

Strategies to ensure prudent use of antimicrobial drugs

Key Points

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

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

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

Prudent-use principles and responsibilities

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

Canada

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

General Principles:

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

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

Specific Principles:

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

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

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

United States

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

International organizations

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

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

Treatment guidelines

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

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

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

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

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

Prudent use

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

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

Incentives

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

Disincentives

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

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

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

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

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

Provincial endorsement

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

Treatment guidelines

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

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

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

Conclusions

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

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

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

Recommendations

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

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Food safety programs used in food-animal production

Key Points

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

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

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

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

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

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

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

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

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

Food safety programs on Canadian farms

Beef

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

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

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

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

Dairy

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

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

Pork

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

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

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

Chicken

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

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

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

Turkey

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

Hatching-egg producers and hatcheries

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

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

Eggs

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

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

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

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

Sheep

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

Bison

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

Deer and elk

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

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

Aquaculture — salmon and trout

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

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

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

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

^a from a variety of sources, including national commodity-group associations, supplemented with information from government sources (Canadian Food Inspection Agency, Agriculture Canada, Department of Fisheries and Oceans and Statistics Canada) and other sources such as CanFax Research Services. In many instances where specific figures were not available or data obtained did reconcile, figures were estimated by mathematical extrapolation.

^b includes veal; ^c metric tonnes; ^d milk includes milk, cream and milk used in milk products (ice cream, yogurt, can/evap milk); ^e million litres; ^f cheese, butter, milk powders; ^g million eggs.

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

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

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

Commercial feed industry

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

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

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

Analysis

Use of drugs on farms

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

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

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

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

Program development and implementation issues

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

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

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

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

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

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

Coordination between production and processing sectors

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

Applicability of HACCP to farms

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

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

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

Imported animals and food products

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

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

Conclusions

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

Recommendations

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

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Monitoring of antimicrobial drugs used in food animals

Key Points

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

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

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

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

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

Monitoring of antimicrobial use

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

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

Monitoring practices in other countries

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

Sweden

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

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

Denmark

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

Norway

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

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

The Rest of the European Union

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

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

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

Australia

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

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

United States

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

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

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

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

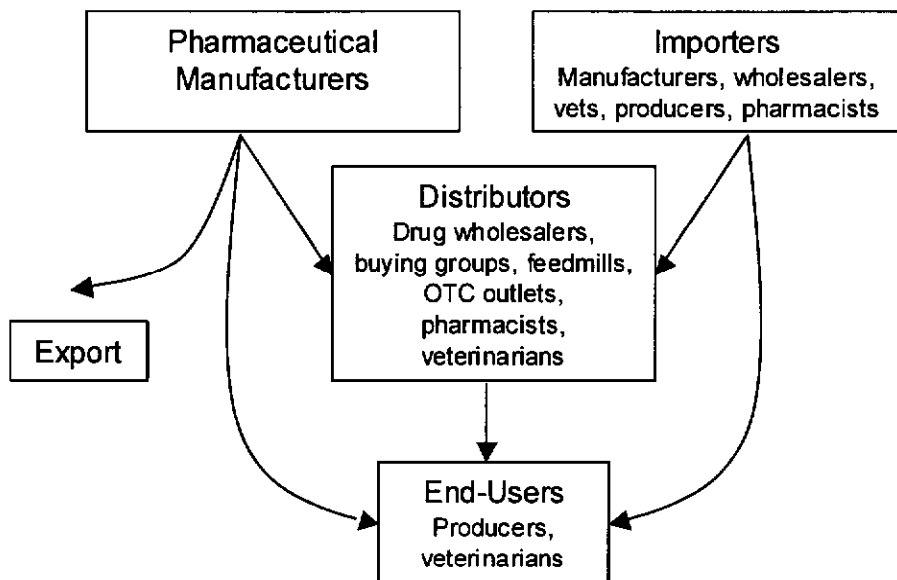
The FDA plans to develop an official monitoring program on antimicrobial use. The nature of this has not been finalized. In the initial proposal, the program will require manufacturers of antimicrobials in the U.S. to provide sales data on an annual basis. The sales data will be recorded on report forms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

Analysis – monitoring of antimicrobial use

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

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

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



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

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

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

Conclusions

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

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

Recommendations

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

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Surveillance of antimicrobial resistance in food animals

Key Points

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

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

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

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

Current practices

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

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

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

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

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

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

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

Surveillance practices in other countries

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

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

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

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

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

Analysis – surveillance of resistance

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

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

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

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

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

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

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

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

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

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

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

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

Conclusions

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

Recommendations

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

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

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

Key Points

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

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

Alternatives to antimicrobials

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

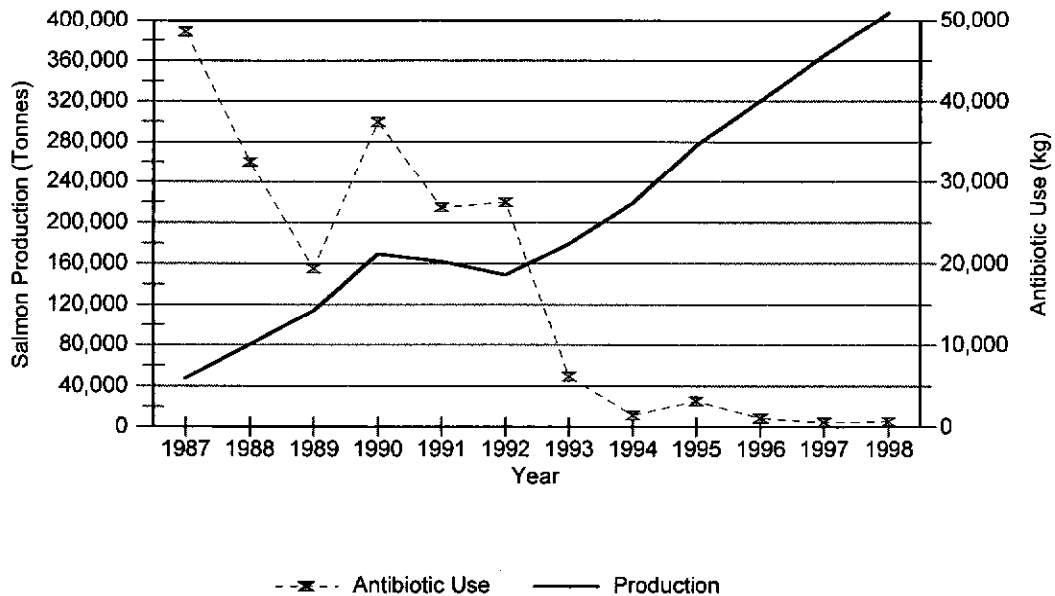
In food-animal production, biosecurity is a term that is used to describe measures for control of infectious disease. These include measures to prevent introduction of new diseases onto a farm and to prevent spread of disease within a farm. Strict disease control programs, such as disease screening of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

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

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

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

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



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

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

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

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

Educational and research needs

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

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

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

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

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

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

Current and proposed practices in other countries

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

Analysis – alternatives to antimicrobials

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

Other research priorities include:

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

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

Conclusions

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

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

Recommendations

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

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