Antibiotic use in animal feed and its impact on human health

Mary D. Barton

School of Pharmacy and Medical Sciences, University of South Australia, GPO Box 2471, Adelaide, South Australia 5001, Australia

Antibiotic resistance in bacteria that cause disease in man is an issue of major concern. Although misuse of antibiotics in human medicine is the principal cause of the problem, antibiotic-resistant bacteria originating in animals are contributory factors, with some types of resistance in some species of bacteria. Antibiotics are added to animal feeds to treat and prevent infections and to improve growth and production. Until recently, the major concerns about incorporation of antibiotics in animal feeds related to antibiotic residues in products from treated animals. Although, in 1969, the Swann (1969) report drew attention to the potential for antibiotic-resistant bacteria to spread from treated animals via the food chain, there was little response until the detection of vancomycin-resistant enterococci in animals fed a related glycopeptide, avoparcin. Subsequently, attention started to focus on the issue and other examples of transfer of resistant bacteria through the food chain, such as enterococci resistant to quinupristin–dalfopristin or to everninomicin, fluoroquinolone-resistant campylobacters and multiresistant *Escherichia coli*, and salmonella such as *Salmonella typhimurium* DT104. Reviews and committees in many countries have highlighted the need for better control of licensing of antibiotics, and codes for prudent use of antibiotics by veterinary practitioners and farmers. The continued use of antibiotic growth promoters has been questioned and there is a need to ensure that antibiotics important in human medicine are not used therapeutically or prophylactically in animals.

Drug resistance: Antibiotics: Animal feeds

Introduction

Over the last three decades there has been concern over the problem of antibiotic resistance in human pathogens, leading to recent widespread debate about these problems. The debate has become more intense over the past 5 years or so. Much of the concern has been directed against the use of antibiotics in animals, with particular focus on antibiotic growth promotors. This

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

Corresponding author: Dr Mary D. Barton, fax +61 (0)8 8302 2389, email Mary.Barton@unisa.edu.au

concern has led to the publication of a number of reports from committees and groups in Europe, the UK, the USA and Australia (Commission on Antimicrobial Feed Additives, 1997; World Health Organization, 1997, 1998; Health Council of The Netherlands, 1998; House of Lords, 1998; Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1999; Ministry of Agriculture, Fisheries and Food, 1998). These reports all emphasised the need for greater control over the use of antibiotics in veterinary medicine and animal husbandry, but there have also been reports suggesting that there is insufficient scientific evidence (Congress of the United States, 1995; Heidelberg Appeal Nederland Foundation 1998; National Research Council, Institute of Medicine, 1998; General Accounting Office, 1999) to support the link between the use of antibiotics in animals and antibiotic resistance in human pathogens. Some reports pointed out that most of the antibiotic-resistance problems in human medicine stem from overuse or from inadequate controls in human medicine. None the less, evidence is mounting that antibiotic-resistant enteric bacteria (for example, *Escherichia coli*, salmonella, campylobacter and enterococci) can transfer from animals to man via the food chain or by direct contact, leading to the establishment of a community reservoir of resistance genes (van den Bogaard & Stobberingh, 1999).

Use of antibiotics in animals

Antibiotics are used largely for three purposes in animals: therapeutic use to treat sick animals; prophylactic use to prevent infection in animals; as growth promoters to improve feed utilisation and production. In general, therapeutic treatment involves treatment of individual animals over a short period with doses of antibiotic exceeding the minimal inhibitory concentration of the known or suspected pathogen. Sometimes, with intensively-farmed animals, therapeutic treatment is delivered by feed or drinking water; however, this treatment can be of doubtful efficacy in some situations, as sick animals often do not drink or eat. Prophylactic treatment again involves moderate to high doses of antibiotic, often given in feed or water for a defined period to a group of animals. Antibiotics used as growth promoters tend to be given in feed at subtherapeutic levels over extended periods to entire herds and flocks, and are available for purchase over the counter by feed manufacturers and farmers. It is important to note that subtherapeutic levels generally still exceed the minimal inhibitory concentration of enteric organisms such as *Clostridium perfringens* and *Enterococcus* spp. (van den Bogaard & Stobberingh, 1999).

Concern about use of antibiotics in animals and the possible impact on human health covers two major issues: the antibiotic agents that are used; the way in which they are used. There is a view that antibiotics that are important in human medicine should not be used therapeutically in food-producing animals, particularly for mass medication. Prophylactic use presents a problem on two grounds: the antibiotic agents used; the lack of definition of what is the appropriate duration of prophylactic use. Growth-promotant use is probably the area of highest concern, as some of the antibiotics used are now regarded as compromising the efficacy of some key human antibiotics and the duration of treatment may be for the whole life of the treated animals.

Regulatory controls

Controls vary from country to country. For example, in Australia there are three points of control of antibiotic use in animals. First, all importations are controlled by a permit system (no

antibiotics are produced in Australia). Second, at the registration level, there are strict regulatory guidelines over which antibiotics can be used in food-producing animals. Since 1970, antibiotics intended for animal use have been assessed for their potential to compromise human health. As a result, fluoroquinolones, amphenicols, colistin and gentamicin have not been registered for use in food-producing animals because of concerns about antibiotic resistance, and the registration of carbadox was withdrawn in the late 1980s and of nitrofurans in 1992 because of concerns about carcinogenicity (Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1999). Finally, there is control-of-use legislation that restricts antibiotics registered for therapeutic or prophylactic use to registered veterinary surgeons, but allows over-the-counter sales to farmers or stock-feed companies of products registered for use as growth promoters.

Agricultural use of antibiotics in the USA and Canada is also regulated. There are three categories of use: as feed antibiotics; as over-the-counter drugs; as veterinary prescription drugs. Feed antibiotics include antibiotics used as growth promotants and those used for subtherapeutic (including prophylactic and some growth-promotant use) and therapeutic purposes (Prescott, 1997). Feed antibiotics are licensed for specific uses such as for meat chickens or young pigs or calves or feedlot cattle. In the USA preregistration assessment specifically addresses human health issues relating to antibiotic resistance in enteric coliforms, salmonella excretion and increased resistance in salmonella, increased virulence and pathogenicity of bacteria, animal disease that is difficult to treat, and residues and risk of hypersensitivity in consumers (Sundlof *et al*. 1997). In Canada, the risk of development of antibiotic resistance is not assessed at this stage (Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1999).

In the UK and other EU countries, antibiotics are authorised as either veterinary medicinal products or zootechnical feed additives. Veterinary medicinal products and growth promoters are subject to assessment for safety, including residues (veterinary medicines) and the risk of emergence of antibiotic resistance, cross-resistance to therapeutic antibiotics and selection for transferable resistance (both veterinary medicines and growth promoters; Rutter, 1997). Other European countries outside the EU have their own regulations.

China has regulated the use of antibiotics in animal feeds since 1989 and only non-medical antibiotics are permitted as feed additives. Antibiotics used include monensin, salinomycin, destomycin, bacitracin, colistin, kitasamycin, enramycin and virginiamycin. However, in practice, other antibiotics such as tetracyclines are used and the mycelial by-products from the production of antibiotics are incorporated into animal feeds (Jin, 1997). Russia also restricts feed antibiotics to non-medical drugs; bacitracin, grizin, flavomycin and virginiamycin are registered for use in this way (Panin *et al*. 1997).

Growth promoters

Antibiotics used for growth-promotant purposes constitute a large proportion of the total antibiotic usage, but the scale of the problem is difficult to estimate since there is little published information on the overall quantities of antibiotics used in animals or human subjects. In Australia import statistics for the years 1992–3 to 1996–7 show that 55·8 % of antibiotics imported were for use in stock feed, 36·4 % for human use and 7·8 % for veterinary use (Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1999). Prescott (1997) reported that 40 % of antibiotic production in the USA was for use in stock feeds, including 55–60 % of penicillin G and tetracycline production. European Federation of Animal Health (1998)

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Table 1. Comparison of glycopeptide (vancomycin and avoparcin) use in man and animals

Country and time period	Glycopeptide (kg)		Reference
	Vancomycin	Avoparcin	
Denmark, 1994	24	24 000	Wegener (1998)
Austria, 1992–1996	582	62 642	Witte (1998)
USA, 1996	11 200	0	Wegener (1998)
Australia*, 1992–3 to 1996–7	643·1	10 029·8	JETACAR (1999)

JETACAR, Joint Expert Technical Advisory Committee on Antibiotic Resistance.
* Recorded as glycopeptides for human and stock feed use rather than as separate antibiotics.

reported that a 2-month survey in Europe had indicated that of 10 493 t antibiotic, 52 % was for medical use, 33 % for veterinary use and 15 % for growth-promotant use. Unfortunately, the definitions of veterinary and growth-promotant use were not given. Some specific data are available for the glycopeptides (see Table 1), showing that more glycopeptides (principally avoparcin) are used in animals than are used in man (vancomycin and teicoplanin).

The chemistry and characteristics of growth promotants registered for use in Europe have been reviewed recently (van den Bogaard & Stobberingh, 1999).

History of the use of growth-promotant antibiotics

The growth-promotant effect of low levels of antibiotics in animal feeds was first described in the late 1940s when chickens fed fermentation waste from tetracycline production grew more rapidly than controls (Stokestad & Jukes, 1950). Over the ensuing 50 years the production-

Table 2. Summary of antibiotics registered for use as growth promotants in Australia, the EU and the USA (adapted from World Health Organization, 1997; Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1998)

Class	Antibiotic	Australia	EU	USA
Arsenicals	3-Nitro-arsonic acid and others	Pigs, poultry		Pigs, poultry
β-Lactams	Penicillin			Pigs
Glycopeptides	Avoparcin	Pigs, meat poultry, cattle	Suspended 1996	
Lincosamides	Lincomycin			Pigs
Macrolides	Erythromycin			Pigs
	Kitasamycin	Pigs		
	Oleandomycin	Cattle		
	Tylosin	Pigs	Suspended 1999	
	Spiramycin		Suspended 1999	
Oligosaccharides	Avilamycin		Pigs, meat poultry	
Pleuromutilins	Tiamulin			Pigs
Polyethers (ionophores)	Lasolocid	Cattle		
	Monensin	Cattle	Beef cattle	Cattle
	Narasin	Cattle		
	Salinomycin	Cattle, pigs	Pigs	
Polypeptides	Bacitracin	Meat poultry	Suspended 1999	Pigs, poultry, cattle
Quinoxalones	Carbadox			Pigs
	Olaquindox	Pigs		
Streptogramins	Virginiamycin	Pigs, meat poultry	Suspended 1999	Pigs, poultry, cattle
Tetracyclines	Tetracycline			Pigs, poultry, cattle
Bambermycins	Flavophospholipol	Pigs, poultry, cattle	Poultry	

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enhancing effects of feeding subtherapeutic levels of a wide range of antibiotics has been described. In this time, the use of growth-promotant antibiotics became entrenched in animal production, particularly in the intensive livestock industries.

Table 2 indicates the growth-promotant antibiotics registered for use in Europe, the USA and Australia. A much wider range is used in the USA than in Australia or Europe. To some extent, this factor reflects the response to the first enquiry into the impact of antibiotic use of animals on human health, the Swann Report (Swann, 1969), and to subsequent investigations in Europe.

The Swann Committee was established in response to concerns about the emergence in the 1960s of transferable antibiotic resistance in human pathogens of animal origin (salmonella) and the possibility of transfer of this resistance to other human enteric pathogens such as *E. coli* and shigella. The committee's report (Swann, 1969) concluded that there was probably a hazard to human health from feeding subtherapeutic levels of antibiotics to food-producing animals. They recommended that antibiotics for use in animal feeds should be restricted to those with little or no therapeutic application in man or animals and which would not impair the efficacy of therapeutic antibiotics because of cross-resistance. In response to the report, a number of countries (including the UK, European countries and Australia) removed penicillin and tetracyclines, at that time the most widely used growth promotants, from the approved list. Interestingly, the USA did not respond in this way because the Food and Drug Administration was unable to demonstrate a threat to public health (Feinman, 1998; see Table 2). In countries conforming to the Swann Report recommendations, other antibiotics rapidly filled the gap.

In parallel with the development of growth promotants in classes of antibiotics at that time of no interest in human medicine, lack of adequate controls on antibiotic use in medical and hospital practice in many countries led to the emergence of antibiotic-resistance problems such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). This factor has prompted interest in the use of antibiotics previously discarded because of lack of suitable systemic formulations (vancomyin) or in classes not used previously in human medicine (virginiamycin, a streptogramin; avilamycin, an orthosomycin). Unfortunately, these antibiotics represent some of the most widely used post-Swann growth promoters.

Despite a steady stream of papers reporting antibiotic resistance in bacterial isolates from animals fed antibiotic-medicated feeds, there was little response from health or industry authorities until 1986 when the Swedish Parliament imposed a ban on antibacterial growth promoters (Commission on Antimicrobial Feed Additives, 1997). There was an initial increase in the therapeutic use of antibiotics, but this situation corrected itself as improvements occurred in animal husbandry, feed formulation and on-farm hygiene (Wierup, 1997). When Sweden joined the EU in 1995, it received derogation from certain EU rules applying to restrictions on antibiotic use in animals until 1 January 1999. This action led to much debate and attempts by other European authorities to refute Swedish claims of reduced antibiotic use on Swedish farms (Viaene, 1997*a*,*b*,*c*). The opponents claimed that the total quantity of antibiotics used in Sweden did not decline because more antibiotics were used therapeutically to treat diseases that had previously been prevented by the use of subtherapeutic levels of antibiotics in feed. The Swedish stance received support from Denmark in 1995, when the detection of vancomycin-resistant enterococci (VRE) in pigs and poultry that had been fed avoparcin-medicated feed was reported (Danish Veterinary Laboratory, 1995). Denmark responded by banning the use of avoparcin as a growth promotant in 1995 and Germany followed suit in 1996. Although expert panels such as Scientific Committee for Animal Nutrition (1996) argued that there was insufficient scientific evidence to support such bans, the use of avoparcin was banned in EU countries from 1 April 1997, pending further work. Subsequently other growth promotants were

scrutinised and, although Scientific Committee for Animal Nutrition (1998*a*,*b*) again questioned the adequacy of scientific evidence, the use for virginiamycin, tylosin phosphate, spiramycin and zinc bacitracin was banned in the EU from 1 January 1999, on the basis of the precautionary principle. It could be argued that the ban was put in place to alleviate political concerns, rather than on the basis of scientific evidence.

Mode of action of growth-promotant antibiotics

The mode of action of antibiotic growth promotants is not known (Commission on Antimicrobial Feed Additives, 1997). Most of the growth promotants are active against Gram-positive organisms (Table 3). However, the concentrations used are lower than therapeutic levels, although they may exceed the minimal inhibitory concentration for the Gram-positive intestinal bacteria. The agents are assumed to exert their effect by acting on the intestinal microflora to cause a range of beneficial changes: causing lethal or sublethal damage to pathogens; causing a reduction in the production of bacterial toxins; reducing bacterial utilisation of essential nutrients; allowing increased synthesis of vitamins and other growth factors; improving the absorption of nutrients by reducing the thickness of the intestinal epithelium; reducing intestinal mucosa epithelial cell turnover and reducing intestinal motility (Prescott & Baggot, 1993). It seems that the addition of growth promotants to feed rations alters intestinal characteristics so that they more closely resemble those seen in germ-free animals (Commission on Antimicrobial Feed Additives, 1997). It is clear that, in many cases, the effects are more noticeable in sick animals and animals housed under conditions of poor hygiene (Prescott & Baggot, 1993). There are also age-related effects, with younger animals showing a greater response to growth promotants than older animals.

Benefits of growth promoters in animal husbandry

Antibiotic growth promoters are given primarily to improve productivity and enhance economic returns to farmers (Taylor, 1999). Improvements on growth rate and feed conversion in

Table 3. Antibacterial activity of growth promotant antibiotics

Class of antibiotic	Commonly used growth promotants	Mode of action
Arsenicals	3-Nitro-arsonic acid	DNA effects?
β-Lactams	Penicillin G	Gram-positive cell-wall synthesis
Glycopeptides	Avoparcin	Gram-positive cell wall synthesis
Lincosamides	Lincomycin	Inhibit protein synthesis in Gram-positive bacteria
Macrolides	Erythromycin, tylosin, kitasamycin, oleandomycin, spiramycin	Inhibit protein synthesis, principally in Gram-positive bacteria
Oligosaccharides	Avilamycin	Inhibit protein synthesis in Gram-positive bacteria
Pleuromutilins	Tiamulin	As for macrolides
Polyethers	Monensin, lasolocid, narasin, salinomycin	Affect bacterial cell permeability; active against Gram-positive bacteria
Polypeptides	Bacitracin	Gram-positive cell-wall synthesis
Quinoxalones	Carbadox, olaquindox	Inhibit bacterial DNA synthesis and denature pre-existing DNA; active against anaerobes
Streptogramins	Virginiamycin	Inhibit protein synthesis in Gram-positive bacteria
Tetracyclines	Tetracycline	Inhibit protein synthesis; broad spectrum
Bambermycins	Flavophospholipol	Interferes with cell wall synthesis in Gram-positive bacteria

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piglets of 9–30 % and 6–12 % respectively have been reported (Thomke & Elwinger, 1997). These authors also evaluated the literature for meat chickens and reported that improvements in growth rate of 3·9 % and feed conversion of 2·9 % could be obtained in birds on medicated feeds. Taylor (1999) indicated that carcass quality is improved when growing animals are fed growth promotants, but that effects are reduced in animals approaching slaughter weight. Improvements in milk, wool and egg production and in fertility have also been reported, but less consistently (Taylor, 1999).

It is now recognised that growth promoters also play a beneficial role in controlling some chronic diseases in intensively-reared animals. Control of such diseases not only improves productivity and economic returns, but also has implications for animal welfare.

C. perfringens causes necrotic enteritis in chickens and this disorder is well controlled by avoparcin, virginiamycin, zinc bacitracin, lincomycin and avilamycin (Wicker *et al.* 1977; Prescott *et al.* 1978; Hamdy *et al.* 1983; Jansson *et al.* 1992; Elwinger *et al.* 1995; Taylor, 1999). Prevention of subclinical necrotic enteritis improves health, welfare and production in meat chickens.

Swine dysentery, caused by *Serpulina dysenteriae*, and porcine proliferative enteropathy, caused by *Lawsonia intracellularis*, can be prevented by the use of medicated feeds. Quinoxalones are effective in controlling swine dysentery (Molnar, 1996; Commission on Antimicrobial Feed Additives, 1997), but resistance appears to emerge with tylosin, lincomycin, monensin and tiamulin (Molnar, 1996). Porcine proliferative enteropathy can be effectively prevented by tylosin or tiamulin (McOrist *et al*. 1996, 1997) or a range of other growth promoters including salinomycin and spiramycin (Tsinas *et al*. 1998). Prevention of these common conditions in pigs is a significant contributor to the improved production and well-being of pigs.

Some researchers have reported that the use of growth-promotant antibiotics reduces the shedding of salmonella (Gustafson & Bowen, 1997); however, other researchers report no effect (Ford *et al*. 1981; Abou-Youssef *et al*. 1983), or even prolonged excretion of pathogens such as thermophilic campylobacters, *Salmonella* spp. and *Listeria* spp. (Gutzman *et al*. 1976; Barrow, 1989; Corpet, 1996). Kaukas *et al.* (1988) reported that the use of growth-promotant antibiotics in chickens selected for *Enterococcus faecium* at the expense of *Enterococcus gallinarum*.

Other benefits attributed to the use of growth promoters include environmental gains such as reduced N and P excretion and therefore less effluent production (Roth & Kirchgessner, 1994; Verbeke & Viaene, 1996; Gropp & Shuhmacher, 1997). Lawrence (1997) noted that significant practical benefits accrue from use of growth promoters, including a reduction in feed, protein and water consumption as well as a reduction in slurry production and N and P excretion. Lawrence (1997) and McOrist (1997) both commented that withdrawal of growth promoters would lead to reduced profitability of farming enterprises through increased capital and operational costs.

Therapeutic and prophylactic in-feed medication

A wide range of antibiotics is used therapeutically in animals. Conventional wisdom suggests that this use does not pose a significant threat to human health, because in countries with developed animal-health systems therapeutic use is under tight regulatory control. Therapeutic use generally involves the treatment of sick animals on an individual basis, but on occasion can require the use of medicated feed or water to treat a group or pen of animals. Importantly, many countries and professional associations have developed (or are in the process of developing)

guidelines and codes for the prudent use of antibiotics (Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1999; Office International des Epizooties, 1999). These guidelines stress the need for accurate diagnosis and specific therapy for a defined period.

In some countries, restrictions apply regarding which antibiotic can be used therapeutically. For example, in Australia fluoroquinolones, amphenicols, colistin and gentamicin are not registered for use in food-producing animals. In addition, approval for use of third-generation cephalosporins is severely restricted. If the recommendations of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (1999) report are accepted by agricultural authorities, these restrictions will be tightened further, with the aim of minimising the use in food-producing animals of antibiotics regarded as important in human medicine.

Prophylactic use is of greater concern. Here, a wider range of antibiotics can be used and the definitions of dose rates and treatment times are subject to manipulation. Most prophylactic use involves mass medication of a group or flock of animals via feed or water. For example, in Australia tetracyclines are registered for prophylactic use for the prevention of respiratory disease in pigs. Evidence from urine-residue monitoring suggests that on occasion higher doses are used for longer periods than intended under the definition 'prophylactic use'.

Some of the antibiotics registered for prophylactic use are in categories that contain antibiotics, or are in a class that contains antibiotics of value in human medicine. Antibiotics registered for prophylactic use in Australia are tylosin, lincomycin, spectinomycin, tetracyclines, neomycin, apramycin, avoparcin, zinc bacitracin, olaquindox, dimetridazole, sulphonamides and 3-nitro-arsonic acid. This list contains most of the growth-promotant antibiotics of concern. Some medical specialists are concerned, therefore, that banning the use of growth promotants will not prevent prolonged in-feed use of such antibiotics, as they will continue to be used prophylactically (Joint Expert Technical Advisory Committee on Antibiotic Resistance, 1999).

Problems associated with antibiotic use in animals

Problems attributed to the use of antibiotics in animals include those of antibiotic residues and antibiotic resistance.

Antibiotic residues

Until very recently, controls on antibiotic use in animals focused almost exclusively on the control of residues in the tissues of treated animals. Concerns about residues revolve around allergic reactions and the possible adverse effects on the flora of the human gastrointestinal tract (selecting for resistance or transfer of resistance). Swann (1969) noted that penicillin residues in milk could provoke allergic reactions in sensitised individuals, but concluded that there were no other adverse effects associated with antibiotic residues. Triggering of allergic reactions in sensitised individuals by penicillin residues is well documented (Dewdney *et al.* 1991), but these authors conclude that there is no evidence that any individual has become sensitised by food residues of either penicillins or macrolides. Confirmed cases of allergy to substances in food are very rare, although adverse reactions to antibiotics have been linked to hypersensitivity (Woodward, 1991) and cases of chronic urticaria (Ormerod *et al.* 1987; Dayan, 1993). A rare fatal blood dyscrasia in individuals sensitised to chloramphenicol could also be triggered by chloramphenicol residues in food (Settepani, 1984).

There is little scientific information on the effect of antibiotic residues on the bacterial flora of the human intestinal tract. Clearly, such studies are very difficult to conduct (Corpet, 1993;

Kidd, 1994), and Gorbach (1993) points out that most human studies have used therapeutic rather than residue-range concentrations and that, to date, results have been confusing. Corpet (1993) also makes the point that most resistant enterobacteria in the human gut of untreated individuals come from bacterial contamination of raw foods.

Many developed countries monitor and survey tissues from animals for antibiotic residues. Acceptable daily intakes for human subjects based on 'no-effect levels' and safety have been calculated for many antibiotics, despite the lack of accurate data. From these values, a tolerance level or maximum residue level is calculated. Established maximum residue levels are modified and often reduced as the techniques for detection of residues improve and become more sensitive. Conversely, some levels have been increased recently as data become available that facilitate better risk assessment.

Antibiotic resistance in bacteria in animals

Resistance to antibiotics associated with the use of antibiotics in animals is the issue of principal concern. First, there are concerns about transfer of antibiotic-resistant pathogens through the food chain and the risk of transfer of antibiotic-resistant genes from animal enteric flora to human pathogens. Second, there is the issue of reduced efficacy of antibiotic therapy in animals colonised with resistant bacteria. There are few comprehensive studies of antibiotic resistance in bacterial isolates from animals. However, since concerns have arisen about growth-promotant antibiotics selecting for resistance in human pathogens, more countries have set up antibiotic-resistance surveillance programmes for bacterial isolates from animals. There has been some surveillance of salmonella in the UK and Sweden since the 1970s (Commission on Antimicrobial Feed Additives, 1997; Ministry of Agriculture, Fisheries and Food, 1998) and more recently in France (Martel & Coudert, 1993) and the USA (Fedorka-Cray *et al*. 1998). Denmark has established very comprehensive surveillance and reporting (Aarestrup *et al*. 1998*a*,*b*). The World Health Organization (1999) organised a meeting to facilitate exchange of information on progress in implementing resistance surveillance in foodborne pathogens. Programmes discussed included: the European survey of antibiotic resistance in *E. faecium* in animals; US national antimicrobial-resistance monitoring system for enteric bacteria; a more general European study on antibiotic resistance in bacteria of animal origin covering *E. coli*, salmonella, enterococci, campylobacter, staphylococci, streptococci and pasteurella; the Danish programme; the European surveillance programme for salmonella and *E. coli* O:157; the Canadian programme for surveillance of antimicrobial resistance in food-borne pathogens; a Japanese programme of monitoring resistance in isolates of animal origin.

One of the difficulties in comparing results from different laboratories and countries is the lack of standardisation of methods used and lack of agreed interpretive criteria. For many veterinary antibiotics, breakpoints of sensitivity and resistance have not been established and, for antibiotics also used in human medicine, medical criteria are used. For example, Riddle *et al*. (2000) have pointed out the errors that can occur when ciprofloxacin is used to assess resistance of veterinary isolates to fluoroquinolones used in veterinary practice.

In general, antibiotic resistance is readily detected in bacterial isolates from animals exposed to antibiotics.

Antibiotic resistance in enteric bacteria

Most concern about antibiotic resistance in animal isolates of bacteria is directed towards the enteric bacteria, *E. coli*, salmonella, thermophilic campylobacters and enterococci. There is

considerable information on antibiotic resistance in *E. coli* and salmonella, as these bacteria are recognised pathogens in animals, but there is relatively little information about antibiotic resistance in thermophilic campylobacters and enterococci, as these bacteria are commensal enteric organisms rather than animal pathogens.

Antibiotic resistance was detected in isolates of *E. coli* from animals soon after antibiotics were incorporated into animal feeds. Studies in the UK found that, in the late 1950s, tetracycline resistance was already detectable in *E. coli* isolates from chickens and pigs fed rations containing less than 100 g tetracycline/t (Smith, 1967). Resistance to other antibiotics was detected as new agents were introduced for therapeutic and growth-promotant purposes (Smith, 1967; Anderson, 1968). Some workers (Linton *et al*. 1988; Lee *et al*. 1993) also noted the occurrence of tetracycline resistance in some piggeries, even though tetracyclines had not been used in those piggeries. A common finding has been that resistance persists after antibiotics are withdrawn (Smith, 1973; Rollins *et al*. 1976; Langlois *et al*. 1983; Hinton *et al*. 1984).

Feeding oxytetracycline to recently-weaned pigs was found to lead to a rapid increase in the incidence of tetracycline resistance, which was widely distributed among all strains of *E. coli* present, rather than being restricted to a few selected clones (Hinton *et al*. 1985). More recently, feeding low doses of ampicillin to chickens was shown to select for high levels of resistance to that antibiotic (El-Sam *et al*. 1993). Marshall *et al.* (1990) have described an elegant experiment that demonstrated that resistant strains of *E. coli* spread among animals (and to other species such as mice), even in the absence of ongoing antibiotic treatment.

In reviewing the published literature, it is clear that resistance to antibiotics has become very common in *E. coli* over the 50 years of use of in-feed antibiotics (Langlois *et al.* 1988; Aalback *et al.* 1991; Adesiyun & Kaminjolo, 1992; Nijsten *et al.* 1993; Dunlop *et al*. 1998*a*; Matthew *et al*. 1998; Sunde *et al.* 1998; Orden *et al.* 1999; Lambie *et al.* 2000). The level of exposure affects the extent of resistance, and there are differences between antibiotics in the time taken for resistance to be evident and in the extent of the resistance that is seen. In herds and flocks treated with tetracycline, aminoglycoside and sulphonamide, widespread resistance is seen (Rollins *et al*. 1976; Williams Smith, 1980; Franklin, 1984; Nijsten *et al*. 1993; Wray *et al.* 1993*b*; Dunlop *et al.* 1998*a*; Matthew *et al*. 1998; Sunde *et al.* 1998). However, resistance to other antibiotics such as ampicillin and olaquindox is less widespread (Dunlop *et al.* 1998*a*,*b*; Linton *et al.* 1988). More recently, resistance to fluoroquinolones has been reported (Blanco *et al.* 1997; Heurtin-Le Corre *et al.* 1999). Resistance to more than one class of antibiotics is the rule rather than the exception in these published studies.

Antibiotic resistance in salmonella was also reported soon after antibiotics began to be fed at subtherapeutic levels to animals (Anderson, 1968). As salmonella is a recognised food-borne pathogen, a number of the published reports of resistance patterns in animal isolates have been linked with studies of human isolates (Threlfall *et al.* 1993; Seyfarth *et al.* 1997) or with concerns about resistance to particular antibiotics (Wray *et al.* 1986; Heurtin-Le Corre *et al.* 1999). Some countries have carried out surveys of resistance in animal isolates of salmonella or have ongoing antibiotic-resistance surveillance programmes (Wray *et al.* 1993*a*; Commission on Antimicrobial Feed Additives, 1997; Seyfarth *et al.* 1997; Baggesen & Aarestrup, 1998; Fedorka-Cray *et al.* 1998; Davis *et al.* 1999; van der Wolf *et al.* 1999). The results are not easy to interpret because some reports do not distinguish between different serovars of *Salmonella enterica* and it is recognised that some serovars such as Typhimurium are much more likely to be resistant than other serovars such as Dublin and Enteritidis PT4 (Ministry of Agriculture, Fisheries and Food, 1998).

As with *E. coli*, as new antibiotics are used, so resistance in salmonella is detected; for example, apramycin resistance was reported in both *E. coli* and salmonella within 3 years of its

licensing for use in the UK (Wray *et al.* 1986) and fluoroquinolone resistance within a few years of enrofloxacin first being used (Griggs *et al.* 1994; Heurtin-Le Corre *et al.* 1999). The overall conclusion is that resistance is generally less prevalent in salmonella, but that resistance to tetracyclines, sulphonamides and streptomycin is quite widespread. Antibiotic resistance in *E. coli* and salmonella poses problems in relation to effective treatment of these infections in animals.

Thermophilic campylobacters are enteric commensal bacteria in animals, so there are few reports on antibiotic resistance. Erythromycin-resistant campylobacters have often been reported in pigs (Elharrif & Megraud, 1984; Hariharan *et al.* 1990; Moore *et al.* 1996), with Moore *et al.* (1996) reporting more frequent resistance in *Campylobacter coli* isolates. Aarestrup *et al.* (1997) found that tetracycline resistance was more common in human isolates than in pig or poultry isolates, and that there was more macrolide and streptomycin resistance in isolates from pigs than in human and poultry isolates. Resistance to ampicillin, spectinomycin, streptomycin, sulphonamides and nalidixic acid (but not fluoroquinolones) was detected in campylobacter isolates in Ireland (Lucey *et al.* 2000), whereas a study in Spain (Saenz *et al.* 2000) reported very high levels of ciprofloxacin resistance in pig and poultry isolates. In addition, there were high levels of resistance to erythromycin, ampicillin, gentamicin and amikacin in pig isolates and high levels of ampicillin and gentamicin resistance in poultry isolates. The difference between these two studies presumably reflects differences in antibiotic usage in the two countries. In an Australian study of 116 isolates, significant levels of resistance to erythromycin, clindamycin, ampicillin and tetracycline were found, but no resistance to fluoroquinolones (which are not registered for use in livestock in Australia; MD Barton and R Pratt, unpublished results).

Enterococci are also enteric commensal bacteria in animals. There was no interest or concern about resistance in these organisms until vancomycin-resistant *E. faecium* were detected in pigs and poultry being fed avoparcin (Danish Veterinary Laboratory, 1995). This finding provoked much interest and debate about the role of animal use of avoparcin in the development of VRE in man (Klare *et al.* 1995; Aarestrup *et al.* 1996; Jensen *et al.* 1998; Kruse *et al.* 1999). Bager *et al.* (1997) found that resistance occurred only on farms where avoparcin was used. Molecular studies of the glycopeptide-resistance element in *E. faecium* isolates from animals and human subjects found that the genetic elements encoding vancomycin resistance were indistinguishable. These findings presumably prompted investigations into resistance to other antibiotics of interest (or potential interest) in human medicine. Other types of antibiotic resistance reported in enterococcal isolates from animals include resistance to the macrolide–lincosamide–streptogramin group (Dutta & Devriese, 1982), to tylosin (Aarestrup & Cartensen, 1998) and to virginiamycin (Hammerum *et al.* 1998). An Australian study (MD Barton and R Pratt, unpublished results) found widespread resistance to: macrolides (erythromycin and tylosin); clindamycin, tiamulin and virginiamycin; aminoglycosides (streptomycin, gentamicin, apramycin); spectinomycin, tetracycline and monensin. These was also moderately common resistance to bacitracin, a low prevalence of resistance to ampicillin and no resistance to vancomycin or teicoplanin. Recently it has been found, in a small study of commercial pig carcasses, that there was no increase in resistance to tylosin or avilamycin in isolates of enterococci from pigs fed those antibiotics as growth promoters (Davies & Roberts, 1999).

Antibiotic-resistant bacteria have been found in environmental samples (Linton, 1986; Morinigo *et al.* 1990; Young, 1993) and wild-caught blue crabs (*Callinectes sapidus;* Marshall *et al.* 1996). Some of this contamination presumably comes from use of antibiotics in aquaculture, but Boon & Cattanach (1999) reported that the incidence of antibiotic resistance was higher in native heterotrophic bacteria isolated from a river than in faecal bacteria from the

same source. Kelley *et al.* (1998) drew attention to the risk of spread of antibiotic-resistant bacteria in poultry litter used as mulch or bedding.

Transfer of resistant bacteria and resistance genes from animals to man

The question of whether antibiotic use and antibiotic-resistant isolates of bacteria from animals have an impact on human health has been under scrutiny since the Swann (1969) report was published. Some of the issues have been reviewed recently (Witte, 1997, 1998; Barton, 1998). Some animal health, farming and pharmaceutical groups are reluctant to accept that there are links between antibiotic use and resistance in animal isolates and resistance in human pathogens (Shryock, 1999). However, scientific evidence is mounting, for at least some organisms and some antibiotics. For example, salmonella is a well-recognised food-borne pathogen, so resistant strains of salmonella, including *Salmonella typhimurium* DT104 do spread from animals to man via the food chain (Threlfall, 1992; Threlfall *et al.* 1993; Wall *et al.* 1995; Glynn *et al.* 1998) and by direct contact (Fone & Barker, 1994). However, antibiotic treatment for human non-typhoidal salmonella enteritis is rarely required, and is probably contraindicated unless there is evidence of systemic infection.

Apramycin resistance in human strains of salmonella and *E. coli* provides evidence of transfer of resistant organisms or resistance genes from animal to human isolates, as apramycin is not used in human medicine (Wray *et al.* 1986; Hunter *et al.* 1993). A similar situation has been reported, with spread of resistance to nourseothricin, an antibiotic growth promoter of a class of antibiotic not used in human medicine. Plasmid-borne resistance was detected not only in *E. coli* from treated pigs, pig farm employees and their families, but also in that from residents of nearby villages and towns (Hummel *et al.* 1986).

Campylobacter is another food-borne pathogen. Fluoroquinolone-resistant strains of *Campylobacter jejuni* were isolated from human subjects soon after enrofloxacin started to be used in poultry in Europe (Jacobs-Reitsma *et al.* 1994; Velazquez *et al.* 1995). A study in the USA documents not only a temporal association between use of fluoroquinolones to treat chickens and resistance in human isolates but also that molecular sub-typing indicated that resistant strains from chickens were very similar to resistant strains from human subjects (Smith *et al.* 1998). A further concern with fluoroquinolone resistance is resistance in animal isolates of salmonella (Griggs *et al.* 1994) or transfer of this resistance from campylobacter (Herikstad *et al.* 1997) or *E. coli* to multiresistant salmonella (Heurtin-Le Corre *et al.* 1999).

There is observational evidence from case studies indicating direct spread of resistant commensal enteric bacteria from animals to man (Levy *et al.* 1976; Hunter *et al.* 1994; Nijsten *et al.* 1994, 1996; van den Bogaard *et al.* 1997; Wegener *et al.* 1997; Stobberringh *et al.* 1999; Fey *et al.* 2000). Although it has been easy to find resistant bacteria in animals and similar resistance patterns in isolates from human subjects, until recently few isolations have been made from food (Klein *et al.* 1998; Manie *et al.* 1998; Quednau *et al.* 1998; Duffy *et al.* 1999).

The early evidence for transfer of glycopeptide resistance from animals to man came from observational studies (e.g. Danish Veterinary Laboratory, 1995; Aarestrup *et al.* 1996), but scientific evidence based on molecular analysis of the distribution of the *van*A resistance determinant Tn1546 is now compelling (Jensen *et al.* 1998; Simonsen *et al.* 1998; van den Braak *et al.* 1998; Descheemaeker *et al.* 1999; Wegener *et al* 1999). Molecular studies have helped clarify the link between avoparcin-resistant enterococci and *van*A VRE in man. Although there is considerable genomic heterogeneity in *van*A-positive VRE from human and animal isolates, indistinguishable patterns are found across pig, poultry and human isolates.

Resistance mediated by *van*B has not been confirmed in non-human enterococci (Woodford, 1998). Resistance mediated by *van*A is the commonest form of vancomycin resistance in human isolates in Europe, whereas *van*B resistance is more commonly seen in the USA (where avoparcin is not used in animal feeds) and Australia.

Currently, there is much debate about resistance in enterococci to some new human antibiotic products. Virginiamycin, a streptogramin antibiotic, has been used for many years as a growth-promotant antibiotic without any concerns, as there were no related human products. As problems with MRSA and VRE grew, a related streptogramin quinupristin–dalfopristin was developed (Bryson & Spencer, 1996; Rubenstein & Bompart, 1997) with specific activity against multiresistant Gram-positive bacteria. However, concerns were soon raised about whether the use of virginiamycin had selected for resistant enterococci, and whether there would be cross-resistance with quinupristin–dalfopristin. A report (Danish Veterinary Laboratory, 1998) indicated that the use of virginiamycin did select for resistant *E. faecium*, and Hammerum *et al.* (1998) and Jensen *et al.* (1998) detected the *sat*A and *vgb* genes, which encode streptogramin resistance, in virginiamycin-resistant *E. faecium* isolates from animals and man. Quinupristin–dalfopristin resistance was detected in a high proportion of a small number of strains of virginiamycin-resistant *E. faecium*, including isolates collected before any quinupristin–dalfopristin had been used but where virginiamycin had been used as a growth promoter for many years (Werner *et al.* 1998). In addition, a recent European study of more than 4000 enterococci reported that 75 % of *Enterobacter faecalis* isolates and 15 % of other enterococci were resistant to quinupristin–dalfopristin (Schouten *et al.* 1999).

Another promising human antibiotic for treating multiresistant Gram-positive infections is everninomicin (SCH 27899). This antibiotic is an orthosomycin, as is avilamycin, which has been used as a growth promoter for some years (when it was introduced there were no related clinical products). Avilamycin-resistant *E. faecium* and *E. faecalis* have been found to have reduced susceptibility to everninomicin (Aarestrup, 1998). However, in the European study mentioned earlier (Schouten *et al.* 1999), all enterococci (mostly *E. faecalis* in this study) were sensitive to everninomicin.

Conclusions

Antibiotic-resistant human pathogens are a major challenge in human medicine (Collignon, 1997; Turnidge, 1998; Williams & Heymann, 1998; Guillemot, 1999). There is some risk that excessive attention to transfer of antibiotic-resistant bacteria or genes from animals to man will divert attention from the need to address problems inherent in the medical use of antibiotics. Antibiotic-resistance problems in human medicine include those of MRSA, VRE, multiresistant *Mycobacterium tuberculosis*, penicillin-resistant pneumococci, multiresistant Gram-negative organisms and extended-spectrum β-lactamase-producing Gram-negative bacteria (Gold & Moellering, 1996; Collignon, 1997). For most of these organisms there is no connection with antibiotic use in animals, but there are exceptions.

An important issue is MRSA, and it was the need in many countries to find an effective treatment for this organism that led to a rapid increase in vancomycin use, particularly in the USA. Kirst *et al.* (1998) reported that vancomycin use in the USA increased from 2000 kg in 1984 to over 11000 kg in 1996, whereas in The Netherlands medical use increased from 9 to 60 kg over the same period. VRE started to emerge as a problem in the late 1980s, particularly in the USA. Vancomycin is frequently the drug of last resort in treatment of MRSA. It is worth noting that, although strains of MRSA with reduced susceptibility to vancomycin have emerged

(Anonymous, 1997; Lessing & Raftery, 1998; Woodford *et al.* 2000), the mechanism of resistance is unrelated to that seen in VRE. A high proportion of the VRE problems in the USA is caused by *van*B VRE, which presumably emerged because of the high selection pressure in American hospitals. As avoparcin is not registered for use in the USA, it is more difficult to account for *van*A VRE there. A survey in the USA failed to isolate VRE from healthy volunteers with no hospital exposure, or from chickens and chicken-farm effluent ponds (Coque *et al.* 1996). However, it is now clear from molecular epidemiological studies that animals carrying *van*A VRE in their intestinal tracts are a source of these organisms for human subjects in countries where avoparcin is (or has been) used as a growth promoter.

Human enteric infections with campylobacter and salmonella are rarely treated with antibiotics; antibiotic resistance is, therefore, less important than it is with some of the other more serious infections. However, it is still not acceptable for individuals to be unnecessarily exposed to resistant strains of bacteria in their food. It is clear that antibiotic resistance is an issue with animal strains of campylobacter, salmonella and *E. coli*, and that these organisms infect individuals as a result of contamination of animal carcasses and meat. One control strategy is to reduce carcass contamination with these enteric bacteria from animals through improvements in on-farm management, transport, abattoir lairage management and killing-floor and chiller practices and controls. However, antibiotic resistance itself must also be controlled.

Farmers as the end-users of antibiotics must be made more aware of the antibiotic-resistance problem, and it is crucial that on-farm Quality Assurance programmes address the responsible use of antibiotics more broadly than by merely trying to reduce the incidence of residues in tissues. Clearly, there is a case for reducing antibiotic usage on farms. Some of this reduction can come from development of, and adherence to, guidelines for the prudent use of antibiotics. It is also essential to strengthen the segregation of antibiotics into those for human use and those approved for animal use. It is difficult to justify the use of potentially-valuable antibiotics as growth-promotant agents, and long-term use of antibiotics for prevention of disease clearly contributes to the antibiotic-resistance problem. Alternatives to antibiotics for disease prevention should be further studied and, if beneficial, implemented. Examples currently under investigation include improvements in housing, management systems and feed formulation, and the development of more vaccines, probiotics and competitive exclusion products. It is important to assess these approaches to ensure, for example, that probiotics and competitive exclusion products do not themselves carry antibiotic-resistance genes. However, it will always be necessary to have available a range of antibiotics for therapeutic use in animals.

It is worth considering that, in many ways, the damage has been done with the currently-available antibiotics, as resistance is already well established in bacterial populations in man, animals and the environment. Salyers & Amábile-Cuevas (1997) point out that, although withdrawal of an antibiotic can lead to a decline in resistance to that antibiotic, resistance levels rapidly rebound if the antibiotic is reintroduced. Bager *et al.* (1999) found that there was a statistically significant decline in glycopeptide resistance in *E. faecium* isolates from pigs and poultry over the 3 years following the withdrawal of avoparcin from use in Denmark. However, resistance to others, particularly tetracyclines, persists for a long time, even in the absence of exposure to the antibiotic (Smith, 1973; Rollins *et al*. 1976; Langlois *et al*. 1983; Hinton *et al*. 1984).

Be that as it may, it is essential to protect the value of antibiotics that have not yet been compromised. For example, countries such as Australia that have not licensed fluoroquinolones for use in food-producing animals and have restricted the use of third-generation cephalosporins should maintain that stance. All new antibiotics or new antibiotic uses in animals should be assessed before licensing for their potential to cause harm to human health, including

the capacity to cause resistance in human pathogens and to select for cross-resistance with important human antibiotics.

Consumers are concerned about the wholesomeness and safety of foods. Increasing litigation based on the premise that individuals should not suffer any harm from food must alert the farming industries to the need to ensure that animal products are safe and healthy for consumers. The aim should be to produce a product with no residues and with minimum levels of bacteria that have no acquired antibiotic resistance. Controls on animal usage will not resolve the current problems in human medicine, but may well help to extend the useful life of any new classes of antibiotics, if and when they are introduced.

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