

# Banning antibiotic growth promoters: Learning from the European experience

***The EU banned the use of avoparcin, a widely used antibiotic feed additive in food-producing animals in 1997, against the advice of a panel of animal nutrition experts. Two years later came a ban on bacitracin, spiramycin, tylosin and virginiamycin. Once more, the ban was imposed against expert advice, again on the basis of fears of antibiotic resistance spreading via the food chain. How have these bans affected the health of animals and humans?***



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**F**rom the first day of 2006, the last antibiotic feed additives (AFAs) were banned from use in food-producing animals in the European Union. Several years have passed since the first ban on AFAs was implemented and some other countries are proposing similar action, so it is worthwhile to assess the results of these bans on antibiotic resistance in microorganisms as well as the health of food-producing animals and humans.

## **Effects on antibiotic resistance**

The oldest and most complete source of data regarding antibiotic use and antibiotic resistance monitoring in animals and people is the Danish database, DANMAP. Data from these reports will be used to illustrate the results and conclusions reached in this article.

As anticipated, the AFA bans have resulted in substantially lower levels of antibiotic resistance for the corresponding antibiotic on indicator bacteria isolated from raw meat products. This was expected as, with a few exceptions, antibiotic use will create antibiotic resistance, whether in animals or people. What the DANMAP data shows, however, is that the improvements seen on indicator bacteria isolated from raw meat have not translated into lower levels of antibiotic resistance in human patients. There is much scientific information that helps to explain this lack of correlation.

The first AFA used in food-producing animals to be banned in the EU was avoparcin, in 1997. It was excluded because it belongs to the glycopeptide class, a critically important group of antibiotics used in human medicine. Vancomycin belongs to the same class, and studies

have shown that glycopeptide-resistant enterococci will develop in animals fed avoparcin. Resistant enterococci have been isolated from the raw meat of animals fed avoparcin, creating a concern for their passage to people via the food chain.

If we look at the incidence of vancomycin-resistant enterococci (VRE, bacteria commonly involved in fatal infections in hospitals), a different picture emerges. VRE infections are more prevalent in US hospitals than those in the EU although avoparcin has never been used as an AFA in food-producing animals in the USA. This suggests that the VRE problem was created by vancomycin use in humans, and that a ban on AFAs in the USA would not improve the critical VRE problem in the hospitals. Studies in Europe have shown that VRE can be isolated from healthy human and animal faeces. However, the relatively low prevalence

of VRE in EU hospital patients indicates that without substantial use of vancomycin in human medicine, the VRE problem would be limited.

Virginiamycin was the AFA banned in the EU in 1999. This antibiotic belongs to the streptogramin class. As in the case of avoparcin, there were concerns over cross-resistance with a new human antibiotic in the same class, Synercid. This drug was developed to treat vancomycin-resistant *E. faecium* (VREF) infections. It prompted EU regulators to call for its ban as an AFA.

However, an extensive sensitivity survey conducted in American and Canadian clinics before Synercid's introduction in North America found that out of more than one thousand clinical isolates of *E. faecium* tested, 99.8 percent were sensitive to the new human antibiotic. So after nearly three decades of continuous use of virginiamycin in food-producing animals in the USA and Canada, there was virtually no evidence of streptogramin-resistant *E. faecium* (SREF) in the human population.

These results are not surprising. Meat is cooked prior to its consumption, and the high temperatures achieved during cooking kill any bacteria that might have contaminated it. Dead bacteria cannot transmit antibiotic resistance. Proper food hygiene and cooking have been highlighted as the most effective ways to prevent not only the transmission of antibiotic-resistant bacteria but also food poisoning in people.

A study published in 2001 failed to prove the transfer of SREF from foods of animal origin to people. Between July 1998 and June 1999, the authors cultured 407 raw chickens obtained from 26 grocery stores in four US states, and isolated SREF from 58% of them. Resistance was defined as a minimum inhibitory concentration (MIC) of at least 4ppm. The authors attributed the high level of resistance to the use of virginiamycin. During the same period, the authors cultured 334 stool samples from outpatients at various medical clinics in the same four states. Only two stool samples (0.6%) yielded SREF. Both samples had an MIC of 4ppm, reported by the authors as a 'low level' resistance.

Despite the results, the authors concluded that 'the low prevalence

and low level of resistance in human stool specimens suggest that the use of virginiamycin in animals has not yet had a substantial influence', and 'food borne dissemination of resistance may increase'. They concluded, 'The Food and Drug Administration (FDA) was in the process of conducting a risk assessment for virginiamycin and that if such assessment demonstrated a role for food borne transmission in the emergence of SREF in humans, restrictions on the continued use of virginiamycin in food animals should be considered.'

Since that paper was published, two risk analyses have been conducted. The first, a quantitative risk analysis,

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showed that if virginiamycin continues to be used as an AFA in food-producing animals, the risk would be less than one statistical life saved for the entire USA population over a 15-year period. The risk is further decreased by the increased use of newer alternatives to Synercid. (This calculation assumes that resistance is transmitted from foods to people, which has not been proven.)

The FDA completed the second risk assessment. It concluded that the risk from the continued use of virginiamycin in food-producing animals is very small – annually somewhere between six chances in 100 million and 1.2 chances in one million. The FDA assessed the risk of a human patient having SREF attributable to animal uses of virginiamycin and impaired Synercid therapy.

A thorough examination of this and many other published research reports led a panel of experts to conclude that there is little or no evidence that resistant enterococci from animals are a risk to human

health. Furthermore, they agreed that a ban on AFAs was not justified on this basis, and would have no impact on the prevalence of VRE in human infections'

### **Effects on animal health & productivity**

A study in Norway published in 2001 reported severely impaired production performance in broiler flocks with high incidence of *Clostridium perfringens*-associated hepatitis (CPAH). The authors analysed production performance data collected from a large processing plant, with the objective of comparing performance data from broiler flocks with high levels of CPAH to those with low levels of CPAH. The study was conducted for the two-and-a-half years following the EU ban of avoparcin. Flocks with high levels of CPAH had 25-43% lower profitability than those with low levels. These effects were mainly attributed to impaired feed conversion and reduced weight at slaughter. Researchers from the same institute had reported earlier that the main effects of experimentally induced subclinical necrotic enteritis were increased feed conversion and retarded growth. So it appears that avoparcin and virginiamycin were preventing clinical and subclinical necrotic enteritis in poultry, even when used at inclusion rates labelled for 'growth promotion'. This observation has been confirmed in other studies.

In another paper, the authors examined data three years after the bans were implemented. They concluded that the only measurable benefit in humans was a reduction in acquired resistance in enterococci isolated from human faecal carriers. However, the authors stated that despite the AFA ban and the reduction of carriage of resistant enterococci in animals and humans, there had been no reduction in the prevalence of resistant enterococcal infection in humans. On the other hand, the AFAs had an important prophylactic activity previously unrecognised, and their withdrawal was associated with a deterioration in animal health. They cited as evidence an increased incidence of diarrhoea, weight loss and mortality in post-weaning pigs, and necrotic enteritis in

broiler chickens. The authors stated, 'The theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences.'

## Effects on human health

An unintended consequence of the EU ban on the prophylactic use of AFAs in food-producing animals may be a greater adverse effect on public health.

A paper published in 2004 indicates that following the EU bans, the incidence of *Cl. perfringens*-associated disease in poultry and its detection in poultrymeat had increased substantially and that it is emerging as a real threat to public health. Toxins formed by *Cl. perfringens* type A and type C present in poultrymeat can cause food poisoning and necrotic enteritis in people, respectively. Since food poisoning by this micro-organism is not a reportable disease, its incidence is greatly underestimated. Nevertheless, it was recognised in Norway as the most common cause of food poisoning during the 1990s. According to one report, the ban on the remaining three AFAs (avilamycin, monensin and salinomycin) with activity against *Cl. perfringens* is likely to increase even more the public threat of food poisoning by that bacterium. Only time will tell whether the AFA bans have consequences on food poisoning in humans.

According to the latest available report by DANMAP, 'the use of antibiotics in humans and animals and the occurrence of resistant bacteria continued to increase through 2004'. In the meantime, the use of antibiotics for therapeutic purposes in food-producing animals has increased every year since the first bans, from 48 tonnes (t) the year after the bans to 112.5t in 2004.

An interesting theory has been proposed on how antibiotic use in food-producing animals may actually reduce consumer risk. A recent paper indicates that virginiamycin in turkey feeds significantly reduced the incidence of *Salmonella* spp. Since virginiamycin has no direct

activity on these bacterial species, it seems that the changes produced in the intestinal microflora were less favourable to its growth. Likewise, the use of antibiotics, whether added to the feed to prevent disease or in the drinking water to treat diseases like airsacculitis of poultry, may also reduce the risk of food poisoning to consumers. In a series of studies to determine the effect of airsacculitis of broiler chickens on the overall quality of the carcass, airsacculitis-positive flocks had lower body weights, more faecal contamination, more processing errors and higher levels of *Campylobacter* spp. This led to the recommendation that broiler chicken companies should emphasise control of airsacculitis in their flocks to help prevent subsequent food-borne bacterial infection.

Concentrations of various AFAs and ionophore anticoccidials used in poultry feeds have been found to have an inhibitory effect on the transfer of a multiresistance-conferring plasmid in *E. coli* in an in vitro test. So it appears that AFAs and ionophores may actually inhibit resistance transfer mechanisms.

## Conclusions

There is little or no evidence to support the claim that the use of AFAs in animal feeds has contributed to the problem of antibiotic resistance in human medicine. Of the 20 most serious bacterial infections exhibiting problems with antibiotic resistance in human medicine, 12 are not acquired via the food chain, and so cannot be linked to AFAs. Of the remaining eight infections, the calculated contribution to antibiotic resistance in all cases is no more than 1%. This assumes that transfer of bacterial resistance from animals to people occurs at all, an unproven assumption in most cases.

The EU banned the use of AFAs at levels labelled for growth promotion. Almost immediately, there was a surge of enteric disease problems in food-producing animals, and a consequent rise in antibiotic use for therapeutic purposes. The antibiotics

used to treat food-producing animals belong to the same classes of antibiotics most frequently used in human medicine. It is conceivable that this might have actually had a greater adverse effect on the creation of antibiotic resistance in people than the regular use of the AFAs.

The increased use of antibiotics for therapeutic purposes in food-producing animals has clearly proven that the prior use of AFAs had positive effects on health promotion and disease prevention in food-producing animals, even when used at concentrations labelled for 'growth promotion.'

The AFA bans implemented by the EU did achieve their objective of reducing the incidence of resistance on indicator bacteria in raw food products of animal origin. However, there has been no measurable improvement in antibiotic resistance in human patients or hospitals. Monitoring antibiotic resistance in raw meat products is not an appropriate measure to represent the bacteria that reach the consumer because cooking destroys these bacteria, and dead bacteria cannot transmit antibiotic resistance.

The incidence of food-borne diseases in the US population has declined, while it continues to increase in the EU, at least for certain bacteria like *Salmonella*, *Campylobacter* and *Cl. perfringens*. It is becoming apparent that the ban AFAs has not made the food supply safer.

Other countries should learn from the EU experience and proceed with caution. Decisions should be taken based on sound science and quantitative risk analysis, or the action that may have effects opposite to those intended.

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