CONTRACT REVIEW

USE OF ANTIBIOTICS IN ANIMALS AND ANIMAL FEEDS—AN OVERVIEW

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Before an antibiotic can be legally marketed in Australia it must be evaluated by the National Registration Authority for safety to the public, the operator, the environment and the target species. The efficacy of the product, its justification for use and the residue profile are also evaluated. Residue and trade issues are assessed and appropriate controls and labelling applied.

While management, housing and husbandry practices are improving and disease control is depending more upon the use of vaccines, there is still a need for the use of antibiotics in animals to control disease to satisfy animal welfare, animal production and human health prevention concerns.

The use of antibiotics for growth promotion, while seen as an important production measure, is controversial, particularly in Europe where hormonal growth promotants are banned. There is a major concern that the use of antibiotics in animals is leading to the transfer of antimicrobial resistance from animal to man. Sweden has had a ban on the use of growth promotion in animal feed for nearly ten years and several other European countries are advocating a total ban on the use of antibiotics as growth promoters in animals.

Current and longstanding NRA practice is that before new antibiotics are registered for animal use in Australia, they are evaluated by the National Health and Medical Research Council's Working Party on Antibiotics (WPA) (previously known as the Expert Panel on Antibiotics), in particular for their potential to transfer microbial resistance from animals to man.

Australia has adopted a conservative approach to the use of antibiotics in animal feed, adhering to the main principles of the Report of the Swann Committee (1969). These are that permission to supply and use drugs without prescription in animal feed should be restricted to antibiotics which:

(a) are of economic value in livestock production under Australian farming conditions,
(b) have little or no application as therapeutic agents in man or animals, and
(c) will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms.

In addition, 'therapeutic antibiotics' should be available for use in animals only if prescribed by a veterinarian who has those animals under his care.

Australia has not registered the fluroquinolone family of antibiotics (enrofloxacin) or gentamycin which are registered for food animal use in Europe and the US. Antibiotics such as chloramphenicol, carbadox and nitrofurans have been banned in Australia for food animals for many years.

In 1996 an outbreak of Vancomycin Resistant Enterococci occurred in several Australian hospitals. Vancomycin is not registered for any use in animals in Australia. There was a suspected link to a growth promotant avoparcin that came from the same family as vancomycin (glycopeptides) based on some European data. Scientists in the EU and the NH&MRC's WPA evaluated the data and concluded that there was insufficient evidence to recommend a ban of avoparcin. The EU Parliament decided, notwithstanding the scientific advice, to ban avoparcin in 1996. The product is still registered in Australia though the chicken industry implemented a withdrawal of the use of avoparcin while the discussions were taking place.

In October 1997, the World Health Organisation hosted a conference in Berlin on Antibiotic Resistance and have issued their report. The report recommends a review of the national policies on antimicrobial use in animals and the development of policies to reduce the risks of selection and dissemination of antimicrobial resistance. The report also recommends replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives and a range of monitoring procedures pre and post registration. The implications of these recommendations for the animal production, processing and retailing industries are considerable.

The challenge for all people associated with animal production is to use antibiotics judiciously, minimising the need for their use by good husbandry and housing, the development of alternative methods of disease prevention and control such as vaccination, use of probiotics and the development of methods to improve feed conversion and weight gain that does not involve the use of antimicrobials.

THE USE OF ORAL ANTIBIOTICS IN FARM LIVESTOCK

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One of the aspects of modern food production, that is the use of antibiotics in livestock, has long come under scrutiny by vocal pressure groups, which has included some medical microbiologists and consumerists. Advocates for the reduction of the use of antibiotics in farm livestock generally claim that this is aimed at improving public health and promoting more 'ethical' practices of animal husbandry. Much of the concern has arisen in northern Europe, particularly in Sweden, leading to the influencing of some public policies.

CURRENT USE OF ORAL ANTIBIOTICS IN FARM LIVESTOCK

Following the initial discoveries of the various classes of antibiotics and their use in the livestock industries in the 1950s and 1960s, the number of classes of antibiotics available for oral use in animals and the quantities used have been declining steadily over the past 35 years (OTA 1995). In Australia, Europe and the USA, only tetracyclines, macrolides, pleuromulins, ionophores and bacitracin are still widely used. Reexamination of the safety data for some other classes of compounds, such as arsenicals, quinoxalines, nitrofurans and nitroimidazoles has led to these being restricted or banned in several countries. Semi-synthetic penicillins, cephalosporins, quinolones or chloramphenicols are not widely used as oral antibiotics in livestock. No new classes of antibiotics have recently been made available to the livestock industry for oral use. All of the few newly developed compounds, such as tilmicosin and valnemulin, are chemical variations on older drugs ('retreads') belonging to long-established classes. This partly reflects the relative lack of overall profit for a pharmaceutical company in respect of the likely return on the research investment required to discover and develop new antibiotics, compared to returns from compounds for other uses, such as heart disease or arthritis. The smaller scale of the health market for animals also tends to reduce the profits from compounds intended for input into that market, compared to the human health market.

The housing or confinement of young animals is often necessary to provide shelter from adverse climate conditions and natural predators, and to aid effective husbandry and monitoring of livestock. The use of antibiotics in medicated premix formulations for modern livestock husbandry systems is mainly limited to these groups of young animals prior to or immediately after weaning. This is due to their ability to prevent the predictable occurrence of infectious bacterial diseases in these animals, as maternally derived passive immunity wanes (Frost 1991). Other antimicrobial agents, particularly those acting on Gram positive organisms, are also widely used orally at low (sub-therapeutic) levels for their consistent ability to improve the growth of livestock. While part of the reason for this is undoubtedly disease prevention, it is also true that the regular oral intake of antibiotics as feed additives increases the efficiency of nutrient utilisation.

BENEFITS OF ORAL ANTIBIOTICS TO LIVESTOCK

The direct beneficial effects of the use of oral antibiotics in medicated premixes for livestock include the prevention and relief of suffering caused by pathogenic bacteria. Specific examples in the Australian livestock industries include prevention of enteric diseases in pigs, such as swine dysentery, enterotoxigenic *E coli* disease and proliferative enteropathy, and lactic acidosis in cattle. In the chicken industry, successful husbandry of broiler chickens raised on standard shed floors is generally dependent on the prudent use of oral ionophores for control of coccidiosis and on anti-Gram positive antibiotics such as bacitracin or avoparcin for control of necrotic enteritis due to *Clostridium* spp. The recent ban on the use of avoparcin in European chicken flocks led to a marked increase in the incidence of necrotic enteritis. Concerns have been expressed that only two antibiotics (a pleuromulin and a lincosamide) are now available in Australia and Europe for swine dysentery, as no alternative antibiotics or vaccine are likely to be available in the foreseeable future.

The use of antibiotics therefore plays an important role in sustaining the health and welfare of large numbers of the world's livestock kept in productive groups, by preventing outbreaks of these and many other diseases. Alternative production of the world's animal food products by low-scale, low-intervention methods, without antibiotics, would lead to widespread suffering and deaths in livestock due to contagious animal pathogens and a decline in available amounts of food (Avery 1995).

As mentioned, the intake of oral antibiotics as feed additives has a nutrient sparing effect, enabling animals to perform closer to their true genetic potential in terms of physical growth. This effect occurs with various antibiotics, even at low intake levels. It has remained a constant feature of dosed animals, since it was first noted 50 years ago, that is, no reduction in response has developed to the nutrient sparing activity (Zimmerman 1986). The oral use and low absorption of these compounds means that they are consistently not detectable in portions of the animal used for human food (Ungemach 1995). Their use can provide food producers with a cost-effective means of enhancing the measurable performance of livestock.

A wider benefit of the modern housing of groups of livestock is the reduced land area required for an equivalent output. This frees the consequently available land for non-farm community needs, such as leisure and tourism. One estimate put the price of a worldwide return to low-scale production without proper housing of animals, as the removal of 10 million square miles of land (Avery 1995). The use of low levels of oral antibiotics in livestock also has wider environmental benefits related to their effect on absorption and excretion of dietary components. The reduced deposition of urea, methane and ammonia in animal faeces gives a substantial benefit in terms of reduced environmental pollution. It has been estimated that a removal of oral antibiotics from European livestock diets would result in an extra 78,000 and 15,000 tonnes of nitrogen and phosphorus pollutants entering the environment each year (Frost 1991, Avery 1995). This intake of oral antibiotics by groups of livestock also significantly reduces the bulk and water content of their faeces, making faecal disposal or re-use easier.

RESISTANCE TO ORAL ANTIBIOTICS IN FARM LIVESTOCK

While the benefits to the food producer of the wide use of oral antibiotics in livestock were quickly accepted, numerous expert committees in Australia, Europe and America have examined whether significant problems can occur with their use. One possible problem was soon identified to be the development of resistance to an antibiotic by pathogenic bacteria. Antibiotic resistance factors are a natural phenomenon with many bacteria (even present in bacteria isolated from Egyptian mummies) and the expert assessments have focused on whether potentially damaging shifts in resistance patterns have occurred.

Because oral antibiotics are almost exclusively used at relatively low levels in young livestock, and are rapidly excreted or metabolized, the actual concentration of drug in the meat or offal at the time the animal finally comes to slaughter ('residues') normally undetectable (Ungemach 1995). Careful monitoring in Australia and elsewhere for residues of antibiotics, over many years, has indicated that only sulphonamides pose any tangible risk of possible intake in edible offal, due to their longer tissue persistence. Partly for this reason, use of sulphonamides in food-producing animals is targeted for replacement with other compounds. The statutory periods prior to slaughter when antibiotics cannot be given ('withdrawal periods') are based on carefully formulated pharmaceutical guidelines derived from experimental dosages of animals. The residue limits imposed by regulatory authorities tend to have a wide safety margin both in terms of standard human food intakes and animal tissue levels after standard usage of antibiotics. The net effect of these procedures is that there is no direct interaction between oral antibiotics used in livestock and those bacteria present in man. The average human consumption of antibiotics is almost exclusively derived from routine community or hospital therapy.

However, there is still a wide body of medical and consumerist opinion which has a negative attitude to the use of antibiotics in animals as posing a small risk to human health. The suggested possibility of the development of antibiotic resistance in human pathogens is usually confined to the interactions between intestinal bacteria in an animal and its exposure to an oral antibiotic, with these bacteria somehow transferring from the animal's intestines to the food of humans. Great care and monitoring procedures (such as the Hazard Analysis Critical Control Point schemes) are now taken routinely by the modern slaughterhouse industry in Australia and elsewhere to ensure that a transfer of potential food-borne bacteria, particularly *Salmonella* spp, *Escherichia coli*, and *Campylobacter jejuni*, does not take place from the intestines or faeces to food items. For a meaningful 'problem' of antibiotic resistance in animal-derived bacteria to exist there must be:

(i) the presence of resistant bacteria in animals;
(ii) the colonization of humans by these bacteria; and
(iii) the occurrence of human disease by these or connected bacteria and the disturbance of relevant therapy by antibiotic resistance.

Presence of resistant bacteria in animals fed oral antibiotics

Following the introduction of oral antibiotics to livestock, there was, inevitably, a detectable rise in the prevalence of antibiotic resistance factors in their intestinal bacteria. The prevalence of tetracycline resistance plasmids in *Salmonella* spp and other coliforms derived from calves rose to around 30 % by 1970. However, these levels of resistance in animal isolates of *Salmonella* spp and coliforms for various antibiotics have remained steady or have fallen over the past 30 years, despite continued use of these antibiotics (Corpet 1996). Seventy-six percent of all *Salmonella* spp isolates from cattle and poultry were still sensitive to all 16 antimicrobial agents tested in recent European surveys. The levels of *Salmonella* spp in Australian livestock are generally lower than those seen in European or American surveys, presumably due to our more extensive livestock systems and clean feed. The ability of *Salmonella* spp to live in a huge variety of organic matters and hosts at a very wide temperature range, means that reduction of this organism in food products requires a vigorous approach.

While the actual numbers of *Salmonella* spp isolates from all livestock species has also remained steady, or has even declined in the past 20 years, the identity of the most common strain varies from time to time. *S. enteritidis*, or *S. typhimurium* definitive types 104 and 204, with multiple antibiotic resistance factors, have all shown apparent increases and decreases in incidence in European livestock over the past 40 years. Although these *S. typhimurium* strains are currently important in European livestock and humans, they have not been widely detected in Australia, despite the unrestricted movement of human and animal travellers. *S. enteritidis* infections in Australia are thought to have largely arisen as the result of human travellers acquiring the infection in South-east Asia. The observed fluctuations in the incidence of *Salmonella* spp infections in livestock are considered to be due to farm hygiene and management factors, such as water purity and faeces disposal, and particularly the mixing operations of animals by dealers in young livestock, rather than any influence of antibiotic use.

Other potential animal-derived food-borne bacteria, such as *E. coli* have also shown variable rates of resistance to antibiotics over the past 10 years. The use of oral aminoglycoside antibiotics in animals was linked to the occurrence of gentamicin resistance in some human *E coli* isolates. However, other studies of *E. coli* and *Salmonella* spp strains derived from cattle and pigs found no homology to human apramycin-resistant strains and only a low and declining level of resistance to the aminoglycoside apramycin, despite its common oral usage in livestock for the past 10 years. Depending on the viewpoint, an observer could derive two attitudes. Firstly that aminoglycoside resistance is now rarely likely to transfer to humans, or secondly that a perceived risk exists which should be removed. Similarly, the use of oral fluoroquinolones in the poultry industries of some European countries was linked with resistance in some human isolates of *Campylobacter jejuni*. The use of oral quinolones for livestock has therefore been limited in Australia and elsewhere.

It is possible to make glib associations between animal isolates with certain antibiotic resistance patterns under one set of test methods, to similar isolates from humans. It is not scientific to draw these associations without proper consideration of all the data, including the age and fate of the originating animal, and the precise identity and resistance methodology used for each isolate. In Europe, the use of the glycopeptide avoparcin in livestock was tenuously linked to van-A resistance in *Enterococcus* sp (Bates *et al.* 1994). However, van-A resistance is normally detected in around five percent of *Enterococcus* sp isolates from livestock (which may have received oral antibiotics), this is an identical or lower carriage rate to that seen than in other animal hosts, such as dogs, cats or horses which do not generally receive oral antibiotics (Deveriese *et al.* 1996). Rather than indicate that glycopeptide use leads to van-A+ isolates in livestock, this indicates that it does not.

While antibiotic resistance in *Salmonella* spp is a possible problem for therapeutics in calves, one key factor in the colonization of these and other intestinal bacteria is whether strains in young animals persist to the age of slaughter. The period between the end of exposure to oral antibiotics and slaughter is usually at least four weeks for chickens, six months for pigs, and two years for cattle. Studies of *S. typhimurium* strains in calves and older cattle, which incorporated markers for the identity of strains and their antibiotic resistance patterns, have indicated that strains acquired by calves, which may show antibiotic resistance, do not in fact persist in the intestine of cattle (OTA 1995). Some medical microbiologists have been guilty of misleadingly quoting resistance patterns from isolates derived from young animals as somehow relating to food-borne bacteria.

Colonization of humans by resistant bacteria derived from animals

Bacteria that are present in food are merely one of the myriad sources of bacterial input into the human body. Antibiotic-resistant bacteria are present on many vegetable foodstuffs, as well as on some animal-derived foods (Corpet 1996). Indeed, vegetarians are usually found to have a higher level of antibiotic-resistant bacteria in their intestines, probably because animal-derived foodstuffs are more likely to be sterilized by cooking than are vegetables (Guinee *et al.* 1970).

Whether animal-derived food-borne bacteria which also contain antibiotic resistance factors, actually set up any sustained infection of the human body has proved elusive to confirm. Studies of *E. coli* in pigs receiving antibiotics, which looked at isolates in humans in contact with these animals, showed no or only limited 'transference' of isolates (Nijsten *et al.* 1996). Similarly, studies of poultry processing plant workers in contact with numerous food-borne bacteria, which also contained antibiotic resistance factors, found only a very low rate of infection by these bacteria in the workers.

Because the intestinal bacteria in animals and humans contain numerous coliforms and enterococci of various groups, specific markers such as restriction endonuclease fragment analysis of genomic or plasmid DNA are necessary to show any purported relationship between the animal and human isolates. Without such markers, it is not valid to draw comparisons between isolates with similar resistance patterns from various sources, as the isolates may belong to separate groups without any direct or indirect contact. Recent studies of van+ enterococci in animals and humans have indicated that they belong to separate genetic groups.

Implications for therapy caused by animal-derived bacteria

The possibility that animal bacteria containing antibiotic resistance factors may transfer, albeit briefly, to humans has been suggested to pose potential problems for therapeutics in humans. However, numerous studies have indicated that the great majority of antibiotic resistance in human isolates originates from use of antibiotics in humans, not animals. The rates of antibiotic resistance in human intestinal bacteria in countries such as India and China, whose livestock industries have a very low consumption of oral antibiotics, are similar to or higher than the rates in the U.S.A and European countries, whose livestock industries have higher consumptions (Guinee *et al.* 1970). While the therapy of *Salmonella* spp, *E. coli* or *Campylobacter jejuni* infections in humans should rarely involve the use of antibiotics, those that are used, such as ampicillin or erythromycin, are still widely effective for the alleviation of clinical symptoms. The clinical resistance of *Enterococcus* spp infections in immunocompromised patients to the action of vancomycin has been an acknowledged problem in certain hospital situations in Australia, Europe and the U.S.A., albeit at a low level, involving a reported risk factor of one in one million chance of death (one-half of that of dying from a plane crash). This has not been even remotely related to the livestock industry in the USA, as glycopeptides have never been used in animals there, and the use of vancomycin in American hospitals increased by 160-fold in the period 1978 to 1992. In contrast, the glycopeptide avoparcin had been widely used in European livestock, at levels such as 24,000 kg per year in Denmark, yet not one death due to vancomycin resistant enterococci has been recorded in humans in Scandinavia. The implication of these data and other epidemiologic studies of hospital practices indicates that vancomycin resistance in human enterococcal infections is due to activation of naturally occuring van-A+ resistant bacteria in humans by use of vancomycin in hospitals. One has to question whether avoparcin use in animals has had, or would have, any appreciable effect on the 'pool' of van-A resistance in humans.

CONCLUSIONS

The increased perception of problems with antibiotic resistance in hospital infections in many situations is likely to be due to the increased numbers of patients now receiving long-term hospital care requiring antibiotic use, unrelated to any use of antibiotics in animals. This is not to say that there is no problem with the use of antibiotics in animals. Animal reservoirs are of considerable importance in *Salmonella* sp and other infections. The formulation of sensible guidelines for the use of antibiotics in livestock in Australia should emphasise the prudent use to limit the development of resistant strains. Some European countries have extended this attitude to include the requirement for a definitive diagnosis prior to a specified antibiotic being approved by a dispensing pharmacist for use by a veterinarian. In the Swedish view, a 'zero tolerance' for possible problems in effective therapy of bacterial infections in humans makes it unethical for widespread use of antibiotics to occur in livestock. However, the restrictions on certain uses of antibiotics in Sweden did not come without costs to animals. The year following the ban of oral antibiotics in 1986 in Sweden, an extra

900,000 weaned pigs (of a four million pig population) were found to suffer diarrhoea, mainly due to enterotoxigenic *E. coli* and swine dysentery. An estimated 50,000 unnecessary pig deaths in 1987 alone were therefore directly due to the removal of antibiotics and the increase in swine dysentery problems in Sweden has remained a continual problem. The same ban has led to an estimated increase of 15 percent in the costs of swine production in Sweden, illustrating the higher costs of production of animal products in low-scale, subsidised operations, with consequential higher food prices for consumers. In contrast, no published studies have clearly indicated any particular benefit to the Swedish public of the antibiotic ban. It is also unfortunately true that the self-interest of scientist groups can foster the 'discovery' of positive associations, particularly in surveillance programs. The emotive aspects of surveillance programs involving suggested transfer of infections from animals to humans were fully illustrated by the recent outbreaks of spongiform encephalopathies in Europe and avian influenza in Hong Kong. The ethics of antibiotic use in livestock must balance the small but possible risk of resistance developing in some bacteria, in relation to the benefits of their use for sustaining animal health and welfare.

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