
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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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 opportunistic 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 considerations 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 sources, 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.

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.asmsusa.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.

References

1. World Health Organization (WHO) (2001). Global strategy for containment of antimicrobial resistance. WHO, Geneva, Switzerland. <http://www.who.int/emc/amr.html> (Accessed May 7, 2002)
2. House of Lords, U. K. (1998). Resistance of antibiotics and other antimicrobial agents. Seventh report of the House of Lords' Select Committee on Science and Technology, 1997–1998. The Stationary Office, London, U.K.
3. Harrison PF, Lederberg J (eds) (1998). Antimicrobial resistance: issues and options, workshop report. Proceedings of the forum on emerging infections of the Division of Sciences Policy, Institute of Medicine (July 1997). National Academy Press, Washington, D.C.
4. Department of Health, U. K. (1998). The path of least resistance. Main report of the Standing Medical Advisory Committee, sub-group on antimicrobial resistance. Department of Health, London, U.K.
5. Bager F (ed) (2002). DANMAP 99. DANMAP, Danish Zoonosis Centre, Danish Veterinary Laboratory, bulowsvej 27 DK-1790, Copenhagen, Denmark. *DANMAP*, <http://www.svs.dk>
6. McEwen S (2001). Improve antibiotic use in animals. *In*: WHO. Antibiotic resistance synthesis of recommendations by expert policy groups. WHO. <http://www.who.int/emc/amr.html> (Accessed May 7, 2002)
7. Food and Drug Administration (FDA) (Dec. 1999). Risk assessment on the human health impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken. <http://www.fda.gov/cvm/default.htm> (Accessed May 7, 2002)
8. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (1999). The use of antibiotic in food-producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth of Australia. <http://www.health.gov.au/pubs/jetacar.htm> (Accessed May 7, 2002).
9. Health Canada and the Infectious Disease Society (Nov. 1997). Controlling antimicrobial resistance: An integrated action plan for Canadians. Canadian communicable disease report - supplement vol23S7. <http://www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr/97vol23/vol23s7/index.html> (Accessed May 7, 2002).
10. Office of the Provincial Health Officer, British Columbia. (2000). Antimicrobial Resistance: A Recommended Action Plan for British Columbia.
11. Healthcare Ontario (2001). Antibiotic Resistance: Emerging Risks and the Partnership Solution. Ontario Ministry of Health and Longterm Care.
12. World Health Organization (WHO) (June 2000). WHO global principles for the containment of antimicrobial resistance in animals intended for food. WHO, Geneva, Switzerland.

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	<i>De novo</i> 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

^aMechanism 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)).

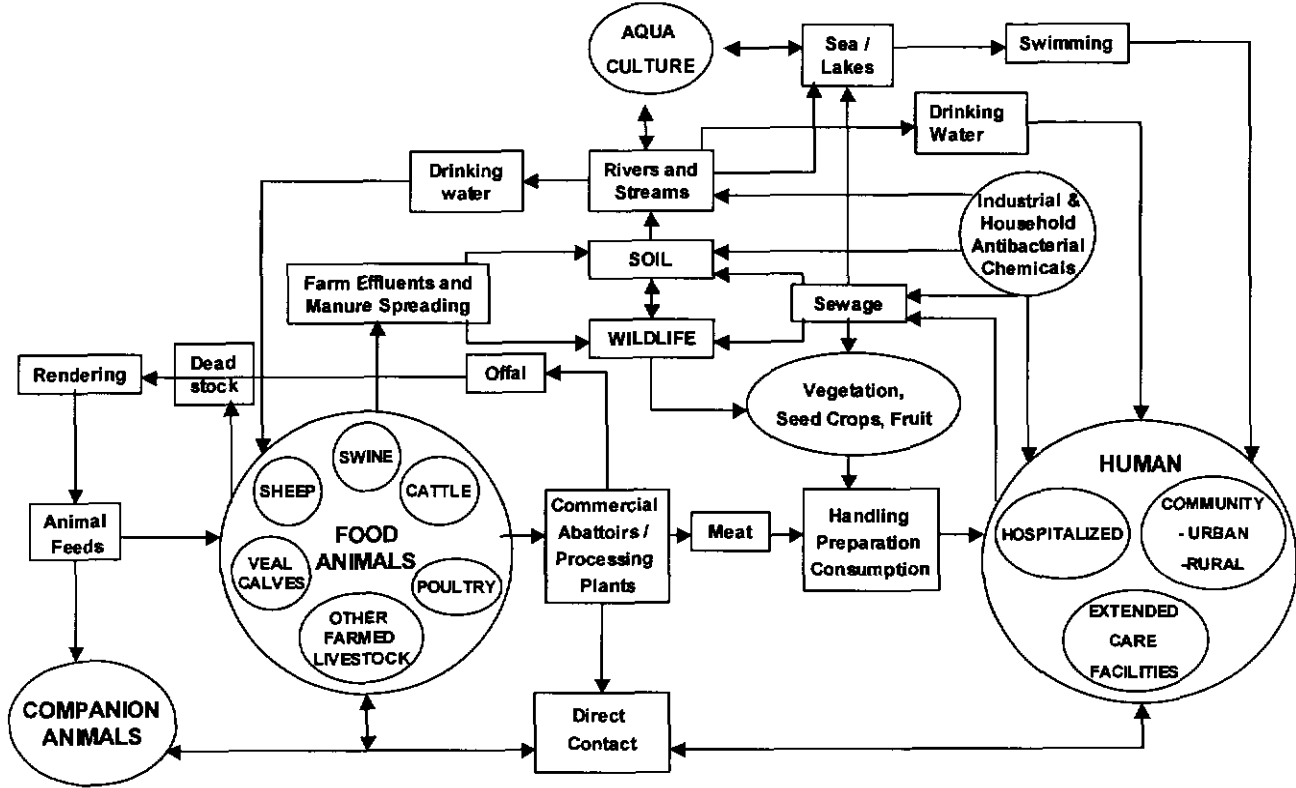


Figure 2.1 describes potential pathways by which resistant organisms may be introduced or transferred between populations of humans, animals, fish, water sources, and plants, and demonstrates the complexity of this ecosystem. The major risk factor for the emergence of resistance among bacterial populations 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).

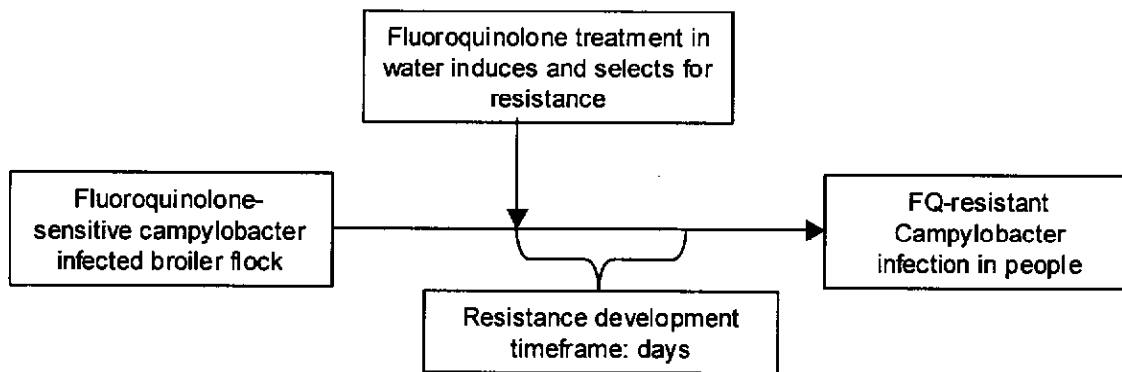
Consequently, antimicrobial resistance in zoonotic enteropathogens is a human health problem because necessary treatments may fail, be delayed or made more expensive, and because resistant infections may be more numerous, severe, and long-lasting than those infections that are more sensitive to the effects 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*

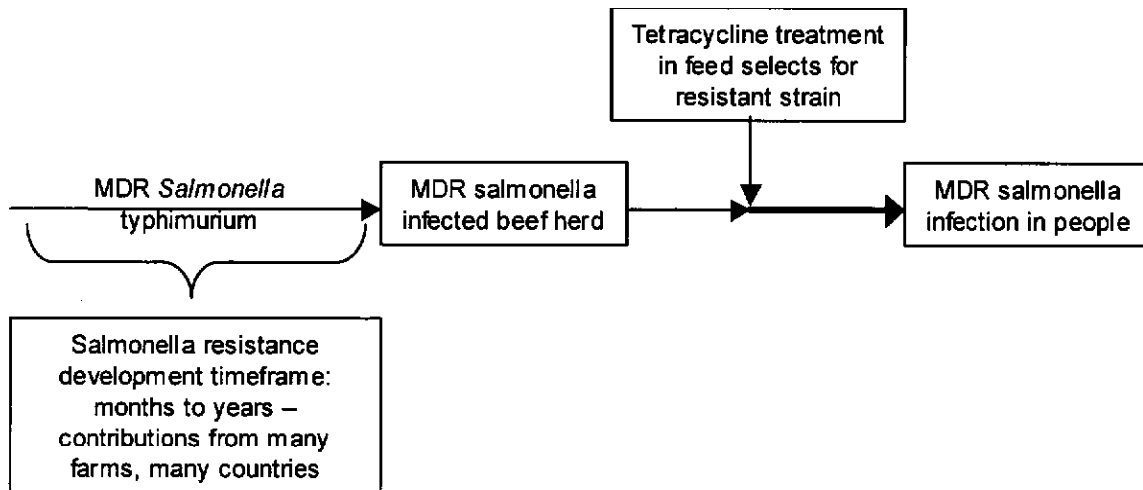
Multidrug-resistant (MDR) strains of *Salmonella enterica* have been a problem in Canada and many other countries for decades (27). A variety of studies have attempted to document the role of antimicrobial use in animals in the development and selection of these organisms (28). Many scientists believe 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 virginiamycin 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)

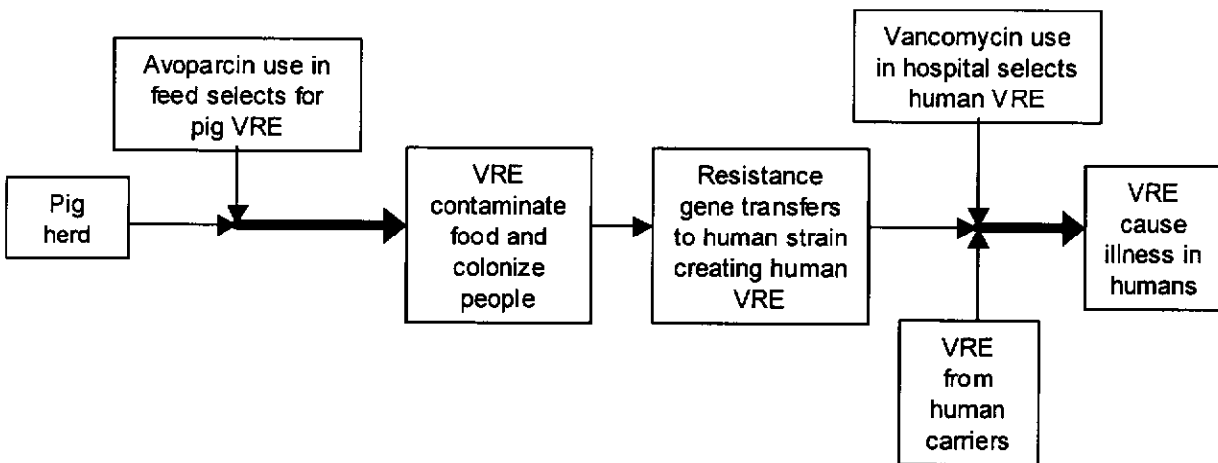
Enterococci are normally found in humans, with the highest concentration in the large intestine (33). They are also found in water, soil, food, a variety of other animals, and the inanimate environment of hospitals. Enterococci are opportunistic pathogens best known for their resistance to antimicrobial 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 introduced 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.

References

1. Health Canada (1996). Notifiable diseases on-line: campylobacteriosis. http://cythera.ic.gc.ca/dsol/ndis/diseases/camp_e.html (Accessed May 7, 2002)
2. Health Canada (Sept. 2000). Notifiable diseases on-line: notifiable disease incidence by year, 1986–1998. http://cythera.ic.gc.ca/dsol/ndis/c_time_e.html (Accessed May 7, 2002)
3. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al (1999). Food-related illness and death in the United States. *Emerg Infect Dis*, 5(5):607–625
4. Schroeder CM, Zhao C, DeRoy C, Torcolini J, Zhao S, White DG, Wagner DD, McDermott PF, Walker RD, Meng J (Feb. 2002). Antimicrobial resistance of *Escherichia coli* 0157 isolated from humans, cattle, swine, and food. *Appl Environ Microbiol*, 68(2):576–581

5. Todd ECD (1989). Preliminary estimates of costs of foodborne disease in Canada and costs to reduce salmonellosis. *J Food Prot*, 52(8):586-594
6. Poppe C, Ayroud M, Ollis G, Chirino-Trejo M, Smart N, Quessy S, Michel P (2001). Trends in antimicrobial resistance of *Salmonella* isolated from animals, food of animal origin, and the environment of animal production in Canada, 1994-1997. *Microb Drug Resist*, 7(2):197-212
7. 1999 National Antimicrobial Resistance Monitoring System (NARMS) Working Group (1999). National antimicrobial resistance monitoring system for enteric bacteria 1999 annual report.
8. Farber J, Mederios D, et al (June 2000). Quinolone resistance among clinical and food isolates of *Campylobacter* spp. Abstract T064 43rd Annual Meeting of the Canadian Federation of Biological Societies. Ottawa, Ontario.
9. Alekshun MN, Levy SB (1999). The *mar* regulon: multiple resistance to antibiotics and other toxic insults. *Trends Microbiol*, 7:410-413
10. Levy SB (2001). Antibacterial household products: cause for concern. *Emerg Infect Dis*, 7:512-515
11. Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, and Bager F (2001). Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother*. 45:2054-2059
12. Prescott JF, Baggot JD, and Walker RD (2000). Antimicrobial therapy in veterinary medicine (3rd ed). Ames, Iowa, Iowa State University Press. 796pp
13. Chee-Sanford JC, Aminov RI, Krapac IJ, Garrigues-Jeanjean N, Mackie RI (2001). Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities. *Appl Environ Microbiol*, 67:1494-1502
14. Linton AH. (1977). Antibiotic resistance: the present situation reviewed. *Vet Rec*. Apr 23;100(17):354-60.
15. Barza M. Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. *Clin Infect Dis* 2002 Jun 1;34 Suppl 3:S123-5
16. Kuschner RA, Trofa AF, Thomas RJ, et al (Sept. 1995). Use of azithromycin for the treatment of *Campylobacter* enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clin Infect Dis*, 21(3):536-541
17. Holmberg SD, Solomon SL, Blake PA (Nov. 1987). Health and economic impacts of antimicrobial resistance. *Rev Infect Dis*, 9(6):1065-1078
18. Helms M, Vastrup P, Gerner-Smith P, Molbak K. (2002). Excess mortality associated with antimicrobial drug-resistant *Salmonella* Typhimurium. *Emerg Infect Dis*, 8(5):490-495
19. Lee LA, Puhf ND, Maloney EK, et al (July 1994). Increase in antimicrobial-resistant *Salmonella* infections in the United States, 1989-1990. *J Infect Dis*, 170(1):128-134
20. Travers K, Barza M. (2002). Morbidity of infections caused by antimicrobial-resistant bacteria. *Clin Infect Dis* 34 Suppl 3:S131-4
21. Barza M, Travers K. (2002). Excess infections due to antimicrobial resistance: the "Attributable Fraction." *Clin Infect Dis*, 4 Suppl 3:S126-30
22. Dunlop RH, McEwen SA, Meek AH, Clarke RC, Black WD, Friendship RM (1998). Associations among antimicrobial drug treatments and antimicrobial resistance of fecal *Escherichia coli* of swine on 34 farrow-to-finish farms in Ontario, Canada. *Prev Vet Med*, 34:283-305
23. Hooper DC (Mar. 2001). Emerging mechanisms of fluoroquinolone resistance. *Emerg Infect Dis*, 7(2):337-341
24. Smith KE, Besser JM, Hedberg CW, Leano FT, Bender JB, Wicklund JH, Johnson BP, Moore KA, Osterholm MT (May 1999). Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. Investigation Team. *N Engl J Med*, 340(20):1525-1532
25. McDermott PF, Bodeis SM, English LL, White DG, Walker RD, Zhao S, Simjee S, Wagner DD (2002). Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. *J Infect Dis*, 185:837-840
26. Wang Y, Huang WM, Taylor DE. (1993). Cloning and nucleotide sequence of the *Campylobacter jejuni* *gyrA* gene and characterization of quinolone resistance mutations. *Antimicrob Agents Chemother* 1993 37(3):457-63
27. Poppe C, Smart N, Khakhria R, Johnson W, Spika J, Prescott J (Sept. 1998). *Salmonella typhimurium* DT 104: a virulent and drug-resistant pathogen. *Can Vet J*, 39(9):559-565
28. Spika JS, Waterman SH, Hoo GW, et al (Mar. 1987). Chloramphenicol-resistant *Salmonella newport* traced through hamburger to dairy farms: a major persisting source of human salmonellosis in California. *N Engl J Med*, 316(10):565-570
29. Swartz MN. (2002). Human diseases caused by foodborne pathogens of animal origin. *Clin Infect Dis*, 34 Suppl 3:S111-22
30. Radostits OM. (1999). The use of antimicrobials in beef cattle health management and production and the development of antimicrobial resistant pathogens and their transfer to humans causing disease which is difficult to treat. *The Bovine Proceedings* No. 32. September, 1999. pp75-110
31. O'Brien TF. (2002). Emergence, spread, and environmental effect of antimicrobial resistance: how use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. *Clin Infect Dis*, 34 Suppl 3:S78-84
32. Witte W (Feb. 1998). Medical consequences of antibiotic use in agriculture. *Sci*, 279:996-997
33. Chenoweth C, Schaberg D (1990). The epidemiology of enterococci. *Eur J Clin Microbiol Infect Dis*, 9:80-89
34. Murray BE (Mar. 1997). Vancomycin-resistant enterococci. *Am J Med*, 102(3):284-293
35. Gray JW, Pedler SJ (1992). Antibiotic-resistant enterococci. *J Hosp Infect*, 21:1-14

36. Endtz HP, van den Braak N, Verbrugh H, van Belkum A (Oct. 1999). Vancomycin resistance: status quo and quo vadis. *Eur J Clin Microbiol Infect Dis*, 18(10):683–690
37. Eliopoulos GM (1993). Increasing problems in the therapy of enterococcal infections. *Eur J Clin Microbiol Infect Dis*, 12:409–412
38. Budavari SM, Saunders GL, Liebowitz LD, et al (Nov. 1997). Emergence of vancomycin-resistant enterococci in South Africa [letter]. *S Afr Med J*, 87(11):1557
39. Zanella RC, Valdeto F, Lovgren M, et al (1999). First confirmed case of a vancomycin-resistant *Enterococcus faecium* with vanA phenotype from Brazil: isolation from a meningitis case in Sao Paulo. *Microb Drug Resist*, 5(2):159–162
40. Bell JM, Paton JC, Turnidge J (Aug. 1998). Emergence of vancomycin-resistant enterococci in Australia: phenotypic and genotypic characteristics of isolates. *J Clin Microbiol*, 36(8):2187–2190
41. Allerberger F, Lass-Florl C, Dierich MP, et al (May 1997). Vancomycinresistente enterokokken in Osterreich [Vancomycin-resistant enterococci in Austria]. *Wien Klin Wochenschr*, 109(9):312–320
42. Kjerulf A, Pallesen L, Westh H (June 1996). Vancomycin-resistant enterococci at a large university hospital in Denmark. *APMIS*, 104(6):475–479
43. Torell E, Fredlund H, Tornquist E, et al (1997). Intrahospital spread of vancomycin-resistant *Enterococcus faecium* in Sweden. *Scand J Infect Dis*, 29(3):259–263
44. Bhat KG, Paul C, Ananthakrishna NC (Apr. 1998). Drug resistant enterococci in a south Indian hospital. *Trop Doct*, 28(2):106–107
45. Hanger HC, Sidwell A, Aitken J, Brett M (Sept. 1999). Vancomycin-resistant enterococci in New Zealand [letter; comment]. *N Z Med J*, 112(1095):347–348
46. Dan M, Poch F, Leibson L, et al (Nov. 1999). Rectal colonization with vancomycin-resistant enterococci among high-risk patients in an Israeli hospital. *J Hosp Infect*, 43(3):231–238
47. Son R, Nimita F, Rusul G, et al (1999). Isolation and molecular characterization of vancomycin-resistant *Enterococcus faecium* in Malaysia. *Lett Appl Microbiol*, 29:118–122
48. Marin ME, Mera JR, Arduino RC, et al (1998). First report of vancomycin-resistant *Enterococcus faecium* isolated in Argentina. *Clin Infect Dis*, 26:235
49. Samet A, Bronk M, Hellmann A, Kur J (Feb. 1999). Isolation and epidemiological study of vancomycin-resistant *Enterococcus faecium* from patients of a haematological unit in Poland. *J Hosp Infect*, 41(2):137–143
50. van der Auwera, Pensart N, Korten V, et al (May 1996). Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. *J Infect Dis*, 173(5):1129–1136
51. Klare I, Badstubner D, Konstabel C, et al (1999). Decreased incidence of vanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microb Drug Resist*, 5(1):45–52
52. Bager F, Madsen M, Christensen J, Aarestrup FM. (1997). Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant *Enterococcus faecium* on Danish poultry and pig farms. *Prev Vet Med*, 31 :95–112
53. Sorensen TL, Blom M, Monnet DL, Frimodt-Moller N, Poulsen RL, Espersen F. (2001). Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. *N Engl J Med*, 345:1161–6
54. Goossens H (Aug. 1998). Spread of vancomycin-resistant enterococci: differences between the United States and Europe. *Infect Control Hosp Epidemiol*, 19(8):546–551
55. Armstrong-Evans M, Litt M, McArthur MA, et al (May 1999). Control of transmission of vancomycin-resistant *Enterococcus faecium* in a long-term-care facility. *Infect Control Hosp Epidemiol*, 20(5):312–317
56. McGeer AJ, Low DE (Dec. 2000). Vancomycin-resistant enterococci. *Semin Resp Infect*, 15(4):314–326
57. Elsner HA, Sobottka I, Feucht HH, et al (Mar. 2000). *In vitro* susceptibilities of enterococcal blood culture isolates from the Hamburg area to ten antibiotics. *Chemother*, 46(2):104–110
58. Coque TM, Tomayko JF, Rieke SC, et al (Nov. 1996). Vancomycin-resistant enterococci from nosocomial, community, and animal sources in the United States. *Antimicrob Agents Chemother*, 40(11):2605–2609
59. Hospitals Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services (June 1999). National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999. *Am J Infect Control*, 27(6):520–532
60. Stosor V, Peterson LR, Postelnick M, Noskin GA (Mar. 1998). *Enterococcus faecium* bacteremia: does vancomycin resistance make a difference? *Arch Intern Med*, 158(5):522–527
61. Garbutt JM, Ventrappagada M, Littenberg B, Mundy LM (Mar. 2000). Association between resistance to vancomycin and death in cases of *Enterococcus faecium* bacteremia. *Clin Infect Dis*, 30(3):466–472
62. Kruse H, Johansen BK, Rorvik LM, Schaller G (1999). The use of avoparcin as a growth promoter and the occurrence of vancomycin-resistant enterococcus species in Norwegian poultry and swine production. *Microb Drug Resist*, 5(2):135–139
63. Wendt C, Krause C, Xander LU, et al (July 1999). Prevalence of colonization with vancomycin-resistant enterococci in various population groups in Berlin, Germany. *J Hosp Infect*, 42(3):193–200
64. Endtz HP, van den Braak N, van Belkum A, et al (Dec. 1997). Fecal carriage of vancomycin-resistant enterococci in hospitalized patients and those living in the community in the Netherlands. *J Clin Microbiol*, 35(12):3026–3031

65. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (1998). JETACAR literature review. Antibiotic resistance in animal enteric bacteria and human disease - a review of the scientific literature, 1998. Department of Health and Aged Care, Australia
66. Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F. (2001). Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother*, 45:2054-9
67. Hammerum AM, Fussing V, Aarestrup FM, Wegener HC. (2000). Characterization of vancomycin-resistant and vancomycin-susceptible *Enterococcus faecium* isolates from humans, chickens and pigs by RiboPrinting and pulsed-field gel electrophoresis. *J Antimicrob Chemother*, 45:677-80
68. Willems RJ, Top J, van den Braak N, van Belkum A, Mevius DJ, Hendriks G, van Santen-Verheuver M, van Embden JD. (Mar. 1999). Molecular diversity and evolutionary relationships of Tn1546-like elements in enterococci from humans and animals. *Antimicrob Agents Chemother*. 43(3):483-91
69. Jensen LB, Hammerum AM, Aarestrup FM, et al (Dec. 1998). Occurrence of satA and vgb genes in streptogramin-resistant *Enterococcus faecium* isolates of animal and human origins in the Netherlands. *Antimicrob Agents Chemother*, 42(12):3330-3331

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. Niessleria 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

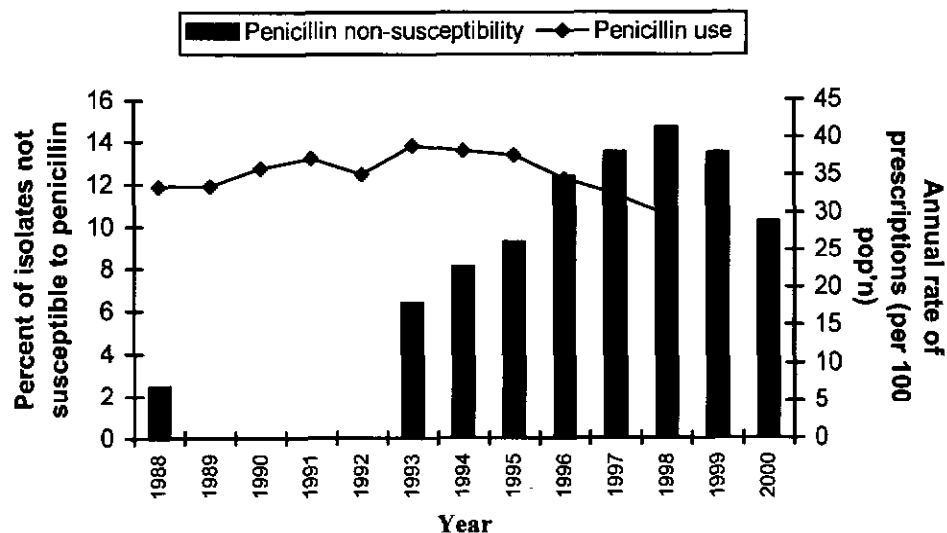
Unlike resistance in the zoonotic enteropathogens, resistance in most non-enteric (*e.g.*, respiratory, skin, genitourinary) bacterial infections of humans is almost entirely attributable to antimicrobial use in humans. These infections are major human health problems in Canada and abroad. The purpose 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)

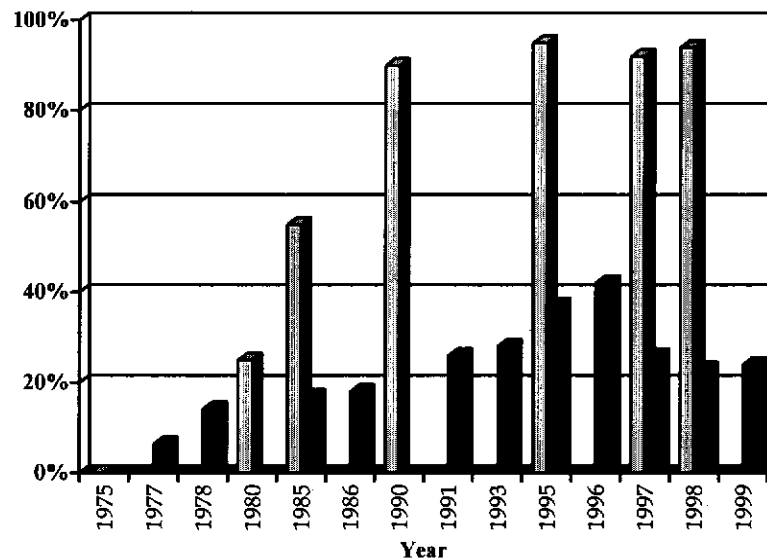


Disturbing information arose from a surveillance study from the U.S. where it was found that strains of *S. pneumoniae* that are highly resistant to the effects of penicillin now occur with greater frequency than intermediately resistant strains (32.5% versus 18%) (3). Resistance in *Haemophilus influenzae* 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 *Neisseria gonorrhoeae* during the 1980s and early 1990s (6). Fluoroquinolone-resistant *N. gonorrhoeae* (ciprofloxacin maximum inhibitory concentration (MIC) greater than or equal to 1.0 $\mu\text{g/mL}$) 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.

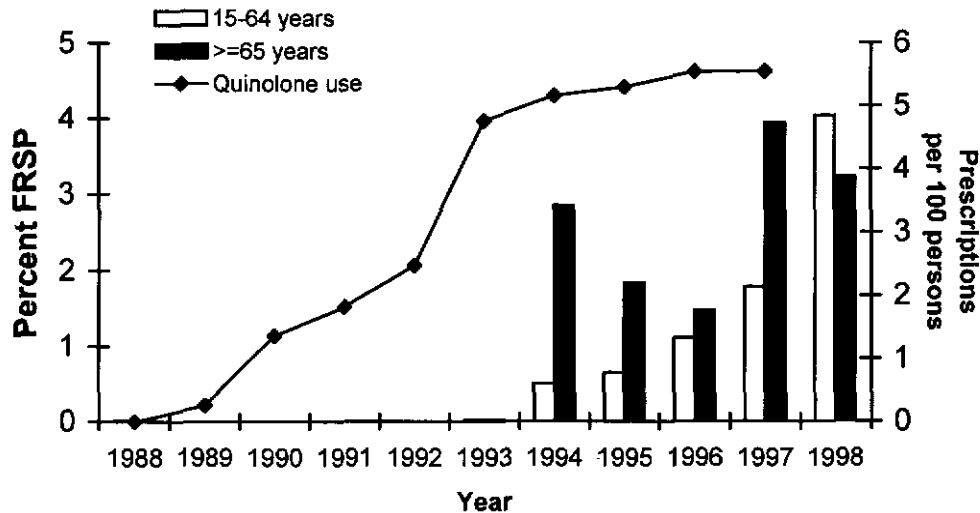
Analysis: impact of efforts to control antimicrobial resistance in the human health sector

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.

References

1. Gonzales R, Malone DC, Maselli JH, Sande MA (2001). Excessive antibiotic use for acute respiratory infections in the United States. *Clin Infect Dis*, 33(6):757-762
2. Gonzales R, Steiner JF, Sande MA (1997). Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA*, 278:901-904
3. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC (1999). Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. *Antimicrob Agents Chemother*, 43:1901-1908
4. Low DE (2001). Antimicrobial drug use and resistance among respiratory pathogens in the community. *Clin Infect Dis*, 15;33 Suppl 3:S206-13
5. Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, Cohn DL, Lambregts-van Weezenbeek CS, Kim SJ, Chaulet P, Nunn P (1998). Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization - International Union against tuberculosis and lung disease working group on anti-tuberculosis drug resistance surveillance. *N Engl J Med*, 338:1641-1649
6. Centers for Disease Control and Prevention (1998). 1998 guidelines for treatment of sexually transmitted diseases. *Morb Mortal Wkly Rep*, 47:1-111
7. Knapp JS, Fox KK, Trees DL, Whittington WL (1997). Fluoroquinolone resistance in *Neisseria gonorrhoeae*. *Emerg Infect Dis*, 3:33-39
8. Low DE, Garcia M, Callery S, Milne P, Devlin HR, Campbell I, Velland H (1993). Methicillin-resistant *Staphylococcus aureus* - Ontario. *Can Dis Wkly Rep*, 7:249-250
9. Roman RS, Smith J, Walker M, Byrne S, Ramotar K, Dyck B, Kabani A, Nicolle LE (1997). Rapid geographic spread of a methicillin-resistant *Staphylococcus aureus* strain. *Clin Infect Dis*, 25:698-705

10. Simor AE, Ofner-Agostini M, Bryce E, Green K, McGeer A, Mulvey M, Paton S (2001). The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance. *CMAJ*, 165:21–26
11. Centers for Disease Control and Prevention (1999). Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus* - Minnesota and North Dakota, 1997–1999. *JAMA*, 282:1123–1125
12. Kim T, Oh PI, Simor AE (2001). The economic impact of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals. *Infect Control Hosp Epidemiol*, 22:99–104
13. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP (1996). Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clin Infect Dis*, 23:1234–1239
14. Office of the Provincial Health Officer, British Columbia. Antimicrobial Resistance: A Recommended Action Plan for British Columbia. 2000
15. Healthcare Ontario. Antibiotic Resistance: Emerging Risks and the Partnership Solution. Ontario Ministry of Health and Longterm Care. 2001
16. Canadian Committee on Antibiotic Resistance (CCAR) (July 1999). Canadian Committee on Antimicrobial Resistance. Ottawa, Ontario. <http://www.ccar-ccra.org/> (Accessed May 7, 2002)
17. National Information Program on Antibiotics (2000). NIPA. Toronto, Ontario. <http://www.antibiotics-info.org> (Accessed May 7, 2002)
18. World Health Organization (WHO) (2001). Global strategy for containment of antimicrobial resistance. WHO, Geneva, Switzerland. <http://www.who.int/emc/amr.htm>
19. House of Lords, U.K. (1998). Resistance of antibiotics and other antimicrobial agents. Seventh report of the House of Lords' Select Committee on Science and Technology, 1997–1998. The Stationary Office, London, U.K.
20. Department of Health, U.K. (1998). The path of least resistance. Main report of the Standing Medical Advisory Committee, sub-group on antimicrobial resistance. Department of Health, London, U.K.
21. European Commission (May 1999). Report of the scientific steering committee on antimicrobial resistance. http://europa.eu.int/comm/dgs/health_consumer/index_en.htm
22. Bager F (ed) (2002). DANMAP 2000. DANMAP, Danish Zoonosis Centre, Danish Veterinary Laboratory, bulowsvej 27 DK-1790 Copenhagen, Denmark. *DANMAP*, <http://www.svs.dk>
23. Department of Health (Jan. 2002). Antibiotics: don't wear me out. London. <http://www.doh.gov.uk/antibioticresistance/index.htm> (Accessed May 7, 2002)
24. Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (US FDA), National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare and Medicaid Services (CMS), U.S. Department of Agriculture (USDA), Department of Defense, Department of Veterans Affairs, Environmental Protection Agency (EPA), Health Resources and Services Administration (HRSA) (Sept. 2001). Antimicrobial resistance: A public action plan to combat antimicrobial resistance. <http://cdc.gov/drugresistance/actionplan/index.htm> (Accessed May 7, 2002)
25. World Health Organization (WHO) (2001). Antibiotic resistance: synthesis of recommendations by expert policy groups. WHO. <http://www.who.int/emc/amr.htm> (Accessed May 7, 2002)
26. Chen D, McGeer A, de Azavedo JC, Low DE (1999). The Canadian bacterial surveillance network, 1999, decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N Engl J Med*, 341:233–239

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.

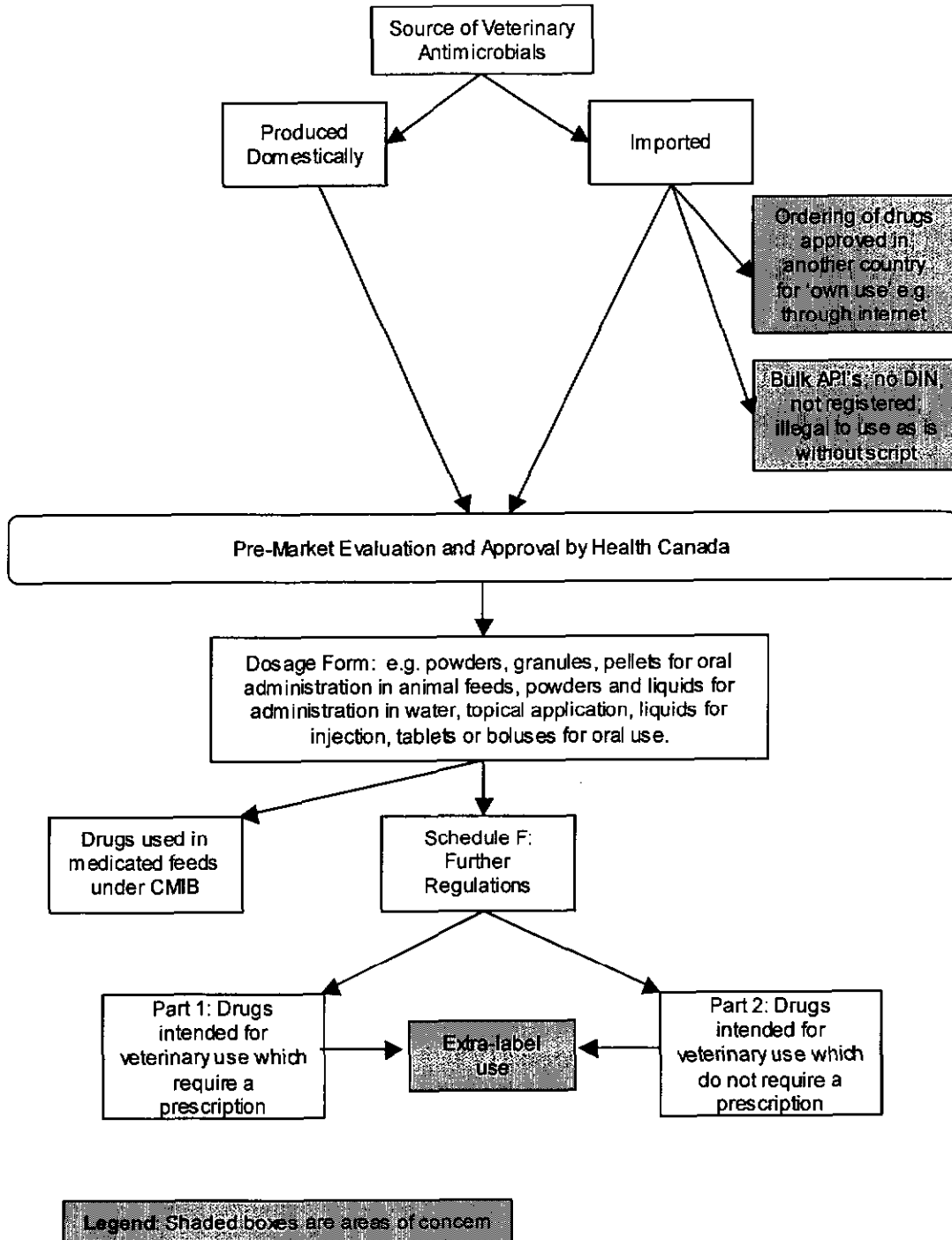
Ontario

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 than 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	<i>Alberta Livestock Disease Act</i> and <i>Veterinary Profession Act</i>	Prescription and OTC ^a (permit holders)	
British Columbia	<i>Pharmacists Act</i>	Prescription and OTC (layperson outlets and feed mills or dealers)	
Manitoba	<i>Pharmaceutical Act</i>	Prescriptions by veterinarians	
Newfoundland and Labrador	Current legislation under review		
New Brunswick	<i>An Act Respecting the New Brunswick Veterinary Medical Association</i>		VCPR ^b needed for prescription drug dispensing
Nova Scotia	<i>Veterinary Medical Act</i> <i>Pharmacy Act</i>		VCPR needed for prescription drug dispensing
Ontario	<i>Livestock Medicines Act</i>	OTC (licensed retail sales outlets)	
Prince Edward Island	<i>Veterinary Medical Act</i> <i>Pharmacy Act</i>		VCPR needed for prescription drug dispensing
Quebec	<i>Veterinary Surgeons Act</i> , <i>Pharmacy Act</i> and the <i>Animal Health Protection Act</i>	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 (EMA) 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, EMA 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 System			
	Prescribed by Veterinarian		OTC sale	Not Medicated feed
	On label	Off label		
Manufactured to regulated, GMP standards	Yes	Yes	Yes	Yes
Product and use approved by regulators	Yes	Approved for label use in at least one species	Yes	Yes
Veterinarian makes decision to use product ^a	Yes	Yes	Maybe	Maybe
Product distributor is trained and licenced	Yes	Yes	Some training of OTC	Yes
Regulations in place to enforce product use	<i>Food & Drugs Act Feeds Act Veterinarians Act</i>	<i>Food & Drugs Act Veterinarians Act</i>	<i>Food & Drugs Act Provincial acts</i>	CMIB
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

^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.

References

1. Mitchell GA (1988). The veterinary practitioner's right to prescribe. *Can Vet J*, 29:689–692
2. Ritter L (May 1991). Safety concerns over extra-label drug use (update). College of Veterinarians of Ontario. p.13
3. Ritter L, Alexander I (1993). Extra-label use policy of the Canadian Bureau of Veterinary Drugs. *J Am Med Vet Assoc*, 202:1623–1626
4. Health Canada's Therapeutic Products Program (Feb. 1999). Therapeutic Products Program, Food Directorate. <http://www.hc-sc.gc.ca/hpb-dgps/therapeut> (Accessed May 7, 2002)
5. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (1999). The use of antibiotic in food-producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth of Australia. <http://www.health.gov.au/pubs/jetacar.htm> (Accessed May 7, 2002)
6. The European Agency for the Evaluation of Medicinal Products (EMA) (1995). EMA. London. <http://www.emea.eu.int/>
7. European Commission (1999). Opinion of the scientific steering committee on antimicrobial resistance. European Commission - Health and Consumer Protection Directorate (General).
8. Food and Drug Administration's Center for Veterinary Medicine (FDA CVM) (2002). Food and Drug Administration Center for Veterinary Medicine. <http://www.fda.gov/cvm> (Accessed May 7, 2002)
9. Food and Drug Administration (FDA) (1999). A proposed framework for evaluating and assuring the human safety of the microbial effects of antimicrobial new animal drugs intended for use in food-producing animals (framework document)
10. Food and Drug Administration's Center for Veterinary Medicine (2000). An approach for establishing thresholds in association with the use of antimicrobial drugs in food-producing animals. <http://www.fda.gov/cvm/default.htm>
11. World Health Organization (WHO) (1997). The medical impact of the use of antimicrobials in food animals. WHO, Berlin, Germany.
12. World Health Organization (WHO) (1998). Use of quinolones in food animals and potential impact on human health. WHO, Geneva, Switzerland.
13. World Health Organization (WHO) (2000). WHO global principles for the containment of antimicrobial resistance in animals intended for food. WHO, Geneva, Switzerland.
14. Office International des Epizooties (OIE) (2000). Office International des Epizooties (OIE). World organization for animal health. <http://oie.int/> (Accessed May 7, 2002)
15. International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (2001). VICH. <http://vich.eudra.org/> (Accessed May 11, 2002)
16. International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (2001). Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance. Draft 1 edition. Bruxelles, Belgium. <http://vich.eudra.org/htm/topics.htm#t8> (Accessed May 7, 2002)
17. Codex Alimentarius Commission (2002). Codex Alimentarius Commission. <http://www.codexalimentarius.net/>
18. Health Canada (1998). Health Canada. Advisory Committees. <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/advcomm.html> (Accessed May 7, 2002)
19. Food and Drug Administration's Center for Veterinary Medicine (FDA CVM) (2001). Veterinary Medical Advisory Committee (VMAC). <http://www.fda.gov/cvm/index/vmac/vmactoc.htm> (Accessed May 7, 2002)
20. Dunlop RH, McEwen SA, Meek AH, Friendship RA, Clarke RC, Black WD (1998). Antimicrobial drug use and related management practices among Ontario swine producers. *Can Vet J*, 39:87–96
21. Miller MA, Flynn WT (2000). Chapter 34: Regulation of antibiotic use in animals. In: Antimicrobial therapy in veterinary medicine (3rd ed.). Iowa State University Press, Ames, Iowa.