CHAPTER

5

Uses of antimicrobial drugs in food animals

Key Points

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

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

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

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

Table 5.1: Types of antimicrobial use in food animals

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

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

Food animal production and antimicrobial use

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

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

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

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

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

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

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

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

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

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

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

Beef

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

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

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

Veal

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

Poultry

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

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

Swine

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

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

Dairy

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

Aquaculture

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

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

Sheep

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

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

Other species

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

Antimicrobials used in feeds

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

Table 5.3: Antimicrobials used in feeds in Canada

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

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

Benefits of growth promoters

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

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

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

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

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

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

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

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

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

Approved products

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

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

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

Antimicrobial treatment practices and policies of other countries

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

Australia

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

Sweden

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

Denmark

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

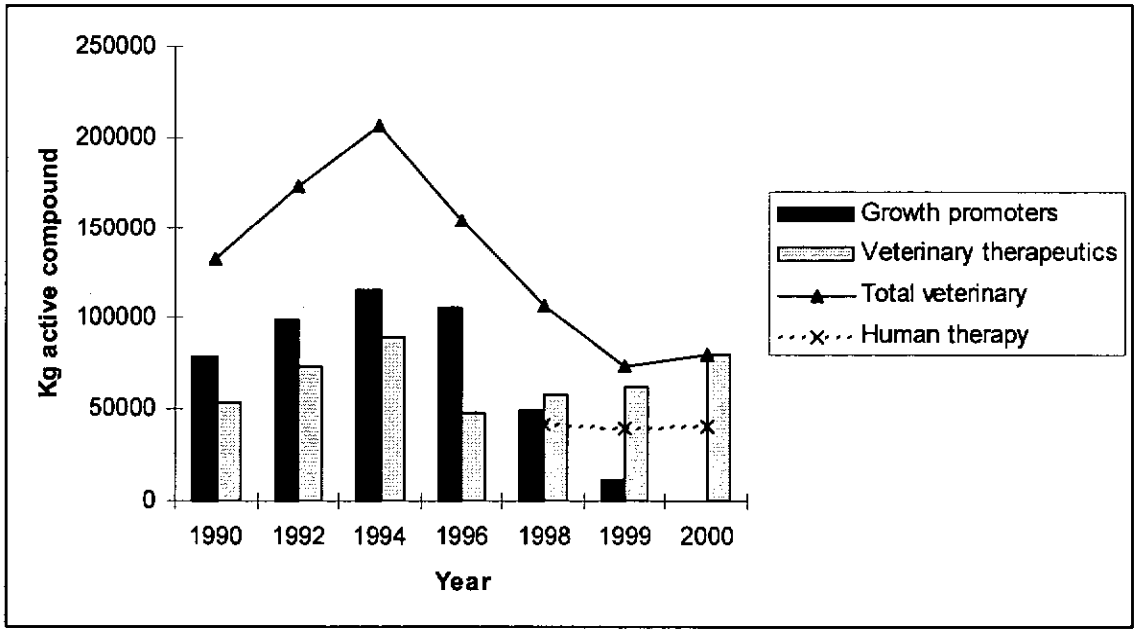
Although the bans were quite recent, some follow-up data are emerging. Total antimicrobial use in Denmark declined steadily from 1994–2000 along with declines in growth promoter use. Quantities of therapeutic antimicrobials increased modestly since 1996; however, total therapeutic quantities remained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

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

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

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

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



Analysis: antimicrobials used in food animals

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

On the positive side:

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

On the negative side:

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

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

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

Conclusions

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

References

1. Committee on Drug Use in Food Animals (1999). The use of drugs in food animals, benefits, and risks. National Academy Press, Washington, D.C.
2. Advisory Committee on the Microbiological Safety of Food (1999). Report on microbial antibiotic resistance in relation to food safety. Synopsis. The Stationery Office, London.
3. National Research Council (NRC) (1999). The use of drugs in food animals: benefits and risks. National Research Council Committee on drug use in food animals. National Academy Press, Washington, D.C.
4. Dunlop RH, McEwen SA, Meek AH, Friendship RA, Clarke RC, Black WD (1998). Antimicrobial drug use and related management practices among Ontario swine producers. *Can Vet J,* 39:87–96
5. Animal and Plant Health Inspection Service (APHIS) (Mar. 1997). Cattle and calves death loss 1995. USDA.
6. Guichon PT, Booker CW, Jim GK (1993). Comparison of two formulations of oxytetracycline given prophylactically to reduce the incidence of bovine respiratory disease in feedlot calves. *Can Vet J,* 34:736–741
7. Harland RJ, Jim GK, Guichon PT, Townsend HGG, Janzen ED (1991). Efficacy of parenteral antibiotics for disease prophylaxis in feedlot calves. *Can Vet J,* 32:163–168
8. Animal and Plant Health Inspection Service (APHIS) (Oct. 1997). Part III: Changes in the U.S. pork industry 1990–1995. USDA.
9. AVMA (June 2001). Judicious therapeutic use of antimicrobials. http://www.avma.org/scienact/jtua/default.asp (Accessed May 8, 2002).
10. Friendship R (2000). Antimicrobial drug use in swine. Antimicrobial therapy in veterinary medicine. Iowa State University Press, Ames, Iowa. p.602–616
11. Office of the Commission for Aquaculture Development, (2001). Legislative and Regulatory Review of Aquaculture in Canada. Communications Directorate, Department of Fisheries and Oceans, Ottawa, Ontario.
12. Canadian Standards Association International, (2000). PLUS 1141. Managing the Regulatory Requirements Facing the Canadian Aquaculture Industry. CSA International, Toronto, Ontario.

13. Sheppard, M. (2000). Antibiotic use in the British Columbia aquaculture industry (1996–998): Is the comparison with Norway realistic? Bulletin of the Aquaculture Association of Canada. 100–1, pp. 13–16.
14. Shryock TJ (2000). Growth promotion and feed antibiotics. In: Antimicrobial therapy in veterinary medicine (3rd ed.). Iowa State University Press, Ames, Iowa.
15. Bafundo KW (2001). The effect of virginiamycin on nutrient digestibility in poultry. Phibro Animal Health, Fairfield, NJ.
16. Hegde SN, Rolls RA, Coates ME (1982). The effects of the gut microflora and dietary fibre on energy utilization by the chick. *Br J Nutr,* 48:73–80
17. Lawrence K (July 1998). Growth promoters in swine. *In:* Proceedings of the 15th IVPS Congress. Birmingham, England.
18. Jukes TH (1986). Effects of low level antibiotics in livestock feeds. *Effects of Antibiotics in Livestock Feeds,* 10:112–126
19. Elwinger K, Berndtson E, Engstrom B, Fossum O, Waldenstedt L (1998). Effect of antibiotic growth promoters and anticoccidials on growth of *Clostridium perfringens* in the ceca and on performance of broiler chickens. *Acta vet scand,* 39:433–441
20. Canadian Food Inspection Agency (Sept. 2000). Compendium of medicating ingredient brochures (8th ed.). Ottawa, Ontario.
21. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (1999). The use of antibiotic in food-producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth of Australia. http://www.health.gov.au/pubs/jetacar.htm (Accessed May 8, 2002)
22. House of Lords, U. K. (1998). Resistance of antibiotics and other antimicrobial agents. Seventh report of the House of Lords' Select Committee on Science and Technology, 1997–1998. The Stationary Office, London, U.K.
23. Aarestrup FM (Oct. 1999). The European perspective on antimicrobial related regulations and trade. *In*: Proceedings: Agriculture's role in managing antimicrobial resistance conference (2nd ed.). Toronto, Ontario. p.170–173
24. Statens Serum Institute (2001). DANMAP 2000. Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods, and humans in Denmark. Danish Veterinary and Food Administration, Danish Medicines Agency, Danish Veterinary Lab.
25. Emborg H-D, Ersboll AK, Heuer OE, Wegener HC (2001). The effect of discontinuing the use of antimicrobial growth promoters on the productivity in the Danish broiler production. *Prev Vet Med,* 50:53–70
26. Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F (2001). Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother,* 45:2054–2059

CHAPTER

6

Managing antimicrobial resistance risks

Key Points

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

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

General principles

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

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

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

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

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

Human health risks from residues and resistance

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

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

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

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

Socio-economics

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

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

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

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

International trade

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

Pharmaceutical industry

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

Who benefits and who bears the risk

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

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

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

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

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

Notion of acceptable levels of risk

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

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

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

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

Consumer perspectives

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

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

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

Animal welfare perspectives

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

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

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

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

Legal/statutory issues

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

The policy requires that federal regulatory authorities ensure that:

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

c. parties proposing equivalent means to conform with regulatory requirements are given positive consideration.

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

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

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

Risk analysis practices

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

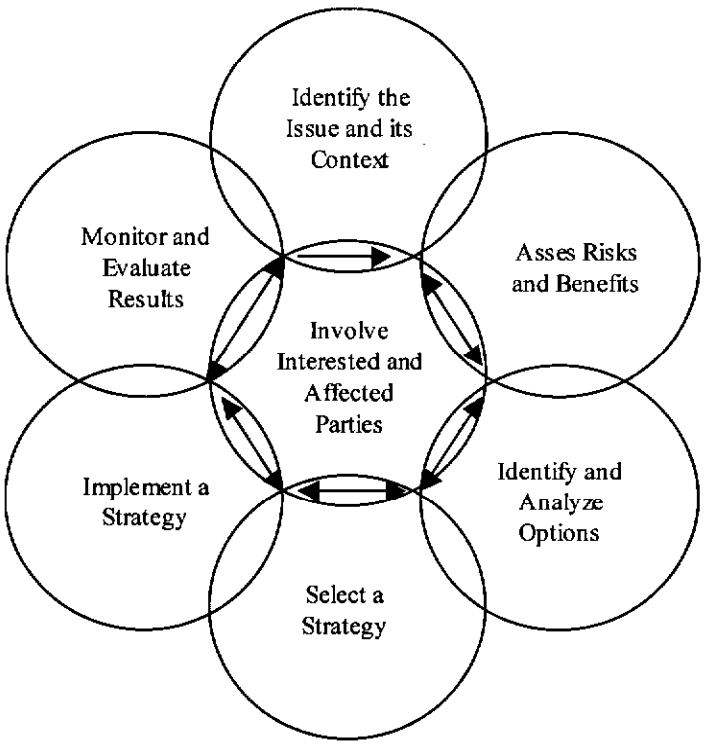
- maintain and improve health as the primary objective;
- involve interested and affected parties;
- communicate in an effective way;
- use a broad perspective;
- use a collaborative and innovative approach;
- make effective use of sound, scientific advice;

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

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

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

Figure 6.1: Decision-making framework (15)



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

Risk analysis practices in other countries

United States

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

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

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

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

Europe

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

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

United Kingdom

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

Office International des Epizooties

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

The "precautionary principle"

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

Science-based policy development: weighing the evidence

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

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

Assumptions

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

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

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

Weight of evidence approach

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

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

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

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

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

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

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

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

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

Committee analysis of resistance risks

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

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

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

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

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

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

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

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

Analysis: managing resistance risks

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other options discussed and favoured by a minority were:

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

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

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

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

Conclusions

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

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

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

Recommendations

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

References

1. The Presidential Commission/Congressional Commission on Risk Assessment and Risk Management (1997). Framework for the environmental health risk management. Final report 1. The Presidential Commission/Congressional Commission on Risk Assessment and Risk Management, Washington, D.C. http://www.riskworld.com/ (Accessed May 8, 2002)
2. Vose D (2000). Risk analysis: a quantitative guide. J. Wiley, Chichester, England.
3. Society for Risk Analysis (SRA) (Dec. 2001). Society for risk analysis. http://www.sra.org (Accessed May 8, 2002)
4. Society for Risk Analysis (2001). Society for risk analysis principles of risk analysis. *RISK Newsletter 2001,* 21(3):6
5. National Research Council (NRC) (1994). Science and judgement in risk assessment. National Academy Press, Washington D.C.
6. Committee on Drug Use in Food Animals (1999). The use of drugs in food animals, benefits, and risks. National Academy Press, Washington, D.C.
7. Canadian General Standards Board (June 1999). Organic Agriculture, National Standard of Canada. *CAN/CGSB,* 32.310.99
8. Council of Europe Parliamentary Assembly (Dec. 1999). Ban on antibiotics in food production.
9. Government of Canada Privy Council Office (Nov. 1999). Government of Canada Regulatory Policy. http://www.pco-bcp.gc.ca/raoics-srdc/default.asp?Language=e&Page=Home (Accessed May 8, 2002)

10. Government of Canada Privy Council Office: Treasury Board of Canada Secretariat (Nov. 1996). Federal regulatory process management standards. http://www.pco-bcp.gc.ca/raoics-srdc/default.asp?Language=e&Page=Home (Accessed May 8, 2002)
11. Government of Canada Privy Council Office (Oct. 1992). International collaboration: options for the regulation of potentially dangerous products. http://www.pco-bcp.gc.ca/raoics-srdc/default.asp?Language=e&Page=Home (Accessed May 8, 2002)
12. Lammerding AM, Ffazil A (2000). Hazard identification and exposure assessment for microbial food safety risk assessment. *Int J Fd Microbiol,* 58(3):147–157
13. Todd E, Ross W, Gellson T, et al. A quantitative risk assessment for *Salmonella enteritidis* in eggs in Canada.
14. Todd ECD, Harwig J (1996). Microbial risk analysis of food in Canada. *J Food Prot (Suppl),* 10–8
15. Risk Management Team (2000). Health Canada decision-making framework for identifying, assessing, and managing health risks. Ottawa, Ontario. http://www.hc-sc.gc.ca/hpb/transitn/rmf_e.html (Accessed May 8, 2002)
16. Committee of the Drug Review Process of the Science Advisory Board to Health Canada (2000). Report of the drug review process. Health Canada, Ottawa, Ontario. http://www.hc-sc.gc.ca/hpb/science/drg_e.html (Accessed May 8, 2002)
17. Krewski D, et al (2001). Managing health risks from drinking water: a background paper for the Walkerton inquiry. The Walkerton Inquiry. Toronto, Ontario. http://www.walkertoninquiry.com/ (Accessed May 8, 2002)
18. Council of Science and Technology Advisors (1999). Science advice for government effectiveness (SAGE). Council for Science and Technology Advisors Secretariat, Industry Canada, Ottawa, Ontario.
19. Food and Drug Administration (FDA) (1998). Proposed framework for evaluating and assuring the human safety of the microbial effects of antimicrobial new animal drugs intended for use in food-producing animals. FDA, Washington, D.C. http://www.fda.gov/cvm/default.htm (Accessed May 8, 2002)
20. Food and Drug Administration (FDA) (Dec. 1999). Risk assessment on the human health impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken. http://www.fda.gov/cvm/default.htm (Accessed May 8, 2002)
21. Food and Drug Administration's Center for Veterinary Medicine (2000). An approach for establishing thresholds in association with the use of antimicrobial drugs in food-producing animals. http://www.fda.gov/cvm/default.htm (Accessed May 8, 2002)
22. Institute of Medicine (1989). Human health risks with the subtherapeutic use of penicillin or tetracyclines in animal feed. National Academy Press, Washington, D.C.
23. The European Agency for the Evaluation of Medicinal Products (EMEA) (1999). Antibiotic resistance in the European Union associated with therapeutic use of veterinary medicines. Report and qualitative risk assessment by the committee for veterinary medicinal products. EMEA http://www.emea.eu.int/index/indexv1.htm (Accessed May 11, 2002).
24. Oxford Economic Research Associates Ltd (OXERA) (2000). Policy, risk, and science: securing and using scientific advice. Contract research report 295/2000 edition. Her Majesty's Stationery Office, Norwich, U.K. http://www.foodstandards.gov.uk/ (Accessed May 8, 2002)
25. May SR (2000). Review of the risk procedures used by the Government's Advisory Committee dealing with food safety. Food Standards Agency, U.K. http://www.foodstandards.gov.uk/ (Accessed May 8, 2002)
26. Office International des Epizooties (OIE) Ad Hoc Group on Antimicrobial Resistance (2000). Risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin. Guideline No.1 edition. Office Internationale des Epizooties, Paris, France. http://www.oie.int/ (Accessed May 8, 2002)
27. Commission of the European Communities (2000). Communication from the Commission on the precautionary principle. Commission of the European Communities, Brussels. http://europa.eu.int/comm/dgs/health_consumer/index_en.htm (Accessed May 8, 2002)
28. Government of Canada. A Canadian Perspective on the Precautionary Principle / Approach. September 2001.
29. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (1998). JETACAR literature review. Antibiotic resistance in animal enteric bacteria and human disease — a review of the scientific literature, 1998. Department of Health and Aged Care, Australia.
30. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) (1999). The use of antibiotic in food-producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth of Australia. http://www.health.gov.au/pubs/jetacar.htm (Accessed May 8, 2002)
31. Bailar III JC, Travers K. Review of assessments of the human health risk associated with the use of antimicrobial agents in agriculture. Clin Infect Dis 2002 Jun 1;34 Suppl 3:S135–43

CHAPTER

7

Impacts of antimicrobial resistance on animal health[a]

Key Points

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

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

Antimicrobial resistance in veterinary medicine

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

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

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

Bacteria of concern

Three categories of animal bacteria are monitored in veterinary medicine:

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

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

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

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

Table 7.1: Recognized bacterial pathogens in food-animal species

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

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

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

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

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

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

Summary of evidence of resistance problems in animals

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

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

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

Evidence from Canada and other countries

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

Pasteurella

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

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

Actinobacillus pleuropneumoniae

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

Salmonella

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Escherichia coli

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

Mastitis staphylococci

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

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

Aeromonas salmonicida ssp salmonicida

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

Analysis: animal health impacts of resistance

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

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

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

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

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

Conclusions

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

Recommendations

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

References

1. Poppe C, Smart N, Khakhria R, Johnson W, Spika J, Prescott J (Sept. 1998). *Salmonella typhimurium* DT 104: a virulent and drug-resistant pathogen. *Can Vet J,* 39(9):559–565
2. Smith KE, Besser JM, Hedberg CW, Leano FT, Bender JB, Wicklund JH, Johnson BP, Moore KA, Osterholm MT (May 1999). Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992–1998. Investigation Team. *N Engl J Med,* 340(20):1525–1532
3. DANMAP 2000 (2000). Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods, and humans in Denmark. DANMAP, Copenhagen, Denmark. *DANMAP,* 56pp
4. Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) (2001). Swedish veterinary antimicrobial resistance monitoring 2000. National Veterinary Institute, Uppsala, Sweden. 46pp
5. Daignault D, Higgins R, Messier S, CoutureY (1997). Sensibilité des isolats de *Pasteurella multocida* et *Pasteurella haemolytica* envers différents agents antibactériens. *Méd Vét Québec,* 27:154–155
6. Nadeau M, Côté G, Higgins R (2000). Surveillance de l'antibiorésistance chez des bactéries d'origine aviaire et porcine de 1993 à 1999 au Québec. *Méd Vét Québec,* 30:195–199
7. Prescott JF, Bhasin JL, Sandford SE, Binnington BD, Kierstead ME, Percy DH, Nicholson VM (1984). Serotypes and antimicrobial susceptibility of *Pasteurella multocida* isolated from cattle and pigs in Ontario. *Can Vet J,* 25:117–118
8. Martel JL (1996). Épidémiosurveillance de l'antibiorésistance des bactéries pathogènes chez l'animal. *Épidémiol Santé Anim,* 29:107–120
9. Raemdonck DL, Tanner AC, Tolling ST, Michener SL (1994). Antimicrobial susceptibility of *Actinobacillus pleuropneumoniae, Pasteurella multocida,* and *Salmonella choleraesuis* isolates from pigs. *Vet Rec,* 134:5–7
10. Vaillancourt JP, Higgins R, Martineau GP, Mittal KR, Larivière S (1988). Changes in the susceptibility of *Actinobacillus pleuropneumoniae* to antimicrobial agents in Quebec (1981–1986). *JAVMA,* 193:470–473
11. DANMAP 98 (1998). Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods, and humans in Denmark. DANMAP, Copenhagen, Denmark. *DANMAP,* 56pp
12. Poppe C, Ziebell K, Michel P (1999). Trends in antimicrobial resistance of *Salmonella* isolated from animals and animal sources in Canada. *In*: Proceedings: Agriculture's role in managing antimicrobial resistance conference. Toronto, Ontario. p.40–50
13. Poppe C, Kollar JJ, Demeczuk WHB, Harris JE (1995). Drug resistance and biochemical characteristics of *Salmonella* from turkeys. *Can J Vet Res,* 59:241–248
14. Abouzeed YM, Hariharan H, Poppe C, Kibenge FSB (2000). Characterization of *Salmonella* isolates from beef cattle, broiler chickens, and human sources on Prince Edward Island. *Comp Immun Microbiol Infect Dis,* 23:253–266
15. Fedorka-Cray PJ, Dargatz DA, Petersen KE, Hollinger K, Wineland NE, Headrick M, Tollefson L, Ferris K (1999). NARMS-EB veterinary isolates 1998 summary. *In*: Proceedings: Agriculture's role in managing antimicrobial resistance conference. Toronto, Ontario. p.279
16. Fairbrother JM, Higgins R, Desautels C (2000). Trends in pathotypes and antimicrobial resistance of *Escherichia coli* isolates from piglets with postweaning diarrhoea in Quebec. *Proc Int Pig Vet Soc Congr,* 16:17
17. Hariharan H, Bryenton JW, St.Onge J, Long JR, Ojo MO (1989). Resistance to trimethoprimsulfamethoxazole of *Escherichia coli* isolated from pigs and calves with diarrhea. *Can Vet J,* 30:348–49
18. Canadian Pork Council's Working Group on Antimicrobial Resistance (July 2000). Antimicrobial resistance in the Canadian Pork Industry: nature, stakes, and solutions. Report submitted to the Canadian Pork Council's Board of Directors Meeting. 47pp

19. Blanco JE, Blanco M, Mora A, Blanco J (Aug. 1997). Prevalence of bacterial resistance to quinolones and other antimicrobials among avian *Escherichia coli* strains isolated from septicemic and healthy chickens in Spain. *J Clin Microbiol*, 35(8):2184–2185
20. De Oliveira AP, Watts JL, Salmon SA, Aerestrup FM (2000). Antimicrobial susceptibility of *Staphylococcus aureus* isolated from bovine mastitis in Europe and in the United States. *J Dairy Sci*, 83:855–862
21. Franklin A (1999). Current status of antibiotic resistance in animal production. *Acta vet scand*, 92 (Suppl):23–28
22. Myllys V, Asplund K, Brofeldt E, Hirvela-Koski V, Honkanen-Buzalski T, Junttila J, Kulkas L, Myllykangas O, Niskanen M, Saloniemi H, Sandholm M, Saranpaa T (2001). Bovine mastitis in Finland in 1988 and 1995 - changes in prevalence and antimicrobial resistance. *Acta vet scand*, 39:119–126
23. Genitilini E, Denamiel G, Llorente P, Godaly S, Rebuelto M, DeGregorio O (2000). Antimicrobial susceptibility of *Staphylococcus aureus* isolated from bovine mastitis in Argentina. *J Dairy Sci*, 83:1224–1227
24. Watts JL, Salmon SA, Yancey RJ, Nickerson SC, Weaver LJ, Holmberg C, Pankey JW, Fox LK (1995). Antimicrobial susceptibility of microorganisms isolated from the mammary glands of dairy heifers. *J Dairy Sci*, 78:1637–1648
25. Dalsgaard I, Nielsen B, and Larsen JL (1994). Characterization of *Aeromonas salmonicida* subsp. *salmonicida* : a comparative study of strains of different geographic origin. *J Appl Bacteriol*, 77:21–30.
26. Høie S, Martinsen B, Sohlberg S, and Horsberg TE (1992). Sensitivity patterns of Norwegian clinical isolates of *Aeromonas salmonicida* subsp. *salmonicida* to oxolonic acid, flumequine, oxytetracycline, and sulphadiazine/trimethoprim. *Bull Eur Ass Fish Pathol*, 12(4):142–144.
27. Inglis V, Yimer E, Bacon EJ, and Ferguson S (1993). Plasmid-mediated antibiotic resistance in *Aeromonas salmonicida* isolated from Atlantic salmon, *Salmo salar* L., in Scotland. *J Fish Dis*, 16:593–599
28. Olivier G (1992). Furunculosis in the Atlantic provinces : an overview. Bull. Aquacul. Assoc. Canada, 1 :4–10.
29. Starliper CE (1998). Biochemical and conjugation studies of Romet-resistant strains of *Aeromonas salmonicida* from salmonid rearing facilities in the Eastern United States. *J Aquat Anim Health*, 10(3) :221–229.
30. Schmidt AS, Bruun MS, Dalsgaard I, Pedersen K, and Larsen JL (2000). Occurrence of antimicrobial resistance in fish-pathogenic and environmental bacteria associated with four Danish rainbow trout farms. *Appl Environ Microbiol*, 66(11) :4908–4915.