed resistance above 10%. In Denmark, more than 70% of the bovine *E. coli* (F5) isolates were resistant to ampicillin, sulfas, and tetracycline (3). A decrease in resistance to fluoroquinolones was observed for the period 1998 to 2000. This surveillance program also detected increased resistance by isolates of porcine *E. coli* O149 to tetracycline, probably associated with the increased use of this antimicrobial drug from 1999 to 2000. A pattern of multidrug resistance involving ampicillin, nalidixic acid, streptomycin, sulfas and tetracycline has also been observed in 30% of the avian *E. coli* isolates. The O78 serotype accounted for 95% (19/20) of these isolates. In the Swedish program, persistent resistance to streptomycin, ampicillin, and chloramphenicol by porcine *E. coli* isolates has been noted, even though few antimicrobial agents are used in Swedish pig populations (4).

Mastitis staphylococci

The surveillance of mastitis staphylococci includes the monitoring of coagulase-negative *Staphylococcus* isolates and especially of *S. aureus* isolates. The latter organism is considered the most significant pathogen affecting the mammary gland of dairy cows. Most studies assess the susceptibility of *S. aureus* to antimicrobial agents found in intramammary antimicrobial infusions. The susceptibility of *S. aureus* isolates is studied within a particular region or by comparing data from various countries (20, 21). Among other findings, the percentage of *Staphylococcus* isolates resistant to penicillin varies from 5% to 90% according to comparative country data from 1986 to 1988 (21). In Sweden, this resistance was found to be most prevalent in isolates of coagulase-negative staphylococci (21). Cloxacillin has been approved for the treatment of mastitis in Canada for many years, but oxacillin, which is a related antibiotic, is tested instead because it allows for better detection of

methicillin-resistant *S. aureus* (MRSA) strains. Of a total 811 *S. aureus* isolates from 11 countries, 12 isolates exhibited resistance to oxacillin (20). It was found that these isolates did not possess the *mecA* resistance gene as in MRSA of human origin but that their resistance was due to the hyperproduction of ß-lactamases. For all the antimicrobial agents analyzed, there was little variation in the susceptibility observed (minimum inhibitory concentration) from one country to the other. Multidrug resistance of staphylococci, most commonly to penicillin, tetracycline, and sometimes neomycin, has also been observed. With coagulase-negative staphylococci in particular, the multidrug-resistance involves penicillin, erythromycin, and occasionally TMP/SXT (22). This latter Finnish study also reported an increase in the proportion of *S. aureus* isolates resistant to at least one antimicrobial agent, from 37% in 1988 to 64% in 1995. For coagulase-negative staphylococci, the proportion increased from 27% to 50%. The Danish surveillance program has reported that *S. aureus* isolates are susceptible to most antimicrobials (3). The researchers noted that the proportion of *S. aureus* isolates resistant to penicillin dropped between 1996 and 2000. They also reported no oxacillin resistance in these isolates. Similar findings have been reported by researchers in Argentina (23) and the U.S. (24). In summary, resistance in bovine *S. aureus* mastitis isolates is not a significant problem.

Aeromonas salmonicida ssp salmonicida

Aeromonas salmonicida ssp. salmonicida is the etiologic agent responsible for furunculosis in salmonids. Antimicrobial resistance of *A. salmonicida* ssp. salmonicida isolates has been described in a number of studies (25–29). Resistance has been observed with the following antimicrobials: ormetoprim-sulfadimethoxine, oxytetracycline, quinolones, streptomycin, sulphamethoxine, trimethoprim, and trimethoprim-sulfadiazine. Some of these are not approved for the treatment of fish. A Danish study examined patterns of susceptibility in isolates from five countries, including Canada and the United States (25), and found increased resistance to quinolones and tetracyclines. Multiple drug resistance has also been observed in *A. salmonicida* ssp. salmonicida isolates from several countries (25–27,30). One significant problem with comparing findings from the various studies is the lack of standardized susceptibility test techniques with recognized guidelines adapted for bacterial pathogens affecting fish. There is also no surveillance program in the world currently monitoring antimicrobial resistance in these bacteria on a continuous basis.

Analysis: animal health impacts of resistance

The lack of coordinated systems to monitor antimicrobial resistance among animal pathogens in Canada makes it difficult to assess patterns of antimicrobial resistance in these pathogens at a regional, provincial, or national scale to identify changes in resistance over time. There should be a Canadian surveillance network to ensure the management and sharing of data from the various laboratories or even the rapid dissemination of information to veterinarians in the event of the emergence of MDR bacteria.

A surveillance system involving diagnostic laboratory data requires the standardization of methodologies to allow for national and international data comparisons. The selection of the bacteria and antimicrobial drugs to be monitored,

processing the antimicrobial resistance data, and supervision of the surveillance system should all be done by the same group or organization. The system would require rapid communication of information to the animal health community, especially during the emergence of drug-specific or multidrug resistance in pathogens.

Ideally, the decision to administer antimicrobial therapy should be supported by the appropriate diagnosis and the choice of antimicrobial drugs should be validated by laboratory analysis. Empirical treatment not guided by laboratory findings is often administered because of the diverse realities of veterinary practice and the desire, by producers, to avoid the significant economic losses that would be caused by the delay in obtaining the results from the laboratory. Some factors may also make the laboratory diagnostic route unpopular, including the distance to centres performing the recommended tests, the associated costs, and the fact that routine susceptibility tests cannot always accurately predict the clinical efficacy of antimicrobials. This results in an incomplete knowledge of existing susceptibility profiles of pathogenic bacteria and the risk of skewed study results due to too many samples obtained from previously treated animals.

Currently, the genetic determinants of resistance among the major animal bacterial pathogens to the main antimicrobial drugs are poorly characterized. With some exceptions, there is also relatively poor understanding of the dynamics of resistance gene transfer between animals, the environment, and humans. In particular, the scale of this transfer is not well characterized. Epidemiological studies based on molecular characterization of resistance genes would usefully contribute to identifying the nature and extent of the interaction. Molecular research involving resistance genes in animal bacterial pathogens needs to be better developed and subsidized in Canada. The findings should then be practically applied to complement surveillance activities to help us better understand and explain observed antibiotic resistance phenomena.

Conclusions

Resistance in important animal pathogens varies widely from near 0% to 90%, depending on the antimicrobial tested, host species of animal, and geographical location. The true impact on animal health is unknown, however, because Canada lacks a coordinated system to monitor antimicrobial resistance among animal pathogens. Antimicrobial resistance is an animal health concern when antimicrobials lose effectiveness for treatment or prophylaxis of bacterial infections. Resistance in animal pathogens can lead to use of more expensive drugs, which increases the costs of animal health care. Resistance in animal pathogens is indirectly of concern to human health when it leads to use of newer drugs important in human medicine, or to extra-label use of drugs. Ideally, the choice of antimicrobial drugs for treatment and control of animal disease should be validated by laboratory analysis.

Recommendations

18. Develop a coordinated, ongoing national surveillance system for antimicrobial resistance in the major pathogens affecting food animals.
19. Ensure the appropriate dissemination of food-animal pathogen resistance surveillance data to concerned parties, *e.g.*, veterinary practitioners and governments. These data should be available in a form that supports prudent use of antimicrobials in food animals.

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CHAPTER

8

Strategies to ensure prudent use of antimicrobial drugs

Key Points

- **Prudent use of antimicrobials optimizes therapeutic effects while minimizing antimicrobial resistance**
- **The Canadian Veterinary Medical Association published general and specific prudent-use principles**
- **These principles are essentially voluntary and "best practice" in nature, and several are consistent with on-farm quality assurance programs**
- **Factors affecting the degree of implementation of prudent-use principles include:**
    - **desire by producers and veterinarians to prolong the useful lifespan of antimicrobials and to reduce the impact of resistance in animals and humans**
    - **willingness to modify prescribing behaviours and treatment practices**
    - **costs of implementation and financial incentives for prescribing and sale of antimicrobials**
    - **costs and advantages of implementing alternatives to antimicrobials**
- **Treatment guidelines are not yet widely used in veterinary medicine, but some have been produced**
- **These guidelines may suggest choices (*e.g.* first, second and third) of antimicrobials for treatment of important bacterial infections of animals, as well as recommended diagnostic procedures**

Prudent use of antimicrobials is central to preserving their long-term effectiveness in animals and humans. It involves "optimal therapeutic effect and/or protection of animals at risk" and "control of antimicrobial resistance in animal and zoonotic bacteria" (1). In a broad sense, prudent use is a very complex phenomenon that is affected by a host of factors including the pharmacological and pharmacokinetic properties of veterinary drugs, indications for use, availability of alternative treatments and disease prevention methods, species and type of animals treated, farm management characteristics, treatment decision-making methods and motivations of

farmers and veterinarians, standards of veterinary practice, antimicrobial delivery mechanisms, pharmaceutical company marketing practices, surveillance infrastructure, and provincial and national drug regulations and enforcement. Many of these factors are discussed in other chapters. This chapter focuses on the principles of prudent use (also called "judicious use") and assesses the degree of implementation and effectiveness of prudent use strategies in minimizing antimicrobial resistance in agriculture.

Prudent-use principles and responsibilities

Student veterinarians are taught the essential elements of prudent use in veterinary school and the associated aspects of antimicrobial resistance, especially among animal pathogens important in clinical veterinary medicine, but also in zoonotic pathogens. In general, these are taught in piecemeal fashion since elements exist in pharmacology, bacteriology, medicine, health management and veterinary public health courses. For the graduate veterinarian, prudent use has not been a priority subject for professional continuing education or veterinary conferences. Only very recently were some veterinary medical organizations prompted to at least begin the process of promoting prudent-use principles and practices. These recent efforts are probably motivated in part by a desire to help the profession improve its service to the public, but also in part as a reaction to the threat resistance issues pose to the availability of drugs to the veterinary profession. In a very few instances, codes of antimicrobial prescription in veterinary practice (therapeutic guidelines) are also under development.

Canada

In 1999, the Canadian Veterinary Medical Association (CVMA) issued a position statement on antimicrobial resistance (2), declaring, "We believe there is a role for antimicrobials in agriculture. We believe the veterinarian is in the best position to work with the animal owner in determining that role. We accept this responsibility and will increase our efforts to ensure the prudent use of all antimicrobials in agriculture." The CVMA established a working group to draft the following general and specific prudent-use principles (3). These were published in the *Canadian Veterinary Journal* and are available on the CVMA website.

General Principles:

1. Veterinarians, animal owners and animal caretakers all share responsibility for minimizing the use of antimicrobial drugs to conserve drug efficacy.
2. Antimicrobial treatment regimens should be designed to maximize therapeutic efficacy while minimizing bacterial resistance.
3. Antimicrobials used in animals should only be used within the confines of a valid veterinarian-client-patient-relationship (VCPR).
4. Veterinarians should continually update their knowledge of methods of disease prevention, new therapeutics, and of other issues such as drug resistance trends, to ensure the prudent use of antimicrobials.
5. All users of antimicrobials should be educated in the proper use of antimicrobials including administration, handling, storage, disposal, and record keeping. Veterinarians have a responsibility to educate staff, clients,

and other animal handlers on the prudent use of antimicrobials and for ensuring such training occurs.

Specific Principles:

1. All antimicrobials, even those not purchased directly through or on prescription from a veterinarian, should be used within the confines of a valid VCPR.
2. Animal owners and caretakers should be instructed in and encouraged to implement management, immunization, housing, and nutritional programs that prevent or reduce the incidence of disease and therefore antimicrobial use.
3. Antimicrobials should only be used therapeutically if a pathogen is demonstrated or anticipated to be present, based on clinical signs, history, necropsy examinations, laboratory data (including resistance testing), and if the pathogen is expected to respond to treatment.
4. The need for prophylactic antimicrobials should be regularly assessed. Prophylactic antimicrobials should only be used when an animal is determined to be at risk and evidence indicates that such usage reduces morbidity and/or mortality. Surgical protocols should emphasize strict aseptic technique instead of prophylactic antibiotics.
5. Antimicrobials should only be used to promote growth and feed efficiency if such use does not compromise therapeutic use in animals and people.
6. Antimicrobial selection should be based on the known or suspected target organisms, their known or predicted antimicrobial drug susceptibility, the site of infection, knowledge of the drug including its pharmacokinetic and pharmacodynamic properties, and other factors such as host immunocompetence. Antimicrobials that specifically target the pathogen should be selected over broader-spectrum agents, and local therapy should be selected over systemic therapy when appropriate.
7. Antimicrobials with unique mechanisms of action or novel resistance profiles in human medicine should not be used in veterinary medicine, particularly food animals, unless other antimicrobials by use or sensitivity testing have been shown to be ineffective and use of the antimicrobial is considered to be life-saving in the animal.
8. Antimicrobials approved for the treatment of the diagnosed condition should be used whenever possible. The dose, frequency and duration stated on the label should be followed whenever possible.
9. Combinations of antimicrobials, compounding of active pharmaceutical ingredients and extra-label use of antimicrobials should be avoided unless safety and efficacy have been documented.
10. Antimicrobials should be used for the shortest time period required to reliably achieve a cure. This minimizes exposure of other bacterial populations to the antimicrobial.
11. Appropriate withdrawal times for antimicrobials used in animals intended for food should be adhered to.
12. Animals treated with antimicrobials may shed resistant bacteria into the environment. If possible, steps should be taken to minimize environmental contamination.

13. Antimicrobial products should be handled and stored properly. This includes proper disposal to avoid environmental contamination by the antimicrobial drug.
14. Veterinarians should alert any person handling antimicrobials of any potential risk to themselves and other species.

The AMR committee reviewed the above CVMA principles on prudent use and generally endorses them. The committee does not believe, however, that compounding of active pharmaceutical ingredients for treatment of food animals is acceptable, as indicated in item (9) under Specific Principles. Also, in item (11), Specific Principles, the committee believes that appropriate withdrawal times for antimicrobials used in animals intended for food must (not should) be adhered to.

United States

The American Veterinary Medical Association (AVMA), in conjunction with the Center for Veterinary Medicine, Food and Drug Administration (FDA), developed judicious-use principles that are tailored somewhat to the major food-animal species (4-11). Other veterinary organizations, such as the American Association of Swine Practitioners (AASP), have also contributed (12). In general, these principles are similar to the CVMA principles already described, but, as expected, are more specific to the American regulatory system. For example, there are more restrictions in the U.S. than Canada on extra-label use in food animals. One AVMA principle states, "Extra-label antimicrobial therapy must be prescribed only in accordance with the *Animal Medicinal Drug Use Clarification Act* amendments to the *Food, Drug, and Cosmetic Act* (AMDUCA) and its regulations." The AVMA guidelines define "therapeutic" as "treatment, control, and prevention," and therefore do not recognize prophylactic or metaphylactic categories. This is at odds with other definitions. Although no explanation is given, the reason may be due to the drug dosages that veterinarians prescribe; these are almost always at therapeutic levels, even when the intent is to prevent or control disease. Non-therapeutic treatments (*i.e.* growth promotion or disease prophylaxis) in North America are almost always available through over-the-counter (OTC) sale.

International organizations

The WHO recently issued recommendations on prudent use of antimicrobials in animals (1); these are largely represented in the above CVMA principles. The OIE also recently issued a guideline on prudent use that outlines, in some detail, the responsibilities of regulatory authorities, the veterinary pharmaceutical industry, pharmacists, veterinarians, and producers (13). The responsibilities of veterinarians are similar to the CVMA Prudent-Use Principles described above. Producer responsibilities include some of these same items, with special emphasis on preparing an animal health plan with their veterinarian, using antimicrobials only under prescription and according to label instructions, employing good management practices that reduce the spread of infection among animals, maintaining good records of antimicrobial use, and using and disposing of drugs in manners that are safe to animals, people, and the environment.

Responsibilities of the veterinary pharmaceutical industry, identified by OIE, include providing appropriate information to regulators for authorization of marketing and marketing and exporting only officially approved veterinary medical products. With respect to advertising, the industry should comply with advertising regulations and discourage direct advertising of products to producers. Training and research responsibilities were also identified (13).

Treatment guidelines

Treatment guidelines, including recommendations on prudent-use practices, are not widely used in veterinary medicine; at least their use is not widely reported. The CVMA is in the process of producing species-specific guidelines. The AVMA has prepared a document entitled, "Guidelines to Judicious Therapeutic Use of Antimicrobials in Poultry" (8). This document classifies approved antimicrobials into three categories of importance to human health corresponding to the system employed in the FDA "Framework Document" (14). The guidelines describe diagnostic, non-antimicrobial interventions and suggest antimicrobial interventions (favouring classes less important to human therapy) that may be used for treatment of colibacillosis in broilers and turkeys, pasteurellosis in chickens, and other important bacterial and mycoplasmal infectious diseases.

The Danish Veterinary Laboratory has prepared an "Antibiotic Use Policy" describing its treatment guidelines (14). The policy document is broadly similar to the AVMA guidelines for poultry, although there are important differences. General principles of prudent antibiotic use are described, and suggestions for choice of antimicrobial agent are given for the most important bacterial infections of cattle, poultry, and swine. First, second, and third choices are given, and no choice is offered if prophylaxis by vaccination is the preferred option. The following criteria were used in identifying the choices:

- Preference for narrow-spectrum antimicrobials
- Priority given to old antimicrobials over newer compounds
- General occurrence of resistance to the given bacterial species
- Expected clinical effect
- Mode of administration
- Limitation to antimicrobial agents that are approved for treatment of the given food-animal species

The document also includes Danish susceptibility data for common bacterial agents for the use of practising veterinarians.

Analysis: gaps in our knowledge and barriers to prudent-use implementation

Prudent use

The CVMA Prudent-Use Principles are appropriate, comprehensive and consistent with those from other countries. No doubt, however, there are gaps between the ideals laid down in these prudent-use guidelines and the reality of antimicrobial use in Canadian farming and veterinary practice. How wide is the gap? Few published data are available to answer that question, although the committee suspects it is

substantial. Furthermore, the impact of simple publication of these guidelines on the behaviour of veterinarians and farmers, and on antibiotic use and resistance themselves, is also unknown. If experience from human health is any indication, they probably have minimal effect if simply published or distributed without other reinforcement, such as using multiple training modalities, training at the work site, use of opinion leaders, and ongoing supervision and monitoring of practice (16). Under present conditions in Canada, there are currently insufficient incentives and many disincentives to full implementation of the prudent-use principles laid down by the CVMA and other national and international bodies.

Incentives

The prudent-use principles and programs described above are essentially voluntary and "best practice" in nature. There are no specific financial and few regulatory incentives for veterinarians or producers to fully implement prudent-use guidelines, or for that matter to employ treatment guidelines. On the other hand, antimicrobials are expensive and producers won't use them unless they are believed to be cost-effective. For producers, several of the prudent-use principles and recommendations are consistent with the on-farm quality assurance programs that are in place or being developed (see Chapter 9), and there are incentives to adhere to these programs. Similarly, most veterinarians would argue that they already adhere to these principles, at least most of them. The committee had no data with which to assess any gaps, and whether any shortcomings are important to antimicrobial resistance.

Disincentives

There are many disincentives and barriers to vigorous and complete application of prudent-use principles. First and probably most important, there is insufficient awareness among veterinarians and food-animal producers about resistance issues in their industry. The preceding chapters discuss the resistance problems in both human and veterinary medicine. In human medicine, there is a belief that such problems constitute a crisis; that if action is not taken soon, serious infections of humans may become untreatable with existing drugs. In contrast, veterinarians seem not to perceive that an animal health resistance crisis (*i.e.*, resistance in animal pathogens) is upon us. This may be explained by fewer reports of treatment failures, poorer surveillance, and also, perhaps, by the anticipation of access to antimicrobials now used in humans, but not yet approved for animals. Many veterinarians and producers believe the main antimicrobial problem is a lack of new drug approvals, not diminished effectiveness of available drugs. It is probable that, due to heightened concerns in human medicine about antimicrobial resistance, the flow of new veterinary antimicrobials onto the market in Canada and most other industrialized countries will not resume to its late twentieth-century level. Increasingly, pharmaceutical companies will have to choose whether to invest in drugs for the human or animal market. Being more lucrative, the human market is the more probable choice. The committee believes this is not sufficiently appreciated within the Canadian veterinary and agricultural communities.

Similarly, many (perhaps most) veterinarians and producers do not really believe that resistance arising from antimicrobial use in food animals has any significant, negative effects on human health. This is probably due to the relative lack (until

recently) of information and studies that clearly document the impacts on human health, and to the ease with which the prescription practices of physicians can be blamed for the build-up of resistance problems in humans. The complexity of the food production, processing, distribution, and food service system in Canada and other countries makes it extremely difficult to trace infections and resistance genes and to "definitively" measure impacts. Essentially, the issue is this: if veterinarians and producers do not believe that their practices and behaviours create human or animal health risks, can we expect them to change these practices and behaviours?

Conflicts in economic interests also impede aggressive implementation of prudent-use practices. There are financial disincentives to using antimicrobials. Drugs are costly and producers will use them only if they believe they are necessary. Furthermore, the presence of antimicrobial resistance may mean that newer, more expensive drugs are the only choice for effective treatement of a disease. On the other hand, substantial financial incentives exist for producers, veterinarians, and pharmaceutical companies to encourage the use of antimicrobials in food animals. Producers treat animals to avoid financial losses from animal morbidity and mortality due to infectious disease and increase their profit margins by using growth promoters. Veterinarians often obtain income from the profitable sale of antimicrobials. To the committee's knowledge, there is no published evidence that profit motive adversely affects the prescription practices of veterinarians, nor is there evidence to the contrary. In any case, it seems wise to remove the opportunity for profit motive to play a role in prescription practice. Pharmaceutical companies are, of course, in the business of selling antimicrobials. Their long-term interests in promoting prudent use to help maintain the effectiveness of their products is somewhat offset by their short-term need for profit and increased market share.

The cost of implementing alternatives to antimicrobials can be a barrier to prudent use. For some producers (the percentage is unknown), using drugs to treat or prevent disease is an attractive, less expensive alternative to improving their management practices. Food-animal producers operate on very narrow profit margins, and the infrastructure costs of instituting animal husbandry or other management changes that could decrease the need for treatment and therefore the risks associated with antimicrobial resistance could be substantial. This makes this type of change very unattractive, unless it is clear the change will produce a tangible benefit. One such benefit is the elimination or a substantial reduction in the impact of infectious disease in a producer's herd or flock. Good producers take steps to prevent and control infectious diseases of animals; for example calf hutches on dairy farms to prevent diarrhoea and pneumonia and all-in-all-out management on hog farms to reduce the spread of infection. These measures will decrease the need for antimicrobial treatment, which could reduce the risk of antimicrobial resistance to human health. However, few disease-control or on-farm biosecurity measures are aimed specifically at foodborne zoonotic pathogens or commensal bacteria, because few of these bacteria cause commercially important disease in animals, and implementation of control measures costs money. Notwithstanding their usefulness in preventing economically important animal disease, these control measures may or may not prevent the spread of resistant bacteria of importance to human health.

Provincial endorsement

There should be improved federal-provincial coordination of endorsement and promotion of prudent-use principles and practices. The CVMA is a national organization, but not all provinces require membership for veterinarians. Furthermore, licensing of veterinarians and self-regulation by the profession is administered at the provincial level. It is important , therefore, that provincial veterinary medical licensing bodies and veterinary medical associations carefully examine and strongly endorse the CVMA Prudent-Use Principles.

Treatment guidelines

As discussed above, treatment guidelines are not widely used in veterinary medicine, presumably due to the perceived absence of a compelling need. The situation may be changing with the prospect of fewer new drugs available for veterinary use. Nevertheless, it seems appropriate to extend the AVMA poultry and Danish swine, cattle, and poultry examples to the Canadian situation. In the human medical field, treatment guidelines have met with some acceptance and success.

Species-specific therapeutics committees should devise guidelines that are (1, 16) :

- evidence based;
- appropriate to the clinical, microbiological and management situation for each species and animal type, and local conditions;
- developed with involvement of practitioners who will be using them and mindful of the incentives or disincentives for their use;
- implemented actively, using interactive strategies;
- subject to peer review; and
- revised at regular intervals

Conclusions

Prudent use of antimicrobials optimizes therapeutic effects while minimizing antimicrobial resistance. The CVMA Prudent-Use Principles are appropriate, comprehensive and consistent with those from other countries. Although these principles are essentially voluntary and “best practice” in nature, they should be helpful if implemented by veterinarians and farmers. Factors affecting degree of implementation include awareness of resistance issues and the desire by producers and veterinarians to prolong the useful lifespan of antimicrobials and to reduce the impact of resistance in animals and humans. Other factors include willingness to modify prescribing behaviours and treatment practices; cost, efficacy and availability of alternatives; and incentives for the prescription and sale of antimicrobials. On-farm quality assurance programs can help achieve prudent use in animals. Treatment guidelines are not yet widely used in veterinary medicine, but are logical for enhanced prudent use.

The recommendations listed below are directed towards veterinarians, veterinary licensing bodies and professional organizations, producers and producer groups, and pharmaceutical companies, in addition to Health Canada. Recommendations relating

to prudent use and drug distribution, education, research, and regulation are found in other chapters

Recommendations

20. Veterinarians and veterinary medical organizations should effectively implement the Prudent-Use Principles developed by the CVMA, and periodically review the principles and their implementation.
21. Provincial licensing bodies and veterinary medical associations should endorse and promote the CVMA's Prudent-Use Principles.
22. Only under exceptional circumstances should antimicrobials with unique mechanisms of action or novel resistance patterns in human medicine be used in veterinary medicine.

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CHAPTER

9

Food safety programs used in food-animal production

Key Points

- **Many national commodity groups are developing on-farm food safety or quality assurance programs**
- **These programs are in many cases based on principles of HACCP (Hazard Analysis Critical Control Points) and GPP (Good Production Practices)**
- **At present, none of these programs specifically targets antimicrobial resistance, but they do focus on antimicrobial residues**
- **They are relevant to resistance control however, because they:**
    - **encourage reduction of disease through good husbandry and management techniques**
    - **advocate a strengthened veterinary-patient-client relationship (VPCR) on farms**
    - **involve keeping of drug-use records**

The issues surrounding the use of antimicrobials in food-animal production and their potential role in the emergence of antimicrobial resistance in human pathogens arise at a time when food safety is one of the primary concerns of Canadians. Over the past decade, several food safety incidents, including salmonellosis, *Escherichia coli* O157:H7 and bovine spongiform encephalopathy (BSE), have all contributed to the public's perception of food safety issues on the farm (1–4). Consumer polls conducted by commodity groups have singled out food safety and quality as a public concern and have suggested that the public's confidence in the safety of food over the last couple of years has declined (5,6). To maintain the public's confidence, many national commodity groups have developed on-farm food safety or quality assurance programs. These programs are designed to manage biosecurity, disease, and biological, chemical and physical food safety hazards that may occur on the farm. A key component of these programs is the safe use of drugs, to ensure drugs used on the farm do not result in a chemical food safety risk (*i.e.* harmful residue). As discussed in the previous chapter, prudent use of antimicrobials is critical in maintaining the long-term effectiveness of currently available drugs and limiting the emergence and

spread of antimicrobial resistance in farm animals. Consequently, on-farm food safety programs that endorse prudent use should ultimately contribute to the control of antimicrobial resistance on the farm. This chapter examines the basic structure of these programs, how they relate (or do not relate) to antimicrobial resistance, and lists the committee's recommendations for improvement.

Hazard Analysis Critical Control Point (often called "HACCP") is a science-based food safety system that focuses on the prevention of problems and the control of risks associated with food. Adopted by the Codex Alimentarius Commission, an agency of the World Health Organization, HACCP has become a standard within the food manufacturing and processing industry around the world. In Canada and the U.S., food processors are generally required to file HACCP plans with regulatory agencies. However, there are currently few, if any, food safety regulatory requirements for food-animal producers. There are several key elements about HACCP that are relevant to resistance. HACCP plans are structured to assess and control risks associated with food safety hazards. Thus, the use of antimicrobials in agriculture falls within any on-farm HACCP program. Residues from antimicrobials can represent a direct risk to food safety, although this risk is easily quantified and readily controlled. On the other hand, antimicrobial resistance is much more difficult to quantify and control.

In Canada, national commodity groups representing farm-animal production, through the Canadian Federation of Agriculture (CFA), developed the Canadian On-Farm Food Safety Program (COFFSP). In partnership with Agriculture and Agri-Food Canada (AAFC), the program was initiated in 1997 and mandated to develop and implement national food safety initiatives on a commodity-specific basis at the farm level. There are currently 14 programs in various stages of development within the food-animal production sector. These include beef cattle, dairy cattle, hogs, sheep, cervids (*i.e.*, deer and elk), bison, chickens, turkeys, hatcheries, hatching eggs, table eggs, honey bees, shellfish, and salmonids (salmon, trout and char).

In June 2001, the Minister of AAFC and the provincial and territorial Ministers of Agriculture agreed that all levels of government have a responsibility for enhancing Canada's integrated food safety systems. The ministers also agreed to work closely together and with industry towards the continued development and implementation of credible On-Farm Food Safety Programs (OFFSP). The committee was advised by the CFIA that, at the national level, it would provide official recognition of the technical soundness, including the requirement to meet regulatory standards (where applicable), and administrative effectiveness of OFFSP in Canada. This level of recognition will include:

1. CFIA-led technical review of program design for adherence to internationally recognized HACCP principles;
2. industry completion and implementation of the OFFSP;
3. independent, CFIA approved, third-party auditing; and
4. CFIA-led assessment and recognition of the OFFSP, which will involve audit of OFFSP national associations' administration, including the third-party auditors.

CFIA anticipates that provincial governments will also play critical roles in the implementation of these voluntary programs.

The OFFSP of the Chicken Farmers of Canada (CFC) is being used by the CFIA as a pilot project aimed at providing a technical review of the program and establishing a process for conducting the review. HACCP plans and the producers' manual of guidelines, including good production practices (often called "GPPs"), will be reviewed for their technical soundness. In February 2002, 17 other National Associations expressed the intention to forward applications for a technical review by the CFIA. Some producer groups believe that CFIA accreditation is important to the national and international credibility of their food safety programs.

Food safety programs on Canadian farms

Beef

The cattle industry in Canada includes over 100,000 producers. Most of their operations consist of small, cow-calf herds with approximately 35 head of cattle. However, the bulk of production (about 80%) comes from approximately 20,000 producers who operate feedlots located primarily in Alberta and Saskatchewan. Just over 50% of Canadian production is exported, mostly to the U.S. (7). In 1995, the Canadian Cattlemen's Association (CCA) developed on-farm, HACCP-based GPPs to improve beef quality and food safety. The "Quality Starts Here" (QSH) program is being implemented across the country. This project is the result of a collaborative effort between all of the various interest groups, including the CCA, provincial industry associations, the CFIA, regional veterinary associations, pharmaceutical manufacturers' associations, and trucking associations, all of whom participate on the QSH management committee.

With respect to the use of antimicrobials, the program includes sections on:

- record keeping;
- pharmaceutical product information, use and testing;
- feed quality assurance principals;
- sanitation; and
- handling of sick animals.

The program includes standard operating procedures (SOPs) to reduce disease in feedlots and for safe feed preparation. The program is both educational and functional, containing blank record sheets, instructions on product use and comprehensive checklists. In addition, the program uses a cd-rom information database. Third-party accreditation and program auditing by a recognized authority is now being integrated into the program.

Dairy

The Dairy Farmers of Canada (DFC) is the national organization that represents over 20,000 producers. The majority (81%) of these producers are located in Quebec and Ontario. At present, the DFC operates under a strict set of testing protocols to ensure food safety. Under the current testing program, all bulk milk shipments are tested for the presence of residues from antimicrobial drugs. When such residues are found, the whole shipment of milk is rejected, with the cost passed on to the farmers involved.

In 1997, the DFC developed GPPs based on HACCP principles and began a pilot study in British Columbia. Critical control points (CCP) identified in the DFC program include the use of medicines and milk storage, especially with respect to temperature. The program will move away from the traditional "end-product testing" and focus on managing the CCPs. These in turn will be monitored through a record-keeping system as required under the overall HACCP system. Preparation of formal manuals and further research and development are currently being co-ordinated through the CFA's OFFSP.

Pork

The Canadian Pork Council (CPC) is the national association for approximately 12,400 pork producers. The majority of farms (80%) represent operations with less than 100 animals per farm. The remaining 20% of producers have operations with greater than 1,000 animals per farm and account for 80% of the production volume.

Pork producers, through the CPC's Canadian Quality Assurance Program, have developed GPPs based on HACCP principals. The two main CCPs identified were feed handling and management of veterinary supplies, primarily antimicrobials. The CPC then developed GPPs specifically for handling drugs and medicated feed. Other relevant areas addressed by the program include barn sanitation, feed mixing, record keeping on feeds and medications used on-farm, and protocols to reduce biological hazards from parasites and bacteria on the farm.

The GPPs were developed over two years and then evaluated on 150 farms in 1997. Preliminary feedback from the test sites suggests that in most instances producer acceptance was high. In general, the larger producers felt that more could be achieved, whereas the smaller producers found the protocols to be burdensome. The program was officially launched in 1998 incorporating certification using herd veterinarians as validators, who are, in turn, subject to auditing. The program incorporates a national quality assurance manager to ensure consistent program delivery. The national quality assurance manager works with a technical committee to review and update the GPPs and to validate procedures. As of December 2001, 3,453 producers were fully recognized in the program. These producers represent 36.5% of hogs marketed in 2001.

Chicken

The Chicken Farmers of Canada represents 2,800 chicken farmers. It has operated since 1989 under a Handling and Practices Code that was subsequently expanded to include biosecurity and HACCP-based GPPs similar to those used by cattle and pork producers. This led to the development of an on-farm food safety and quality assurance program called "Safe, Safer, Safest," which was launched as a pilot program in 1998.

The focus of the program is record keeping and traceability through the entire production cycle. The main CCPs identified in chicken farming are feed and water medication. The Safe, Safer, Safest manual includes a set of record-keeping forms used to monitor key areas such as farm access, facilities maintenance, watering and feeding systems, cleaning and disinfection, bird health and shipping to the processor.

CFC is now working with other poultry groups to develop a compliance auditing model and protocols for on-farm validations.

Turkey

The Canadian Turkey Marketing Association (CTMA) represents approximately 564 turkey producers and has an on-farm HACCP-based program similar to that managed by the CFC. The program, which began development in 1997, is now in the pilot phase with an implementation target of 2002. The GPPs and biosecurity measures are similar to those used in the CFC program. The CCPs identified cover the use of medicines, vaccines, rodent and pest controls, cleaners and disinfectants. Information and reporting forms cover topics such as medication withdrawal, medicines used, number of birds, bird weight, and past health problems.

Hatching-egg producers and hatcheries

In general, there are two types of hatcheries — those that supply to grower farms for meat production and those that supply to layer farms for egg production. The Canadian Hatchery Federation (CHF), which represents 50 hatcheries, is working with the CFA's OFFSP to develop a generic HACCP-based program for the sector. The goal is to ensure that on-farm safety management extends through the complete life cycle of the poultry industry from hatching-egg production through to chicken and table-egg production.

The Canadian Broiler Hatching Egg Producers Association (CBHEPA), which represents 300 members, is developing an OFFSP. It will be based on the existing Canadian Hatching Egg Quality (CHEQ) program. The goal is to create a manual for producers that lists the program requirements, including bird and feed supplier accreditation, health monitoring, medication and medicated feed handling and record keeping, hygiene and sanitation and record keeping. CBHEPA is currently working with other groups including the CFC, the CTMA, and the Canadian Egg Marketing Agency (CEMA) to develop a common approach to audit, compliance, and validation.

Eggs

Egg producers are represented by CEMA. The industry is relatively small (1,200 registered producers with more than 100 birds). CEMA has been developing an on-farm, HACCP-based program since 1990. The program, "Start Clean — Stay Clean," launched in 1999, was developed from an inspection and rating system that had been in operation for over five years. Inspectors employed by CEMA specifically for this inspection program implement program auditing. The CEMA inspectors are provided with HACCP and audit training.

The development of CEMA's HACCP program was facilitated by the fact that few, if any, CCPs were identified. For example, according to CEMA, drugs and additives (*i.e.*, colourings, hormones) are not used in laying hens, which eliminates the primary CCPs encountered on a meat-production farm site. One of the biggest challenges was to develop a trace-back system, given the large number of eggs involved. *Salmonella* contamination remains the principal safety issue, and a provincially funded testing

program is in place that involves 82% of the producers. CEMA also has developed a unique HACCP incentive program to promote active participation by its members. The HACCP program is linked to a national-provincial insurance program that compensates farmers for lost wages if birds test positive for *Salmonella* and the birds are destroyed for disease control purposes.

The CEMA program has been highly successful. During the last four years, national average inspection scores have risen from 70% to 80%. The program has allowed CEMA to track potential problems and provide producer education where necessary.

Sheep

The Canadian Sheep Federation (CSF), which represents approximately 10,000 producers, is currently evaluating its on-farm safety program through a national pilot program. The program features HACCP-based GPPs, which have been incorporated into a manual for producers. Preparations are underway to develop a training program for validators.

Bison

The Canadian Bison Association (CBA) represents approximately 1,800 bison producers. While the size of the bison herd is relatively large (approximately 100,000), only a small portion (6.4%) are presently slaughtered for human consumption. The CBA has recently completed a pilot study of its on-farm safety program that incorporates HACCP-based GPPs, record keeping and auditing/compliance protocols. The program should be launched nationally in 2001/2002.

Deer and elk

The Canadian Cervid Council (CCC) represents 2,494 elk and deer farmers. This sector has grown considerably in the last several years. Principal species grown include elk, fallow deer, red deer, white deer and others (mainly reindeer). The market is complex, as animals are grown for venison and antler velvet, and as trophy animals. Furthermore, animals such as elk, while representing a large proportion of the cervid herd, are principally grown for antler velvet. Deer, on the other hand, while contributing to antler velvet production, represent the bulk of venison produced in Canada. Total antler velvet production for 2000 was approximately 70 metric tonnes (MT).

The CCC has approached the COFFSP with an application to develop an OFFSP covering the production of both antler velvet and venison, due to increasing concern over chronic wasting disease. While a national strategy has been developed, the group is still in the research and development phase pending availability of funds to develop the program.

Aquaculture — salmon and trout

Canada's diverse aquaculture industry is represented by the Canadian Aquaculture Industry Alliance (CAIA). Salmonids (salmon, trout and char) are farmed in all 10

provinces and the Yukon Territory in fresh and salt water, depending on the species. Canada currently produces approximately 77,500 MT of salmon, the majority of which are grown in large marine net-pens. Production of trout and char is 7,000 MT, from a very large number of small fresh-water pond sites and a small number of lake-based cage sites.

Table 9.1: Summary of farm-animal commodity-group statistics 2000/2001 (ranked by production)[a]

Group	Estimated Number of Farms	Estimated Herd Inventory (million)	Estimated Production	Estimated Per-Capita Consumption (lbs) – 1999
Pork	14,920	12.3	1,638,218 MT[c]	60.4
Beef[b]	123,570	13.2	1,207,573 MT	71.2
Chicken	2,800	572	874,400 MT	61.3
Turkey	564	21.2	151,700 MT	4.3
Salmon	300	25	77,400 MT	1.5
Lamb	10,665	0.7	10,788 MT	1.8
Trout	900	10	6,800 MT	n/a
Bison	1,800	0.1	3,101 MT	0.02
Deer/Elk	2,000	0.15	355 MT	n/a
Dairy-Milk[d]	20,624	1.4	7,490 ML[e]	108.1
Dairy-Cheese[f]				61.7
Eggs	1,200	186	5,400 ME[g]	182.4 (# eggs)

[a] from a variety of sources, including national commodity-group associations, supplemented with information from government sources (Canadian Food Inspection Agency, Agriculture Canada, Department of Fisheries and Oceans and Statistics Canada) and other sources such as CanFax Research Services. In many instances where specific figures were not available or data obtained did reconcile, figures were estimated by mathematical extrapolation.
[b] includes veal; [c] metric tonnes; [d] milk includes milk, cream and milk used in milk products (ice cream, yogurt, can/evap milk); [e] million litres; [f] cheese, butter, milk powders; [g] million eggs.

To address the issue of drug use on salmon and trout farms, the "Healthy Salmon" program was developed by the Salmon Health Consortium (SHC), which represents salmon growers, animal product manufacturers, feed manufacturers, and other provincial aquaculture extension offices. From a HACCP perspective, the principal hazard identified was drug use on farms, which represents the focus of the program.

The program verifies that the use of drugs is compliant with all regulatory requirements and, most importantly, that producers employ prudent-use practices for drugs. This is achieved through a semi-annual or annual evaluation of fish health management practices, therapeutic handling, storage and use, as well as record systems used for tracking treatments, withdrawal times and harvest. The certification

component provides independent auditing (through the local association), and certificates (date limited) are issued to farms that meet all of the program requirements.

Commercial feed industry

The Animal Nutrition Association of Canada (ANAC) is the national association representing manufacturers and suppliers of approximately 90% of the animal nutrition products commercially manufactured in Canada. In 1996, ANAC launched a national Feed Safety Program to assist feed manufacturers in implementing GMPs and HACCP programs in feed manufacturing facilities.

Similar to the on-farm programs, the ANAC program focuses on prevention by applying controls throughout the manufacturing process: from reception of ingredients at the feed mill to delivery of finished products to the farm. The program also incorporates key elements of the CFIA's Food Safety Enhancement Program (FSEP), the U.S. FDA program and the European Union's HACCP protocol. A significant component of the program with respect to antimicrobial usage focuses on chemical hazards associated with proper use of medications in the feed manufacturing process: weighing the right quantity of the right drug, proper mixing of the drug in the feed, and prevention of cross contamination and residues throughout the manufacturing process.

The program incorporates a "Good Manufacturing Practices Manual for Feed Manufacturers" and a generic HACCP model, both of which are reviewed and updated on a regular basis, industry training sessions on both GMPs, HACCP, auditing, and independent third party accreditation. An estimated 40% of commercial feed products are currently being manufactured in HACCP-certified feed mills. As is the case with the national OFFS programs, ANAC will seek recognition by the CFIA for the program.

Analysis

Use of drugs on farms

A comprehensive review of all of the current OFFSPs reveals that none specifically targets antimicrobial resistance. However, a direct goal of all programs is to promote and implement several elements of prudent antimicrobial use on farms with the aim of reducing residues. Although not specifically targeting resistance issues, this could reduce the amount of antimicrobials used on farms and, as a consequence, reduce selection pressure.

In general, OFFSPs seek to promote the following elements of prudent antimicrobial use:

1. minimize the incidence of disease through good husbandry and management techniques;
2. advocate a strengthened veterinary-patient-client relationship (VPCR) on farms;
3. veterinary involvement in disease diagnosis, appropriate drug use, more accurate dosing, and proper application regimens;

4. careful preparation of medicated feed on farms;
5. monitoring of antimicrobial withdrawal times to reduce risk of residues in animal products; and
6. record keeping of drug use.

Program development and implementation issues

All commodity groups developing OFFSPs experienced many of the same problems. These include:

- funding and resources
- volume — dealing with large numbers of farms
- regional differences
- coordination between producer and processing sectors
- program accreditation

Development of a national program is time consuming and impossible without adequate financial and human resource commitments. This is a critical time for all sectors that are struggling with implementing their own programs, particularly for some of the smaller industries, such as elk, deer, salmon and trout.

When the CTMA was developing its program, the original board was set up with representation from five grower regions, all of which had different husbandry practices. This approach eventually contributed significantly to producer acceptance of the program. The developers of the Healthy Salmon program had a similar experience. This emphasizes the need to have a consistent national policy that works for all participants.

Several groups noted that implementation of their program was contingent on accreditation from CFIA. In essence, the intention has been to allow the industry to develop programs to allow self-regulation, but to "regulate the regulators" through program auditing and accreditation by a government agency such as the CFIA. Without this third-party oversight, the programs lose a large degree of credibility in the eyes of the public and the farmers who participate in the programs. Traditionally, it has been cost prohibitive for the government to inspect farms. The benefit of self-regulation in this manner is that it allows farms to regulate themselves at their own cost. Validating the programs ensures that producers meet an acceptable national standard on an individual basis. This would not only encourage producers to participate in legitimate programs, but, more importantly, it would prevent illegitimate programs from being developed and sold to commodity groups or individual producers.

It is clear from a review of other voluntary regulatory programs in other industries that those that are most successful receive a strong commitment from the industry associations and the government. One example is the Canadian Chemical Producers' Association's Responsible Care Program, or the Accelerated-Reduction of Toxics (ARET) program, which manages toxic emissions from various sources.

Coordination between production and processing sectors

Under the current system, processors are legally responsible for product quality under various meat, fish, and poultry inspection acts and regulations. However, they have little control over what occurs at a farm. The use of on-farm GPPs and HACCP-based protocols would give food packers and processors better verification of product quality and certification. This is where OFFSPs provide a great benefit. However, it is critical that packers and processors work together with producers to ensure consistency throughout the food production/processing system.

Applicability of HACCP to farms

One of the issues facing on-farm, HACCP-based programs is the applicability of HACCP. This is the main reason the GPPs are HACCP-based. All commodity groups would like to move from GPPs based on HACCP principles to a full HACCP system. However, there is debate over the validity of a true HACCP system on the farm, where not all inputs can be controlled. Under a HACCP system, all control measures should have a food safety outcome, or, in other words, control measures should provide predictable results. There is often not enough research to know the risks and outcome of control measures in certain situations.

Antimicrobial and other veterinary drug residues are widely recognized by industry to be food safety issues in need of control on the farm. Currently, however, HACCP-based programs are not designed to directly control resistance. GPPs indirectly control resistance by requiring producers to use all management techniques available to reduce the incidence of disease and by applying prudent-use practices. This, in turn, should reduce the use of antimicrobials. It must be pointed out, however, that controls aimed at residues are not necessarily the same as controls aimed at resistance. For example, adhering to withholding times prior to slaughter is a critical method of preventing residues, because that is their purpose. However, these withholding times may do little or nothing to prevent resistance. On the other hand, treatment of animals in the nursery may be important from a resistance perspective, but not important from a residues perspective. On-farm food safety programs must be designed with both in mind to be truly useful.

Program auditing models are perhaps the element that varies most amongst the OFFSPs. At one end of the spectrum, programs are voluntary and contain no mechanism to verify that producers are meeting program standards. At the other end, farms are issued certificates following an audit by an independent auditor. At a minimum, program managers/developers should maintain a national list of registered participants and, depending on the program, what level of registration the farm has within the program (*i.e.*, registered, recognized, or certified).

Imported animals and food products

Antimicrobial resistant bacteria may be imported with host animals or animal products from other countries. This is a concern, especially because there are differences in drug availability and licensing between Canada and its trading partners. It makes little sense to limit the availability of antimicrobials to Canadian farmers if farmers in other countries raise animals under less restrictions and then

export their products to Canada. One solution is to focus on validating source animals that were produced according to a HACCP-based, on-farm GPP program. This would follow the lead of the food packing and processing industry engaged in trade with the U.S., which requires processors to have a HACCP plan in place regardless of the source country.

Conclusions

Although OFFSPs do not yet specifically seek to control antimicrobial resistance on the farm, these programs do promote elements of prudent antimicrobial use, and for this reason they are clearly in the interest of Canadians. Most commodity groups have, or are in the process of developing an on-farm food safety program. These programs incorporate Good Production Practices that seek to minimise disease on farms and therefore the need to use antimicrobials, and they incorporate third-party auditing.

Recommendations

23. Food animal industries should develop OFFSPs that address antimicrobial resistance issues, subscribe to CVMA Prudent-Use Principles, and be audited. Programs that successfully address these matters should be acknowledged (and ideally, accredited) by appropriate government agencies.
24. Encourage food-animal industries to develop OFFSPs that are audited, maintain a national registry of participating farms and provide accurate information on antimicrobial use. Use this drug-use information to assist national surveillance.
25. Encourage measures to reduce transmission of zoonotic infections from animals to humans throughout the food production and processing system.

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CHAPTER

10

Monitoring of antimicrobial drugs used in food animals

Key Points

- **In Canada, we do not know the quantities of various antimicrobials used in animals, and we do not collect use data in a manner that helps to further our understanding of resistance and its impact on human health**
- **Such data are needed for:**
    - **interpretation of trends in antimicrobial resistance**
    - **use in human health risk analyses**
    - **the development and evaluation of programs designed to contain antimicrobial resistance**
- **An integrated approach combining data from several sources will probably be necessary, and should include:**
    - **annual antimicrobial sales data from pharmaceutical manufacturers and importation data**
    - **periodic monitoring of antimicrobial use by producers and veterinarians**
    - **information from other points in the distribution system (*e.g.*, feed mills, pharmacies, over-the-counter (OTC) outlets, and wholesalers)**

Publicly available data on antimicrobial use in food animals are scarce in Canada. This gap makes it difficult to state which drugs are used, in what quantities, and for what purposes in various animal species. This gap also impedes progress in understanding the relationship between antimicrobial use and the emergence and spread of resistance among animals and between animals and humans.

A number of organizations, including the World Health Organization, Health Canada and the United States Department of Health and Human Services have stated that monitoring the use of antimicrobials in animals is an essential component in controlling the development of antimicrobial resistance in bacteria affecting the health of humans and animals (1,2,3).

In general, data should be available to the public, along with a description of the methods used to collect and collate the data. Systems that monitor antimicrobial use should provide credible and accurate data:

1. for the interpretation of antimicrobial resistance surveillance data from human, animal, food, and environmental sources;
2. for the development and evaluation of programs designed to contain antimicrobial resistance and to maintain and promote a wholesome and nutritious food supply (*e.g.*, through surveillance of antimicrobial resistance; producer, veterinarian, and stakeholder education; prudent-use and clinical-practice guidelines; target setting for use reduction; and setting restrictions on the availability of antimicrobials);
3. that allow comparisons of antimicrobial use at different jurisdictional levels (*e.g.*, regional, national, international) and between different sectors (*e.g.*, livestock growth promotion, veterinary medicine, human medicine);
4. for use in risk analyses relating to the use of antimicrobials in food-animal production and the protection of human health; and
5. for use in identification of agricultural antimicrobial use practices that are likely to result in the development of antimicrobial resistance of veterinary or human medical significance.

Monitoring of antimicrobial use

In Canada, there is, for the most part, no existing mechanism by which data on the consumption of antimicrobial drugs by food-producing animals is collected, analyzed, and reported (an exception is the monitoring of antimicrobial use in aquaculture feed by the B.C. Ministry of Agriculture Food and Fisheries (4,5). Canada differs very little from most countries in this regard. As a result, there are no comprehensive estimates of antimicrobial consumption in livestock production for Canada, although some data are available from targeted research studies (6-8).

The committee was advised that a number of projects investigating methodologies for collecting quantitative data on antimicrobial use, as well as the behaviour patterns of veterinarians and food-animal producers relative to antimicrobial use, have been undertaken by Health Canada (Laboratory for Foodborne Zoonoses) and various research partners, including the University of Guelph, the Centre for Coastal Health, several provincial ministries of agriculture, and food and livestock commodity groups.(8-13) These studies will provide some preliminary information on antimicrobial use in Canadian livestock production and will contribute to the development of a system for monitoring antimicrobial use in food animals.

Monitoring practices in other countries

Some of the following information is derived from the WHO Consultation on the Monitoring of Antimicrobial Usage in Food Animals for the Protection of Human Health, in Oslo, Norway (September 10–13, 2001). A final report of the consultation should be published soon.

Sweden

Sweden was the first country to develop a system for monitoring antimicrobial consumption in animals. All veterinary use of antimicrobials in Sweden requires a prescription. The 1986 *Feedstuffs Act* restricted the use of antimicrobials to veterinary use only. Prescriptions can be filled only by pharmacies or feed mills, which are supplied by two drug wholesalers. Sales data have been available from the drug wholesalers and compiled by the Swedish National Veterinary Institute (SVA) since 1980, although the data do not report consumption by species. Species-specific information has been accessible since 1996 in a centralized database maintained by the National Corporation of Swedish Pharmacies (Apoteket AB), which contains information on all veterinary prescriptions. These two sources are used to determine the use of antimicrobials in animals. Currently, only antimicrobial use in birds is reported by species/class. An additional system, developed in 1999, is used to record data on all visits by veterinarians to food-producing animals. Although this system does not provide information on antimicrobial use, it has the potential to do so. Despite its early progress in recording antimicrobial use data, Sweden has not clearly defined the roles and responsibilities of stakeholders for implementing an antimicrobial use monitoring program (14,15).

Sweden has developed the Anatomical Therapeutic Chemical veterinary classification (ATCvet) system, which includes classification and codes for antimicrobial drugs. This system has greatly facilitated standardization in recording drug use, which is key to providing credible, accurate data and to facilitating comparisons of data from different jurisdictions and/or countries. The ATCvet system has been adopted by the European Union and is being considered by the WHO as a possible international standard. It is currently administered by the WHO Collaborating Centre for Drug Statistics Methodology, in Oslo (14,16).

Denmark

In Denmark, veterinarians can only prescribe antimicrobials for use in practice or for re-sale to food-animal producers through a pharmacy. Denmark has developed a monitoring system of antimicrobial use similar to Sweden's, but with more resources dedicated to the task. The system has two components: 1) collection, since 1995, of antimicrobial sales data from pharmaceutical companies and importers, reflecting sales to veterinary drug wholesalers, and 2) collection of antimicrobial prescription data from veterinarians through the newly developed VETSTAT system. Also, Denmark is recording on-farm antimicrobial use, beginning with dairy producers. Antimicrobial use data are reported annually, along with human consumption data and animal, food, and human antimicrobial resistance data in the DANMAP report. The data are broken down by ATC code and route of administration but, to date, not by species (17,18).

Norway

In Norway, use of antimicrobials in animals requires a prescription. These are filled by pharmacies, which are supplied by drug wholesalers or feed mills authorized by the Norwegian Medicines Agency. Sales data collected from Norwegian drug wholesalers and registered feed mills represent all antimicrobial use in agriculture. In

July 2001, reporting of sales data from these two sources was made mandatory. Additionally, since 1989, a program monitoring antimicrobial use in aquaculture has collated data from prescribing veterinarians and the dispensing pharmacy or feed mill. In order to augment and validate the data collected from the wholesalers and feed mills, a program requiring veterinarians to register all prescriptions will begin in 2002 or 2003. Furthermore, Norway has plans to institute on-farm recording of antimicrobial use. In 2000, the Norwegian Zoonoses Centre, in collaboration with the Norwegian School of Veterinary Science, launched NORM-VET. This official monitoring program reports antimicrobial use data and antimicrobial resistance surveillance data from animals and humans on an annual basis (19,20).

The Rest of the European Union

In 1997, the European Commission requested that Fedesa (European Federation for Animal Health) provide information on antimicrobial use in Europe. Reported total sales volume was 10,494 MT of active ingredients. Of this, 5,400 MT(52%) was for human use, 3,494 MT(33%) for animal health, and 1,599 MT(15%) for growth promotion). They estimated that 90% of antimicrobials for animal use were administered in feed; 60% were used in pigs, 20% in poultry and rabbits, 18% in ruminants, and 1% each in fish and pets. Within the animal health category (therapy, prevention and control), 66% were tetracycline, 12% macrolide, 9% penicillin, and 12% other drugs (21).

An attempt was made to compare use figures between European countries based on the size of animal populations (antimicrobials used by tonne of live weight of slaughter animals). Based on animal census and production data, countries could be classified into three groups: in the highest use group were U.K., Greece, Spain, and the Netherlands; the lowest group comprised Sweden, Denmark, and Finland; with remaining countries in the middle group. These differences were attributed to varying husbandry conditions, but antimicrobial regulatory and distribution policies within countries were probably also contributing factors. Much has happened in Europe to change the situation since these data were assembled, including the removal of several growth promoters from the market.

The European Union has proposed that all member states and the broader European Community should monitor consumption of antimicrobials within veterinary medicine. Several member states, including he U.K., France and the Netherlands, have initiated programs and pilot projects to this end (22-24). A community system to collect data on the supply and consumption of antimicrobial feed additives was initiated in January 2000 (25).

Australia

All antimicrobials are imported either in end-product or bulk form. Since 1992, importers have been required to identify the intended end use (human, stock feed, veterinary therapeutic). Data have been compiled since 1992 by the Therapeutic Goods Administration (TGA). There are several data quality issues related to completeness and accuracy of the importation records, especially situations in which the importer is unaware of the intended end use of imported antimicrobials. However, the data are considered reasonably representative of overall consumption. At present

there is no mechanism for separating the stock-feed category into growth promoter and prophylactic uses, nor for reporting use by species. No formal collection of end-use data has been undertaken or planned (26,27).

United States

As is the case for Canada, there is no existing mechanism for the routine collection of quantitative data on the use of antimicrobials in agriculture. Some estimates have been made by various organizations. The most widely quoted estimate of total use is found in the 1989 Institute of Medicine (IOM) report (28), which estimated that approximately 50 million lb. of antimicrobials are produced annually in the U.S., and that approximately 50% is used in animals. This estimate was made over 10 years ago and was based on extrapolations from uncertain sources. Recently, the Union of Concerned Scientists (UCS), a non-profit organization representing consumer issues, estimated that approximately 35 million lb. of antimicrobials are used annually in the U.S.; 4.5 million lb. (9%) in humans and 30.6 million lb. (87%) in animals (29). The vast majority (24.5 million lb.) of this estimate was classified as non-therapeutic (*e.g.*, growth promotion, prophylaxis) in three types of food animals: cattle, swine, and poultry. To estimate human use, UCS cited outpatient prescription data from the National Center for Health Statistics and inpatient data from the U.S. Hospital Anti-Infective Market Guide. For animal estimates, UCS used an indirect method based on animal population estimates from agricultural census data, coupled with expert opinion and the results of USDA surveys of on-farm treatment practices and lists of FDA-approved antimicrobials.

The FDA does require pharmaceutical manufacturers to report quantities of drugs marketed as part of the annual Drug Experience Report. However, this reporting program was not designed to be the basis of a monitoring system of antimicrobial use. The reports are issued for each drug based on the drug's approval date, not the calendar year, so compilation of use data is virtually impossible. Furthermore, domestic sales are not distinguished from export sales, and there is no information on animal species, actual use conditions, commodity distribution, or geographic region (30).

Since 1999, the FDA and the Centers for Disease, Control and Prevention (CDC) have requested antimicrobial sales data from the Animal Health Institute (AHI), an organization that represents manufacturers of animal health products in the United States. A third-party research company collects the data provided by AHI. The data are categorized in three ways: kilograms (kg) of active ingredient; use — therapeutic/preventive (14.7 million lb., or 83% of the total in the 1999 survey), or growth promotion (3.1 million lb., or 17% of the total); and antimicrobial drug class (aminoglycosides, fluoroquinolones, ionophores/arsenicals, penicillins, sulfonamides, tetracyclines). AHI has been collecting this type of data for its own use since 1980 (31). There are several issues that complicate the usefulness and interpretability of the AHI data. Not all manufacturers of antimicrobials for agricultural use belong to the AHI. Also, members of the AHI are not required to give actual sales figures, and in some cases estimates are provided. The way in which the estimates are derived has not been presented. In cases where a given product is labelled for both growth promotion and therapeutic/preventive use it is classed as therapeutic/preventive (31-33).

Antimicrobial use data are available also from the USDA's National Animal Health Monitoring System (NAHMS). NAHMS administers surveys to food-animal producers covering various aspects of animal health, including the use of antimicrobials (34). These surveys are conducted annually on a rotational basis. The data are primarily qualitative/descriptive but the mechanism could be used to collect quantitative data. These data cannot be used to develop total-use data, but could be used to interpret antimicrobial sales data.

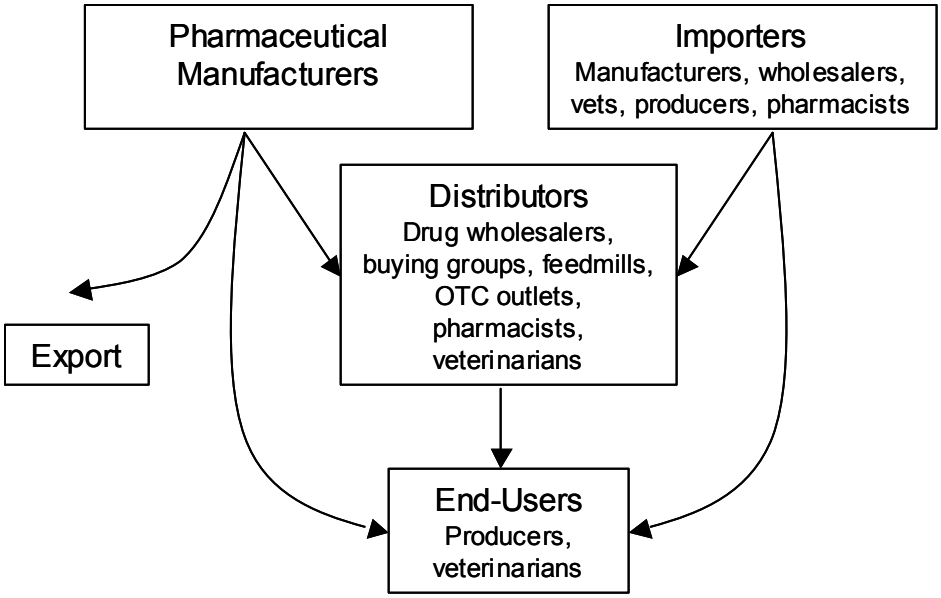
The FDA plans to develop an official monitoring program on antimicrobial use. The nature of this has not been finalized. In the initial proposal, the program will require manufacturers of antimicrobials in the U.S. to provide sales data on an annual basis. The sales data will be recorded on report forms and returned to the FDA for analysis. The report forms will include the following elements: 1) market pack container sizes and number of marketable units sold within the calendar year (by month), 2) estimates of drug use within each labelled species or target animal, 3) estimates for the actual dose regimen use, 4) active drug units sold within the calendar year (by month). The possibility of breaking this information down by geographic region is being considered. The resulting data will be reported annually, while maintaining manufacturer product confidentiality as stated under U.S. law (30).

Analysis – monitoring of antimicrobial use

In Canada, we do not know the quantities of various antimicrobials used in animals, and we do not collect use data in a manner that helps to further our understanding of resistance and its impact on human health. The committee believes Health Canada should be responsible for collection, interpretation, and reporting of monitoring data on antimicrobial use; however, it may partner with the CFIA, provinces, and industry groups. When collecting such data, it is common to encounter concerns about confidentiality and proprietary interests. Confidentiality agreements and laws should be respected, but barriers to reporting these data must be resolved. In order to protect confidentiality, data on antimicrobial use may be aggregated prior to reporting by Health Canada.

Because of the complexity of the Canadian distribution system (Figure 4.1) for antimicrobial drugs, an integrated approach combining data from several sources will probably be necessary (Figure 10.1). For example, the monitoring baseline could be provided by annual antimicrobial sales (including export) data from pharmaceutical manufacturers and importation data, including "own-use importation" and the importation of bulk chemicals. A model could be developed using information from end-users and the baseline manufacturer/import data to develop annual use estimates reported by drug class and species/livestock class. End-user data could be verified by periodic monitoring of antimicrobial use by producers and veterinarians. This could be done through a rotating sentinel site system, possibly making use of quality assurance program records. Additional information from other points in the distribution system (*e.g.*, feed mills, pharmacies, OTC outlets, and wholesalers) could be used to validate the model and/or adjust the model estimates.

Figure 10.1: Monitoring of the patterns of use of antimicrobial drugs



The following information is essential for a functional, meaningful and comprehensive monitoring system on antimicrobial use:

- volume produced (kilograms of active ingredient);
- volume imported (including "own-use" and API);
- volume exported;
- quantitative data at end-use and use patterns (by species, use, drug, region); and
- quantitative data collected at various points in the antimicrobial distribution system (*e.g.*, feed mills, drug wholesalers, pharmacies).

To facilitate the development of a monitoring system on antimicrobial use, Health Canada must improve its knowledge of the provincial legislation surrounding antimicrobial sales and determine the points in the distribution system where meaningful and useful data can be collected in an ongoing and logistically feasible manner. It must carefully plan how it will use, classify and report the data. It is very important that Health Canada develop useful methods to integrate antimicrobial use and resistance surveillance data from animals and humans.

Conclusions

The quantities of various antimicrobials used in animals in Canada are unknown, but it is important that this information be available in the future. These data are needed to interpret changes in resistance over time, to assess the impact of resistance on human health, and for development and evaluation of programs designed to contain antimicrobial resistance. Given the way that antimicrobials are distributed and used in Canadian agriculture, an integrated approach combining data from several sources will probably be necessary. This should include annual antimicrobial sales data from pharmaceutical manufacturers, importation data, periodic monitoring of antimicrobial

use by producers and veterinarians, and information from other points in the distribution system (*e.g.*, feed mills, pharmacies and wholesalers).

Recommendations

26. Design and implement a national surveillance program of antimicrobial use in food animals that provides valid data in a timely and methodologically transparent fashion. Design the program to support risk analysis related to human health and policy development related to antimicrobial use. The data should be publicly available.
27. Provide an annual report of antimicrobial use monitoring by appropriate means (*e.g.*, website, paper report).

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CHAPTER

11

Surveillance of antimicrobial resistance in food animals

Key Points

- **Canada does not have an active or an organized passive surveillance program for monitoring the presence of resistance in enteric bacteria in food animals**
- **Available data on resistance in bacteria derived from food animals is highly fragmented**
- **Recently, preliminary attempts have been made to develop a systematic monitoring program federally and in some provinces**
- **Surveillance of resistance in selected animal pathogens, particularly those that reach people through the food chain, is needed to:**
    - **identify the potential public health impact of antimicrobial drug use in food animals**
    - **undertake human health risk analyses**
    - **develop and evaluate programs designed to contain antimicrobial resistance**
- **Surveillance should be integrated with activities underway in both the human and agri-food sectors**

Assessment of the full impact on human health of antimicrobial drug use in food animals has been hampered by the relative lack of reliable data on antimicrobial resistance. As a generalization, on a global basis, data on antimicrobial resistance in bacteria of animal origin is fragmentary, often biased because it is commonly derived soley from diagnostic laboratories, focused on a narrow and variable range of bacterial pathogens, collected in an unsystematic way, and not generally comparable between laboratories and/or countries because the methods used for testing resistance have not been standardized. This unhappy state is changing in the wealthier countries, spurred on by the antimicrobial resistance crisis in medicine. Some countries, notably Denmark, have developed excellent surveillance data on antimicrobial resistance. They have used these data to assess when intervention is needed to control resistance rates, and, in these instances, to support the removal of certain antimicrobial drugs from use in growth promotion and to monitor resistance in bacteria, post-withdrawal of the drug(s).

The benefit of having reliable data on antimicrobial resistance in bacteria derived from food animals is that it can be used for a number of important purposes:

1. To document changes in resistance in important bacterial pathogens that can be acquired through the food chain by humans from animals. Examples of bacteria that cause acute diarrhoeal and other illness in generally healthy humans include *Campylobacter jejuni*, *Escherichia coli* O157:H7, and *Salmonella enterica* serovars, including *Salmonella* Typhimurium. Examples of bacteria causing serious illness in immunocompromised people include *Enterococcus faecium* and other *Enterococcus* species, including vancomycin-resistant enterococci (VRE).
2. To document changes in resistance in commensal bacteria (*e.g.*, *E. coli)* that can be acquired through the food chain by humans from animals. These bacteria, however, also have the ability to transfer resistance genes to human bacterial pathogens.
3. To document the efficacy of interventions taken to reduce antimicrobial drug use in animals by demonstrating the magnitude of the change in resistance in important pathogenic and commensal bacteria.
4. To provide justification, direction, and impetus for research into the mechanisms and transfer of resistance.
5. To provide the information necessary to conduct pre- and post-market evaluations of veterinary drugs.
6. To integrate with data on antimicrobial resistance in bacteria from human sources to evaluate the risk to Canadians of exposure to antimicrobial resistance through the food chain.

Current practices

There has never been a program of systematic monitoring of antimicrobial resistance of bacteria originating from food animals in Canada. Data on resistance in bacteria derived from food animals, when available, tends to be highly fragmented and opportunistic. Recently, preliminary attempts have been made to develop a systematic monitoring program, federally and in some provinces.

The work of scientists at the Laboratory for Foodborne Zoonoses in Guelph (1,2) provides a possible exception to the above, since it is related to the importance of the relationship between antimicrobial use in food animals and human health. The laboratory conducts ongoing monitoring of serovars of *Salmonella* isolated from animals, including the highly virulent *Salmonella* Typhimurium definitive phage type 104 (DT 104). Resistance testing is performed on a proportion of these *Salmonella*. However, the *Salmonella* currently received are from diagnostic and research submissions; therefore, they are not systematically collected and the findings may be biased. A project is currently underway to build on this existing passive system and improve the geographical representation of its diagnostic submissions. Typically, Canadian data on antimicrobial resistance in animal pathogens has addressed resistance only in the context of its adverse affect on treatment of infections in animals. Similar data obtained from individual animal health diagnostic laboratories also have been published sporadically, but with no intent to relate such findings to human health. As described in this report, veterinary diagnostic laboratories in Canada are not organized at the national level. Therefore, there are no formal

mechanisms to standardize methodologies and interpretation of tests for antimicrobial susceptibility, or, on a regular basis, to collate and publish data obtained across the country. Because resistance data from diagnostic laboratories originates from the identification of problems in specific herds/animals, it has an inherent bias that may suggest the presence of a greater degree of resistance than actually exists in the bacterial population. Therefore, these data may not be representative of exposure of Canadians to antimicrobial resistance in the food chain. However, if a standardized national reporting system for diagnostic laboratories is established, it may provide an early warning of emerging resistance issues.

Work in Canada that documents the relationship between antimicrobial drug use in animals and its effect on resistance in bacteria found in these animals was done in the early 1990s (3-6). Not only did this work document the extensive nature of antimicrobial drug use on farrow-to-finish hog farms in Ontario, it clearly identified the relationship between drug use and resistance in intestinal *Escherichia coli*, an easily isolated bacterium used as a "marker" organism to indicate the extent of resistance. Follow-up studies to this work were performed (Table 11.1) and showed an apparent increase in resistance on the same farms.

Table 11.1: Temporal changes in the antimicrobial resistance pattern of intestinal *Escherichia coli* isolated from pigs in Ontario (percentage resistance) (7).

Antimicrobial drug	1992	1999
Ampicillin	40%	53%
Spectinomycin	39%	53%
Streptomycin	55%	50%
Sulfisoxazole	50%	55%
Tetracycline	78%	92%

Recently, the Ontario Ministry of Agriculture and Food (OMAF) undertook a pilot project to document patterns of antimicrobial resistance among bacteria isolated from foods of animal origin. Isolates obtained from a diagnostic laboratory and from healthy food animals at slaughter were examined following the methodology used by the National Antimicrobial Resistance Monitoring System (NARMS) of the U.S. (8). The Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec took a similar approach, but with greater emphasis on potential human pathogens (9). Also, the Laboratory Centre for Foodborne Zoonoses recently examined antimicrobial resistance in *Campylobacter jejuni* isolated from poultry samples and from human infections in Ontario (10).

Surveillance practices in other countries

Although Canadian data on antimicrobial resistance in animal pathogens, including those important for human health, are fragmented, the lack of data is typical of other developed countries, with two notable exceptions. Denmark leads the way as the country with the most valuable data on antimicrobial resistance in bacteria isolated from animals. The Danish Veterinary Laboratory has had, for a number of years, a

consistent program of surveillance of antimicrobial resistance in normal intestinal bacteria obtained from animals as well as in selected animal pathogens, some significant for human health (11). This work is of exceptional quality, and includes detailed molecular analysis of genes involved in resistance in animal pathogens (12-14). Their assessments of the contribution of antimicrobial growth promoters to resistance in important human pathogens are of particular value. The Danes found that feeding the antimicrobial growth promoter, avoparcin, to chickens, pigs, and calves led to widespread resistance to vancomycin by species of fecal *Enterococcus* isolated from these animals. The finding led to the withdrawal of avoparcin as a growth promoter from use in Danish animals and, subsequently, in the entire E.U. The same laboratory also documented the relationship between use of virginiamycin as a growth promoter and resistance of enterococci to streptogramin antimicrobials, including quinupristin-dalfopristin. The latter drug was recently introduced into human medicine specifically for the treatment of VRE. These data have been used also in the E.U. to support the removal, in late 1999, of virginiamycin as a growth promoter (together with other antimicrobials: bacitracin, spiramycin, and tylosin). Also, they have been used to document the decline in vancomycin resistance in faecal enterococci in chickens and pigs following withdrawal of avoparcin as a growth promoter (15). In summary, the availability of very high quality Danish data, based on resistance surveillance, with subsequent detailed investigation of specific areas once apparent problems are identified, illustrates the value of well-designed resistance surveillance in support of important policy decisions on antimicrobial drug use in food animals.

In the U.S., NARMS was established in 1996 as a collaborative effort among the Food and Drug Administrations' Center for Veterinary Medicine (FDA, CVM), the U.S. Department of Agriculture (USDA), and the Centers for Disease Control and Prevention (CDC). The NARMS program monitors changes in susceptibilities of human and animal enteric bacteria to 17 antimicrobial drugs. Bacterial isolates are collected from human and animal clinical specimens, healthy farm animals, and food-animal carcasses. The objectives of the system include provision of descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from human and animal populations; facilitation of the identification of resistance in humans and animals as it arises; and provision of timely information to veterinarians and physicians. The ultimate goal of these activities is to prolong the lifespan of approved drugs by promoting prudent and judicious use of antimicrobial drugs and to identify areas for more detailed investigation (16). The NARMS program is designed as two nearly identical parts: an animal arm and a human arm. Human-origin isolates are submitted by 17 state and local Departments of Health for testing that is conducted at the National Center for Infectious Disease (NCID), CDC, in Atlanta, Georgia. Animal-origin enteric isolate susceptibility testing is conducted at the USDA Agricultural Research Service's (ARS) Russell Research Center in Athens, Georgia. Animal and human isolates currently monitored in NARMS are non-typhoid *Salmonella*, *Campylobacter*, *E. coli*, and *Enterococci*. The CDC/NCID and USDA/ARS provide the NARMS results annually in comprehensive summary reports. Data acquired through this well-established surveillance system, with other data, were used to document the marked rise in fluoroquinolone resistance of *Campylobacter jejuni*, an important cause of human diarrhoeal and other illness, isolated from broiler chickens. This resistance has been attributed to the use of enrofloxacin and sarafloxacin in the control of septicemic

Escherichia coli infections in chickens for at least the last five years. [This drug was approved for use as an egg-dip in Canada in 1988 but voluntarily withdrawn by the manufacturer in 1997]. These data were used in the "Risk assessment on the human health impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken," conducted for the U.S. FDA CVM in October, 2000 (17), which led to the proposal to withdraw approval for the use of fluoroquinolones in poultry in the U.S. This is therefore another example of the value of antimicrobial resistance surveillance in supporting policy changes based on scientific data.

In the U.S., the "Framework Document" proposed to be used for assessment or re-assessment of approval of antimicrobial drug use in food animals includes the development of "thresholds" for resistance in selected target microorganisms. If resistance exceeds a certain preset threshold, then steps would be implemented to reduce such resistance, for example by reduced use of the drug (18). If the Framework Document proposal is accepted, a reliable resistance surveillance system, such as NARMS, would thus be essential in determining when such thresholds are reached.

Analysis – surveillance of resistance

Canada does not have an active or an organized passive surveillance program for monitoring the presence of resistance in enteric bacteria in food animals. Therefore, Canada has no way of identifying potential problems, or the impact of any changes in antimicrobial drug use policies in food animals. In the absence of national surveillance data, policy changes can still be made, but based on data obtained in other countries, and with less confidence in the applicability of the information for Canadian conditions.

Surveillance of resistance in selected animal pathogens, particularly those that reach people through the food chain, has proven useful in other countries in assessing where interventions are needed and, in these cases, supporting removal or proposed removal of certain antimicrobial drugs from use in food animals. Bacteria isolated from healthy animals are more representative of the population entering the food chain than those isolated from treated animals. Bacteria selected for surveillance are foodborne pathogens (*Campylobacter, Salmonella*), commensal, Gram-negative, enteric pathogens (*Escherichia coli*) and commensal, Gram-positive bacteria (*Enterococcus*). The latter two bacteria are regarded as "generic" examples of robust Gram-negative and Gram-positive intestinal inhabitants, which can reach the human population through the food chain, as well as in other ways. Because of their potential to colonize the human intestine, these organisms may be a source of resistance genes for human pathogens as well as potential agents of opportunistic infection.

The methods used within a surveillance program must meet international standards. For example, they should be compatible with, if not identical to, those methods used by NARMS. A program of active collection of animal-derived bacteria followed by testing for antimicrobial resistance is more valid than a passive system for determining the broad range of resistance in clinically normal animals and in animal-derived food products. Passive collection of resistance data, based on diagnostic laboratory material, while useful for identifying clinically important problems,

generally provides information that is less representative of the majority of animals and farms than a program of active surveillance. Development of the infrastructure for an active surveillance system would mean that additional bacteria could be added on an occasional, as needed basis, and also that the system could be fine-tuned over time.

The objectives of an active, national surveillance program for antimicrobial resistance in foodborne pathogens and in "indicator" bacteria should be as follows:

1. to identify the potential public health impact of antimicrobial drug use in food animals;
2. to trigger changes in national antimicrobial drug use policy and to monitor the effect of such changes;
3. to identify the need for targeted studies into identified problems;
4. to be part of an integrated global system addressing the human health impact of antimicrobial drug use in animals;
5. to provide data relevant to the development of new antimicrobial products in food animals and to ongoing monitoring of resistance to new products once they have been approved for use in food animals; and
6. to identify possible illegal use of antimicrobial drugs in food animals.

The advantage of a national system of active surveillance is that it could be used to support policy changes over time; this has proven to be valuable in other countries. If an approach similar to the "Framework Document" approach in the U.S. was adopted, an active surveillance system would be absolutely necessary. The disadvantage of an active surveillance system is the cost. It is expensive to commit the labour and laboratory resources required for a long-term program.

If such a system is developed, then it should be integrated with activities underway in both the human and agri-food sectors. There are several directorates within Health Canada's Population and Public Health Branch with activities related to antimicrobial resistance. The Centre for Infectious Disease Prevention and Control (CIDPC) hosts individuals working on surveillance for human enteric illness, sexually-transmitted diseases, respiratory, bloodborne and nosocomial infections. The Laboratory for Foodborne Zoonoses (LFZ) in Guelph has the mandate to perform research, surveillance, and risk assessment activities related to the human-animal interface. The Canadian Science Centre for Human and Animal Health in Winnipeg provides research, specialized diagnostic services and laboratory disease surveillance. An integrated surveillance program will require these directorates to partner with the Canadian Food Inspection Agency (CFIA) and provincial food inspection agencies. The CFIA reports to the Minister of Agriculture and Agri-Food Canada (AAFC) and is responsible for federal food safety inspection and compliance activities and national animal and plant health programs. Their provincial counterparts are responsible for similar programs at the provincial level.

The Laboratory for Foodborne Zoonoses is currently involved in a small number of pilot projects. For example, all Canadian meat packers and processors who export or supply companies that export products to the U.S. are required to meet USDA requirements for HACCP programs. This involves the systematic collection of samples that are cultured for *Salmonella* and *E. coli*. This testing is done privately and the results are proprietary. The Canadian Meat Council and the Canadian Poultry

and Egg Processors Council are collaborating on a voluntary basis with LFZ to have the *Salmonella* isolates forwarded to LFZ for resistance testing. Experience gained with this and other pilot programs might assist in the development of a national surveillance system of antimicrobial resistance in bacteria of animal origin.

LFZ has recently acquired the laboratory infrastructure to conduct antimicrobial resistance testing on a significant scale. This technology is utilized by the NARMS system. The Veterinary Drug Directorate supported the purchase of this equipment and its technical support. This will allow for harmonization of Canadian and NARMS results.

LFZ has developed a comprehensive and epidemiologically sound sampling plan for a national antimicrobial resistance surveillance system in food animals and retail products. This was done under the guidance of the National Steering Committee for Antimicrobial Resistance Surveillance in Enterics, which has representation from Health Canada, the CFIA, Alberta, Quebec, and Ontario. Health Canada and the CFIA are currently in negotiations to pilot the abattoir portion of this plan at a national level in 2002. Discussions are also underway between LFZ and several provinces to pilot the retail portion of the plan in this fiscal year. Resources provided by Health Canada's Veterinary Drugs Directorate have been instrumental in moving these projects forward. These pilot projects will provide vital information on logistics and resources as well as facilitating refinement of the sampling plan.

Conclusions

Identifying the magnitude of the resistance problem in Canada is hampered by the lack of an ongoing, representative, active or passive resistance surveillance system. Available data on resistance in bacteria derived from food animals is highly fragmented and drawn from a few regions and targeted studies. Recently, preliminary attempts have been made to develop a systematic monitoring program federally and in some provinces. Surveillance of resistance in selected animal pathogens, particularly those that reach people through the food chain, is needed to identify the potential public health impact of antimicrobial drug use in food animals, to undertake human health risk analyses, and to develop and evaluate programs designed to contain antimicrobial resistance. Surveillance in animals and food should be integrated with activities underway in both the human and agri-food sectors.

Recommendations

28. In consultation with the provinces, other federal agencies and industry groups, design and implement an ongoing, permanent, national surveillance system for antimicrobial resistance arising from food-animal production. Surveillance should include indicator and pathogenic bacteria isolated from animals, foods, and imported animal products.
29. Collect, interpret, and publish resistance surveillance data, ideally in partnership with other groups. Approach the food-animal and pharmaceutical industries to provide support for pilot or special studies.

30. Design the program to support human health risk analysis and policy development on antimicrobial use.
31. The bacteria chosen for active surveillance and the laboratory methods used within the surveillance program should be comparable to those of NARMS, so that Canada can participate in a global system of surveillance of antimicrobial resistance in bacteria of food-animal origin.
32. Integrate the surveillance system with the national surveillance of antimicrobial resistance in human enteric bacterial pathogens conducted by Health Canada.

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CHAPTER

12

Alternatives to antimicrobial drugs in food animals, plus research and education needs

Key Points

- **Producers and veterinarians already have a variety of non-antimicrobial methods to control infectious disease:**
  - **biosecurity (on-farm practices and procedures to limit the introduction and spread of disease)**
  - **quarantine**
  - **vaccination**
  - **selective sourcing of animals (e.g. from disease-free herds)**
  - **all-in-all-out management**
  - **laboratory testing**
  - **sanitation of premises, farm entry restrictions**
- **To reduce dependence on antimicrobials, research is needed to develop additional alternative methods of disease control, and to improve on existing ones (*e.g.* vaccines, genetic resistance to disease, health management)**
- **Some alternative methods of promoting growth and enhancing feed efficiency are available and others are being researched (*e.g.* probiotics, feed additives)**
- **National resistance research priorities and improved coordination of research and transfer of technology are needed**
- **The Canadian Veterinary Medical Association (CVMA) and Canadian Committee on Antibiotic Resistance (CCAR) contribute to promotion of prudent-use practices and national coordination of activities to control resistance**
- **Improvements are needed in the education of veterinarians, producers and the public with respect to antimicrobial resistance in animals and impacts on human health**

Calls to reduce antimicrobial use in food animals provide incentives to search for alternatives that may achieve similar goals, *i.e.*, to prevent or control infectious disease, promote growth, and increase feed efficiency. Furthermore, there are important educational and research efforts required to effectively implement many of the recommendations made in previous chapters. The purpose of this chapter is to review and provide recommendations on alternatives to antimicrobials, as well as to highlight research and educational needs.

Alternatives to antimicrobials

There are a myriad of potential approaches that can be used to promote the health and productivity of food animals without the use of antimicrobial drugs. In general, these include management practices that reduce the likelihood and impact of infectious diseases (biosecurity), probiotics, enzymes, oligosaccharides, minerals, herbs, acidification, vaccines, novel peptides, novel antibodies, immune potentiators, and selective breeding. Canadian producers are quick to adopt practices that are humane and environmentally sound in addition to being cost-effective and profitable. It should be noted that alternative products may themselves be subject to safety assessment for possible human or animal health risks.

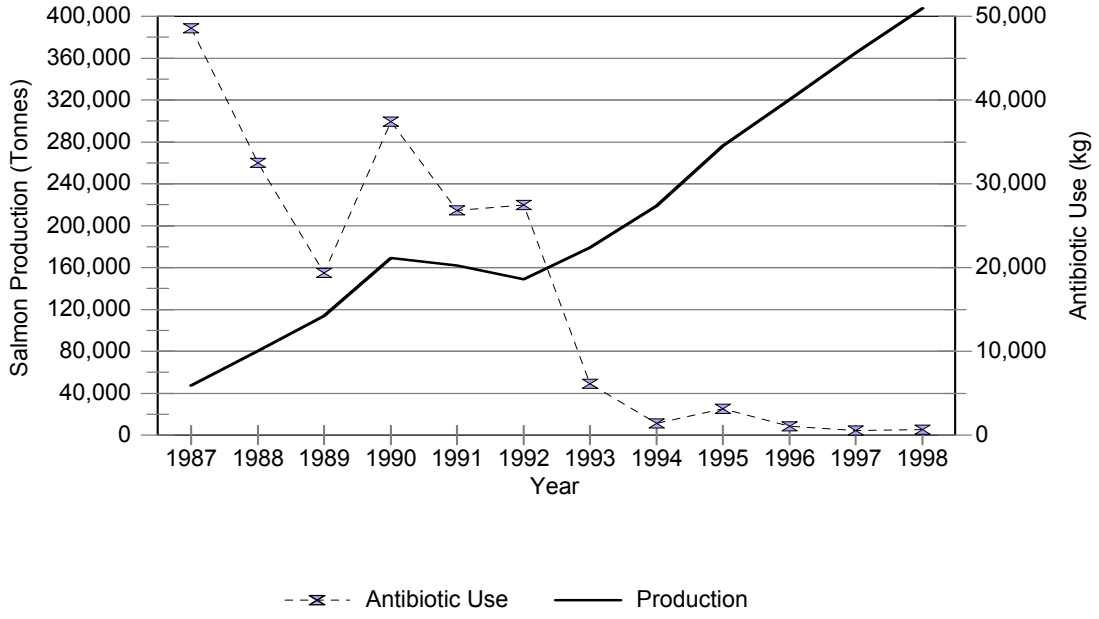
In food-animal production, biosecurity is a term that is used to describe measures for control of infectious disease. These include measures to prevent introduction of new diseases onto a farm and to prevent spread of disease within a farm. Strict disease control programs, such as disease screening of hatcheries and artificial insemination centres, can reduce or prevent vertical transmission of pathogens. Special attention is also paid to introduction of new animals onto farms and reducing the number of sources of replacement animals. Quarantine or laboratory screening tests can be useful for detecting some diseases. A variety of measures can be used to limit contact with carrier animals on neighbouring farms, or with wildlife and rodents. Some farms (particularly poultry and swine) practice “all-in-all-out” management. This enables cleaning and disinfecting of facilities between groups of animals and reduces the risk of introduction and maintenance of pathogens within herds that is seen in “continuous-flow” management. Biosecurity is widely used in the swine and poultry industries, and increasingly in the dairy industry, but it is used less in the beef industry, where animal movements between farms (*e.g.* from ranches to feedlots) and mixing from multiple sources is more common. Spread of endemic disease on farms (*e.g.*, mastitis in dairy cows) can be reduced by improved sanitation (washing of teats and dipping with sanitizers) or by segregating animals at high risk (*e.g.* using outdoor hutches for dairy calves). Most food animals are susceptible to respiratory disease, especially when kept in confinement, so maintenance of air quality is important.

Some diseases can be at least partially controlled or prevented by vaccination (*e.g. E. coli* diarrhea, viral and bacterial respiratory disease in pigs and cattle). Controlling viral disease can help reduce the need for antimicrobial treatment of secondary bacterial infections. The most dramatic example of vaccines reducing the need for antimicrobial treatment occurred in the Norwegian salmon-farming industry. After vaccines were introduced to control *Vibrio salmonicida* and *Aeromonas salmonicida* in salmon, fish farmers dramatically reduced antimicrobial use (1) (Figure 12.1).

Some mineral oxides and salts (*e.g.*, zinc oxide, copper sulfate) have antibacterial activity and also exert growth-promoting effects when fed at pharmacologic doses. These products have enjoyed widespread use, but have been criticized due to their potential build-up in the

environment. In Canada, this practice is limited because of regulatory constraints on the mineral levels allowed in feed.

Figure 12.1. The effect of multivalent *Aeromonas salmonicida*/Vibrio vaccines on antimicrobial use in the Norwegian salmon-farming industry (source: Norwegian Directorate of Fisheries).



Probiotics, or bacterial cultures of beneficial organisms, have been investigated as feed additives. Under proper circumstances such additives can be effective, although their use in pelleted feeds is problematic since the temperatures commonly reached during processing are high enough to kill living organisms. The exact nature of the organisms used is also important. Non-living derivatives of cellular organisms, such as cell-wall components of yeast, have also been used as nutritional additives. For example, mannan oligosaccharide (MOS) is derived from yeast cell walls and provides decoy attachment sites for Gram-positive pathogens, thereby preventing attachment to enterocytes and subsequent colonization. Studies have shown MOS to be equally as effective as bambermycins and virginiamycin in promoting growth in turkeys (2).

Enzymes have been used to enhance the digestive efficiency of animals and thus promote growth. At the same time, alterations in microbial flora of the gastrointestinal tract have been reported. A recent review (3) gives further details regarding the use of enzymes and their effects on animal production efficiency.

Organic acids, essential oils and herbal extracts have been investigated for their growth-promoting and/or bacterial-inhibiting effects. Some of these compounds may hold promise as

growth enhancers (4,5). It is a common misconception that because these materials are natural extracts they are harmless, or without deleterious effect. This remains to be seen, since many powerful pharmaceutical agents in regular use today were originally isolated from natural plant extracts. Regardless of the nature or source of alternative materials, all ingredients used in livestock feed must be approved by the Feed Section of the CFIA prior to their use.

Educational and research needs

In the educational arena, some governments, veterinarians and producer organizations have assumed leadership roles in enhancing efforts to evaluate the use of antimicrobial drugs in animals. Table 12.1 provides examples of national and provincial educational activities that respond to this issue.

Table 12.1: Examples of national and provincial activities by different organizations that address education and research needs in antimicrobial resistance

Organization	Date	Activity
Expert Committee on Animal Nutrition of the Canadian Agri-Food Research Council	2001	Workshop: Alternative Products and Practices to Antibiotic Growth Promotants.
Canadian Pork Council	2000	Research Priorities: (6) “management/husbandry to negate the need for antibiotic therapy in the future” (7,8); “alternatives to antimicrobials”; participation in Bacterial Pathogen Research network.
Poultry Industry Council	2001	“need for a national research strategy on Anti-microbial Resistance (AMR)...national funding initiative for AMR research.”
Beef Cattle Research Council, Canadian Cattlemen’s Association	2000	Strategies and Priorities: “antibiotics and antimicrobial resistance.”
Canadian Veterinary Medical Association	2000	Three pamphlets: “Antimicrobial Resistance: the Canadian Perspective. Information for the Practising Veterinarian”; “Guidelines on the Prudent Use of Antimicrobial Drugs in Animals”; and “Superbugs and Veterinary Drugs.”
	2002-present	Approval of prudent-use guidelines for different species-specific veterinarians.
Banff Pork Seminar (Alberta Pork; Alberta Agriculture, Food and Rural Development; University of Alberta)	2000	“Antimicrobial drugs: Miracle drugs or pig feed”; “Producing pigs without antibiotic growth promoters.”
Ontario Ministry of Agriculture, Food and Rural Affairs	1999	Major conference: Agriculture’s role in managing antimicrobial resistance (Toronto).
Animal Nutrition Association of Canada	1998–2000	Nutrition conference topics on alternatives to and/or antimicrobial-free production.
Alberta Cattle Commission	1999–present	Canada Alberta Beef Industry Development Fund: study of antimicrobial resistance in beef cattle and impact on human health.

While such activities could be regarded as exploratory, they illustrate the impact that criticism of agriculture's use of antimicrobial drugs has had on the industry. Also, they illustrate that these groups are open to change or to promote change. The Ontario Ministry of Agriculture and Food (OMAF) has developed and evaluated an innovative Swine Medicines Course for pork producers (6). Participants who successfully complete the course and pass an examination, receive a certificate. This certificate could be used, and in Ontario it is expected to be used, as a basic requirement in the future for those wanting to purchase antimicrobials OTC. Other livestock producer organizations are interested in, or are developing, similar courses for their commodities.

The Canadian Committee on Antibiotic Resistance (CCAR), financially supported by Health Canada, has a mandate to facilitate the implementation of an "Integrated Action Plan for Canadians on Controlling Antimicrobial Resistance." The plan promotes control strategies across all sectors, including antimicrobial use in agricultural production (7). This is an important multidisciplinary group, which collates and coordinates national activities to address the issue of antimicrobial resistance. CCAR has provided funds for initiatives such as that of the Canadian Veterinary Medical Association (CVMA) to educate its members about prudent use of antimicrobial drugs. The CVMA identified antimicrobial resistance as a national priority in 1999 and has an ongoing Antimicrobial Resistance Committee that promotes prudent-use guidelines, among other activities.

The Canadian Agri-Food Research Council (CARC) is charged with the coordination of publicly funded agri-food research across Canada. CARC builds consensus on research priorities and oversees a coordination system for agri-food research and technology transfer in Canada. CARC's committee system includes participants from industry, universities and governments; the committees identify issues and opportunities to be addressed through research. One of CARC's activities is maintaining a national database of agri-food research efforts. It does not provide funds for active promotion of research or education.

Current and proposed practices in other countries

The World Health Organization's Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food outlined the importance of veterinary undergraduate, postgraduate, and continuing education on preventive medicine, prudent antimicrobial use and antimicrobial resistance, as well as the need to evaluate the effectiveness of educational strategies for prudent use (8). The WHO also emphasized the need to educate producers and stakeholders about prudent-use principles, as well as about the importance of optimizing animal health through disease prevention programs and good management practices. The WHO also described the need to develop guidelines on prudent use of antimicrobials in animals in a multidisciplinary, peer-reviewed manner. This is happening. For example, in the U.S., the American Veterinary Medical Association (AVMA) has coordinated efforts by each of the major species-specific national veterinary associations to develop and publish prudent-use guidelines.

Analysis – alternatives to antimicrobials

Producers need evidence that animals reared in commercial conditions using antimicrobial drugs only for disease treatment can perform as well as those animals where antimicrobial drugs are used for disease treatment and for growth promotion and disease prevention. In Canada, more studies, similar to that described by Van Lunen and others (9), are needed to complement the research information coming from other countries (10). The experiences of countries such as Sweden and Denmark, which have had considerable success with the husbandry of animals after the market withdrawal of antimicrobial drugs used for growth promotional and feed efficiency purposes, need to be carefully analyzed. Also, a study of the broader European experience, following the withdrawal of major growth promotional antimicrobials in 1999, would be useful.

Other research priorities include:

- characterizing, more specifically, antimicrobial resistance in animal bacteria by determining the genes responsible for this resistance
- understanding the mechanisms of transmission for antimicrobial resistant microbes (zoonotic pathogens and commensals) and resistance genes from animals to humans, and vice versa
- understanding the link between therapeutic and non-therapeutic uses of antimicrobials and the development of antimicrobial resistant pathogenic bacteria in food animals
- developing better tools to determine antimicrobial resistance and to better understand the spread of resistant bacteria among animals
- developing animals that are more resistant to infectious diseases in order to decrease the need for antimicrobials
- identifying the design and construction of husbandry system(s) and livestock buildings that minimize disease transmission while maximizing livestock health and performance without the use of antimicrobial drugs for growth promotion or sub-therapeutic purposes.

The challenge lies, first, in identifying existing research in Canada and elsewhere; second, in addressing the inherent gaps at both the basic and applied research levels; and third, in ensuring that the infrastructure exists for continued research and the development of new products. In Canada, there is already agricultural, provincial, and federal funding for research related to antimicrobial resistance. The research needs to be quantified and the results documented so that gaps and duplication can be avoided. In an ideal world, all funding sources would agree to a national set of priorities so that the investment could be maximized.

Conclusions

Antimicrobials are important to animal health management, but they are not the only means of disease control. Biosecurity, quarantine, age-segregation, limitations on animal movements between farms, vaccination, selective sourcing of animals, all-in-all-out management, sanitation and farm entry restrictions are some of the methods used to prevent and control infectious disease in livestock. Nevertheless, to reduce dependence on antimicrobials, research is needed to develop additional alternative methods of disease control and to improve on existing ones (*e.g.* vaccines, genetic resistance to disease, health management).

Some alternative methods of promoting growth and enhancing feed efficiency are available and others are being researched (e.g. probiotics, feed additives). National resistance research priorities and improved coordination of research and transfer of technology are needed. The Canadian Veterinary Medical Association (CVMA) and Canadian Committee on Antibiotic Resistance (CCAR) contribute to promotion of prudent-use practices and national coordination of activities to control resistance. Improvements are needed in education of veterinarians, producers and the public with respect to antimicrobial resistance in animals and impacts on human health.

Recommendations

33. Assume a leadership role in encouraging agriculture-related research on antimicrobial resistance, particularly on alternatives to antimicrobial drug use, including management systems that reduce dependence on antimicrobials. Governments, producer associations, research foundations and national funding agencies should give high priority to supporting research in these areas.
34. Support demonstration projects to evaluate programs that use multiple interventions to promote prudent use of antimicrobial drugs and reduce infection rates.
35. Give priority in the regulatory assessment process for antimicrobial drugs and related products that are unlikely to result in antimicrobial resistance in human pathogens and to products that will reduce the use of antimicrobial drugs in animals.
36. Encourage partners (including Agriculture and Agri-Food Canada, the CFIA, commodity organizations and provincial authorities) to improve education strategies to provide veterinarians and producers with information about the roles and benefits of prudent use of antimicrobial drugs and the risks of inappropriate use. Evaluate the effectiveness of educational programs on prudent use so they may continually be improved.
37. Enhance funding to CCAR to support its mission in promoting strategies aimed at preventing antimicrobial resistance. CCAR should also educate consumer groups about the human health aspects of antimicrobial use in food animals and efforts underway to reduce adverse effects.
38. Encourage Canadian veterinary colleges and veterinary associations to ensure that preventive medicine, prudent use and antimicrobial resistance are given high priority in veterinary undergraduate, postgraduate, and continuing education programs.

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Appendix 1: Terms of Reference

Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health

Purpose

In conjunction with the Canadian Food Inspection Agency (CFIA) and other stakeholder groups, Health Canada - Veterinary Drugs Directorate will develop comprehensive overarching policies aimed at identifying and managing the impact on resistance and human health associated with the animal uses of antimicrobial agents.

Scope

The primary focus of the advisory committee will be to provide information relevant to reducing the potential resistance and human health and safety impacts associated with animal uses of antimicrobial agents. This will include the identification and prioritization of relevant issues surrounding antimicrobial uses and their contribution to resistance as well as the development of strategies to track usage of antimicrobials.

Role and Mandate of the Advisory Committee

The role of the advisory committee will be to provide advice and assistance to the Director General, Veterinary Drugs Directorate, in the development of policy options related to the animal uses of antimicrobial agents by:

- Identifying and prioritizing issues relevant to a broad range of stakeholders.
- Overseeing, reviewing, commenting on, and providing expertise during the preparation of draft policy documents, based on the issues previously identified.
- Identifying sources of, and facilitating access to, information and expertise relevant to the policy development project.
- Acting as stakeholder representatives to analyze issues, generate options and make recommendations concerning potential solutions.
- Providing feedback to stakeholder groups as appropriate.
- Recommending approaches to communicating risks associated with the animal uses of antimicrobial agents and the strategies identified to mitigate the risks.
- Reviewing, in consultation with the Bureau of Microbial Hazards and the Veterinary Drugs Directorate (Health Canada) and the CFIA, draft policy papers prior to general public consultation and subsequent implementation as policy documents.

Responses to the media regarding committee activity should be handled by the Chairperson (in English) and a designated francophone spokesperson. Individual committee members are free to comment to the media for their organization, but should refer any questions about the committee to committee spokespeople.

As an independent advisory committee, the group can make statements to the media on its own behalf without involvement from Health Canada. However, the committee cannot comment on behalf of the Department. Any communications that attempt to speak for the Department would need to be approved in advance by the Department.

Following each meeting, the committee may wish to write an update that can be used by each member to share information in their organizations or constituencies. This paragraph or letter could be inserted in information letters to members, or sent to media. If possible, Health Canada would appreciate knowing when this information is shared with the media so it can be prepared for follow-up questions.

Reporting Structure

Provides advice to the Director General, Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada.

Membership

A small multi-sectoral group of knowledgeable individuals capable of providing advice and assistance to the Veterinary Drugs Directorate. It will incorporate a balanced perspective from a wide range of interested external parties, including representatives from the agriculture and aquaculture industries, the pharmaceutical industry, animal health organizations, animal welfare organizations, the Canadian Veterinary Medical Association, health professionals, academia, consumer groups, provincial governments, etc.

Term

Members are appointed by the Director General, Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada, for the duration of the project (expected to be approximately three years).

Meetings

A large portion of the work will be conducted through a variety of communication means, including telephone or video conference interaction with the steering committee and various working groups. It is anticipated that there will be three to four advisory committee meetings per year.

Management and Administration

The Health Products and Food Branch - Veterinary Drugs Directorate primary contact are the Project Managers, who can be reached as follows:

Dr. Rebecca Irwin
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4th Floor, 1 Stone Road West
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Tower A, Ground Floor
11 Holland Avenue
Ottawa, ON K1A 0K9
Address Locator: 3000A

Unfortunately, it will not be possible to pay a per diem for the time spent on work for this committee. Reimbursement of expenditures by committee members related to meeting attendance will be in accordance with Treasury Board guidelines on travel and accommodation.

Appendix 2: Membership of Advisory Committee and Secretariat

Committee Member	Affiliation
Dr. Scott McEwen (chair)	Department of Population Medicine, University of Guelph
Dr. Paul Hasselback (co-chair)	Medical Officer of Health, Chinook Health Region, Lethbridge, Alberta
Ms. Brenda Nunns Shoemaker (co-chair)	Consumers' Association of Canada, North Saanich, British Columbia
Dr. Rejean Bouchard	Dairy Farmers of Canada, Ottawa, Ontario
Ms. Stephanie Brown	Animal Welfare Representative, Toronto, Ontario
Dr. Ron Clarke	Canadian Cattlemen's Association, Hague, Saskatchewan
Dr. Paul Dick	Canadian Animal Health Institute, Guelph, Ontario
Dr. Patricia Dowling	Western College of Veterinary Medicine, Saskatoon, Saskatchewan
Dr. Lyn Ferns	Veterinary Pathology Laboratory, Nova Scotia Department of Agriculture and Marketing, Truro, Nova Scotia
Dr. S. K. Ho	CARC, c/o Agiculture and Agri-Food Canada, Ottawa, Ontario
Dr. Yves Labbé	Chicken Farmers of Canada and CFIA, Ottawa, Ontario
Dr. Don Low	Mt. Sinai and Princess Margaret Hospitals, Toronto, Ontario
Dr. Keith McMillan	Lilydale Co-operative Ltd. Edmonton, Alberta
Mr. Carl Moore	Canadian Pork Council, Ottawa, Ontario
Dr. Marie Nadeau	Ministère de l'Agriculture, des Pêcheries et de l'Alimentation, Sainte-Foy, Québec
Dr. John Prescott	Department of Pathobiology, University of Guelph
Dr. Bill Revington	New-Life Mills Ltd., Cambridge, Ontario
Dr. Myron Roth	Salmon Health Consortium, Ottawa, Ontario
Dr. Deborah Stark	Canadian Veterinary Medical Association, Ottawa, Ontario

Secretariat Member	Affiliation
Dr. Lateef Adewoye	Health Canada, Ottawa, Ontario
Ms. Estelle Bernier	Health Canada, Ottawa, Ontario
Dr. Shiv Chopra	Health Canada, Ottawa, Ontario
Dr. Anne Deckert	Health Canada, Guelph, Ontario
Dr. Lucye Galand	Health Canada, Ottawa, Ontario
Dr. Rebecca Irwin	Health Canada, Guelph, Ontario
Ms. Catherine Italiano	CFIA, Ottawa, Ontario
Dr. Manisha Mehrotra	Health Canada, Ottawa, Ontario
Dr. Richard Reid-Smith	Health Canada, Guelph, Ontario
Ms. Annie Savoie	CFIA, Ottawa, Ontario
Ms. Linda Webster	CFIA, Ottawa, Ontario
Dr. William Yan	Health Canada, Ottawa, Ontario

Appendix 3: Extra Tables for Chapter 5

Table A.3.1: Growth promoter claims in the CMIB: (8th edition, 1998)

CMIB #	Compound	Species	Level in Feed	Claima[a]
4	Arsanilic acid	1. Broilers	99 mg/kg	growth, f.c.
		2. Pullets	99 mg/kg	growth, f.c.
		3. Layers	99 mg/kg	growth, f.c.
		4. Turkeys	99 mg/kg	growth, f.c.
		5. Swine	50–99 mg/kg	growth, f.c.
10.1	Chlortetracycline HCl	1. Chickens	5.5 mg/kg	growth, f.e.
		2. Turkeys	5.5 mg/kg	growth, f.e.
		3. Swine	5.5 mg/kg	growth, f.e.
		4. Calves	11 mg/kg	growth, f.e.
		5. Lambs	11 mg/kg	growth, f.e.
		6. Mink	27 mg/kg	growth, f.e.
10.2	Bacitracin (Zn or MD)	1. Chickens	4.4 mg/kg	gain, f.e.
		2. Turkeys	4.4 mg/kg	gain, f.e.
		3. Swine	4.4 mg/kg	gain, f.e.
10.5	Lincomycin HCl	1. Broilers	2.2 mg/kg	growth, f.u.
10.7	Procaine Penicillin	1. Chickens	2.2 mg/kg	growth
10.1	Tylosin Phosphate	1. Swine	44/22/11 mg/kg[b]	growth, f.e.
10.11	Virginiamycin	1.Swine	11 mg/kg	gain
		2. Chickens	11 mg/kg	gain, f.e.
10.12	Bambermycins	1. Chickens	2 mg/kg	gain, f.e.
		2. Turkeys	2 mg/kg	gain
10.13	Salinomycin[c]	1. Swine	25 mg/kg	gain
		2. Swine	25 mg/kg	f.e.
10.14	Zinc Bacitracin and	1. Chickens	3.3/1.1 mg/kg	gain, f.e.
	Procaine Penicillin	2. Turkeys	3.3/1.1 mg/kg	gain, f.e.
		3. Swine	3.3/1.1 mg/kg	gain, f.e.
21	3-nitro-4-hydroxy-phenylarsonic acid	1. Chickens	50 mg/kg	gain, f.e.
		2. Chicken-r[d]	50 mg/kg	gain, f.e.
		3. Chicken-l[e]	50 mg/kg	f.e.
		4. Turkeys	50 mg/kg	gain, f.e.
		5. Swine	25–50 mg/kg	gain, f.e.
34	Chlortetracycline HCl	Various	See Table 5.6	
35, A	Oxytetracycline	Various	See Table 5.7	

CMIB #	Compound	Species	Level in Feed	Claima[a]
	HCl			
38	CTC, Sulfamethazine & Proc. Penicillin	Swine	See Table 5.8	
41	Erythromycin thiocyanate	Breeding Chick.	220 mg/kg	gain, egg prod'n
49	CTC & Sulfamethazine	Beef Cattle	350/350 mg/h/d	gain, f.e.
53	Carbadox	Swine-w[f]	55 mg/kg	gain, f.e.
55	OTC & Neomycin Sulfate	Beef Cattle	500/500 mg/h/d	gain, f.e.
57	Monensin sodium	3. Beef Cattle	11/33 mg/kg	f.e.
		5. Cattle[g]	200 mg/h/d	gain
66	Lasalocid sodium	3. Beef Cattle	36 mg/kg	gain, f.e.
		4. Cattle[g]	200mg/h/d	gain
69	Salinomycin sodium	2. Beef Cattle	11,13,16 mg/kg	f.e.

[a] Growth and increased rate of gain are taken to be synonymous. Feed conversion (f.c.), feed efficiency (f.e.) and feed utilization (f.u.) are taken to be synonymous and are generally defined as feed intake per unit of live weight gain.
[b] 44 mg/kg for use in starters, 22 mg/kg in growers, and 11 mg/kg in finishers.
[c] The efficacy for improvement of feed efficiency in swine has not been established with mash feed;
Claim 2 is for pellet feed only.
[d] Replacement chickens (pullets intended for lay).
[e] Laying (mature) chickens.
[f] Weaner pigs up to 35 kg body weight; carbadox is currently under a federal "stop sale" in Canada.
[g] For cattle on pasture (slaughter, stocker and feeder cattle; beef and dairy replacements).

Table A.3.2: Summary of CMIB 34 chlortetracycline HCl

Species	Total Claims	GP Claims[a]	GP Plus…[b]	Prophylactic[c]	Rates[d]	Notes
Broilers	8	7	5	1	220 (2)	5
					110 (5)	
					55 (1)	
Layers	6	6	4	1	110 (5)	
					55 (1)	
Pullets	7	6	4	1	220 (1)	5
					110 (5)	
					55(1)	
Turkeys	12	7	5	2	220 (3)	5
					110 (7)	
					55 (2)	
Lambs	1	0	0	0	22(1)	
Swine	4	2	1	1	110 (2)	
					55(2)	
Beef and NL Dairy[e]	1	0	0	1	0.22mg/kg BW[f]	
Calves	2	0	0	2	55 (2)	

[a] growth promoter claims are claims that refer to growth and/or feed efficiency, but not a recognized disease condition. Typically, these claims refer to “stress due to…” or similar phrasing.

[b] growth promoter plus… refers to growth and/or feed efficiency but also mentions another recognized disease condition such as chronic respiratory disease, atrophic rhinitis, synovitis, non-specific enteritis. These are a subset of the growth promoter claims.

[c] Prophylactic claims are claims that refer to the expected exposure of target species to a named disease condition. This is the 55 mg/kg level except for one claim in turkeys (110 mg/kg for synovitis/infectious sinusitis) and for beef and non-lactating dairy cows.

[d] Rates given as mg/kg of diet unless otherwise indicated; the number of claims at that rate are given in brackets.

[e] Non-lactating dairy animals.

[f] BW = body weight; claim also allows 70 mg/head/day.

Table A.3.3: Summary of CMIB 35 oxytetracycline HCl

Species	Total Claims	GP Claims[a]	GP Plus…[b]	Prophylactic[c]	Rates[d]	Notes
Broilers	8	7	5	1	220 (2)	5
					110 (5)	
					55 (1)	
Layers	6	6	5	1	220 (1)	
					110 (4)	
					55 (1)	
Pullets	7	6	5	1	220 (2)	5
					110 (4)	
					55(1)	
Turkeys	9	7	6	2	220 (2)	
					110 (6)	
					55 (1)	
Lambs	2	0	0	0	110(1)	
					22 (1)	
Swine	5	2	2	1	550 (1)	
					110(2)	
					55(2)	
Beef	1	0	0	1	75mg/hd/d[e]	
Calves	2	0	0	2	55 (2)	

[a] growth promoter claims are claims that refer to growth and/or feed efficiency, but not a recognized disease condition. Typically, these claims refer to “stress due to…” or similar phrasing.

[b] growth promoter plus… refers to growth and/or feed efficiency but also mentions another recognized disease condition such as chronic respiratory disease, atrophic rhinitis, synovitis, non-specific enteritis. These are a subset of the growth promoter claims.

[c] Prophylactic claims are claims that refer to the expected exposure of target species to a named disease condition. This is the 55 mg/kg level except for one claim in turkeys (110 mg/kg for synovitis/infectious sinusitis) and for beef and non-lactating dairy cows.

[d] Rates given as mg/kg of diet unless otherwise indicated; the number of claims at that rate are given in brackets.

[e] 75 mg/head/day for prevention of bloat.

Table A.3.4: Summary of CMIB 38 chlortetracycline/sulfamethazine/procaine penicillin

Species	Total Claims	GP Claims[a]	GP Plus…[b]	Prophylactic[c]	Rates[d]
Swine	6	4	2	0	110/110/55 (6)

[a] growth promoter claims are claims that refer to growth and/or feed efficiency, but not a recognized disease condition. Typically, these claims refer to "stress due to…" or similar phrasing.
[b] growth promoter plus… refers to growth and/or feed efficiency but also mentions another recognized disease condition such as chronic respiratory disease, atrophic rhinitis, synovitis, non-specific enteritis. These are a subset of the growth promoter claims.
[c] Prophylactic claims are claims that refer to the expected exposure of target species to a named disease condition. This is the 55 mg/kg level except for one claim in turkeys (110 mg/kg for synovitis/infectious sinusitis) and for beef and non-lactating dairy cows.
[d] Rates given as mg/kg of diet unless otherwise indicated; the number of claims at that rate are given in brackets.

Appendix 4: Presentations Made to Committee

Presenter	Date	Topic
Diane Kirkpatrick, Health Canada	December 13, 1999	Background on the Policy Development Process
Jean Breton, Kelly Butler, Health Canada	March 20, 2000	Veterinary Drug Regulation and Approval Process in Canada
Don Low, Mt Sinai Hospital	March 20, 2000	Antibiotics Important in Human Medicine
Richard Reid-Smith, Health Canada	March 20, 2000	Antimicrobial Use Surveillance
Anne Deckert, Health Canada	March 20, 2000	Antimicrobial Resistance Surveillance
Scott McEwen, University of Guelph	March 20, 2000	Risk Assessment
Ian Alexander, Health Canada	June 19, 2000	Extra Label Drug Use
Bruce Wozny, Health Canada	June 19, 2000	Sale of Active Pharmaceutic Ingredients as Drugs for Veterinary Use
Mansen Yong, Health Canada	June 19, 2000	Human Health Safety Assessment of Veterinary Drugs
Myron Roth, Aqua Health Ltd	June 19, 2000	Antimicrobial Use in Canadian Aquaculture
Bill Revington, New Life Feeds	January 15, 2001	Use of Antimicrobials – Feed Producer's Perspective
Stephen Sundlof, U.S. Food and Drug Administration, Rockville MD, U.S.A.	June 7, 2001	The United States Perspective on Agricultural Antimicrobial Resistance Issues
John Turnidge, Women and Children's Hospital, Adelaide, Australia	June 7, 2001	The Australian Perspective on Agricultural Antimicrobial Resistance Issues
Paula Fedorka-Cray U.S.D.A., Athens, GA, U.S.A.	June 7, 2001	National Antimicrobial Resistance Monitoring System and Related Research Activities in the United States

Appendix 5: List of Abbreviations

AAFC	Agriculture and Agri-Food Canada
AASP	American Association of Swine Practitioners
AHI	Animal Health Institute
AIDS	acquired immunodeficiency syndrome
AMDUCA	*Animal Medicinal Drug Use Clarification Act*
AMR	antimicrobial resistance
API	active pharmaceutical ingredients
ARET	Accelerated/Reduction of Toxics
ARS	Agricultural Research Service
ARO	antibiotic resistant organisms
ATC vet	Anatomical Therapeutic Chemical Veterinary Classification
AVMA	American Veterinary Medical Association
BCMAFF	British Columbia Minister of Agriculture, Fisheries and Food
BSE	bovine spongiform encephalopathy
BVD	Bureau of Veterinary Drugs
CAHI	Canadian Animal Health Institute
CAIA	Canadian Aquaculture Industry Alliance
CARC	Canadian Agri-Food Research Council
CARD	Canadian Adaptation and Rural Development Fund
CBA	Canadian Bison Association
CBHEPA	Canadian Broiler Hatching Egg Producers Association
CCA	Canadian Cattleman's Association
CCAR	Canadian Committee on Antimicrobial Resistance
CCC	Canadian Cervid Council
CCP	critical control point
CDC	Centers for Disease Control and Prevention
CEMA	Canadian Egg Marketing Agency
CIDPC	Centre for Infectious Disease Prevention and Control
CFA	Canadian Federation of Agriculture
CFC	Chicken Farmers of Canada
CFIA	Canadian Food Inspection Agency
CHEQ	Canadian Hatching Egg Quality
CHF	Canadian Hatchery Federation
CMIB	Compendium of Medicated Ingredients Brochure
CNISP	Canadian Nosocomial Infection Surveillance Program
COFFSP	Canadian On-Farm Food Safety Program
CPC	Canadian Pork Council
CSF	Canadian Sheep Federation

CTMA	Canadian Turkey Marketing Association
CVM	Center for Veterinary Medicine
CVMA	Canadian Veterinary Medical Association
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DFC	Dairy Farmers of Canada
DIN	Drug Identification Number
DNA	deoxyribonucleic acid
DT	definitive phage type
E.C.	European Community
e.g.	exempli gratia
E.U.	European Union
EAGAR	Expert Advisory Group on Antibiotic Resistance
EDR	emergency drug release
EMEA	European Medicines Evaluation Agency
EPA	Environmental Protection Agency
et al.	et alii
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
GATT	General Agreement on Tariffs and Trade
GMP	good management practices
GPP	good production practices
HACCP	Hazard Analysis Critical Control Point
HCl	hydrochloric acid
HIV	human immunodeficiency virus
HUS	haemolytic uremic syndrome
i.e.	id est
IOM	Institute of Medicine
JETACAR	Joint Expert Technical Advisory Committee on Antimicrobial Resistance
MDR	multidrug-resistant
MDRP	multidrug-resistant *Streptococcus pneumoniae*
MDRTB	multidrug-resistant *Mycobacterium tuberculosis*
MIC	minimum inhibitory concentration
MOS	mannan oligosaccharide
MRL	maximum residual levels
MRSA	methicillin-resistant *Staphylococcus aureus*
MT	metric tonne
NAFTA	North American Free Trade Agreement
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NAS	National Academy of Sciences
NCID	National Center for Infectious Disease
NIH	National Institutes of Health
NIPA	National Information Program on Antibiotics

NNIS	National Nosocomial Infections Surveillance
NRC	National Research Council
OFFSP	On-Farm Food Safety Program
OIE	Office International des Epizooties
OMAF	Ontario Ministry of Agriculture and Food
OTC	over-the-counter
PAAB	Pharmaceutical Advertising Board
PT	phage type
QREC	quinolone-resistant *Escherichia coli*
QSH	Quality Starts Here
R factors	resistance factors
R plasmids	resistance plasmids
RSPCA	Royal Society for the Prevention of Cruelty to Animals
SAGE	Science Advice for Government Effectiveness
SHC	Salmon Health Consortium
SOP	standard operating procedure
SRA	Society of Risk Analysis
SVA	Swedish National Veterinary Institute
TB	Tuberculosis
TDD	Therapeutic Drugs Directorate
TGA	Therapeutic Goods Administration
TMP/SXT	trimethoprim/sulfamethoxazole
TPD	Therapeutic Products Directorate
TPP	Therapeutic Products Program
UCS	Union of Concerned Scientists
U.K.	United Kingdom
U.S.	United States
USDA	United States Department of Agriculture
VCPR	veterinarian-patient-client-relationship
VDD	Veterinary Drugs Directorate
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medical Products
VMAC	Veterinary Medical Advisory Committee
VMD	Veterinary Medicines Directorate
VRE	vancomycin-resistant enterococci
WHO	World Health Organization