The Use of Antimicrobials in Beef Cattle Health Management and Production and the Development of Antimicrobial Resistant Pathogens and their Transfer to Humans Causing Disease Which is Difficult to Treat

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Introduction

In food-producing animal health management and production, antimicrobials are used for the treatment and prevention of infectious diseases, and to enhance growth promotion. These uses of antimicrobials represents one of several important health management strategies which contribute to animal health and well-being and to the economical production of wholesome meat and milk products. The control of animal disease also means control of certain infectious diseases which may be transmitted to humans. However, there are some potential human health hazards associated with antimicrobials used in food animals. Residues of drugs may occur in meat and milk and could enter the human food chain and increase the risk of ill-health in persons who consume products from treated animals. Of greater current importance is the potential for the emergence of antimicrobial resistant enteric bacteria which could be transferred to humans resulting in clinical disease which may be difficult to treat.

This paper will review the evidence that the use of antimicrobials in beef cattle health management and production in North America allows the emergence of antimicrobial resistant bacteria, which may be transferred to humans and subsequently cause disease which is difficult to treat because of antimicrobial resistance. Some of the scientific publications and other documents which have examined the various aspects of antimicrobial resistance over the last 30 years will be summarized and their conclusions examined. Some historical aspects are included in an attempt to better the understand the problem. Some references to the use and effects of antimicrobials in health and production management in swine and poultry will be made for comparative purposes.

Antibiotic Resistance in Human and Veterinary Medicine and the Media

No other issue between human and veterinary medicine has generated so much concern as antibiotic resistance (CBC 1999). The public media is attracted to the problem and sensationalizes the issue of antibiotic resistance and the dangers of "superbugs" to human health.

A constant flow of scientific papers, documents, essays, and editorials on antimicrobial resistance appear in the medical and veterinary literature which creates a media feeding frenzy lasting a few days for each episode. Review articles such as "Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria" (Khachatourians 1998), and "Agricultural antibiotics and resistance in human pathogens: Villain or scapegoat" (McGeer 1998) published in the Canadian Medical Association Journal attract the attention of the media which results in headline news of how the use of antimicrobials in food animals pose a threat to human health. The huge amounts of antimicrobials used in food animals are also commonly reported but out of context. For example, the following statement is made: "Nearly half of all antimicrobial use in North America is in agriculture, and the great majority of such use is for promotion of growth in farm animals, rather than for crop treatments or therapy. The volumes used, and the fact that the low doses of antibiotics used for growth promotion may be more effective in inducing

resistance than the higher doses used in therapy, mean that this use of antibiotics contributes significantly toward selection for antimicrobial resistance in human pathogens." (McGeer 1998). No data are provided to support such a conclusion.

In a recent review article (Khachatourians 1998), it is stated that "Microbial resistance to antibiotics is on the rise, in part because of inappropriate use of antibiotics in human medicine but also because of practices in the agricultural industry. Intensive animal production involves giving livestock animals **large quantities** of antibiotics to promote growth and prevent infection. These uses promote the selection of antibiotic resistance in bacterial populations. The resistant bacteria from agricultural environments may be transmitted to humans, in whom they cause disease that cannot be treated by conventional antibiotics" "The use of antibiotics to promote growth in livestock animals is one of the culprits" What is the evidence that large quantities of antibiotics are given to livestock? What does large quantities mean? These statements are very attractive to the media and create considerable unnecessary anxiety in the minds of the public who do not understand the technicalities of the agricultural use of these drugs and the complexities of antimicrobial resistance (Prescott 1997).

Use of Antimicrobials in Food Producing Animal Production

In modern food-producing animal production, animals are kept in groups of varying sizes so that the individuals share a common air and ground space, in close contact with one another and exposed to feces and urine, allowing the spread of microbial agents to occur easily. Under such conditions, it is rational to provide medication when necessary to the entire group whether the size is 20 or 20,000 because the source and occurrence of infection would be the same. In fact, the use of subtherapeutic levels of antimicrobials is one of the methods of health and production management which has allowed confinement housing, and large numbers of animals to be maintained in production facilities of a given size. This has contributed significantly to the lower costs of production and ultimately to the lower cost to the consumer for meat, milk and eggs (Dupont & Steele 1987).

About 40% of the antimicrobials produced in the United States are used in animal feed, but exact figures are unavailable. This represents 55% to 60% of the total production of penicillin G and tetracyclines, with 50% of the total animal feed medication being tetracyclines. In the United States, this may represent up to 8500 tons, a very large amount in terms of the microgram antibacterial potency of these chemicals (Table 1). However, on an individual animal basis, the amounts are small. Moreover, contrary to popular misconception, agricultural use of antimicrobials is extensively regulated. Under the food and drug legislation in both Canada and the United States, there are 3 uses of antimicrobials in agriculture: as **feed antimicrobials**, as **over the counter (OTC) drugs,** and as veterinary **prescription drugs** (Prescott 1997).

Table 1. Estimated annual antibiotic use in livestock in the United States, 1985 ('000 kg)

Species use	Therapeutic use	Subtherapeutic promotion	Growth
Cattle[a]	458	1100	340
Swine	250	3578	1391
Poultry[b]	304	580	315

[a] Mostly beef cattle
[b] Mostly meat chickens

Feed antimicrobials are those which livestock producers can order without a veterinary prescription through licensed feed mills for growth promotion (2-50 g/ton), for subtherapeutic use (200 g or less/ton of feed), or for disease treatment (over 200 g/ton of feed). Subtherapeutic use, the most contentious and the largest of the uses, encompasses prevention of specified diseases but includes growth promotion in the face of certain diseases. Most feed antimicrobials are used for this purpose, particularly in swine. Many of the feed antimicrobials are unique to agriculture (carbadox, flavomycin, monensin, salinomycin, viriginiamycin). Other feed antimicrobials in common use in animals (bacitracin, lincomycin, sulfonamides, tetracyclines, tylosin) are not commonly used in human medicine. Only penicillin G, which is often used in swine feed in combination with sulfonamides and tetracyclines, is commonly used in human medicine (Table 2).

Table 2. Antimicrobial agents prescribed to people in Canada, 1996

Antimicrobial	Number of prescriptions (millions)
Amoxicillin	6.78
Cephalosporin	3.31
Erythromycin	2.72
Trimethoprim-sulfonamide	1.76
Quinolones	1.66
Extended-spectrum macrolide	1.48
Other broad-spectrum penicillin	0.95
Antifungals	0.93
Tetracyclines	0.89

Antimicrobials Used in Beef Cattle Health Management and Production

Antimicrobials are used in beef cattle health management and production in North America for the treatment of clinical disease in cattle of any age, for prophylaxis of certain diseases, and for growth promotion of young growing animals, usually feedlot animals. The successive stages of the production life cycle in cattle include the nursing calf from birth to weaning at 6-8 months of age, the weaned beef calf, the growing yearling on pasture, the feedlot animal fed high energy rations for 6 to 12 months, breeding females, and bulls of various ages.

Treatment of Clinical Bacterial Diseases in Individual Animals

The therapeutic use of antimicrobials occurs after a diagnosis of a disease is made, and treatment is governed by label instruction.

Cattle of all ages from the young calf to the mature cow may require treatment with antimicrobials for clinical disease caused by bacteria. The most common diseases are caused by bacterial infections of the respiratory and alimentary tracts, the mammary gland, the reproductive tract.

Oxytetracycline, florfenicol, tilmicosin, and trimethoprim-sulfonamides are used parenterally for the treatment of acute undifferentiated respiratory tract disease of feedlot cattle (Guichon et al. 1993; Harland et al. 1991; Hoar et al. 1998). It is noteworthy, that in spite of the intensive use of the common antimicrobials for more than 30 years, Pasteurella haemolytica, a primary cause of fibrinous pneumonia in cattle, has not developed significant antimicrobial resistance.

Therapeutic Medication of High Risk Groups of Individual Animals (Metaphylaxis) Respiratory Disease

Feedlot animals at high risk of acute undifferentiated bovine respiratory disease, most of which is bacterial pneumonia, are administered antimicrobials at therapeutic doses upon arrival at the feedlot to reduce morbidity and mortality (Harland et al. 1991). Long-acting oxytetracycline (20 mg/kg BW) and tilmicosin (10 mg/kg BW) are the parenteral antimicrobials currently used (Morck et al. 1993). It is estimated that 10% to 20% of feedlot animals receive prophylactic/metaphylactic tilmicosin and 20% to 40% of feedlot animals receive prophylactic/metaphylactic long-acting oxytetracycline. When oxytetracycline is used, it is sometimes used with a "follow-up" injection 3 days later.

Florfenicol is also used for the treatment of acute bovine respiratory disease and is considered superior to tilmicosin when feedlot calves have previously received tilmicosin prophylaxis on arrival (Jim et al. 1999).

Subtherapeutic Medication of Feed

The subtherapeutic dose of an antimicrobial is defined in the United States as the use of the drug at less than 200 g per ton of feed. Antimicrobials used at these levels are intended to control certain infectious diseases and are provided most commonly in the feed, and occasionally in the water supply. Some of the common disease complexes controlled with subtherapeutic medication of the feed of feedlot cattle are outlined here.

Respiratory Disease (Shipping Fever Pneumonia)

It is common practice to feed chlortetracycline (350 mg/hd/day) and sulfamethazine (350 mg/hd/day) (Aureo S-700 G) to high risk feedlot animals during the first part of the feeding period (typically 50 to 60 days) due to significant ($p<0.05$) reductions in the Haemophilus somnus disease complex associated mortality under commercial field trial conditions. Aureo S-700 G is licensed for the first 4 weeks of the feeding period "as an aid in the maintenance of weight gains and feed efficiency in cattle during periods of stress, due to weaning, shipping or handling". It is estimated that 20% to 30% of feedlot animals receive this type of program.

The inclusion of a feed additive containing 350 mg chlortetracycline and 350 mg sulfamethazine each per head/day in the feed of feedlot cattle from arrival in the feedlot to day 56 of the feeding period significantly improved average daily gain and reduced the incidence rate of respiratory disease, the rate of relapses, and the rate of chronic respiratory disease (Gallo & Berg 1995). Performance and health improvements from using the feed additive were cost effective.

Coccidiosis

Decoquinate in the feed is occasionally used to prevent coccidiosis in feedlot cattle.

Foot Rot

Oxytetracycline or chlortetracycline in the feed are occasionally used to provide mass medication to control outbreaks of foot rot (1 g/hd/day).

Liver Abscesses

Liver abscesses in beef cattle are the result of high level grain-feeding programs (Nagaraja & Chenagappa 1998). The incidence, averaging from 12 to 32% in most feedlots, is influenced by several dietary and management factors. Liver abscesses represent a major economic liability to producers, packers, and ultimately

consumers. Economic losses are due reduced feed intake, reduced weight gain, decreased feed efficiency, and decreased carcass yield. Fusobacterium necrophorum, a member of the ruminal anaerobic bacterial flora is the primary etiologic agent. Ruminal lesions resulting from acidosis are generally accepted as the predisposing lesions for liver abscesses. Virulence factors of the organism permit its penetration and colonization of the ruminal wall and subsequent entry and establishment of infection in the liver. Control of liver abscesses in feedlot cattle on high-level grain feeding has depended on the use of antimicrobials. Five antimicrobials, bacitracin methylene disalicylate, chlortetracycline, oxytetracycline, tylosin and virginiamycin are approved for prevention of liver abscesses in feedlot cattle. Tylosin is the most effective and the most commonly used feed additive and reduces liver abscesses by 40% to 70%.

Virtually all feedlot animals receive antimicrobials to reduce the incidence of liver abscesses. In most situations, they are fed for the entire feeding period. However, if they are used to control bovine respiratory disease or undifferentiated fever or the Haemophilus somnus disease complex for a portion of the feeding period, then the antimicrobial for liver abscess reduction is often excluded from the ration. It should be noted that although a reduction in the incidence of liver abscesses is the licensed claim for these products, the inclusion of these products results in significant improvements in average daily gain and/or feed efficiency. It is currently not known whether or not the observed improvements in average daily gain and/or feed efficiency are a direct result of antimicrobial usage, an indirect result of the reduced incidence of liver abscesses, or a combination of both. The antimicrobials used include tylosin, oxytetracycline, and chlortetracycline. Of these antimicrobials, tylosin is the only compound licensed to reduce the incidence of liver abscesses. However, a series of commercial feedlot studies have demonstrated that both oxytetracycline and chlortetracycline are effective at reducing the incidence of liver abscesses and both are licensed in the US for this claim. Oxytetracycline and chlortetracycline are also licensed to improve average daily gain and feed efficiency in the US. In Canada, tylosin (11 ppm) is the most commonly used antimicrobial to reduce the incidence of liver abscesses (estimate is 40% to 60% of feedlot animals) and tylosin is co-cleared with monensin at 33 ppm. Oxytetracycline (11 ppm) is the next most commonly used antimicrobial to reduce the incidence of liver abscesses (estimate is 30% to 50% of feedlot animals). Chlortetracycline (11 ppm or 350 mg/hd/day) is occasionally used to reduce the incidence of liver abscesses (our estimate is less than 5% of feedlot animals). Both oxytetracycline and chlortetracycline require veterinary prescription in Canada for this use and the combination with monensin.

Laidlomycin propionate in the feed of cattle fed high-grain finishing diets can reduce the severity of ruminal acidosis during adaptation to a 100% concentrate diet (Bauer et al. 1995).

Growth Promotant Antimicrobials in the Feed

Various antimicrobials used as feed additives, and hormonal implants are approved in North America for use throughout the feeding period of feedlot cattle to enhance growth rate and feed efficiency. Antimicrobial feed supplements for growth promotion have been used extensively in almost every major livestock-producing country for the past 40 years. It is generally accepted that their use has contributed to lower animal production costs and ultimately to lower costs to the consumer for meat, milk and eggs.

The antimicrobials used as growth promoters are grouped broadly into **ionophores** and **nonionophores**. **Ionophores** are compounds which beneficially modify ruminal fermentation activity. Monensin, lasalocid, laidlomycin, and salinomycin are the most commonly used. Monensin was the first ionophore approved in 1976 for increasing feed efficiency in feedlot cattle and in 1978 was approved for increasing rate of gain of pasture cattle. It was also shown later that monensin is effective in preventing coccidiosis. Generally, in grain-fed animals, ionophores depress feed intake, but body weight gain is increased or unaffected and feed efficiency (feed/gain) is improved. In pasture-fed cattle, ionophores do not reduce feed intake but body weight gain is increased, thus resulting in improved feed efficiency.

The effectiveness of ionophores in achieving increased efficiency of feed conversion and, under some conditions, improving the rate of gain is attributed to alterations in ruminal fermentation (Nagaraja 1995). Ionophores are not used in human medicine and do not pose a risk to human health from the development of antimicrobial resistance in animal pathogens which may be transferred to humans.

All feedlot animals receive ionophores for the entire feeding period to control coccidiosis and to improve feed efficiency. The Canadian options include monensin, lasalocid, and salinomycin; however, the overwhelming majority (our estimate is 95% plus) of feedlot animals receive monensin. Monensin is generally fed at levels from 22 ppm to 33 ppm, with several post-licensing studies conducted under commercial feedlot conditions demonstrating that 25 ppm is significantly ($p<0.05$) more cost-effective than 33 ppm. However, including monensin at 25 ppm requires a veterinary prescription in Canada as the product is licensed at 33 ppm for the entire feeding period or 11 ppm for 28 days followed by 33 ppm for the remainder of the feeding period to improve feed efficiency and at 22 ppm for the prevention of coccidiosis.

Combining different ionophores such as monensin and lasalocid in the same ration at 50 or 75% of the recommended feeding level for each compound or feeding both in a daily rotation program does not improve performance over that of continuously feeding either compound at recommended levels (McKinnon et al. 1992).

Nonionophore antimicrobials are the conventional antimicrobials used as feed supplements including avoparcin, bacitracins, chlortetracycline, sulfonamides, flavomycin (bambermycin), neomycin, oxytetracycline, spiramycin, tylosin, and virginiamycin. These antimicrobials are a diverse group which differ in chemistry, primary antibacterial spectrum, mode of action of bacterial inhibition, molecular weight, and ability to be absorbed from the intestine. Those which are not absorbed from the intestine or poorly absorbed at the low dosage used are more acceptable as feed additives, because of the absence of residues in milk and meat and because there is no need for a withdrawal period before slaughter.

Antimicrobials used in the feed, decrease the amount of feed needed, increase the rate of weight gain, and improve feed efficiency. The growth promotion response in cattle is much more varied than in swine or poultry depending on the level of subclinical infection, level of management and nutrition, and environmental and managemental stressors such as recent shipping and mixing feedlot animals from many sources. They are used as feed additives for growth promotion in growing cattle at continuous low levels (2 to 50 g per ton of feed). Most studies indicate that chlortetracycline, oxytetracycline and zinc bacitracin are the most effective nonionophore antimicrobials for improving the performance of beef cattle. Chlortetracycline is used at 11mg/kg of complete feed as an aid in stimulating growth rate and improving feed efficiency in calves. Oxytetracycline hydrochloride is used at 11mg/kg of complete feed for growth promotion in calves.

The mechanism of action of antimicrobials in improving growth and enhancing feed efficiency is not fully understood. The most commonly accepted explanation is that the growth response is due primarily to actions on the microbial flora of the intestine. This is supported by the observation of a lack of improved growth under germ-free conditions. At least four general modes of action have been postulated to account for growth promotion by antimicrobials: metabolic effect by directly influencing the rate or pattern of metabolic processes; nutrient sparing effect by altering the bacterial populations and conservation of nutrients; control of subclinical disease by suppressing bacteria causing clinical or subclinical infections; modification of ruminal fermentation by altering rumen population to improve fermentation efficiency. Most feed additive antimicrobials have their antibacterial activity against Gram-positive bacteria but some Gram-negative bacteria are also susceptible. The tetracyclines are inhibitory to both Gram-positive and Gram-negative bacteria. It is important to note that antimicrobials have a beneficial effect on growth rate other than through their effect on enteric microflora.

The feed additive antimicrobials approved for use in beef cattle production in the United States and Canada are summarized in Appendix I.

Current Antimicrobial Usage in Livestock and Humans

For this paper, it was not possible to obtain the data on the total amount of antimicrobials used for disease prevention or growth promotion in the beef cattle industry in North America. The amounts of antibiotics used in livestock production in the United States are summarized in Table 1 and the amounts of antimicrobial agents prescribed to people in Canada in 1996 are shown in Table 2 (Prescott 1997).

Other Health Management Practices in Beef Cattle Production

Cattle are vaccinated for several infectious diseases caused by bacteria and viruses. However, vaccines are available for only about 10% of the commonly occurring bacterial diseases and some of the vaccines are not efficacious The most commonly used and effective vaccines for use in cattle are the clostridial bacterins and toxoids. There are many more vaccines for the control of viral diseases in cattle. Anthelmintics are used in some geographical areas for the control of intestinal helminthiasis, and insecticides are used for the control of ectoparasites. Hormonal implants are administered to growing calves and feedlot animals as growth promotants. A study of the use of drugs to prevent disease in beef cow-calf herds in Tennessee found that antimicrobials were seldom used compared to anthelmintics and insecticides (Kelch & New 1993). However, chlortetracycline was used to prevent anaplasmosis, diarrhea of unknown causes, and non-specific respiratory infections.

Antimicrobial Use in Swine Herds

Some information is available on the use of antimicrobials in swine herds. They are used extensively in newly weaned pigs, a critical time for infections in young animals, and to a lesser extent in growing and finishing pigs, where their use may not be effective (Prescott 1997). Raising pigs under intensified conditions has similarities to beef feedlots where large numbers of animals are fed under intensified conditions.

A mail survey of swine herds in Ontario, Canada, in 1991, found that 86% of herds added antimicrobials

Appendix I.

Growth Promotion and Prophylactic Indications. United States. Feed Additive Compendium, 1997

Bacitracin methylene disalicylate (reduce number of liver condemnations due to abscesses).

Bacitracin zinc (increased weight gain and improved feed efficiency.To aid in stimulating growth)

Bambermycin (for increased rate of weight gain and improved feed efficiency).

Chlortetracycline (for increased rate of weight gain and improved feed efficiency; treatment of bacterial enteritis; control of bacterial pneumonia; control of Anaplasmosis; aid in maintenance of weight gain in presence of respiratory disease such as shipping fever).

Laidlomycin (for improved feed efficiency and increased rate of weight gain in cattle being fed in confinement for slaughter).

Lasalocid (for improved feed efficiency in cattle fed in confinement for slaughter; for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle and dairy and beef replacement heifers).

Lasalocid and oxytetracycline (for improved feed efficiency and reduction of incidence of and severity of liver abscesses in cattle fed in confinement for slaughter).

Lasalocid and melengestrol acetate (for increased rate of weight gain, improved feed efficiency and suppression of estrus in heifers fed in confinement for slaughter).

Lasalocid sodium and melengestrol acetate and tylosin (for increased rate of weight gain and improved feed efficiency; reduction of liver abscesses).

Monensin (improved feed efficiency; prevention and control of coccidiosis caused by Eimeria bovis and Eimeria zuernii; increased weight gain in cattle (pastured slaughter, stocker and feeder cattle), and dairy and beef replacement heifers; cattle (mature, reproducing beef cows on pasture or in dry lots).

Monensin and melengestrol acetate (for increased rate of weight gain and improved feed efficiency).

Monensin and tylosin (Improved feed efficiency; reduction of liver abscesses).

Oxytetracycline (for calves up to 250 lb for increased rate of gain and improved feed efficiency; treatment of bacterial enteritis; reduction of liver abscesses; prevention and treatment of the early stages of shipping fever complex).

Oxytetracycline and neomycin (aid in prevention and treatment of bacterial enteritis).

Oxytetracycline and lasalocid (aid in reducing incidence and severity of liver abscesses; improved feed efficiency).

Oxtetracycline and melengestrol acetate (for increased rate of weight gain, improved feed efficiency; suppression of heat and reduction of liver abscesses in heifers fed in confinement for slaughter).

Tylosin (for reduction of incidence of liver abscesses in beef cattle).

Chlortetracycline (for stimulating growth rate and improved feed efficiency in calves).

Monensin sodium (for improved feed efficiency in beef cattle (steers and heifers) fed in confinement for slaughter).

Growth Promotion and Prophylactic Indications. Canada. Medicating Ingredient Brochure, 1998

Oxytetracycline hydrochloride (reduce incidence of bloat in young cattle on pasture and in feedlots; aid in prevention of foot rot in beef and non-lactating dairy cattle; prevention of bacterial diarrhea in calves weighing up to 136 kg; aid to prevention of diarrhea in milk replacer fed calves).

Tylosin phosphate (reduce incidence of liver abscesses).

Chlortetracycline hydrochloride and **sulfamethazine** (aid in maintenance of weight gains and feed efficiency in cattle during periods of stress, due to weaing, shipping or handling).

Decoquinate (aid in the prevention of coccidiosis caused by Eimeria bovis and Eimeria zuernii in ruminating cattle and non-ruminating calves).

Oxtetracycline hydrochloride and **neomycin sulfate** (aid in the maintenance of weight gains and feed efficiency in beef cattle during periods of stress due to weaning and shipping or handling).

Monensin sodium (aid in the prevention of coccidiosis caused by Eimeria bovis and Eimeria zuernii in cattle; for increased rate of weight gain in growing cattle on pasture (slaughter, stocker and feeder cattle, and beef and dairy replacement heifers) of greater than 180 kg body weight).

Lasalocid sodium (improved feed efficiciency and increased rate of weight gain in beef cattle fed in confinement for slaughter; for increased rate of weight gain in pasture cattle (stocker, feeder cattle, and beef and dairy replacement heifers); as as aid in the prevention of coccidiosis caused by Eimeria bovis and Eimeria zuernii in calves up to 360 kg body weight being fed in confinement).

Salinomycin sodium (for the improvement of feed efficiency in steers fed in confinement for slaughter).

to starter (weanling pig) rations, and only 29% added these drugs to finishing pig rations (Dunlop et al. 1998). The most commonly used antimicrobials were tylosin, carbadox, and furazolidone in weanling pigs, and tylosin, lincomycin, and tetracycline in finishing pig rations. Water medication of grower-finisher pigs was practiced on 25% of farms; 80% of farms had injected at least some grower-finisher pigs with antimicrobials in the 12 months preceding the survey. Approximately 20% of herds which added antimicrobials to finisher rations did so for growth promotion purposes only, while others used them for the treatment of disease, prevention, control, or a combination of both. Among those not using antimicrobials in finisher rations, 83% did not consider they were necessary and 37% were concerned about the potential for residues in marketed pigs.

Antimicrobial use during swine production is associated with increased resistance to those antimicrobials among fecal E. coli of finisher pigs (Dunlop et al. 1998). Antimicrobial treatment of groups of pigs was more important than individual medication in increasing the risk of resistance among E. coli but there was little evidence that group treatment practices increased the risk of resistance to gentamicin which was used only for individual animal therapy. Antimicrobial use in starter rations was associated with resistance to ampicillin, carbadox, nitrofurantoin, sulfisoxazole, and tetracycline. Antimicrobial use in grower-finisher rations was significantly associated with resistance to ampicillin, spectinomycin, sulfisoxazole, and tetracycline. The results suggest that antimicrobial medication of rations of post-weaning pigs selects for and maintains antimicrobial resistance among E. coli of finisher pigs. Antimicrobial resistance was also common on farms which did not medicate rations of post-weaning pigs, the results indicate that antimicrobial use does increase the risk of resistance to antimicrobials studied. It was concluded that reducing group medication with broad-spectrum antimicrobials of weanling and grower-finisher pigs might reduce the prevalence of resistant E. coli in market pigs. Thus, antimicrobials should be used only when necessary and the swine industry should continue to invest in the maintenance of a healthy population of pigs in which the need to treat with antimicrobials is reduced.

Information on the use of feed additives in swine herds was collected from 710 farms (Dewey et al. 1997). Of all the feeds, about 79% contained feed additives used in the labelled manner. For all classes of pigs, the prevalence of labelled feed additive use was greater than 75%. Penicillin was used according to its label most often, followed by apramycin, bacitracin, tetracyclines, lincomycin, and tylosin. Carbadox had the highest prevalence of off-label use. Of the 699 feeds that included feed additives in an off-label manner, about 57% included additives at greater than the recommended concentrations or were fed to an incorrect class of pig. About 56% of the feeds had off-label combinations of additives. Small farms were more likely to use rations with no feed additives than intermediate or large farms. Of those farms using feed additives, the odds of a small farm using all feed additives in the labelled manner was 7.7 times that of an intermediate or large farm. After controlling for herd size, producers who used a veterinary consultant were 2.1 times more likely to use feeds with feed additives.

Benefits of Antimicrobials Used in Beef Cattle Health Management and Production

Antimicrobials are among the few classes of drugs used in food animal production both therapeutically to treat disease and subtherapeutically to prevent certain infectious diseases, to increase production performance, to increase efficiency of use of a feed for growth or product output, and to modify the nutrient composition of an animal product.

Acute respiratory disease caused by Pasteurella haemolytica is the most commonly treated infection of feedlot cattle in North America. The recovery rate using antimicrobials therapeutically usually exceeds 90%, which is a major health and welfare benefit and is also economical. It is remarkable that the commonly occurring bacterial pathogens causing acute respiratory disease in cattle have not developed significant resistance to most of the commonly available antimicrobials in the last 25 years (Bateman 1993; Prescott & Baggott 1993). A four-year survey of antimicrobial susceptibility trends of 880 isolates of Pasteurella haemolytica, Pasteurella multocida, and Haemophilus somnus from cattle with bovine respiratory disease in North America indicated resistance to older antimicrobials including ampicillin, tetracycline, erythromycin, and sulfamethazine (Watts et al. 1994). The widespread resistance to erythromycin may reduce the effectiveness of tilmicosin because of cross-resistance. Of the drugs tested, ceftiofur was the most active, with no strains that were resistant to ceftiofur emerging over the four years. The isolates were obtained from treated animals which may reflect selection of resistant bacteria and may not be a true reflection of the drug sensitivity of the population of Pasteurella haemolytica.

The benefits of feed antimicrobials in agriculture are considerable in terms of increased growth rates and increased feed efficiency, particularly in young animals (Dupont & Steele 1987). Estimates vary and indeed, the beneficial effects of antimicrobials in feed may be declining. In pigs, their subtherapeutic use may improve the average daily gains of young pigs from 10 to 23% and feed efficiency by 6 to 8% (Hays 1986).

Feeding chlortetracycline at subtherapeutic levels can benefit nonstressed finishing cattle by improving

performance and carcass characteristics (Beacom et. al. 1988). The responses may be equal to or greater than those observed with monensin or lasalocid.

Risks of Antimicrobials Used in Beef Cattle Health Management and Production

The use of antimicrobials in livestock has been associated with two potential risks to human health; **antimicrobial residues** and **antimicrobial resistant bacteria**.

Antimicrobial Residues in Meat and Milk

The therapeutic use of antimicrobials in food-producing animals may result in residues in the meat and milk of treated animals if the withdrawal or withholding times for the drugs used following treatment are not followed. The human consumption of meat containing more than the tolerable levels of residues of antimicrobials could cause hypersensitivity reactions if the person is already sensitive to that particular antimicrobial because of previous exposure, usually through medication. Remarkably, however, since the introduction of antimicrobials some 40 years, on a world-wide basis there have been only a few reports of suspected cases of hypersensitivity reactions due to residues in meat. Direct human toxicity caused by the ingestion of meat containing more than the tolerable levels is unlikely because the levels are so low.

Whether the drug to which the animals are exposed will reach the consumer depends upon a number of factors, including the specific drug involved, its absorbability and pharmacokinetics, the interval from administration of the last dose of the drug until slaughtering, the tissue to be eaten, and the degree of cooking of the meat.

Antimicrobial residues in meat above the maximum tolerable levels occur extremely rarely and are usually the result of the slaughter of cattle which were treated therapeutically and not retained on the farm until expiry of the withdrawal period for the drug in question. The percentage of drug residue violations in beef in Canada is extremely low and continues to decrease as producers become more knowledgeable about the judicious use of antimicrobials and their withdrawal period. **Feedlot owners want to produce wholesome meat free of harmful residues of any kind.** Statistically valid random sampling and testing of beef carcasses are done routinely in federally inspected abattoirs across Canada. In addition, carcasses with evidence of drug injection sites are tested as suspect and if positive for antimicrobials are condemned. A follow-up investigation is conducted and future shipments from the farm are examined specifically for violations.

There is no evidence that the subtherapeutic or prophylactic use of antimicrobials in the feed of beef cattle has resulted in residues in the tissues of treated animals. In large part this is due to the low levels of drug which are achieved in the tissues compared to the higher levels following therapeutic use of the drug. Adherence to the stated withdrawal periods will allow for the elimination of the drug and there is no public health hazard (NRC 1999). In a study done by the Food Safety Inspection Service Residue Violation Information System of violative chemical residues in US beef in 1991-93, most of the animals found to have violative residues were bob calves and culled cows. In bob calves, neomycin was the most frequently identified violative chemical, followed by tetracycline, gentamicin, oxytetracycline, and penicillin, In culled cows, penicillin was the most frequently identified violative chemical and was most frequently found in combination with other chemicals in cows with multiple violative residues (Gibbons et al. 1996).

In summary, there is no evidence that the judicious therapeutic, prophylactic or subtherapeutic use of antimicrobials in beef feedlot animals, which use includes strict adherence to the withdrawal times, constitutes a human health hazard associated with drug residues in tissues.

Antimicrobial Resistant Bacteria

A public health concern, which has been expressed for about the last 35 years, about the use of antimicrobials in animal agriculture is the potential to select for antimicrobial resistant enteric pathogens which may be transferred to humans by direct contact with the animals through the fecal-oral route, or by the improper handling or consumption of inadequately cooked meat contaminated with the resistant bacteria. Infection of humans with antimicrobial resistant pathogens may cause disease which may be difficult to treat.

Mechanisms of acquired antimicrobial resistance. The use of antimicrobials in any host species such as man, animal, poultry, aquatic life at therapeutic or subtherapeutic levels, and regardless of the routes of administration, can result in the selection and emergence of strains of antimicrobial resistant bacteria. In most populations of bacteria there are antimicrobial susceptible and antimicrobial resistant bacteria and, in those same populations there are pathogenic and non-pathogenic bacteria. Antimicrobial resistance of bacteria can be natural or acquired. Certain species of bacteria are naturally resistant to certain antimicrobials and others are highly sensitive. The intestinal tract of man and animals contains a mixture of many different species of both resistant and sensitive bacteria and exposure of the intestinal flora to antimicrobials will eliminate the antimicrobial sensitive bacteria and allow the emergence of the antimicrobial resistant bacteria which will tend to predominate the population during exposure to the antimicrobials. This process is called **selection**, and changes

in the resistance or sensitivity patterns can be detected by examination of the sensitivity patterns of the bacteria of the feces within a few days following the addition of the antimicrobial to the feed of the animal. Antimicrobials will select out from a bacterial population those bacteria which are already resistant and which in the presence of the antimicrobial may develop into a dominant antimicrobial resistant population.

Bacteria transmit resistance traits to other members of their own species and to other species. Genetic traits for antibiotic resistance are coded in two locations in bacteria: the chromosomes and the extrachromosomal elements (plasmids and transposons). Resistant bacteria arise by random mutations in the genes of the bacteria which are then inherited by all daughter progeny, if as is usual, the gene is chromosomal.

The **resistance factor** can be passed between the same or different species of bacteria through the process of conjugation or transformation in which resistance (R) plasmids and transposons (transferable genes), which are extra-chromosomal elements in bacteria, are transferred from one bacterium to another. This process is also known as infectious drug resistance and the R plasmids may confer resistance to several antimicrobials simultaneously. The bacteria of major concern are the Salmonella spp., Escherichia coli, and Campylobacter spp. which are exposed to subtherapeutic levels of antimicrobials in the feed of food-producing animals. The emergence of drug-resistant strains of bacteria to several antimicrobials is known as **multiple drug resistance**.

Resistance plasmids from animal enteropathogens can be transferred by the process of conjugation to human enteropathogens. In published reports which claim that this chain of events has occurred, the human patients which became ill in association with the consumption of beef which was apparently contaminated with antimicrobial resistant bacteria were also on physician-prescribed oral antimicrobials for a previously diagnosed illness. Oral medication with antimicrobials will interfere with naturally present competitive antagonism between species of bacteria and allow the colonization of recently introduced bacterial species which the patient may have ingested from food-borne sources (Nord 1993).

Definition of Sensitivity and Resistance: The Break-point Concentration

Antimicrobial sensitivity and resistance are relative terms and provide an interpretation of the clinical significance of concentrations of an antimicrobial which inhibit the growth of an organism or kill it laboratory systems. The commonly used measure of such concentrations is the Minimal Inhibitory Concentration (MIC). This is defined as the lowest concentration of an antimicrobial which will inhibit the visible growth of a microorganism after overnight incubation. The point at which a MIC is sufficiently high to indicate resistance is the break point and is critical to the objective evaluation of sensitivity and resistance of bacteria and for comparing results between laboratories and countries. Different laboratories will use different breakpoints to determine resistance.

The published information on the resistance of Salmonella typhimurium DT 104 is an example of the variations in resistance reported from different laboratories. Since 1993, the Laboratory of Enteric Pathogens, Central Public Laboratory, London, England, have reported on the increased incidence of Salmonella typhimurium DT 104 which are resistant to ciprofloxacin. It has been suggested that the use of fluoroquinolones in animals is associated with increased resistance in the organism isolated from humans. Resistance of the isolates was based on a minimum inhibitory concentration for ciprofloxacin of at least 0.25 ug/ml. The standard MIC breakpoint for resistance in Europe and the United States, however, is 4.0 ug/ml. Using U.S. and European guidelines, over 99% of the DT 104 isolates termed "resistant" by the British workers are actually susceptible to ciprofloxacin (CAHI 1998).

Historical Aspects of Antimicrobial Resistance (1969-1980)

The historical aspects of antimicrobial resistance related to livestock production are summarized here as background information.

Discovery of Antimicrobials.

In the 1930s, antibacterials were discovered and used in human and veterinary medicine. One of the first to be useful for treatment of systemic infections in man and animals was penicillin. Penicillin and its early successors were found to have a certain spectrum of activity, being effective against some genera of bacteria but not others. Therefore, there was a need to continue the search for new antimicrobials so that a range would be available from which to select the most effective for the treatment of a given infection.

After the introduction of penicillin other antimicrobials were discovered which extended the range of bacterial infections which could be treated effectively. Clinical experience, however, indicated that when an antibimicrobial was introduced, a given bacterial species would develop resistance to it. However, this was not alarming because the infection could usually be treated with another antibiotic. Further experience, however, also found that resistance to one antibiotic frequently extended to related antimicrobials. It also became apparent that the use of antimicrobials exerted

selection pressure favoring resistant strains of bacteria which consequently multiplied more than did sensitive strains. It was thought that the development of resistant strains of bacteria might outrun the development of new antimicrobials.

Along with the success of antimicrobials in human medicine, the veterinary use of antimicrobials provided a similar success story for the treatment and control of disease in domestic animals. The use of antimicrobials in animals was very effective and contributed greatly to animal welfare and to a marked increase in the efficiency of livestock production since the 1950s.

Unidentified Growth Factors for Livestock.

In the late 1940s, there was considerable interest in the United States in "unidentified growth factors" which caused increased growth rate and improved feed utilization, particularly in growing food-producing animals (poultry, cattle and swine). The addition of small amounts of antimicrobials to the feed of animals increased their growth rate and feed conversion efficiency. Although it was noted that these feed additives resulted in an increase in the emergence of resistant bacteria isolated from the feces of these animals, there was little concern because of the continuing supply of new antimicrobials and the fact that few pathogenic species of bacteria from the digestive tract of animals could colonize the human intestine. The use of specific antimicrobials in restricted amounts to promote growth in certain classes of livestock was therefore approved and has been in common use in the North America since 1949 and in 1953 in the U.K.

Increased Incidence of Strains of Antimicrobial Resistant Bacteria.

In the 1960s, in Britain, an increase in the incidence of strains of bacteria resistant to antimicrobials was recognized in both human and veterinary medicine.

The Netherthorpe Committee was convened "to examine the possible consequences of the feeding of antimicrobials to farm animals and to consider whether such use posed any threat to human or animal health". The Committee reported in 1962 that it saw no reason to discontinue the approved usage of feed additives. It even recommended that the use of feed additives could be extended to young calves, which was never implemented. The Committee recommended that the usage of antimicrobials should be monitored and if a new antimicrobial were to be developed with comparable efficacy in growth promotion to those for use in feed additives in Britain (penicillin, chlortetracycline and oxytetracycline), but with little or no therapeutic application, the continued use of the permitted antimicrobials should be reconsidered.

In the mid 1960s, a new factor known as **infectious** or **transferable drug resistance** was described. In certain circumstances, a bacterium resistant to one or more antimicrobials could transfer its resistance to other bacterial species although these organisms may not have been exposed to the antimicrobials. This provided a mechanism whereby resistance might be transferred more widely and rapidly than originally thought possible. Several investigations of epidemics of human illness indicated that antimicrobial-resistant bacteria from animals could cause infections in humans (Anderson 1968).

This new finding raised for consideration the following observations:

- The growing incidence of antimicrobial resistance among strains of Salmonella, especially those associated with calf diseases;
- The emergence in these strains of a new pattern of multiple resistance against several antimicrobials;
- The discovery that these resistant patterns could be transferred to previously sensitive strains, not only of Salmonella but also Shigella and E. coli.

The Netherthorpe Committee Report of 1966 found evidence for concern in these new discoveries but did not find evidence to suggest that the use of the three specified antimicrobials permitted in pig and poultry feeds had played a part in developing the situation. However, it recommended that an appropriate committee with wider terms of reference should consider the evidence about these uses of antimicrobials.

In the mid-1960s in England, a single antibiotic resistant strain of Salmonella typhimurium phage type 29, caused an extensive outbreak of disease in cattle and salmonellosis in some farm personnel. Antimicrobials had been used prophylactically and therapeutically for the treatment of sick cattle and it was thought that this may have selected for the proliferation and dissemination of the strain. Subtherapeutic levels of drugs had not been used. Following this outbreak in Britain, the Minister of Agriculture, Fisheries and Food and the Minister of Health appointed a Joint Committee on the Use of Antimicrobials in Animal Husbandry and Veterinary Medicine. The committee, chaired by Dr. M. Swann, was asked to collate the available information on the use of antimicrobials in animal husbandry and to determine its impact on animal and human health.

Swann Committee 1969.

The Swann Committee examined evidence from published literature, public and private organizations, professional bodies, trade associations, research workers, and others known to have interest in the use of antimicrobials, animal husbandry, or veterinary medicine. The following items were considered:

- Use and value of antimicrobials in animals
- Possible dangers of antimicrobials
- The transfer of organisms from animals to man

- Nature of resistance to antimicrobials
- Antimicrobial resistance of bacteria isolated from animals
- General principles of antimicrobial use
- Real and potential dangers to man

Swann Committee Report.

The Committee concluded and recommended the following:

- The administration of antimicrobials to farm livestock, particularly at subtherapeutic levels, posed certain hazards to human and animal health.
- There had been a dramatic increase in the numbers of strains of enteric bacteria of animal origin which were resistant to one or more antimicrobials, and, these resistant strains were able to transmit this resistance to other bacterial species.
- There was ample and incontrovertible evidence to show that man may commonly ingest enteric bacteria of animal origin. This usually occurred through consumption of food of animal origin, such as meat and meat products, but those in close contact with animals could acquire the bacteria more directly.
- Some enteric bacteria, particularly of the salmonella group, were able to cause disease in man and in some species of farm livestock.
- The ingestion by man of antimicrobial resistant E. coli from animals may not be pathogenic for man but the resistance may be transferred to strains of bacteria which are normal inhabitants of the human intestine and could be transferred either directly or indirectly to such highly dangerous organisms as the typhoid bacillus. While these are theoretical possibilities there is little recorded evidence of such situations.
- It would be undesirable to allow situations to arise in which the treatment of human illness is limited because of antibiotic resistance in the causal organisms.
- The limited evidence available does not indicate that antibiotic residues in food of animal origin pose any public health hazard.
- The use of antimicrobials, particularly the tetracyclines, for growth promotion has been of major importance in the development of antibiotic resistance in the enteric bacteria of the animals in which they have been used for this purpose and for the resulting hazards to the human population.
- The economic effects of using antimicrobials as growth promotants in livestock production are obvious but it is evident that similar effects may be obtained with antimicrobials which have little or no therapeutic application in man and animals. Thus the use of antimicrobials that have therapeutic uses is no longer necessary and, because of the problems that have arisen from their use, is clearly undesirable.

After release of the report, antimicrobials were officially classified into two groups in England. The first consisted of agents approved for use in animal feeds as growth promotants and included bacitracin, virginiamycin, and bambermycins. The second consisted of antimicrobials which were used as therapeutic agents in human or animal medicine such as penicillin and the tetracyclines. These were banned for use in the feeds of animals unless prescribed by a veterinarian. Later, the unrestricted sale of the macrolide antibiotic tylosin for growth promoting purposes was allowed, and this agent was retained as a prescription antibiotic for therapeutic purposes in animals. It also recommended a much wider surveillance of the bacteria of animals, animal products and humans, including their antimicrobial resistance.

Changes in Antimicrobial Resistance Following Restrictions.

Antimicrobial resistance in salmonellas has been monitored at the Central Veterinary Laboratory since 1970 using disc diffusion tests (Wray et al. 1993). Most salmonella isolates in the U.K. (75%) are still sensitive to all the antimicrobials used for testing (Wray et al. 1991). Most resistance is associated with S. typhimurium and multiple-resistance is present only among a few phage types.

The results of large scale surveys have indicated that in general terms antimicrobial resistance in bacteria has not increased, especially in Europe and North America. In summary, the United Kingdom's experience with restricting the use of antimicrobials in feeds has shown that resistance in bacteria probably develops in spite of the controls on "feed" (subtherapeutic concentrations) antimicrobials not used in humans. Thus, prohibition of subtherapeutic doses of antimicrobials in animals has not prevented or even affected the prevalence of resistant bacteria in the United Kingdom. It is also difficult to ascertain the effectiveness of the Swann Committee recommendations, because animal health and production practices have improved substantially and, the therapeutic use of antimicrobials may be a more important factor in the selection of resistant organisms than subtherapeutic use. Resistant strains of salmonellae and other bacteria have persisted; some have increased in incidence, and others have decreased. The reasons for the changes are unknown, but do not appear to be related solely to the presence of antimicrobials in the gastrointestinal tract.

An important factor which confounds the study of the effects of subtherapeutic use of antimicrobials in animal feeds is that a significant proportion of antimicrobial resistance in human medicine can be the direct result of the therapeutic use of antimicrobials in man and not from their use in agriculture. The use of very effective antimicrobials simply eliminates a large pro-

portion of the sensitive ones and allows the emergence of the resistant bacterial species. Similarly, antimicrobial resistance in veterinary medicine is usually the result of the therapeutic use of antimicrobials in animals. When the prevalence of resistance to any species of bacteria has increased it has usually been associated with the introduction of a new antimicrobial, whether in human or veterinary clinical practice.

National Research Council. 1980.

In 1980, the National Academy of Sciences, Washington, D.C., commissioned a Committee to study **The Effects on Human Health of Subtherapeutic Antimicrobial Use in Animal Feeds.** After reviewing the evidence, the committee concluded that "the postulated hazards to human health from the subtherapeutic use of antimicrobials in animal feeds were neither proven or disproven". The report also noted that "the lack of data linking human illness with this subtherapeutic use must not be equated with proof that the proposed hazards do not exist". The research necessary to establish and measure a definite risk has not been conducted. The committee also concluded that it is not possible to conduct a feasible, comprehensive epidemiological study of the effects on human health arising from the subtherapeutic use of antimicrobials in animal feeds, partly because it is impossible to determine the antimicrobial history of the animal from which a particular piece of meat came.

Reports of Investigations of Disease Outbreaks in Humans Which Concluded Transfer of Antibiotic Resistant Bacteria from Animals to Man

Some papers published in the medical literature in the 1980s concluded that feeding subtherapeutic levels of antimicrobials to animals or therapeutically treating animals with certain antimicrobials resulted in an increase in the frequency of isolation of Salmonella spp. and E. coli which became resistant to those antimicrobials and, that these bacteria were transferred to humans and caused illness. These papers have become known as the **"irrefutable papers"** which provided the evidence for the **link** between the use of antimicrobials in food producing animals and antibiotic resistant bacteria causing disease in humans (Apley 1998).

Holmberg 1984.

Holmberg et al (1984) reported on a human outbreak of clinical disease caused by Salmonella newport resistant to ampicillin, carbenicillin, and tetracycline which occurred in several midwestern states. Food histories and plasmid profiles of the organisms isolated from both affected humans and some of the animals led the authors to conclude that the resistant organisms infecting the patients were of animal origin and that the probable source was contaminated hamburger, the meat of which was derived from a single herd. An editorial published in the same journal the next month suggested that the study provided " the important missing link" between human disease and resistance in the infecting bacteria due to the feeding of subtherapeutic antimicrobials to animals. The editorial entitled, "In Search of Salmonella's Smoking Gun" with a subtitle "Epidemiologists trace the circuitous path of Salmonella newport, directly linking for the first time human illness to animals fed low doses of antibiotics" (Sun 1984). However, the evidence was incomplete to come to such a conclusion. **First**, the pathogenic bacterial strain was not recovered from the slaughterhouse facilities, or from the hamburger all of which had already been consumed. Also, no cases of Salmonella newport disease occurred in the cattle or in the people associated with the farm. **Second**, another processing plant in another state received half the carcasses from this herd and had no apparent problem. **Third**, the only Salmonella newport isolated from an animal and of a strain identical with the outbreak strain was isolated from a calf that died in an adjacent dairy herd. With regards to the use of antimicrobials in the feed of the feedlot animals, the report stated that "The beef cattle had been fed subtherapeutic amounts of chlortetracycline throughout 1982 for growth promotion and disease prevention, but no therapeutic concentrations of antimicrobials. The farmer added chlortetracycline to the feed by hand, approximately 100g per ton of feed". However, this was not analyzed nor proven and there is no indication of how long the drug was used. (Adding an antimicrobial to the feed by hand at a rate of 100g per ton is likely to very imprecise).

Spika 1987.

Spika et al in 1987, claimed to have provided firm evidence that an outbreak of multiple-resistant Salmonella newport in humans in California in 1985 demonstrated the entire chain of transmission of resistant bacteria from animals to man. The authors claimed to have found the missing link! The outbreak strain was resistant to chloramphenicol, tetracycline, kanamycin, ampicillin, and sulfisoxazole and was characterized by a single large plasmid. Epidemiologic studies associated ground beef as the suspect food vehicle, because the patients had consumed ground beef at fast-food restaurants. Microbiologic and epidemiologic studies traced the epidemic strain through the hamburger, back to meat processing plants, and ultimately back to the farms from which the animals were sent for slaughter. The isolates were from ill calves and cows in several dairy herds. Isolation of chloramphenicol-resistant salmonellae was apparently associated with the use of chloramphenicol in

the herds. However, no information was provided **(none)** on how the drug was used, when it was used, for how long, and if it was used at all. Its use was not documented.

In these two outbreaks of human illness, the patients were receiving physician prescribed oral medication of antimicrobials for a previously diagnosed illness. Oral medication with antimicrobials can interfere with competitive bacterial antagonism which is a natural defence mechanism for the control of populations of bacteria (OTA 1995).

Lyons 1980.

An epidemic of Salmonella heidelberg infection in an infant nursery was associated with infected calves on a dairy farm where the mother of the index patient lived (Lyons et al. 1980). The Salmonella isolates were resistant to chloramphenicol, sulfamethoxazole, and tetracycline. Approximately 20% of the calves had been ill at one time or another and required intravenous fluid therapy and nitrofurantoin orally. No information was given about the use of antibiotics in the feed but the abstract concluded, "Verification of the spread of infection from the farm animals to a hospital population is unusual and raises questions about the hazards of antibiotic animal-feed preparations that may induce infection with resistant organisms in humans."

Tacket 1985.

Several cases of salmonellosis occurred in humans who had consumed raw milk contaminated with multiple-antimicrobial-resistant Salmonella typhimurium in Arizona (Tacket et al. 1985). One of the cases was a 72-year-old woman who died with Salmonella enteritis and sepsis and had not responded to treatment with chloramphenicol. The outbreak strain and isolates were resistant to ampicillin, kanamycin sulfate, streptomycin, sulfoxazole, and tetracycline. The outbreak demonstrated the ability of drug-resistant Salmonella to spread from the animal to the human reservoir and, in a suitable host, produce a fatal infection.

Sweden Bans Use of Antibiotic Feed Additives—1986

In 1986, the Swedish Parliament imposed a ban on antibacterial growth promoters and made them available for use by veterinary prescription only (Report from the Commission on Antimicrobial Feed Additives, 1997). The basis of the ban was the controversy surrounding the routine addition of antibacterials to animal feeds. The knowledge of the transmissibility of resistance between bacteria through plasmids led to calls for a restrictive use of antibacterials in animals. A working group of the Board of Agriculture concluded, among other things, that **"the use of antibacterial feed additives entails a risk of increased resistance in bacteria but as the substances in use are mainly active against the Gram-positive bacteria from which resistance is not transferred, the impact of such development is negligible"**. On the other hand, a negative attitude to all kinds of additives among consumers was noted. The benefits, in terms of increased production and prevention of certain diseases, were also acknowledged. At the same time, the farmers were growing increasingly skeptical towards feed antimicrobials. They were concerned that the continued use of antimicrobials might harm consumer confidence. The Federation of Swedish Farmers made a policy statement, declaring that Swedish agriculture aimed towards a more restricted and controlled use of antimicrobials. In a letter to the Ministry of Agriculture in 1984, the Federation of Swedish Farmers requested a ban on the use of antibacterials as feed additives. The Feedstuffs Act was amended so that the use of antibacterials in feed be restricted to treatment, prevention or cure of diseases, and their use for growth promotion should not be allowed. The grounds cited for this amendment was the risk for increased resistance, especially the risk for cross-resistance to other substances and the risk of increased susceptibility of animals to salmonella and other enteric pathogens. From 1986 to 1996 the total usage of antibacterial drugs in Sweden decreased and stabilized at approximately 35 tons of active substance annually, a level of about 35% lower than before the new law was implemented (Bjornerot et al. 1996). The lower consumption is reflected in a comparatively favorable resistance situation in most animal bacteria.

Institute of Medicine—1989

The report **"Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed"** by the Institute of Medicine, National Academy of Sciences, 1988, concluded that it was not possible to find a substantial body of direct evidence establishing conclusively the presence of a human health hazard that resulted from the use of subtherapeutic concentrations of penicillin and the tetracyclines in animal feeds.

The major obstacle to determining whether antimicrobial-resistant bacteria often arise from food-animal sources and present an important threat to human health has been the difficulty in tracing all the postulated steps from farm practice to human disease (Holmberg et al. 1984). Individual events in the complicated sequence have been documented, such as the selection for and persistence of resistant bacteria in food-producing animals resulting from the use of subtherapeutic doses of antimicrobials, the frequent presence of resistant Salmonella in products of animal origin, the transmission of resistant microorganisms to

humans, and human disease resulting from multiple resistant bacteria. However, outlining all these steps in a sequence is rarely possible and does not indicate the relative frequency with which resistant bacteria arise from animal and human populations.

Impacts of Antibiotic Resistant Bacteria. 1995. Office of Technology Assessment. Washington.

The Food and Drug Administration, the National Academy of Sciences, the Office of Technology, and official boards and committees overseas have examined the evidence for the contribution that agricultural uses of antimicrobials make to human diseases or to the prevalence of antibiotic-resistant bacteria. None was able to pinpoint data that show the extent of the problem, and all emphasized the difficulties in studying this problem (OTA 1995).

The uncertainty about agricultural uses of antimicrobials is their contribution to antibiotic-resistant bacteria and to complications in the treatment of human diseases. Years of review and analysis of the literature testify to the difficulty of coming to any generally accepted conclusions about the effects of long-term, low-level feeding of antimicrobials to food animals and the appearance of antimicrobial-resistant bacteria in humans, and it is unreasonable to expect that another review of existing data would provide resolution (OTA 1995).

The following **three options**, if adopted, would provide for the collection of new information. Importantly, however, careful analysis needs to precede any study because it is quite possible that no study can produce information sufficiently definitive to justify the expense of the study, and that analysis would have to involve agricultural interests, pharmaceutical companies, farmers, farmer organizations, public health officials, environmental organizations, organic food processors, and scientists from all those organizations as well as universities and the government.

1. Collect information about associations between animal husbandry uses of antimicrobials and antibiotic-resistant bacteria in humans.

Does the agricultural use of antimicrobials contribute 2, 5, or 10% of the antibiotic-resistant bacteria in humans?

2. Design a study to determine the sources of antibiotic-resistant bacteria in the human diet.

Investigate the sources of antibiotic-resistant bacteria. Collect samples of marketed foods, isolate bacteria from the foods, and characterize their antibiotic resistance.

3. Study the benefits of antibiotic use in animal husbandry.

Research on the costs and benefits of subtherapeutic uses of antibiotics in livestock production need to be redone given the advances made in animal nutrition and genetics in the last two decades. What is the evidence that the use of antimicrobials as growth promotants is still effective in beef cattle feedlots and under what conditions?

World Health Organization—1997

In October 1997, WHO held a workshop in Berlin on **"The medical impact of the use of antimicrobials in food animals "** (WHO 1997).

The press release stated, "Excessive use of antimicrobials, especially as growth promoters in animals destined for human consumption, presents a growing risk of human health and should be reduced...Healthy practices in animal husbandry reduce the need for antimicrobials, the experts emphasized, and antimicrobials should never be used as a substitute for adequate hygiene..." Particular concern was expressed about widespread use of fluoroquinolones and the rapid increase in fluoroquinolone resistant Campylobacter spp. and the emergence of fluoroquinolone resistant salmonella.

The recommendations included:

- The use of any antimicrobial agent for growth promotion in animals should be terminated if it is used in human therapeutics or known to select for cross-resistance to antimicrobials in human medicine.
- National authorities should define threshold levels of resistance in bacteria and circumstances where mitigation procedures should be instigated and, if such procedures are unsuccessful, when approval should be withdrawn.
- No antimicrobial should be administered to a food animal unless it has been evaluated and authorized by competent national authorities. This evaluation should include a thorough risk assessment which includes the development of resistance that may impact public health, and, post market monitoring program to detect emergence of resistance of public health significance. If such emergence is detected, appropriate action should be taken, which may include the withdrawal of the antimicrobial.
- Increased concerns regarding risks to public health resulting from the use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth promoting antimicrobials with safer non-antimicrobial alternatives.
- National authorities should maintain records of export/import figures of bulk chemicals with potential antimicrobial use, as such information is vital for quantitative assessments of the medical risks related to the use of antimicrobials in livestock production.
- WHO should take the lead in coordinating international efforts in resistance monitoring in bacteria

isolated from food of animal origin and food animals as part of the WHO program on Antimicrobial Resistance Monitoring. Training on antimicrobial resistance testing and national policy framework development activities within the medical sector should involve participation of the veterinary sector.

• Strengthening of microbiological laboratories which are capable of developing networks on resistance monitoring must be given preference, as regional and international resistance monitoring depends on reliable, quality assured and standardized susceptibility testing in individual laboratories.

Danish Integrated Antimicrobial Resistance Monitoring and Research Program (1997)

In 1995, the Minister of Health and the Minister of Agriculture and Fisheries in Denmark initiated an elegant program to conduct a coordinated national surveillance and research program to monitor resistance in bacteria from animals, foods and humans to antimicrobials used for therapy and/or growth promotion (Bager 1997). The program has the following objectives:

• To monitor the use of antimicrobials for treatment in humans and in animals and for growth promotion.

• To monitor the occurrence of antimicrobial resistance among bacteria isolated from food animals, foods and from humans.

• To demonstrate associations between such use and the occurrence of resistance.

• To record trends in the above mentioned parameters.

The results were as follows:

Food animals:

Use of antimicrobials. No official data on usage were available. Aminoglycosides, macrolides, penicillins and tetracyclines accounted for 80% of the total. Tylosin accounted for more than 50% in pigs.

Antimicrobial resistance. Resistance to all antimicrobials occurred. There was considerable variation in the occurrence of resistance associated with the pattern of antimicrobial use. Resistance to antimicrobials was most frequently observed in bacteria isolated from pigs compared to bacteria isolated from cattle and broilers. Resistance to growth promoters occurred in indicator bacteria from all animals. Resistance was less frequent in zoonotic and pathogenic bacteria. Co-resistance to therapeutic antimicrobials was frequently observed in bacteria resistant to growth promoters which are structurally related to therapeutic agents (avoparcin, virginiamycin, spiramycin and tylosin). There was a relatively high level of resistance to Salmonella and Campylobacter, especially multi-resistance in those bacteria isolated from pigs which is a cause for concern. There was a high occurrence of resistance to tetracycline among some strains of bacteria from pigs. The levels of resistance of Salmonella isolated from animals have increased in Denmark during recent years, possibly as a result of therapeutic use of antimicrobials in animals. Continued surveillance will show to what extent changes in levels of resistance in zoonotic bacteria from different animals and foodstuffs affect the levels of resistance observed in zoonotic bacteria isolated from human infections. The level of resistance among Salmonella typhimurium isolated from humans was unchanged from 1993 to 1996.

Foods:

Antimicrobial resistance. Resistance was demonstrated to all therapeutic antimicrobials and most of the growth promoting antimicrobial agents. The only growth promoting agents to which no resistance was recorded were carbadox and salinomycin. The highest frequencies of resistance from foods were among bacteria isolated from poultry. Resistant bacteria commonly occurred in pork.

Humans:

Use of antimicrobials. It is possible to account for approximately 95% of the antimicrobials used in humans in Denmark. Denmark has the lowest consumption per capita among the Nordic countries.

Antimicrobial resistance. Generally, there is a very low level of antimicrobial resistance in bacteria isolated from humans in Denmark.

Association between use of antimicrobials and occurrence of resistance. Tetracyclines are used to treat chlamydial infections and acne in humans and the level of resistance of E. coli isolated from humans to tetracyclines is 22%. The levels of resistance of E. coli to tetracyclines isolated from cattle and pigs was 78% and 57%, respectively.

World Health Organization. 1998. Use of Quinolones in Food Animals and Potential Impact on Human Health, Geneva, Switzerland

It was concluded that the use of fluoroquinolones in food animals resulted in the emergence of fluoroquinolone-resistant Campylobacter and Salmonella with reduced susceptibility to fluoroquinolones (WHO 1998). There has been little documented evidence of this resistance in human health to date, but there is concern about the potential human health consequences if resistance were to increase and spread. The report recommended the prudent use of antimicrobials in food animal production. Prudent use of quinolones is defined as practices which maximize therapeutic effect while

minimizing the emergence of resistance. It is recommended that quinolones be approved only for therapeutic use and not for growth enhancement. No quinolones should be administered to a food animal unless the product has been evaluated including an assessment of the potential for development of resistance which may affect public health. A post-approval monitoring program to detect trends toward the emergence of resistance of public health significance is recommended.

Ministry of Agriculture, Fisheries and Food. United Kingdom. 1998. A Review of Antimicrobial Resistance in The Food Chain

This was an extensive review of the literature dealing with the scientific issues surrounding the use of antimicrobials in food animals and to examine the risks of the transfer of antimicrobial resistant organisms from the food chain to man.

The conclusions were:

- Resistance to antimicrobials is selected in animal pathogens following the introduction of veterinary medicines or growth promoters and is well documented.
- Resistance also develops in bacteria comprising the normal bacterial flora of animals but is not so well documented.
- Bacteria are transmitted on meat, in unpasteurized milk and on some vegetable crops from animals to man. This transfer is documented. Transfer of antibiotic resistant bacteria from man to animals in wastes is poorly documented.
- Some animal bacteria transmitted to man in food are resistant to antimicrobials.
- Bacteria such as salmonella and campylobacter from animals may cause disease in man. If antibiotic resistance confers resistance to antimicrobials used in treatment of disease in man, the infection may become difficult to treat. This transfer is well known.
- Bacteria from the normal animal flora may colonize man and the few publications on this suggest that they colonize normal individuals briefly. Some bacteria from the normal flora are antibiotic resistant.
- Bacteria resistant to antimicrobial growth promoters used in animals have been found in the feces of people in the community. The duration of this colonization has not been clearly established.
- Resistant bacteria of animal origin may transfer their resistance to human pathogens or normal flora. This transfer has been documented in a few experimental studies using human volunteers, and from analyses of the DNA sequences of resistance genes. Data reported at the workshop suggests that this occurs between animal and human enterococci.
- The major risk to man is the food-borne pathogens such as salmonella and campylobacter species some of which are multi-antibiotic resistant.
- Verocytotoxigenic E. coli 0157H:7 generally are not resistant to antimicrobials. Antimicrobials are currently not used in treatment of patients clinically affected with E. coli 0157H:7.
- Antimicrobials to which resistance is of particular concern in the literature include the fluoroquinolones (Salmonella and Campylobacter spp.), macrolides (Campylobacter spp.), virginiamycin (Enterococci spp.) and avoparcin (Enterococci spp.).
- Some antimicrobial growth promoters have no implication for the development of resistant bacteria important in human medicine.
- The sterilization of food for high risk human patients and the development of antimicrobial resistance management on farms will reduce the development and spread of antimicrobial resistance to humans.

European Community Bans Four Antibiotic Feed Additives. 1998

At a meeting in Brussels, December 14, 1998, agriculture ministers from 12 of 15 EU member countries, including Britain, voted to ban the use of four antimicrobials in animal feedstuffs (Anonymous 1998); three countries-Belgium, Portugal and Spain abstained. The products banned as of January 1, 1999, are **virginiamycin**, **tylosin phosphate**, **spiramycin** and **zinc bacitracin**. The ban was imposed as a precautionary measure to minimize the risk of development of resistant bacteria and to preserve the efficacy of certain antimicrobials used in human medicine. The ban will be reviewed before December 31, 2000, on the basis of information from further investigations, particularly the report of the EU's Scientific Steering Committee, and the results of surveillance for bacterial resistance. The Minister of Agriculture of Britain said, "On the precautionary principle, it is right to suspend the use of these four growth promoters until more evidence emerges." Representatives of the European animal nutrition industry said, "To have a decision such as this made without regard to the scientific facts at hand is fundamentally wrong".

A recent report of the EU's own Standing Committee on Animal Nutrition reviewing all recent data on one of these products concluded that there is no scientific basis for such a suspension.

Institute of Medicine. 1998. Antimicrobial Resistance: Issues and Options. (National Academy Press, 1998).

This workshop identified the following issues and options:

- Costs of antimicrobial resistance: The Centers

for Disease Control and Prevention estimated these costs at $4.5 billion in the United States annually.

- Surveillance systems: The need for information and laboratory systems at the local, national and international levels.
- Understanding the use of antibiotics in food production.
- Prolonging effectiveness of antimicrobials through education, law and regulations.
- Developing new products by providing incentives for industry, research, and education.
- Legal and regulatory approaches to monitor use of antibiotics.
- Agricultural use requires research support.

National Research Council 1999. The Use of Drugs in Food Animals: Benefits and Risks.

In response to growing public concern over food safety in relation to the use of drugs in food animals, the U.S. Department of Agriculture and the Center for Veterinary Medicine of the Food and Drug Administration asked the National Research Council to form a committee to examine and review the benefits and risks associated with drug use in the food-animal industry (National Research Council, 1999). The National Research Council assigned the task to the Board on Agriculture, and the Committee on Drug Use in Food Animals was convened. The committee was charged with reviewing, evaluating, and making recommendations related to the need for drugs and their availability and accountability in agriculture, the benefits and risks to human health and food safety associated with food animal drugs, the development of food animal drugs and the process of approval of their use, and the emerging trends in animal health care and the availability of alternative management practices for raising food animals. In particular, the sponsors stressed the importance of evaluating the class of drugs known as antimicrobials.

The committee concludes that the use of drugs in the food animal production industry is not without some problems and concerns, but it does not appear to constitute an immediate public health concern; additional data might alter this conclusion. The greatest concern is associated with the use of antimicrobials in food animals in such a way that there is a potential for antibiotic resistance to develop in or be transferred to pathogens that can cause disease in humans. This report acknowledges that there is a link between the use of antimicrobials in food animals, the development of bacterial resistance to these drugs, and human disease—although the incidence of such disease is very low. The link between the animals fed antimicrobials and transfer of antibiotic resistant enteric pathogens to humans has not yet been demonstrated.

A substantial change in the human health risk posed by antibiotic use would affect not only how animal drugs are reviewed, approved, and used, but also how food animals are produced. It should be noted that antimicrobials are still effective for their intended purposes at the recommended dosages.

Bacterial resistance to antimicrobials will be the most important motivating factor in the development of new drugs to fight infections and in the modification of processes by which drugs are approved. Regulatory agency approval practices have improved in recent years and continue to do so. Reasonable balance in accountability, oversight, and veterinarians' access to alternative drugs has increased with the passage of Animal Drug Availability Act (ADAA) and Animal Medicinal Drug Use Clarification Act (AMDUCA). However, those are only temporary solutions to a continuing problem.

Unless new antimicrobials become available, even the extra-label use of antimicrobials is expected to become ineffective. There is a great need to understand better both the magnitude of the risk and the options available to minimize the risk while maintaining the benefits these drugs confer on agriculture. Constant vigilance in monitoring trends in antibiotic resistance in farm animals and humans is strongly encouraged.

New antibiotic drugs are needed to combat emerging animal diseases that do not respond to traditional drugs and so threaten public confidence in animal agriculture and human medicine. Professionals in human health care should be concerned that they do not have enough specialty antimicrobials to treat resistant and emerging infections in humans, as should veterinarians. The question is, should newly discovered medications be held in reserve for human or animal use only? Antimicrobials should be available to treat specific human and animal diseases with proper accountability and oversight of the drugs used. Information gaps hinder the decision- and policy-making processes for regulatory approval and antibiotic use in food animals. A data-driven scientific consensus on the human health risk posed by antibiotic use in food animals is lacking.

Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals. Food and Drug Administration. November 1988. March 1999.

The Food and Drug Administration has proposed a framework to ensure microbial safety of new drug submissions for use in food animals. The objective is to evaluate the human health impact of the microbial effects associated with all uses of all antimicrobial new animal drugs in food-producing animals. It is proposed to divide antimicrobial drugs into three categories based on their unique or relative importance to human medi-

cine. The FDA believes it is crucial to determine the importance of an antimicrobial in human medicine before it can determine what effect the development of resistance to that drug from food-producing animal use will have on human health. Drugs would be divided into two groups according to two factors: importance to human medicine and potential human exposure to resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their resistance to human pathogens.

A. Categories of Drugs

Antimicrobial drugs would be divided into three categories based on the following criteria:

Category I

- Essential for treatment of a serious or life threatening disease in humans for which there is no satisfactory alternative therapy.
- Important for the treatment of food-borne diseases in humans where resistance to alternative antimicrobial drugs may limit therapeutic options.
- The drug is a member of a class of drugs for which the mechanism of action and/or the nature of the resistance-induction is unique, resistance to the antimicrobial drug is rare among human pathogens, and the drug holds potential for long term therapy in human medicine.
- In addition, any antimicrobial drug that can induce or select for cross-resistance to a Category 1 drug would be considered a Category 1 drug. Similarly, if an antimicrobial is not used in human medicine, and if it can be demonstrated to the agency's satisfaction that it does not induce cross-resistance to any antimicrobials in the same class used in human medicine that are Category 1, then it would not be considered a Category 1 drug.

The following examples would be considered to be included in Category 1:

Quinolones for serious infections caused by multidrug resistant Salmonella spp. (resistant to Category II drugs).

Vancomycin for serious infections caused by methicillin resistant S. aureus, and ampicillin resistant enterococci.

Dalfopristin/quinupristin for vancomycin-resistant enterococcal infections.

Third generation cephalosporins used to treat food-borne infections.

Category II

These would not meet any of the criteria for Category 1 and they or drugs in the same class meet the following criterion:

- They are the drugs of choice or important in the treatment of a potentially serious disease, whether food borne or otherwise, but satisfactory alternative therapy exists.
- Any drug which can induce or select for cross-resistance to a Category II drug. If an antimicrobial is not used in human medicine, and if it can be demonstrated to the agency's satisfaction that it does not induce cross-resistance to any antimicrobials in the same class used in human medicine that are Category II, then it would not be considered a Category II drug.

The following are examples of drugs which would be included in Category II:

Ampicillin for treatment of infections due to Listeria monocyogenes.

Cephalosporins not in Category I which do not induce cross resistance to those in Category I; beta lactams and beta lactamase inhibitor combinations because they represent both drugs of choice and alternative therapies for many life threatening Gram-negative infections.

Erythromycin for treatment of Campylobacter infections.

Trimethoprim-sulfamethosaxole for treatment of a wide range of serious enteric infections including susceptible Salmonella and Shigella infections.

Category III

These do not meet the criteria for Categories I or II but meet the following criteria:

- Have little or no use in human medicine
- Are not the drug of choice or a significant alternative for treating human infections including food borne infections.

The following are examples of drugs which would included in Category III:

Ionophores which have no use in human medicine.

The **polymixins** since they have significant toxicities and have been replaced by other drugs for virtually all human use.

B. Evaluating Potential Exposure of Humans

The potential for exposure of humans to antimicrobial resistant bacteria from animals given antimicrobials would be categorized into **high, medium,** and **low** based on the **drug attributes, use of the drug,** and **potential human contact.**

With different uses of the drug, the relative contributions of factors to the likelihood of human exposure may vary.

High potential human exposure. An antimicrobial which induces significant cross-resistance to an antimicrobial used in human medicine is used for growth or feed efficiency in cattle, swine or poultry.

Drugs used in the feed throughout the life of the animals on a herd or flock basis are considered high potential for human exposure.

Medium potential human exposure. An antimicrobial used for the control, prevention, mitigation, or treatment of disease where use duration is between 6 and 21 days.

Low potential human exposure. An antimicrobial used for individual treatment of short duration, where the disease requires treatment of only a small percentage of the animals in a flock or herd.

C. Microbial Safety.

The combination of categories of drugs and potential for human exposure are combined to determine what actions would be considered necessary to assure the safe use of the drug.

Epidemiology of Antimicrobial Resistance in Veterinary and Human Medicine

Sources of Antimicrobial Resistance

Several origins. The development and spread of antimicrobial resistance in bacteria is usually attributed to overuse or misuse of antimicrobials. However, antimicrobial resistance is not a single phenomenon, and although many resistance mechanisms have been identified and analyzed for most clinical pathogens and almost all antimicrobials for clinical use, the origin and sources of antibiotic resistance have remained neglected subjects of investigation (Bergogne-Berezin, E. 1997). Antibiotic resistance probably has many different origins in nature and must be as ancient as antibiotic synthesis. **Resistance genes pre-existed** in nature, in soil and water, prior to the antibiotic era and their presence was probably related to the production of antibacterial agents, synthesized naturally in the environment by saprophytic organisms such as actinomycetes. These organisms are found in large numbers in soil and biologically active substances are synthesized by the actinomycetes, including the majority of the antimicrobials in use today. Thus, self protection of these organisms is essential. Chromosomal resistance genes have been characterized and cloned for many antibiotic-producing organisms. Extrachromosal resistance plasmids have been recovered from bacteria isolated and stored in the pre-antibiotic era and organisms producing beta-lactamases have been revived from plant specimens stored in the 17th century. As a result, soil and the natural environment constitute a very large reservoir of antibiotic resistance genes, and various potential mechanisms of resistance existed long before clinical use of antimicrobials commenced 50 years ago with the advent of penicillin.

Acquired Resistance. Several factors contribute to the emergence of resistance. The discovery, production and use of large quantities of antimicrobials in human and veterinary medicine have undoubtedly contributed to the selection of bacterial clones possessing resistance genes. The use of antimicrobials in animal agriculture contributes to resistance. The normal intestinal flora in healthy animals is a reservoir of resistance genes. Microorganisms may transfer their plasmids to pathogenic or non-pathogenic intestinal flora and then to the intestinal flora of other individuals. As the risk of infection increases when large numbers of animals are concentrated together, large quantities of antimicrobials are used for prevention of infection, with increased risk of resistance selection. Thus antibiotic resistance in animal enteric flora is a risk to human health via the food chain.

Contaminated animal feed. Contaminated animal feed is a potential source of antibiotic-resistant bacteria. Even in the absence of selective pressure resulting from antibiotic use for growth promotion, animals carry large numbers of resistant strains originating from the environment and feed. Contaminated water (fecal contamination), irrigation of agricultural land by animal or human waste, and contaminated feed for animals are unavoidable factors favoring plasmid carriage and transfer of resistance genes in the intestinal flora of animals (Haapapuro et al. 1997).

Antimicrobial Resistance in Human Medicine

The major cause of antimicrobial resistant bacteria in the human population is associated with the widespread use of antimicrobials prescribed by physicians for patients who insist on being treated for a variety of common infectious diseases for which antimicrobials are not required (OTA 1995). Many physicians comply with the request of patients who demand antimicrobials for the treatment of the common cold and other viral infections which cannot be cured by drugs (Levy 1998). There is general agreement that antibiotic resistance in human medicine is associated with the use of antimicrobials in the community and the hospital setting. It is suggested that only 25% of the antimicrobials prescribed by physicians in North America are necessary. In addition, the rate of non-compliance among human patients is high because many patients fail to take their prescribed antimicrobials for the full prescribed course.

There is a relationship between resistance and antibiotic usage (OTA 1995; Levy 1992 & 1998). Drugs are often prescribed to treat either the wrong kind of infection or to treat infections which do not respond to antimicrobials. Inappropriate doses of oral antimicrobials may achieve serum and tissue concentrations that are lower than the MICs for the infecting pathogens which exerts a potent selective pressure for the emergence of resistant clones that pre-exist in the bacterial populations.

Any kind of usage of antimicrobials selects for resistant organisms. The question for human medicine is, to what extent has the problem of antimicrobial resistance in human pathogens been influenced by the use of antimicrobials for purposes other than for human therapy? Or, in other words, what is the risk in using antimicrobials outside human medicine compared with the risk in using them by treating or preventing human infections with respect to the problem of antimicrobial resistance? This question can be easily answered for pathogens which colonize and infect mainly humans, such as the gonococci, meningococci, H. influenza and pneumococci. The resistance problem in these organisms solely is due the use of antimicrobials in human medicine.

Nosocomial infection. The development of antibiotic resistance in humans in the hospital environment is the result of multiple factors including epidemic Gram-negative bacilli which are known to be inherently resistant to many antimicrobials. Because of their structure they can be selected by antibiotic selective pressure and emerge as opportunist multiresistant pathogens. Emergence of resistance in pathogens during antibiotic treatment can occur by chromosal mutations. In-vivo transfer of plasmids coding for multiple resistance may occur into species or genera previously susceptible. Spread of resistant Gram-positive bacteria, such as MRSA and penicillin-resistant pneumococci, is an increasing problem.

Vancomycin-resistant enterococci. Enterococci have emerged as important human pathogens in recent years and during the last 20 years have been reported to carry antimicrobial resistance. With the recent emergence of vancomycin resistance, enterococci may be resistant to all currently approved antimicrobials. Enterococci is the second most commonly isolated nosocomial (hospital-acquired infections) pathogen and the third most commonly isolated pathogen associated with nosocomial bacteremias in human patients (Ofner-Agostini et al. 1997). The National Nosocomial Infection Surveillance system in the United States reported a 20-fold increase in the percentage of nosocomial enterococcal isolates that were vancomycin-resistant between 1989 and 1993. In 1996, in Canada, a study of vancomycin-resistant enterococci found a prevalence of 0.1% in non-epidemic hospitals, 3.7% in endemic hospitals and 5.3% in endemic patient groups within endemic hospitals (Ofner-Agostini et al. 1997). Several risk factors were associated with acquiring VRE, and most were related to prolonged hospital stay of patients who had multiple surgeries and severe underlying disease or immunosuppression and prior nosocomial infections.

Vancomycin-resistant Enterococci faecium (VREF) may cause serious therapeutic problems in hospitalized patients (Devriese et al. 1996). Until recently, the possible presence of such strains in animals was unknown and remain uninvestigated, probably because glycopeptide antibiotics are not used therapeutically in veterinary medicine. In Europe, one member of this antibiotic group, avoparcin, is used for growth promotion in farm animals, and vanA-carrying vancomycin-resistant Enterococcus faecium strains are cross-resistant to avoparcin. A broad survey has found that vancomycin-resistant enterococci strains are widespread among isolates from horses, chickens and pigs (Bates 1994; Devriese et al. 1996). Samples from pigeons, cage birds and ruminants were negative.

In a number of countries in Western Europe and Australia, avoparcin is widely used as a feed additive to promote growth and feed utilization in pigs and poultry (Bager et al. 1997).

Studies in Denmark, Norway and Sweden provide strong evidence that the use of avoparcin as a growth promoter in poultry and pig farms is associated with the occurrence of vancomycin-resistant enterococci in domestic animals (Bager et al. 1997).

The number of resistant isolates was higher on farms which had been exposed to avoparcin. All resistant isolates examined were co-resistant to avoparcin and contained the vanA gene which supports the contention that avoparcin and vancomycin resistance in Enterococcus faecium is most probably mediated by the same gene. The vanA gene is located on a transposon, a highly mobile genetic determinant of resistance, and the presence of VREF on farms in the absence of a specific selective pressure is similar to the persistence of antibiotic resistance in other bacteria. For example, in Danish pig isolates of E. coli, resistance to chloramphenicol is still widespread, even though this antibiotic has not been used in production animals for more than 15 years. This may indicate that VREF cannot be expected to disappear rapidly in domestic animals after the use of avoparcin has been discontinued. It is suggested that the use of avoparcin as a growth promoter is associated with the occurrence of vancomycin-resistant enterococci in domestic animals. There is little information available on the transfer of these isolates to humans either by direct contact with the animals (farmers and animal attendants) or through the food chain. An undocumented reference indicated that VREF were isolated from the feces of three of six broiler farmers attending to broiler flocks which had used avoparcin (Bager et al. 1997).

Food-Borne Pathogens and Antimicrobial Resistance

Transfer of antibiotic-resistant bacteria such as E. coli, Salmonella spp., Campylobacter spp., and enterococci can occur through the food chain or close contact with animals carrying resistant organisms.

It is important to consider the circumstances of food-borne illness in humans in the context of any discussion of antimicrobial resistant bacteria being transferred from animals to man. Meat and meat products are **not bacteria free** and most food-borne illnesses are due to the improper handling of food and inadequate cooking. **Moreover these bacteria may be pathogenic for humans whether or not they are resistant to antimicrobials. Thus the proper handling and cooking of food for human consumption must be given high priority.**

The major food-borne pathogens are Salmonella spp., Campylobacter jejuni, and E. coli. There is worldwide concern about the emergence of antimicrobial resistant bacteria emerging in the production of poultry, swine and beef cattle. However, the proportion of cases of food-borne illness due to antimicrobial resistant bacteria is unknown.

The USDA National Animal Health Monitoring System collected nearly 12, 000 fecal samples from 100 volunteer feedlots across 13 states to determine the prevalence of E. coli 0157H:7 and Salmonella (USDA 1995). Overall, 5.5% of the fecal samples were positive for Salmonella. Samples collected from pens of cattle which had been on feed for longer periods of time yielded a higher positive culture rate (7.4%) than those samples from pens of cattle which had recently arrived in the feedlot (3.5%).

In a Canadian study, verotoxins were detected in 42.6%, E. coli 0157H:7 in 7.5%, and Salmonella in 0.08% of the fecal samples of yearling cattle and cull cows at slaughter (Van Donkersgoed et al. 1999). The prevalence of E. coli 0157H:7 in fecal samples was higher in yearling cattle than in cull cows and highest in summer months. The prevalence of verotoxins in fecal samples of cull cows was highest in those from auction mart and farm/ranch and lowest in cows from the feedlot. In rumen samples, the prevalence of verotoxins was 6.4%, 0.8% for E. coli 0157H:7, and 0.3% for Salmonella (Van Donkersgoed et al. 1999).

Salmonella spp. The Salmonella species are one of the most common food-borne pathogens. Economic costs associated with human salmonellosis are nearly one billion dollars annually in the United States. It has been proposed that there are six lines of evidence which taken together, demonstrate that foods of animal origin are the dominant source of human salmonellosis and that person-to-person transmission is an uncommon source of human salmonellosis in the United States (Angulo et al. 1998)

Humans can become infected by most serotypes of Salmonella. In the United States, the most common serotypes among isolates recovered from humans annually are S. typhimurium, S. enteritidis, S. heidelberg, S. hada and S. **newport.** Poultry is the food animal reservoir for S. enteritidis and eggs provide a source of the organism for humans. Cattle are the reservoir for S. newport and S. dublin. Salmonella is also an important pathogen to cattle and the organism can be found in the feces of about 5% of feedlot cattle (Losinger et al. 1997).

S. typhimurium is not host specific and is equally infectious to both animals and man. Infection with salmonella does not always cause clinical disease. A localized gastroenteritis is most common and spontaneous recovery without treatment is common. The very young, the elderly, immunocompromised patients, and those already taking oral antimicrobial medication are most at risk of developing systemic illness with septicemia.

In addition to clinical disease which may occur in humans with salmonellosis, there is the major concern that an increasing number of infections are being caused by antimicrobial resistant strains.

Since 1993 a multiple antibiotic resistant strain of Salmonella typhimurium DT 104 has accounted for most cases of salmonellosis in cattle in the U. K (Evans & Davies, 1996; Threlfall et al. 1994 and 1998; Wall et al. 1995), in the U.S.A. (Besser et al. 1997; Akkina et al. 1999), in Australia (Mackie et al. 1996), and in Canada (Poppe et al. 1998). Originally isolated in England in 1984 from a human specimen, Salmonella typhymurium DT 104 remained very rare until about 1990 when there was a rapid increase in isolation rates in humans and the first isolation in livestock. Cattle are thought to be the main reservoir of infection (Calvert et al. 1998). The herd associated risk factors for disease caused by multiple-resistant Salmonella typhimurium DT 104 in cattle herds in Great Britain have been examined (Evans 1996). The epidemic strain is classified as R-type ACSSuT through being resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline. Some strains of S. typhimurium DT 104 have chromosomally integrated multiple drug resistance (Threlfall et al. 1994). Since 1994, the percentage of DT 104 with additional resistance to trimethoprim and reduced sensitivity to ciprofloxacin has increased. The emergence and dissemination of multiresistant DT 104 with reduced sensitivity to ciprofloxacin (a fluoroquinolone) has occurred since the licensing for veterinary use in the U.K. in 1993 of the related fluoroquinolone, enrofloxacin, which has subsequently been used for treatment and prophylaxis in both cattle and poultry in the U.K. (Frost et al. 1996; Threlfall et al. 1998). In contrast to the U.K., while multiresistant strains of DT 104 have been isolated in the U.S. none of the human or veterinary isolates of DT 104 has been resistant to fluoroquinolones (Besser et al. 1997; Glynn et al. 1998). Since chromosomal integration has been cited as a method whereby bacterial cells can retain antimicrobial resistance genes in the absence of selective pressure, it is unlikely that

withdrawal of antimicrobials would have any significant effect on the current epidemic of DT 104 ACSSuT in cattle in Britain (Threlfall et al. 1994).

Nalidixic acid is a first generation quinolone antimicrobial now used to detect changes in susceptibility to other more modern fluoroquinolones such as enrofloxacin. In the Great Britain, nalidixic acid resistance in salmonellae was rare and sporadic until 1994, when increasing resistance in DT 104 isolates was noted in most of the livestock species except ducks and sheep. By 1995, there had been a rapid increase in the proportion of resistant S. typhimurium isolates from turkeys and a more gradual increase, largely as a result of increasing resistance in DT 104, in isolates from other species (Davies et al. 1999). In 1997, 72.7% of other S. typhimurium DT 104 isolates from turkeys were resistant to nalidixic acid compared with zero and 16.1% from chickens.

In the U.S., multidrug resistant Salmonella typhimurium DT 104 has been isolated from cattle, sheep, goats, pigs, wild birds, dogs, cats, mice and horses (Dargatz et al. 1998). Serotyping, phage typing, and antibiograms must be done in order to identify isolates as DT 104.

Compared with most other countries antimicrobial resistance among S. enterica isolated from Danish pig herds is uncommon (Baggesen & Aaestrup 1998) and the number of multiresistant isolates is still small. The prevalence of multiple-resistant Salmonella typhimurium DT in Danish pig herds is still low.

In Denmark, the frequency of antimicrobial resistance and epidemiological relatedness among 473 isolates of Salmonella enterica subsp. enterica serovar typhimurium from humans and veterinary sources have been examined (Seyfarth et al. 1997). The human strains were isolated from patients with diarrhea, and the animal strains from clinical and subclinical infections in cattle, pigs, or poultry. All strains were tested against 22 antimicrobials used in both human and veterinary medicine with the tablet diffusion method. Strains were phaged typed and the plasmid content determined in all resistant strains. Ribotyping was done on selected strains. Of 228 human isolates tested, 19.3% of the strains were resistant to one or more antimicrobials compared with 10.4% of strains from cattle, 11.1% of strains from pigs and 9.2% of strains from poultry. Multiple resistance, to at least 4 antimicrobials, was found in 9.2% of the human strains, but in only two of the cattle isolates. The majority of the multi-resistant strains in humans were from infections contracted outside Denmark, most often in southern Europe or southeast Asia. Resistance in human strains was most common against tetracycline (13%), ampicillin (12%), sulphonamide (12%), streptomycin (10%), and chloramphenicol (8%). The resistance pattern differed somewhat in animal isolates. Poultry strains were usually resistant only to ampicillin, while pig and cattle isolates were most often resistant to sulphonamides, tetracycline and streptomycin. Typing of the strains found some animal strains and human strains were indistinguishable.

Multiple resistant organisms of serotypes other than S. typhimurium occur at a very low frequency (0.002 percent) in Scottish isolates (Rankin 1998).

E. coli. Several different virotypes of E. coli can cause disease in humans and animals (Su & Brandt 1995). The most important one causing disease in humans is the enterohemorrhagic type known as E. coli 0157H:7 which causes hemorrhagic colitis (HC) and the hemolytic uremic syndrome (HUS) (Whipp et al. 1994).

Serotype E. coli 0157H:7 is classified as an enterohemorrhagic *E. coli* because it causes hemorrhagic colitis, produces a Shiga-like toxin, does not produce either heat-stable or heat-labile toxin which is characteristic of enterotoxigenic *E. coli*, and it is not invasive. *E. coli* 0157H:7 is considered the epidemic strain because it has been responsible for major outbreaks reported in the United States, Canada, and the United Kingdom (Whipp et al. 1994).

Cattle are a source of E. coli 0157H:7 which causes food-borne disease in humans in North America, Europe and the United Kingdom. Transmission of the organism occurs through the ingestion of **uncooked** ground beef and consumption of raw milk although outbreaks have been associated with fresh-pressed apple cider, unchlorinated drinking water, and person-to-person transmission. Investigations of outbreaks of disease in man have linked most of the cases to consumption of hamburgers from fast-food restaurant chains. *E. coli* 0157H:7 was isolated from ground hamburger supplied to restaurants by meat suppliers. This has been followed by recall of the incriminated meat.

The prevalence of E. coli 0157H:7 in the cattle population is low. In a survey in the United States, the prevalence in dairy heifers and in all cattle was 0.37 and 1.85%, respectively. Person to person spread also occurs. Overall, E. coli 0157H:7 was recovered at higher rates from pens of cattle which had been on feed for the shortest period of time (3.01%). Samples from pens of cattle which had been on feed the longest time, and were closer to slaughter, were less likely to give positive results for E. coli 0157H:7 (1.08%) (USDA 1995). Other studies found that 0.33% of the fecal samples and 10% of feedlot pens sampled gave positive results for E. coli 0157H:7 (Hancock et al. 1994).

Contamination of carcasses during slaughter and processing may explain how beef and beef products become contaminated and thereby transmit the organism to man. The organism can survive in bovine feces for long periods and still retain its ability to produce verotoxins. In-vitro studies of the growth of the organ-

ism in rumen contents indicate that the organism does not grow well in rumen fluid collected from fasted cattle, suggesting that well-fed animals appear less likely to become reservoirs for pathogenic E. coli. The organism has been isolated from dairy calves less than 8 weeks of age and calves were three times more likely to shed the organism after weaning.

The persistence of E. coli O157H:7 in dairy cattle is transient and persistence of the organism cannot be demonstrated from farm environment sites tested. The duration of detected E. coli O157H:7 by individual cattle is usually less than one month.

In Washington State, the organism was found in 0.28% of fecal samples from dairy cattle in 8.3% of herds. Fecal samples, bulk milk samples, and milk filters were negative for the organism. The strain was also isolated from 0.71% of fecal samples from pastured cattle of 16% of herds sampled. The organism has also been isolated from the feces of cattle and deer on a ranch in Texas, which suggests that wild ruminants may shed verocytotoxic E. coli. In beef feedlots the prevalence was 0.33%. Drinking water on dairy farms in Wisconsin has also been identified as one source.

E. coli 0157H:7 are not resistant to antimicrobials and antimicrobials are not used for the treatment of patients clinically affected with the disease.

Campylobacter. Campylobacter jejuni is a common food-borne pathogen and a leading cause of food borne disease in humans in the United States and other industrialized countries (Altekruse et al. 1998). Most outbreaks are associated with raw milk or surface water whereas most sporadic cases are often associated with mishandling and consumption of undercooked poultry or cross-contamination of foods by raw poultry. Most retail chicken for human consumption contains C. jejuni. The organism may be present in bulk milk samples, tissue specimens of beef cattle, and in raw ground beef. Other foods associated with campylobacteriosis include barbecued sausage and shellfish. The organism can be found in poultry, cattle, pigs, sheep and other food animal species. Several species of birds and rodents may also carry the organism

In the United States, the incidence of disease is highest in infants and young adults. Most Campylobacter-related deaths occur among infants, elderly, or immunosuppressed people. Many Campylobacter spp. are resistant to several antimicrobials and the resistance varies worldwide (MAFF 1998). Campylobacter infections are not treated in farm animals. The MICs of antimicrobials for campylobacter are therefore of no significance. Critical antimicrobial resistances for human campylobacters are to fluroquinolones, and erythromycin and related macrolides. Several reports have described the high prevalence of multiple antimicrobial resistant Campylobacter coli and C. jejuni in Spain (MAAF 1998).

In a Minnesota study, the proportion of quinolone-resistant C. jejuni isolates from humans with gastroenteritis increased from 1.3% in 1992 to 10.2% in 1998 (Smith et al. 1999). A large part of the increase in the incidence of resistance was associated with infections acquired during foreign travel, but the number of resistant infections acquired domestically also increased. Ciprofloxacin-resistant C. jejuni were isolated from 14% of domestic chicken products obtained from retail markets during a two-month period in 1997. Molecular subtyping found an association between resistant C. jejuni strains from chicken products and domestically acquired infections in Minnesota residents. In the United States, fluoroquinolones were first licensed for use in poultry in 1995. On the basis of their results, the authors concluded that "the number of quinolone-resistant infections acquired domestically has also increased, largely because of the acquisition of resistant strains from poultry." Such a conclusion is totally unacceptable and is an example of bad reasoning. The premises of isolating quinolone-resistant strains of the organism in humans and in poultry can be accepted as true but the conclusion that the increased incidence of resistance in human isolates over a 6 year period is due to the use of the antimicrobial in poultry production without additional data is not sound. Furthermore, it is a classical example of conclusions based on assumptions.

Microbial Contamination of Beef as a Source of Pathogens for Humans

During the slaughter and processing of cattle for beef, the surfaces of the carcasses are contaminated by aerosol microorganisms immediately after removal of the hide following slaughter (Gill et al. 1996). Surface sites of the carcass contaminated by direct fecal contact or hides contaminated with feces may have very high colony counts of E. coli (Bell 1997). Bacterial contamination of meat products can influence the keeping quality of meats and may be hazardous to public health, if the food chain is without adequate hygienic controls. Deposition of bacteria on carcasses on the kill-floor occurs during and after removal of the hide. Many activities and conditions before and after the animal reaches the kill-floor affect the level of contamination of the carcasses and, consequently, of final products of processing lines. Cold water carcass washing is ineffective in removing microbial contamination and tends to spread a posterior to anterior contamination, resulting in increased counts at forequarter sites (Jericho et. al 1995).

Hot water spray at 95°C effectively reduces the bacterial count of carcasses experimentally contaminated with E. coli 0157H:7 and Salmonella typhimurium (Castillo et al. 1998). The use of a combination of hot wa-

ter and lactic acid is also very effective in reducing bacteria of fecal origin on beef carcasses (Castillo et al. 1998).

Steam-vacuuming systems can reduce microbial counts on carcasses with no visible signs of contamination (Kochevar et al. 1997). Steam pasteurization of commercially slaughtered beef carcasses at 82.2°C for 6.5 seconds effectively decreases the bacterial load on carcasses during slaughter, and the technology can serve as an important step in the process of improving the safety of and reducing the risk associated with beef and beef products (Nutsch et al. 1998). Chemical dehairing of the skin of cattle is being evaluated as a method of reducing pathogenic bacteria and bacteria of fecal origin (Castillo et al. 1998).

Cooling of the carcasses immediately after leaving the slaughter floor reduces viable aerobic bacteria, coliforms, and generic E. coli on carcasses (Jericho et al. 1998). The control of bacteria during processing of beef may be verified by aerobic bacterial counts as a direct measure of cleanliness or E. coli counts as an indirect measure of fecal contamination (Jericho et al. 1997). The microbiological verification of the control of the processes of dressing, cooling and processing of beef carcasses at a high line-speed abattoir have been examined (Jericho et al. 1996). Manufactured beef obtained from culled cow carcasses are generally less heavily contaminated with E. coli than the trimmings obtained from carcasses of feedlot cattle (Gill et al. 1996). General hygienic conditions of hamburger patties could be improved by their being manufactured from only manufacturing beef of superior hygienic quality, and by better management of chilled patties at retail outlets (Gill et al. 1997).

Ground beef produced at the retail level traditionally uses store trim and/or commercial beef trimmings that are vacuum packed and distributed to retailers for fine grinding. It is then aerobically packaged for the retail display case. Ground beef produced in this manner has a highly variable total bacterial load, ranging from 10^3 to 10^7 colony forming units (CFU) per gram with coliform bacteria usually exceeding 10^3 per gram. The bacterial load of retail ground beef often exceeds 10^7 CFU per gram (Worobo, et al. 1997).

Pathogen Reduction, Hazard Analysis Critical Control Point Systems (HACCP)

Hazard Analysis Critical Control Points is a system which identifies potential food safety risks, prevents or corrects them, records what was done, and verifies that the system works (Hogue et al. 1998). The objective is to improve food safety for meat and poultry. It is assumed that a reduction in carcass contamination leads to a proportionate reduction in illness and death. Pathogens can contaminate meat and poultry at any step from production through consumption, including final food preparation and handling. The primary focus of the Pathogen Reduction and HACCP regulation is slaughter and processing operations. Slaughter plants will respond by improving methods for separating the viscera and hides or feathers of animals without contamination of carcasses, and by using final rinses of carcasses to remove pathogens. In the U.S. as of 1996, the USDA adopted the Pathogen Reduction HACCP system which includes four major elements: 1. Every plant must adopt and carry out its own HACCP plan which systematically addresses all significant hazards associated with its products. 2. Mandatory E. coli testing in slaughter plants. Every plant must regularly test carcasses for E. coli to verify the effectiveness of the plant's procedures for preventing and reducing fecal contamination. 3. Pathogen reduction performance standards for Salmonella. All plants and plants producing raw ground products must ensure that their Salmonella contamination is below the current national baseline prevalence. 4. Sanitation standard operating procedures. Every plant must adopt and carry out a written plan for meeting its sanitation responsibilities. Effective sanitation in slaughter and processing plants is essential to prevent adulteration of meat and poultry products.

The general hygienic conditions of meat will be improved only if effective HACCP systems can be developed for meat production, preparation and distribution processes (Gill 1995). The development of effective HACCP systems is impeded by the uncertain commitment of managements to product improvement, the lack of defined procedures for the objective identification of hazardous practices, and the persistence of the subjective assessment of the hygienic condition of product.

Risk Reduction Rather Than Complete Risk Reduction. Many opportunities exist during production, processing, distribution, retail, marketing, and consumption for pathogens to find their way into beef and beef products. Eliminating pathogens, and, therefore, the risk of contracting a food-borne illness from beef products is a monumental, if not impossible task. Therefore, the approach must be to explore methods of risk reduction, rather than complete risk elimination. This can be done by effective risk communication (Powell & Leiss 1997).

Antimicrobial Resistance Surveillance Programs

United States. In 1996, the Centers for Disease Control (CDC), United States Department of Agriculture (USDA), and Food and Drug Administration (FDA) established the National Antimicrobial Resistance Monitoring System to prospectively monitor changes in antimicrobial susceptibilities of zoonotic pathogens from human and animal clinical specimens, healthy farm animals, and carcasses of food-producing animals at slaugh-

ter plants (Tollefson et al. 1998). This will facilitate the identification of resistance in humans and animals as it occurs, provide timely information to veterinarians and physicians; prolong the life span of approved drugs; and identify areas for more detailed investigations.

Denmark. Acquired resistance to all current and previously used growth promoting antimicrobials was found among selected indicator bacteria, zoonotic bacteria and pathogenic bacteria from broilers, pigs and cattle in Denmark (Aarestrup et al. 1998). Antimicrobials used for growth promotion include: avilamycin, avoparcin, bacitracin, carbadox, flavomycin, monensin, olaquinodox, salinomycin, spiramycin, tylosin, and virginiamycin. Following these observations, the Danish Ministry of Agriculture and Fisheries decided to ban avoparcin and establish the surveillance of resistance to antimicrobial agents for growth promotion and therapy in Denmark. Since then the use avoparcin has been banned in all EU countries.

Acquired resistance to all antimicrobials currently used for animal therapy was found among selected indicator bacteria, zoonotic bacteria and pathogenic bacteria (Aarestrup et al. 1998). These include: ampicillin, penicillin, apramycin, ceftiofur, chloramphenicol, colistin, gentamicin, neomycin, quinolones, spectinomycin, streptomycin, sulfonamides, tetracycline, and trimethoprim, This provides a baseline for future prospective studies and enables the determination of trends over time.

Critical Analysis of the Link Between Subtherapeutic Use of Antimicrobials in Food Animals and Antibiotic Resistance

Some important questions include the following:

Does the subtherapeutic use of antimicrobials in the feed of feedlot cattle contribute significantly to antimicrobial resistance in human medicine?

An equally important question could be, "If the subtherapeutic use of antimicrobials in food-producing animals is responsible for the emergence of resistant bacteria, in significant numbers, why do we not see regular community-based epidemics of food borne illness due to resistant enteric bacteria, from animals, in the human population?"

A sequence of events can be postulated to explain the contention that the prolonged subtherapeutic use of antimicrobials in the feed of beef cattle allows the emergence of certain species of enteric pathogens or non-pathogens to become resistant to the antimicrobials. However, to date there is insufficient evidence to support the conclusion that the subtherapeutic use of antimicrobials, as growth promoters, in the feed of feedlot cattle is associated with antimicrobial resistance in human medicine. There is no evidence that the use of antimicrobials as growth promotants in beef cattle will result in antimicrobial resistance. No case control studies have been done as were recommended 20 years ago by 1980 Report of NAS. Conversely, there is no published evidence that it does not occur. This is a major gap in our knowledge base.

It has been proposed that there are four lines of evidence that support the conclusion that most antimicrobial resistance among salmonella isolates in humans results from the use of antimicrobials in food animals (Angulo et al. 1998). They are:

1. Trace backs of selected food borne disease outbreaks. Several outbreaks of antimicrobial resistant salmonella infections in humans have combined epidemiological fieldwork and laboratory subtyping techniques to trace back antimicrobial resistant salmonella through the food distribution system to the farms, and to the use of antimicrobials on the farm (Holmberg et al. 1984; Spika et al. 1987).
2. Emergence of Salmonella typhimurium DT 104 R-type with decreased susceptibility to fluoroquinolones in humans in the U.K. provides increasingly strong evidence that antimicrobial-resistance among Salmonella isolates in humans results from the use of antimicrobials in food animals.
3. Comparisons of patterns of antimicrobial resistance of Salmonella isolates from animals and humans.
4. Comparison of antimicrobial usage and resistance in animals and humans.

The salient features of the evidence available for the several links in the food chain from cattle to humans is presented here.

1. Subtherapeutic Use of Antimicrobials in Feed of Feedlot Cattle

Approximately 80% of feedlot cattle in North America receive subtherapeutic levels of antimicrobials in their feed throughout the feeding period.

2. Presence of Zoonotic Bacteria in Intestinal Tract of Feedlot Cattle

Some data is available on the prevalence of zoonotic enteric pathogens in the intestinal tract of feedlot cattle in North America. The USDA National Animal Health Monitoring System collected nearly 12, 000 fecal samples from 100 volunteer feedlots across 13 states to determine the prevalence of E. coli 0157H:7 and Salmonella (USDA 1995). Overall, 5.5% of the fecal samples gave positive results for Salmonella. Samples collected from pens of cattle which had been on feed for longer periods of time yielded a higher positive culture rate (7.4%) than those samples from pens of cattle which had recently

arrived in the feedlot (3.5%). There are currently no scientifically defined critical management points or critical points to manage food-borne pathogens at the pre-harvest level. **In general, the prevalence of food-borne pathogens is low in feedlot cattle.**

3. Antimicrobials in Feed Select for Emergence of Resistant Enteric Bacteria in Feedlot Cattle

No published information is available on the effects of subtherapeutic use of antimicrobials in the feed of feedlot cattle on the antimicrobial resistance of the enteric bacteria, either commensal bacteria or zoonotic pathogens. It can be assumed that the prolonged use of subtherapeutic levels of non-ionophore antimicrobials would result in the emergence of resistant bacteria, either commensals or zoonotic pathogens.

4. Contamination of Beef Carcasses with Antimicrobial Resistant Enteric Bacteria During Slaughter Process

Beef carcasses are contaminated with enteric bacteria, both non-pathogenic and pathogenic, after the hide is removed following slaughter. The incidence of contamination with Salmonella and E. coli 0157H:7 is low.

5. Transfer of Enteric Bacteria From Beef Cattle to Humans

Enteric bacteria can be transferred directly to farm animal attendants (Levy 1976; Linton 1985; 1986). The bacteria may also be transferred to humans indirectly through the handling of contaminated meat or inadequate cooking of meat, especially ground beef. It is also biologically possible for non-pathogenic animal enteric bacteria to become resistant to the antimicrobials, be transferred to humans and wherein the bacteria transfer their resistance factors to human enteric pathogens. Furthermore, the resistance may be to multiple antimicrobials.

The ecology of the majority of food-borne pathogens is such that, if proper hygiene and cooking practices are followed, the likelihood of human infections is much reduced and virtually eliminated. Outbreaks of salmonellosis are commonly associated with the consumption of uncooked meat (Thornton et al. 1993).

Those at most risk include the elderly, the immunocompromised and those taking oral medication for previously diagnosed disease.

There is little appreciation by the public that fresh meat contains bacteria and that it must be handled hygienically and must be cooked properly. The general public is not well informed about the proper handling of meat, and the necessity to adequately cook ground beef and poultry. Unpasteurized milk is still consumed by some people and is a major risk to human health.

6. Colonization and Infection of Humans with Antimicrobial Resistant Bovine Enteric Bacteria

Colonization and infection of humans with the bovine enteric pathogens may cause clinical disease. However, colonization and infection occurs primarily in high risk people such as the elderly, the immunocompromised, and those already taking oral antimicrobials for a previously diagnosed infectious disease. Oral medication results in the elimination of many species of enteric bacteria and allows the intestinal colonization of pathogens such as Salmonella which under normal conditions would not occur. Several pathogen and host risk factors influence whether or not the animal organism will colonize and infect humans. Patients taking oral antimicrobials are highly susceptible because the antimicrobials disrupt the normal microflora (Nord 1993).

When considering bacterial species which infect both animals and humans, there is limited information. The reasons for the lack of experimental evidence are the difficulty in quantifying the transfer of whole organisms or of resistance traits from animals to humans, the difficulty in quantifying the establishment of these bacteria or these traits in humans or human pathogens, respectively, and the difficulty to demonstrate the role of resistant organisms of animal origin or of human pathogens carrying R-genes of nonhuman origin in causing human disease. Although it has been shown that resistant bacteria can move from farm animals to humans being in close contact with the animals and that these organisms can colonize the human intestinal tract for a certain period of time as part of the human flora, only in the case of the Salmonellae has it been shown that transfer of resistant Salmonella through the food chain finally resulted in human clinical disease. Adequate data to quantify the risk for other food-borne pathogen, such as C. jejuni, Yersinia enterocolitica or enteropathogenic E. coli, are lacking (Kayser 1993).

"How is it possible to know the origin of an antimicrobial resistant strain of pathogen isolated from a human with clinical disease?" Given the origin of such strains in hospitals, long-term care facilities, how is it possible to distinguish between strains from animals and those of hospital origin?

7. Clinical Disease in Humans Difficult to Treat Because of Antimicrobial Resistance of Pathogens

The majority of food-borne infections are self-limiting and treatment with antimicrobials is unnecessary. However, although the incidence of septicemic salmonellosis in humans is low, when certain salmonella strains become systemic, antibiotic therapy may be necessary. If the strains are multiple resistant, the choice of drugs may be limited.

There is no published information which documents that human patients which have died due to a clinical

disease associated with an antimicrobial resistant pathogen have actually died primarily because of the resistant organism. Many other complications are possible.

Conclusions Based on Assumptions

Attributing the problem of antimicrobial resistance in human medicine to the subtherapeutic use of antimicrobials in food animals has been based on assumptions. **There is insufficient data to conclude that the subtherapeutic use of antimicrobials in the feed of feedlot cattle for disease prevention or growth promotion contributes significantly to antimicrobial resistance in human medicine.** The increased incidence of resistance to individual antimicrobials and to multiple antimicrobials in salmonellas isolated from humans and animals cannot be linked directly to the use of antimicrobials in animals because such evidence has not been provided. Researchers have commonly reported on the increased incidence of drug resistant bacteria from humans and animals, and then concluded that it was due to the use of antimicrobials in animals. The increased incidence has not been directly associated with the use of antimicrobials in the feed. It is not good reasoning to conclude that because there is an increased incidence of antimicrobial resistance in certain isolates of bacteria in a certain geographical area that the cause is the use of antimicrobials in food animals. As a result, conclusions about the effects of the use antimicrobial use in food animals are based on assumptions and do not constitute a strong inductive argument.

The Need for Logic

Logic is the study of the methods and principles used to distinguish good (correct) from bad (incorrect) reasoning (Copi & Cohen 1994).

A **proposition** is a declarative statement, either true or false, in this they differ from questions, commands, and exclamations.

Inference is the process by which one proposition is arrived at and affirmed on the basis of one or more propositions accepted as the starting point of the process.

An **argument** is any group of propositions of which one is claimed to follow from the others, which are regarded as providing support or grounds for the truth of that one.

The **conclusion** of an argument is the proposition that is affirmed on the basis of the other propositions of the argument, and these propositions, which are affirmed (or assumed) as providing support or reasons for accepting the conclusions, are the premises of that argument.

Arguments are traditionally **deductive** or **inductive**. Every argument involves the claim that its premises provide some grounds for the truth of its conclusion, but only a deductive argument involves the claim that its premises provide conclusive grounds for its conclusions. When the reasoning in a deductive argument is correct, the argument is valid, when the reasoning of a deductive argument is incorrect, the argument is invalid.

A **deductive argument** is valid when its premises, if true, do provide conclusive grounds for the truth of its conclusion. In a valid deductive argument, premises and conclusions are so related that it is absolutely impossible for the premises to be true unless the conclusion is true also. In every deductive argument, either the premises succeed in providing conclusive grounds for the truth of the conclusion, or they do not succeed. Therefore, every deductive argument is either valid or invalid. If a deductive argument is not valid, it must be invalid; if it is not invalid, it must be valid.

A **deductive argument** is one whose conclusion is claimed to follow from its premises with absolute necessity, this necessity not being a matter of degree and not depending in any way on whatever else may be the case.

In the realm of deductive logic, the central task is to clarify the relation between premises and conclusions in valid arguments, and thus to allow us to discriminate valid from invalid arguments.

An example of a deductive argument is the classic one as follows:

- All humans are mortal
- Socrates is a human
- Therefore, Socrates is mortal.

An **inductive argument,** in sharp contrast, is one whose conclusion is claimed to follow from its premises only with **probability**, this probability being a matter of degree and dependent upon what else may be the case. The terms valid and invalid do not apply to inductive arguments. An **inductive argument** makes a very different claim. Its premises can only provide some support for the conclusion. Inductive arguments, therefore, cannot be valid or invalid in the sense in which these terms are applied to deductive arguments. Inductive arguments can be evaluated as better or worse, according to the degree of support given to their conclusions by their premises. Thus, the greater the likelihood, or probability, that its premises confer on its conclusions, the greater the merit of an inductive argument. But that likelihood, even when the premises are all true, must fall short of certainty.

The essential difference between deductive and inductive arguments lies in the strength of the claim that is made about the relation between the premises of the argument and its conclusion.

The argument that the use of antimicrobials in food animals and antimicrobial resistance in human medicine, is a complex one containing several arguments. In

a complex argument, often, the conclusion of one argument serves as the premise for another. More than two arguments may be present, and they may be so articulated that an extended line of reasoning cascades through several arguments to reach a final conclusion. In such passages there is a flow, a general direction, from the initial event to the final conclusion. The development of the argument that the use of antimicrobials in the feed of food animals contributes to antimicrobial resistance in human medicine is a complex passage containing several premises, some of which are conclusions which serve as premises for subsequent conclusions. Thus probability is important.

Calculation of Probability

Probability is defined as the relative frequency with which members of a class exhibit a specified attribute. The probability of an event is thus expressed as a fraction, of which the denominator is the number of equipossible outcomes that would successfully yield the event in question. For example, in an honest lottery with one thousand tickets sold, there are one thousand equipossible outcomes. The probability of any one's ticket winning that lottery is 1 over 1000.

Probability calculus is a branch of pure mathematics that can be used to compute the probabilities of complex events from the probabilities of their component events. A complex event can be regarded as a whole of which its component events are parts. Even a hypothesis that fits all the available facts is not thereby established conclusively; only with probability.

The probability that the subtherapeutic use of antimicrobials in the feed of feedlot cattle will result in the emergence of antimicrobial resistant enteric zoonotic pathogens which will be transferred to humans, directly or indirectly, and cause clinical disease which will be difficult to treat because of resistance is unknown.

Calculating the probability that the use of antimicrobials in the feed of feedlot cattle will ultimately result in the occurrence of antimicrobial resistant clinical disease in humans could be done using probability estimates of each event as outlined in Table 3. The probabilities of occurrence of each event are hypothetical estimates based on the information available for each event. The calculated probability is 0.000000031!. Such a low probability could explain why epidemics of human illness associated with antimicrobial resistant enteric bacteria from food animals is not more common.

It is interesting to note that if consumers handled their meat products hygienically and cooked their meat adequately, the probability of transfer of any potentially antimicrobial resistant enteric bacteria would be extremely low, probably less than 0.01, and the final probability of transfer and illness would approach zero.

Conclusions

Insufficient Evidence

Based on the available information it is not possible to conclude with a strong inductive argument that the subtherapeutic use of antimicrobials in the feed of feedlot cattle contributes significantly to antimicrobial resistance in human medicine. It is also possible that the probability of a cause and effect relationship is extremely low because of the complex nature of the events which must occur.

The failure to make progress with this problem may be due to the lack of a multi-disciplinary approach to a complex problem and perhaps, failure of adequate risk communication. Antimicrobial resistance involves many stakeholders including the livestock producer, feed manufacturing industry, pharmaceutical industry, microbiologist, pharmacologist, epidemiologist, medical and veterinary clinicians, animal scientist and nutritionist, logician, agricultural economist, regulatory agencies, meat scientists and meat packing industry, food retail outlets, food scientists, and the consumer. Most disciplines have worked on the problem on their own with little attempt to coordinate activities among the so-called stakeholders; in other cases, some disciplines like mathematicians have not been involved.

Steps must be taken to obtain the data required to better assess the risks associated with the subtherapeutic use of antimicrobials. There is a need for active cooperation of many agencies and industries to address the problem. There are risks associated with using antimicrobials in animal production as well as not using them. The relationships between risks is dynamic and ever changing as more information is gathered. Through partnership and communication among stakeholders, the effect of the changing of risks inherent in the use of antimicrobials can be identified and intervention strategies can be formulated before a true crisis develops (NRC, 1999). Risk analysis, assessment and communication are necessary in order to minimize risk communication failure (Powell & Leiss 1997).

Recommendations

Principles and Methods of Epidemiology

The principles and methods of epidemiology need to be applied to this complex problem. The complex chain of events of the emergence of antimicrobial resistant bacteria and their transfer, or transfer of the resistance genes, from the animals to humans requires precise sampling methods of populations of animals receiving antimicrobials, measurement of the risk factors for the transfer of bacteria to humans through the handling of beef, precise observations of the details of human illness, and correlation of resistance with the use of antimicrobials. Causal reasoning will be necessary to arrive at sound conclu-

Table 3. Probability that subtherapeutic use of antimicrobials in feedlot cattle results in emergence of resistant bacteria which are transferred to humans in which disease may occur and be difficult to treat

(Some values used in this table are hypothetical; others are based on some scientific evidence.)

1	Subtherapeutic antimicrobials used for growth promotion (80% of feedlot cattle).	0.80
2	Presence of zoonotic pathogens in intestinal tract of animals (Salmonella spp., Campylobacter spp.)	0.05
3	Antimicrobials in feed select for emergence of resistant enteric pathogens.	0.50
4	Contamination of beef with antimicrobial resistant enteric bacteria.	0.10
5	Transfer of antimicrobial resistant enteric pathogens from animals to man either directly by personal contact with animals or indirectly by contaminated meat supply due to unhygienic handling or inadequate cooking (ground beef). Alternately, transfer of non-pathogenic enteric bacteria which carries resistance factor.	0.05
6	Colonization of antimicrobial resistant animal enteric bacteria in humans.	0.05
7	Infection of humans with antimicrobial resistant enteric bacteria which are pathogenic and cause disease or the bacteria may be non-pathogenic but transfer the resistance factor to an pathogenic enteric bacteria in humans which causes disease.	0.05
8	Clinical disease which is difficult to treat because of antimicrobial resistant animal enteric bacteria.	0.10
9	Human patient dies because of disease intractable to treatment.	0.05
	Final Probability???	0.000000001

sions. System analysis and modelling may be useful techniques. Field investigations of food-borne disease outbreaks in humans must be continued and improved.

Encourage Risk Communication

Risk communication is the process of exchanges about how best to assess and manage risks among scientists, regulatory agencies, public interest groups, and the general public (Powell & Leiss 1997). Risk is the probability of harm in any given situation, and this probability is determined by two factors: (a) the nature of a hazard and (b) the extent of anyone's exposure to that hazard. The product of the two factors (hazards and exposures) adds up to the overall risk.

Risk communication does not mean denying that a potential problem exists. They must be acknowledged and evaluated.

The work of risk communication occurs within the great divide that often separates two evaluations of risks: those of scientific experts on the one hand, and those of members of the public on the other. Good risk communication practice seeks to bridge that divide by ensuring that the meaning of scientific risk assessments is presented in understandable terms to the public–and, equally, by ensuring the nature of the public's concerns is known to and respected by risk managers. Often there is little or no effort by either group, and a risk information vacuum interposes itself between experts and the public. Trapped in the resulting solitudes, experts bemoan the public's irrationality while being repaid with the public's contempt for their indifference and arrogance (Powell & Leiss 1997). These solitudes represent risk communication failure.

Problems in communicating about risks originate primarily in the marked differences that exist between the two languages used to describe our experience with risks: the scientific and statistical language of experts on the one hand and the intuitively grounded language of the public on the other.

There is a need to narrow the gap between what people's perception of the risk is and what the risk re-

ally is, and what measures people can take to protect themselves. How many people die annually in North America due to disease caused by antimicrobial resistant enteric zoonotic bacteria transferred from food animals fed subtherapeutic levels of antimicrobials? The question cannot be answered but the numbers must be very, very low.

The veterinary profession must become proactive and promote effective communication and understanding of the risks associated with the use of antimicrobials in food animals, including the risks of improper handling and inadequate cooking of ground beef and poultry.

All of the players in the food chain, from producer to consumer, have a responsibility to recognize the risks of antimicrobial resistance and food safety and to use judicious and prudent methods to minimize the risks to human health.

Many opportunities exist during production, processing, distribution, retail, marketing, and consumption for pathogens to find their way into beef and beef products. Eliminating pathogens, and, therefore, the risk of contracting a food borne illness from beef products is a monumental, if not impossible task. Therefore, the approach must be to **explore methods of risk reduction, rather than complete risk elimination.**

Comprehensive Food Safety Education Program

Food-borne illness in humans due to the improper handling, preparation and inadequate cooking of meat and poultry occurs because poultry and fresh meat, especially hamburger, is not bacteria free. Comprehensive food consumer food safety education programs are necessary and must be promoted, encouraged and supported. Ground beef may contain E. coli 0157H:7 and must be cooked adequately to avoid human illness.

Hazard Analysis Critical Control Points. The risk of food-borne illness can be reduced and excellent progress is being made to produce an even cleaner meat and poultry product using Hazard Analysis Critical Control Points strategies. The real problem is to determine what proportion of food-borne illness is caused by antimicrobial resistant bacteria which emerged in cattle because of the use of antimicrobials as feed additives.

Food Irradiation. The American Dietetic Association has stated that food irradiation is one way to enhance the safety and quality of the food supply (Loaharanu et. al. 1994). The Association has encouraged the government, food manufacturers, food commodity groups, and qualified dietetics professionals to continue working together in educating consumers about this technology.

Antimicrobial Resistance Surveillance Programs

A National Antimicrobial Monitoring System to prospectively monitor changes in antimicrobial susceptibilities of zoonotic pathogens from human and animal clinical specimens, healthy farm animals, and carcasses of food-producing animals at slaughter plants should be encouraged and supported.

Monitoring programs are now being developed to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in Salmonella and other enteric bacteria from human and animal populations (Tollefson et al. 1998). Continued surveillance for quinolone-resistant Salmonella is necessary, particularly after recent approval of a fluoroquinolone for use in food animals in the United States.

A zoonoses monitoring system has been suggested to meet the changing nature of food-borne illness in the United States. The purpose would be to collate information on the incidence of zoonoses, and to develop methods of reduction as part of a national food safety policy (Hogue et al. 1998).

A risk assessment of the human health hazard associated with the use of antimicrobials in the feed of food-producing animals is currently being done by the Center for Nutrition and Food Policy, Georgetown, University.

Antimicrobial Use in Human Medicine

The problems caused by antibiotic-resistant bacteria in human medicine can be reduced through two major strategies: 1) prolonging the effectiveness of currently available antimicrobials through infection control and optimal use of antimicrobials, and 2) developing new antimicrobials to treat resistant bacteria (OTA 1995). Human patients should refrain from demanding antimicrobials for colds and other viral infections. Physicians should educate their patients about the treatment of the common colds and not accede to patients' demands for unneeded antimicrobials. Hospital patients with multidrug resistant bacterial infections should be isolated. Physicians should become knowledgeable with the local data on antibiotic resistance.

Availability and Approval of New Antimicrobials for Food Animals

There is a need for increased research funding for the development, approval and availability of new classes of food-animal drugs. The further development and use of antimicrobials in both human and food-animal practices should be monitored by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy, the animal production industry, research, epidemiology, and the regulatory agencies.

A framework for evaluating and assuring the human safety of the microbial effects of new antimicrobial drugs for use in food-producing animals has been proposed by the Food and Drug Administration. Drugs would be categorized and approved for use in animals according to their use and value in humans. However, this may severely restrict the use of certain antimicrobials in food animals without good reason.

There is a need for the establishment of integrated national data-bases to support a rational, visible, science-driven decision-making process and policy development for regulatory approval and use of antimicrobials in food animals, which would ensure the effectiveness of these drugs and the safety of foods of animal origin.

Clinical Research on Subtherapeutic Use of Antimicrobials in Feedlot Cattle

There is a need for well designed field trials to evaluate the effects of subtherapeutic antimicrobials in the feed of feedlot cattle on the susceptibility of enteric pathogens over the length of the feeding period. Control animals not being fed antimicrobials are also necessary. There is an obvious lack of information on the effects of feed additive antimicrobials used in feedlot beef cattle in North America on the antimicrobial sensitivities of the enteric pathogens in those cattle. Furthermore, we do not know how these feed additives are being used in feedlots (amounts, duration of use, combinations of different additives, and if their use is considered economically beneficial). The antimicrobial susceptibility of the bacterial flora of the beef carcasses would also be determined at the time of slaughter and processing to determine the flow of the bacteria. It is important to examine the relationship between the use of antimicrobials and the emergence of resistant enteric bacteria and their dissemination at slaughter of the cattle and processing of the carcasses.

Recommendations of National Academy of Science (1999)

The Committee on Drug Use in Food Animals. Panel on Animal Health, Food Safety, and Public Health (National Academy Press, 1999) made the following recommendations which are comprehensive and appropriate to address the issue using a multidisciplinary approach.

Major Recommendations

Development, Approval, and Availability of Food-Animal Drugs

• The committee recommends that the Center for Veterinary Medicine continue procedural reform to expedite the drug approval review process and broaden its perspective on efficacy and risk assessment to encompass review of data on products already approved and used elsewhere in the world.

• The committee recommends that, to improve drug availability, worldwide harmonization of requirements for drug development and review be considered and further enhanced among the federal agencies that are responsible for ensuring the safety of the food supply.

• The committee recommends that the Center for Veterinary Medicine base drug use guidelines on maximal safe dosage regimens for specific food animals, consider greater emphasis on the pharmacokinetics of drug elimination from tissues that are consumed in large quantity, and set drug withdrawal times accordingly.

• The committee recommends increased funding for basic research that explores and discovers new or novel antimicrobials and mechanisms of their action, including the development of more rapid and wide-screen diagnostics to improve the tracking of emerging antibiotic resistance and zoonotic disease.

Resistance to Antibiotic Drugs

• The committee recommends establishment of integrated national databases to support a rational, visible, science-driven decision-making process and policy development for regulatory approval and use of antimicrobials in food animals, which would ensure the effectiveness of these drugs and the safety of foods of animal origin.

• The committee recommends that further development and use of antimicrobials in both human medicine and food-animal practices have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy, the animal production industry, research, epidemiology, and the regulatory agencies.

Alternatives to Drug Use in Food Animals

• The committee recommends increased public- and private-sector research on the effect of nutrition and management practices on immune function and disease resistance in all species of food animals.

• The committee recommends increased public- and private-sector research on strategies for the development of new vaccination techniques, on a better understanding of the biochemical basis of antibody production, and on genetic selection and molecular genetic engineering for disease resistance.

Summary

Antimicrobial Use in Food Animals.

Antimicrobials are used for the treatment and control of some economically important bacterial and protozoal infections of food-producing animals. They are also used as feed additives for growth promotion.

The use of antimicrobials for these purposes contributes to the economical production of wholesome beef. No documented information is readily available on how antimicrobials used as feed additives are being used in feedlots in North America (amounts, duration of use, combinations of different additives). Both non-ionophore and ionophore antimicrobials are used as feed additives for the control of certain diseases and for growth promotion, particularly in growing and finishing feedlot cattle. Even after many years of use, feed additive antimicrobials for feedlot cattle continue to be effective and economical.

Prudent Use of Antimicrobials in Food Animals. The prudent use of antimicrobials in food animal production has been recommended in order to control the emergence of antimicrobial resistance. However, no document has made specific recommendations.

Antimicrobial resistance is not a problem for most of the commonly occurring bacterial diseases of food animals. Remarkably, the bacterial pathogens which cause the common diseases such as shipping fever pneumonia and several other infections have remained relatively susceptible to the common antimicrobials such as penicillin, tetracyclines, trimethoprim-sulfonamides, and in recent years, tilmicosin and florfenicol.

Potential Human Health Risks of Antimicrobial Use in Food Animals. The potential risks from using antimicrobials in food producing animals are antimicrobial residues in meat and milk, and the emergence of antimicrobial resistant enteric bacteria in animals which may be transferred to humans and cause clinical disease which is difficult to treat because of antimicrobial resistance.

Antimicrobial Residues in Beef. There are no significant antimicrobial residues in beef which pose a human health hazard.

Antimicrobial Resistance. The problem of the increasing incidence of antimicrobial resistance in human medicine is commonly attributed to the subtherapeutic use of antimicrobials in the health and production management of food-producing animals, and to the overprescribing of antimicrobials by human physicians. The scientific medical literature and the public media attribute a significant part of the resistance problem in human medicine to the agricultural use of antimicrobials, but with uncertain evidence.

For the last three decades, there has been considerable concern that the subtherapeutic use of antimicrobials in food-producing animals results in the emergence of antimicrobial resistant bacteria (Salmonella spp., Campylobacter spp.) which may be transferred to humans who may develop clinical disease which is difficult to treat because of antimicrobial resistance of the pathogens.

The **Swann Committee Report** in the U.K. in 1969, in response to concerns about an increased incidence of antimicrobial resistance in human and veterinary medicine, recommended that antimicrobials used in human medicine not be permitted for use as feed additives in food-producing animals without a veterinary prescription. The banning of certain antimicrobials as feed additives did not result in a decline in the incidence of antimicrobial resistant bacteria in human and veterinary medicine.

From 1969 to 1999, several major committees examined the evidence that the subtherapeutic use of antimicrobials in the feed of food animals contributes to antimicrobial resistance in human medicine. All of the committees concluded that there is insufficient evidence to demonstrate a direct link between the use of antimicrobials in food animals and antimicrobial resistance in human medicine.

Several disease investigations in the 1980s claimed to have shown the link between the use of antimicrobials in farm animals and the isolation of antimicrobial resistant bacteria from humans affected with salmonellosis. However, the evidence was incomplete to demonstrate a link.

Insufficient Evidence. There is a very large literature base on antimicrobial resistance of both human and animal pathogens. Many studies by panels of medical, veterinary and agricultural scientists in last 30 years have examined the potential human health hazards of using antimicrobials in the feed of livestock. In general, there is no evidence that the use of antimicrobials in the feed of cattle contributes significantly to antimicrobial resistance in humans. It has been difficult to trace the postulated steps from the use of the antimicrobial in the feed of cattle to the emergence and transfer of antimicrobial resistant bacteria to humans where it may cause disease. Those who argue that the use of antimicrobials in agriculture contributes to antimicrobial resistance in human medicine are unable to quantify the relative contributions to resistance made by their use in human and veterinary medicine. How much is due to use in agriculture? (Is it 5%, 10%, 25%, 50%?) It has not been evaluated.

Antimicrobial Resistance in Human Medicine. Antimicrobial resistance is a major problem in human medicine, particularly nosocomial (hospital acquired) bacterial infections where the incidence of resistance has increased most dramatically due to the intensive use of drugs. There is general agreement in the medical profession that the major cause of antimicrobial resistance in human medicine is the over-pre-

scribing of antimicrobials by physicians. Patients commonly expect physicians to prescribe antimicrobials for a wide variety of common infections for which antimicrobials are unnecessary. The failure of many human patients to comply with the prescription recommendations by not taking the complete course of the antimicrobials also contributes to the resistance problem. The incidence of antimicrobial resistance of several human pathogens has increased and continues to increase. Some multiple-drug-resistant strains of bacteria emerge in different parts of the world, persist for several years, and then disappear.

People at Most Risk. The people at greatest risk of developing clinical disease due to antimicrobial resistant bacteria of animal origin are those already taking oral antimicrobial medication for a previous illness, immunocomprised patients, and the young and elderly. Increased resistance is a problem in several pathogens which are not zoonoses and thus the resistance is unlikely associated with the use of antimicrobials in food animals but rather intensive and extensive use in human medicine.

The most common and significant cause of disturbances in the normal intestinal microflora of humans is the administration of antimicrobials orally. Bacterial overgrowth occurs and the emergence of resistant bacteria occurs which may lead to serious infections.

Banning Use of Growth Promotant Antimicrobials. The use of antimicrobials which are deemed valuable in human medicine has been banned as growth promotants for livestock in some countries. Banning their use in the U.K. in 1969 did not result in a decrease in the incidence of antimicrobial resistant bacteria. In 1986, **Sweden** and **Denmark** banned the use of the use antibiotics as feed additives. In 1999, the **European Community** banned four antibiotic feed additives (virginiamycin, tylosin, zinc bacitracin, spiramycin) as a precautionary public health measure.

Food Borne Illness

Food borne illness in humans caused by the animal enteric pathogens are usually the result of the improper handling and/or inadequate cooking of ground beef and poultry. More than 90% of such human patients with food-borne gastroenteritis experience an episode of diarrhea and recover without the need for antimicrobials. Fresh ground beef contains variable numbers of E. coli, some strains of which are highly pathogenic (E. coli 0157H:7) and rarely, may be contaminated with Salmonella spp. Poultry is commonly contaminated with Campylobacter or Salmonella.

Beef Carcasses at Slaughter. The surfaces of beef cattle carcasses are contaminated with enteric bacteria immediately after removal of the hide during processing following slaughter.

There is very little information available on the prevalence of antimicrobial resistant bacteria on the surface of beef carcasses. Major progress has been made in the last decade in the processing of beef carcasses following slaughter to reduce the microbial contamination of beef using the Hazard Analysis Critical Control Points System.

Cooking of Meat. Adequate cooking of meat such as hamburger eliminates all potential risks from bacterial contamination. Inadequately cooked beef hamburger is a major risk factor for infection with E. coli 0157H:7.

Antimicrobial Resistance Surveillance Systems

A National Antimicrobial Monitoring System to prospectively monitor changes in antimicrobial susceptibilities of zoonotic pathogens from human and animal clinical specimens, healthy farm animals, and carcasses of food-producing animals at slaughter plants should be supported. The antimicrobial susceptibilities of indicator and zoonotic bacteria should be correlated with the use of antimicrobials used in the sampled herds.

Clinical Research

There is a need for well designed field trials to evaluate the effects of subtherapeutic antimicrobials in the feed of feedlot cattle on the susceptibility of enteric pathogens over the length of the feeding period. Control animals not being fed antimicrobials are also necessary. The antimicrobial susceptibility of the bacterial flora of the beef carcasses would also be determined at the time of slaughter and processing to determine the flow of the bacteria. It is important to examine the relationship between the use of antimicrobials and the emergence of resistant enteric bacteria and their dissemination at slaughter of the cattle and processing of the carcasses.

Risk Communication

There is a need for risk communication between the scientists and the public to improve the understanding of antimicrobial resistance in food animals how to reduce the risks of food borne illness associated with the improper handling and inadequate cooking of red meat and poultry. Every effort should be made to explore risk reduction rather than risk elimination which is not possible.

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