A REVIEW - THE USE OF ANTIBIOTICS IN FOOD PRODUCTION ANIMALS - DOES THIS CAUSE PROBLEMS IN HUMAN HEALTH?

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Abstract

One of the frequent consequences of antibiotic use is the development and spread of resistant bacteria in people and animals. If animals carry resistant bacteria, then food produced from these animals will often be colonised with these bacteria. After ingesting these foods, people can then carry these resistant bacteria and in some cases develop infections from them.

Some of this resistance can be to antibiotics that are 'last-line' agents needed to treat life-threatening infections in people. The development and spread of these multi-resistant bacteria can follow the use of 'last-line' (or similar) antibiotics in food production animals. Examples include ciprofloxacin-resistant strains of *Salmonella spp, Campylobacter spp*. and *E. coli*, vancomycin-resistant strains of enterococcus (VRE) and third generation cephalosporin-resistance in Gram-negative bacteria.

In Denmark, pig and poultry producers voluntarily ceased the routine use of in-feed antibiotic for growth promotion and prophlaxis purposes in 1998. Poultry production was unaffected other than a one percent increase in feed intake (there were no effects on weight gain or mortality). In finisher pigs there were also no important detrimental effects. In weaners there was a 0.5% increase in mortality and a small decrease in daily weight gain. However there were no detrimental effects on overall pork production or exports which both continued to rise.

If three basic principles of antibiotic use were adopted in the agriculture sector, most of the driving factors for unnecessary antibiotic resistance would be substantially reduced or eliminated. This can be done without compromising the therapy of sick animals or the economic production of food animals. These principles are:

- Antibiotics that are 'critical' or 'last-line' for serious human infections should not be used in food production animals or agriculture.
- The use of antibiotics for prophylactic purposes in animals should be kept to a minimum. The use of methods (other than antibiotics) to prevent infections should be expanded and developed.
- Antibiotics should not be used as growth promoters.

Introduction

Antibiotics are used extensively in both humans and animals. The majority of the problems arising from antibiotic resistance in humans is due to the over-use of antibiotics in people and (frequently) the sub optimal infection control and hygiene practices that enable these bacteria to then spread easily from person to person. There are, however, also antibiotic resistant bacteria that can be ingested by people via foods and concerns about this have generated many international reports and recommendations (JETACAR 1999; WHO 1997; WHO 1998; WHO 2000; WHO 2001). Some of these resistant bacteria are 'super-bugs' - multi-resistant bacteria for which there may be few or no therapeutic options available. In Australia, the amount of antibiotic used in animals is much greater than in humans (JETACAR 1999). The three main uses of antibiotics in livestock are for growth promotion, prophylaxis and to treat sick animals (Collignon 1999b; JETACAR 1999; WHO 2001).

Antibiotic use in animals, however, is a potential problem for human medicine because antibiotic resistant bacteria can pass through the food chain to people (JETACAR 1999, WHO 1997). In the past, the main bacterial concerns we were aware of were those involving food-borne bacteria that produced either frequent or severe disease in people (eg gastroenteritis with *Salmonella spp*. or *Campylobacter spp*.). However more recently there have been growing concerns about bacteria that only infrequently cause disease in people but which are transferred more frequently via the food chain (eg *Escherichia coli* and *enterococci*). These latter bacteria

frequently carry genes encoding for antibiotic resistance (as do *Salmonella* species and *Campylobacter* species) (JETACAR 1999; Collignon 1999b; WHO 2000; Witte 2000).

Vancomycin resistance is linked to antibiotic use in animals

In Europe there is strong evidence (Collignon 1999a, Witte 2000) that one type of the vancomycin-resistant enterococci (VRE - vanA) developed in animals fed an antibiotic called avoparcin (a glycopeptide or vancomycin-like antibiotic). VRE carrying the vanA gene-cassette remained on the carcasses of animals after slaughter. VRE was also frequently found on foods that were sold at the retail level (for example, in the Netherlands in one experiment over 70% of chicken tested at the retail level had VRE present (Collignon 1999a). In studies of the European population, between 2 - 17% of people had these multi-antibiotic resistant bacteria present in their bowel (Collignon 1999a, Witte 2000). The conclusion from these data was that VRE was wide spread in the general population in Europe and that avoparcin use in animals was a major cause of this and the consequent spread of vanA VRE via the food chain. Vancomycin resistance is a concern in human medicine in Australia because it is a 'last-line' antibiotic for some hospital-acquired infections of enterococci and staphylococci that have become resistant to the more commonly used antibiotics for these infections. Thus, should bacterial resistance develop to vancomycin we will have no or few alternate antibiotics available to treat people if they develop such infections. Another major concern regarding this type of bacterial resistance is that the vancomycin-resistance genes can spread from VRE to bacteria that are much more common and aggressive such as the multi-resistant strains of *Staphylococcus aureus* (MRSA). Experimentally, this has occurred *in vitro* and has now also occurred with patients in the USA (Sievert 2002). However, currently the most common form of vancomycin resistance in *S-aureus* is caused by a completely different genetic mechanism and is related to the extensive use of vancomycin in hospitals. The amount of vancomycin (or other antibiotics that co-select for VRE) used in hospitals is the main driving force behind how many vancomycin-resistant bacteria amplify and spread. One of the most common and aggressive bacteria causing human infections (*Staphylococcus aureus*) may be untreatable with currently-available antibiotics if vanA spreads from VRE in hospitals to staphylococci and if these MRSA isolates pick up vancomycin-resistance genes and genetic material that allows them to spread more easily. In Australia we have much less data than Europe on the spread of VRE through the food chain. There is, however, suggestive evidence that spread of VRE via foods has occurred (especially with VRE carrying the vanA gene). Recently in Australia, Choice magazine found that 11-14% of chicken meat sold at the retail level in Sydney and Brisbane contained VRE (Australian Consumers Association 2002). We also know that VRE in Australia in hospitalised patients is geographically widespread and has been found in small community hospitals as well as large hospitals (Collignon 1999a, JETACAR 1999). Van A VRE has been isolated in food production animals and foods in Australia (mainly chickens but not from pigs; Barton 1999; Barton and Wilkins 2001, JETACAR 1999, Australian Consumers Association 2002). The most logical explanation of this diverse spread in Australia is that many strains of VRE have been spread through the food chain.

Wherever antibiotics are used, we know that one of the consequences of their use is that resistance can develop. The amount of resistance that eventuates is related to the total amount of antibiotic used. In 1992 over 120,000 kilograms of avoparcin (10% active ingredient by weight) was used in animals in Australia (predominantly as a growth promoter), while only 68 kilograms of vancomycin was used in people (JETACAR 1999). There is debate as to whether antibiotics used as growth promoters still lead to any significant economic benefits (eg weight gains and improved feed efficiency) and in many recent studies, no or minimal benefits were measured (Engster *et al.* 2002; Emborg *et al.* 2001; WHO 2003). In Denmark there has been no decrease in weight gains of poultry or pigs at slaughter time since the use of antibiotic growth promoter (AGP) ceased (Emborg *et al.*, 2001; WHO 2003). In the USA one of the largest poultry producers found the weight gain from the use of AGPs was, at most, only 0.4% (Engster *et al.* l 2002). This is much lower than the general belief and expectation in industry that weight gains with the use of AGPs are between 5 to 10%. At best, with good farming methods, (and relying on figures produced by the pharmaceutical companies themselves) this economic gain is only a few percent in weight gain (JETACAR 1999).

It is also important to note that in much of the promotional material from pharmaceutical companies about their own AGPs, figures are presented which shows their competitors' AGPs

often have a very poor weight gain associated with their use! However, these claimed optimistic benefits usually translate to no more than three cents per chicken or a few cents per kilogram in pork (JETACAR 1999). When it was available, the large amounts of avoparcin used (which is in the class of antibiotics that are 'last line' or 'critical' to humans) appear to have been a waste of a precious resource. Avoparcin has not been registered for use in Australia since 2000. There have been no reports of major losses in production or increases in disease in food animals since the withdrawal of avoparcin. It appears that the use of avoparcin was therefore a waste as it was not essential for the agriculture sector and is now associated with the development, spread and persistence of VRE in food animals and on foods.

Avoparcin was banned in the EU in 1995 and is no longer registered for use in Australia. It is, however, an important antibiotic to study because even after its ban there is continued evidence of the development of avoparcin resistance and the subsequent spread of these resistant bacteria to people along with co-selection of VRE by the use of other antibiotics (eg tylosin) (Aarestrup 2001). There is no reason to believe that resistance in other bacteria following the use of antibiotics different to avoparcin, will develop and spread via similar mechanisms (Witte 2000).

From a medical perspective, any small economic benefits that may have flowed to the agricultural sector from the use of antibiotics as growth promoters appears to have been more than outweighed by the potentially wide-spread circulation of these multi-resistant bacteria throughout the food chain. Antibiotic use in animal production has also resulted in the public perceiving food as a possible source of 'super-bugs'. From a livestock perspective, however, the value of these antibiotics in prevention and control of serious diseases must be factored in. Clearly, it would be much better to remove any ambiguity or misunderstanding about their use and register them as therapeutic agents and not as growth promoters. Failure to do so could potentially compromise their use to treat sick animals if it induces inappropriate changes in laws or regulations in the future.

Ciprofloxacin resistance is linked to antibiotic use in animals

Throughout most of the world, a fluoroquinolone similar to ciprofloxacin (enrofloxacin) has been associated with the spread to humans (through the food chain) of ciprofloxacin-resistant *Salmonella* and *Campylobacter* species and resistant *E. coli* (Molbak *et al.* 1999; Glynn *et al.* 1999; Smith *et al.* 1999). This has resulted in infections of *Salmonella spp.* in humans that are multi-resistant and in some cases for which there are no available antibiotics (ciprofloxacin is also a 'last-line' human antibiotic). In Australia, fluoroquinolones are not approved for use in food production animals and as a consequence, Australia appears to be one of the few countries in the world where there is not a major problem with fluoroquinolone resistant *Salmonella* and *Campylobacter* species (JETACAR 1999).

The Danish Experience

In May 1995 Denmark banned the anti-microbial growth promoter avoparcin (a glycopeptide) because of concerns that its use contributed to the creation of an animal reservoir of VRE, which then posed a potential risk to public health. In December 1997 the EU banned avoparcin in all member states. In January 1998 Denmark also banned the anti-microbial growth promoter, virginiamycin, (a streptogramin) because of concerns that its use contributed to creation of an animal reservoir of streptogramin-resistant *Enterococcus faecium* that posed a potential risk to public health. In February 1998 the Danish cattle and broiler chicken industries voluntarily stopped the use of all anti-microbial growth promoters in response to consumer concerns that the use of anti-microbial growth promoters posed a potential risk to public health. At that time, the Danish swine industry also voluntarily stopped the use of all anti-microbial growth promoters in pigs over 35 kg (finishers). In July 1999 the EU banned another four anti-microbial growth promoters (tylosin, spiramycin, bacitracin and virginiamycin), because they belonged to classes of anti-microbial drugs also used in human medicine. In December 1999, the Danish swine industry voluntarily stopped the use of all remaining anti-microbial growth promoters in pigs under 35kg (weaners). The effects of the terminations of all antibiotics as growth promoters have recently been reviewed (WHO 2003).

In 2001, Denmark had a population of 5.35 million people. It remains a net exporter of both poultry and pork (about 50% of poultry production and 85% of pork production). Broilers and pigs are raised intensively and more than 130-million broilers are produced annually. Typically,

broilers are raised using 'all-in-all-out' (AIAO) management and barns that are cleaned and disinfected between flocks. About 13,500 pig producers raise 22.5 million pigs annually and 95% are slaughtered in two farmer-owned cooperative slaughterhouses. Most new pig facilities use AIAO management.

There has been a substantial reduction in the total amounts of antibiotic used in food production animals in Denmark since the cessation of all AGPs in 1998-99 (eg 99,650 kg of AGPs were used in 1992, 115,786 in 1994, 105,548 kg in 1996, 49,294 kg in 1998 and none in 2000; (DANMAP 2001). The therapeutic use of antibiotics has been variable from year to year, but it appears that similar levels were used before and after the termination of AGPs (range 48,000 – 89,900 kg between 1986–96 to 57,300 – 80,600 kg between 1998-2000; (DANMAP 2000). Despite arguments that the therapeutic use of antibiotics would replace the discontinued use of antibiotics as growth promoters and routine in-feed prophylaxis, the therapeutic use of antibiotics in Denmark remains much lower per kilogram of meat produced than in nearly all other countries in the EU. Danish use of antibiotics is also much lower than in other EU countries that have continued to use some in-feed antibiotics (EMEA 1999). The total use of antibiotics (that is both as AGPs and therapeutically) fell from a peak of 205,686 kg in 1994 to 80,600 kg in 2000 (DANMAP 2001).

Impact of the ban on anti-microbial growth promoters on anti-microbial resistance in Denmark

In Denmark there has been a substantial reduction in the levels of antibiotic resistant bacteria carried by food production animals since the cessation of AGP use (Aarestrup *et al.* 2001, Aarestrup *et al.* 2002). This reduction occurred for most antibiotics relatively soon after the removal of the in-feed antibiotics. With virginiamycin, resistance in isolates of enterococcus from pigs dropped from 60% in 1998 to 5% in 2000 (DANMAP 2001). There were some exceptions, however. Relatively high levels of VRE persisted in pigs at a level of 20% even after avoparcin use was ceased in 1995. It was not until the cessation of another antibiotic in a different class in 1998 (which was co-selecting for the resistant strains – tylosin and a macrolide) that rates dropped to only a few percent in 2000 (Aarestrup *et al.* 2001, DANMAP 2001).

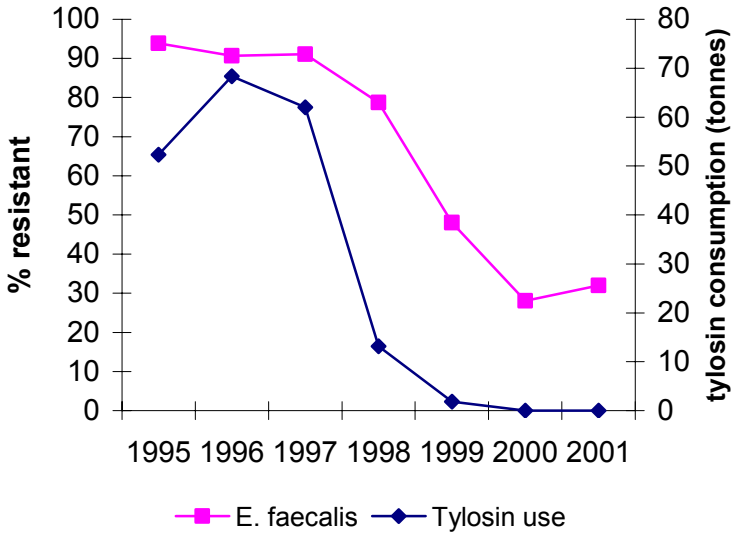

Figure 1. *Trends in tylosin use for growth promotion and erythromycin resistance among Enterococcus faecalis isolated from pigs at slaughter from 1995 to 2001 (WHO 2003; Aarestrup et al. 2001).*

Despite concerns that ceasing AGP use would result in an increased carriage of *Salmonella* in food production animals and/or an increase in human disease caused by *Salmonella*, this was not seen in Denmark. In fact, human cases of *Salmonella* infection have decreased since the termination of AGP-use from 100 cases per 100,000 population in 1997, to 55 cases per 100,000 in 2001. The carriage of *Salmonella* in food animals has shown a steady decrease since 1990 and this downward trend appears to have been unaffected by the termination of AGP use (Evans *et al.* 2003; WHO 2003).

The termination of anti-microbial growth promoters in Denmark has had no major impact on animal production. The amount of pig meat produced in Denmark has continued to rise since 1960 with no obvious effects from the termination of AGPs in swine production in 1998-99 (Figure 2). There were also no effects on pork exports, which have continued to increase over the last 10 years. The number of pig producers continued to decline in Denmark from 1972-2001 but there were no obvious effects following the termination of AGPs in 1998-99 (WHO 2003).

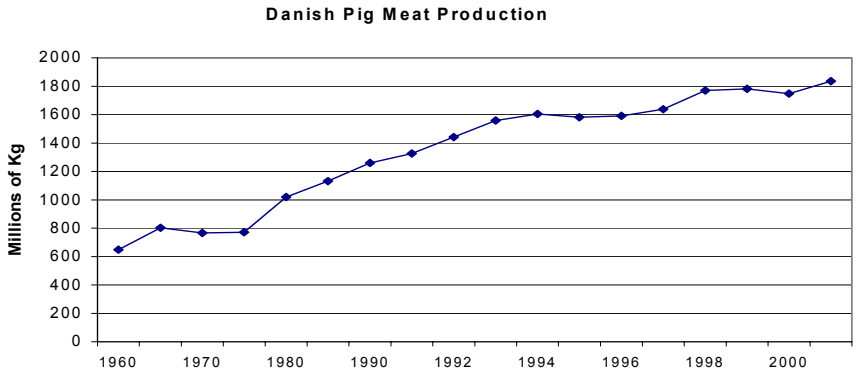

Figure 2. *Total production of pork in Denmark between 1960 and 2001*

The termination of AGPs in swine production in 1998-99 had no effect on production parameters in finisher pigs. Feed efficiency improved between 1995 and 2001 (from 2.95 to 2.89 feed units/weight gain). In weaners however, there were effects with an increase in mortality of about 0.5% and a decrease in daily weight gain (WHO 2003). Feed efficiency also decreased over the periods 1995 to 2001 (97.9 to 99.3 feed units per produced pig). Some of these effects in weaners may have been due to the ban on the use of olaquindox and carbadox, rather than the termination of other antibiotic growth promoters. Before the ban on quinoxaline-based anti-microbial growth promoters (e.g., carbadox and olaquindox), olaquindox was the most commonly used anti-microbial growth promoter in weaners, in terms of total kilograms of anti-microbial growth promoters used (WHO 2003). One of the major reasons for the increased morbidity in weaners appeared to be an increase in diarrhoea due possibly to *E. coli* and/or *Lawsonia intracellularis* infections (Jensen 2002; WHO 2003).

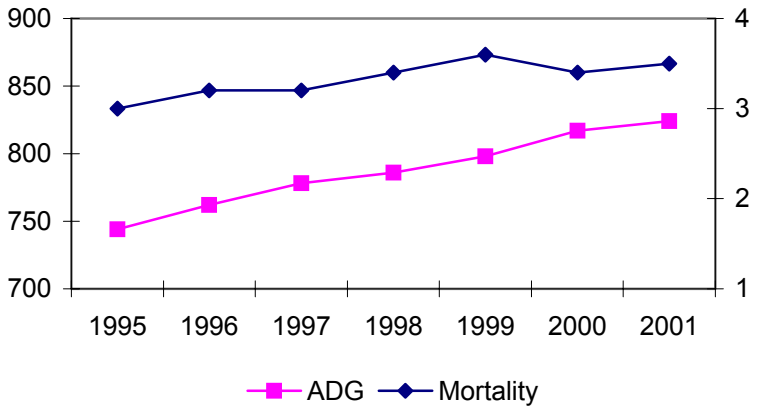

Figure 3. *Productivity of finisher-pigs (average daily weight gain). (% Mortality right axis; Average daily weight gain (ADG) left axis in g. (WHO 2003).*

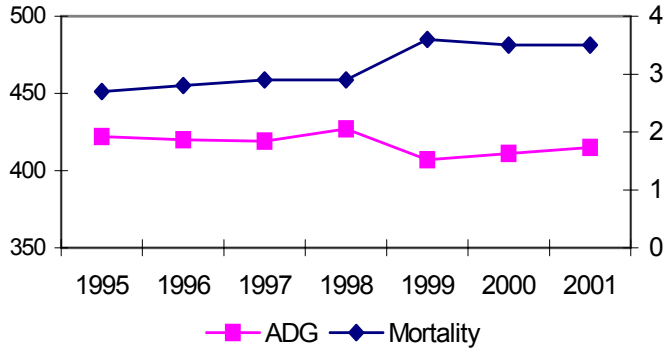

Figure 4. *Productivity in weaner pigs (average daily weight gain): (% Mortality right axis; Average daily weight gain (ADG) left axis in g. (WHO 2003).*

What can we do to limit the amount of antibiotic resistance that occurs?

There will always be new antibiotics and there will always be controversy about the economic and medical costs of their use compared to their benefits (both in humans and in animals). It is important that some antibiotics are available for use to treat sick animals. However, we need to limit the ways that antibiotics are used in food production animals. In particular, antibiotics should not be used for growth promotion and they should be used only sparingly for prophylaxis. Antibiotics that are 'critical' or 'last-line' for human use should not be used in food production animals at all. These 'critical' antibiotics are only a small percentage of the total amount of antibiotics that are used in humans in Australia. If these 'last-line' antibiotics were reserved for human use alone this would be unlikely to compromise animal welfare.

Antibiotics (or similar agents in the same class as antibiotics) that are 'critical' or 'last-line' antibiotics for serious human infection, should not be used in animals or agriculture. There are many serious infections in humans where there are few or, in some cases, no alternate antibiotics that can be used if antibiotic resistance develops to these agents. These can therefore be classified as 'last-resort' or 'critical'. As a group, most of these antibiotics are only used in people in Australia in small volumes by weight. There are also many alternatives to these antibiotics that can be used to treat animals successfully that are sick (for example, penicillins, tetracyclines). Antibiotic classes that can be classified as 'critical', 'last-resort' or 'reserve' include:

Class of antibiotic	**examples (mainly human but with some animal antibiotics)**
glycopeptides	(vancomycin, teicoplanin, avoparcin)
3rd and 4th generation cephalosporins	(eg cefotaxime, ceftriaxone, ceftiofur, cefipime),
anti pseudomonal penicillins	(eg piperacillin, ticarcillin),
anti tuberculosis drugs	(eg rifampicin, isoniazid, ethambutol, pyrazinamide),
fluoroquinolones	(eg ciprofloxacin, levofloxacin, enrofloxacin),
aminoglycosides**	(eg amikacin),
carbapenems	(eg imipenem, meropenem),
streptogramins	(eg Synercid, virginiamycin),
oxazidolones	(eg linezolid)

**(only those with a relative extended spectrum and/or a much lower susceptibility to enzymatic destruction eg amikacin)

Because of increasing antibiotic resistance in many important human pathogens new antibiotics have recently been developed and released (eg linezolid). It is critical that if any other new classes of antibiotics are developed for human use that these are not used in animals unless it is established they are not 'critical' for human use.

These 'critical' antibiotics (or others in the same class) should not be used for therapy or any other purpose in food producing animals. Fluoroquinolones have been approved for use in food production animals in many countries. The use of enrofloxacin has resulted in the development of ciprofloxacin-resistant strains of *Salmonella spp* and *Campylobacter spp*. These resistant bacteria have subsequently caused human infections. When the glycopeptide, avoparcin, was used as a growth promoter in food animals in Europe this resulted in the development and amplification of vancomycin resistant enterococcus (VRE) and subsequent colonisation by a significant percentage of the human population via the food chain (between 2 and 17%). After the ban of avoparcin use in food animals in the EU, the percentage of the general population carrying VRE in their bowel showed a marked reduction (WHO 2003).

The basic principles we need to follow in order to maintain or facilitate this approach not only now, but also in the future are given below.

- Antibiotics that are 'critical' or 'last-line' antibiotics for serious human infections should not be used in food production animals or agriculture.
- The use of antibiotics for prophylactic purposes in animals should be kept to a minimum. The current usage for this purpose should be significantly reduced. The use of methods (other than antibiotics) to prevent infections should be expanded and developed.
- Antibiotics should not be used as growth promoters.

Conclusion

Antibiotics are a precious but non-renewable resource. They are of major benefit to people who have serious and life threatening bacterial infections. We are currently squandering this resource by using antibiotics much more widely than we need to and in inappropriate ways (both in people and in animals). This has resulted in antibiotic resistance developing and then spreading not only from person to person but also via the food chain from animals to humans. It is essential that we use antibiotics wisely and prudently, otherwise these miracle drugs of the 20th century will lose their effect with the wide spread development and amplification of resistant bacteria and the genes that encode for this resistance.

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