

The European ban on growth-promoting antibiotics and emerging consequences for human and animal health

Mark Casewell^{1*}, Christian Friis², Enric Marco³, Paul McMullin⁴ and Ian Phillips¹

¹University of London, London; ⁴Poultry Health Services Ltd, Thirsk, North Yorkshire, UK; ²Royal Veterinary and Agricultural University, Copenhagen, Denmark; ³B & M Consulting, Barcelona, Spain

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Following the ban of all food animal growth-promoting antibiotics by Sweden in 1986, the European Union banned avoparcin in 1997 and bacitracin, spiramycin, tylosin and virginiamycin in 1999. Three years later, the only attributable effect in humans has been a diminution in acquired resistance in enterococci isolated from human faecal carriers. There has been an increase in human infection from vancomycin-resistant enterococci in Europe, probably related to the increased in usage of vancomycin for the treatment of methicillin-resistant staphylococci. The ban of growth promoters has, however, revealed that these agents had important prophylactic activity and their withdrawal is now associated with a deterioration in animal health, including increased diarrhoea, weight loss and mortality due to *Escherichia coli* and *Lawsonia intracellularis* in early post-weaning pigs, and clostridial necrotic enteritis in broilers. A directly attributable effect of these infections is the increase in usage of therapeutic antibiotics in food animals, including that of tetracycline, aminoglycosides, trimethoprim/sulphonamide, macrolides and lincosamides, all of which are of direct importance in human medicine. The theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences.

Keywords: growth promoters, Europe, antibiotic use

The bans on growth promoters and their immediate effects

Following the ban on all growth-promoting antibiotics in Sweden in 1986, and the ban on avoparcin and virginiamycin in Denmark in 1995 and 1998, the European Union (EU) banned the use of avoparcin in 1997 and the four remaining antibiotics used for growth promotion in 1999, on the basis of the 'Precautionary Principle'. These four antibiotics were bacitracin (a polypeptide), spiramycin and tylosin (macrolides), and virginiamycin (a streptogramin combination). The driving forces behind these bans were consumer and political opinion, and a scientific concern that resistance selected in animals might be transmitted to humans to the detriment of their health. Experience in Sweden had already shown that the bans might have adverse consequences for animal health and welfare, and economic consequences for farmers.¹ There were also suggestions that human health is unlikely to benefit and that it might even be adversely affected.^{2,3} Careful perusal of the scanty published literature of events in Europe since the EU ban shows that these concerns were well founded.

The ban has resulted, as intended, in the complete removal of the banned compounds as growth promoters. In Denmark, for example, where over 105 metric tonnes of antibiotics were used for growth promotion in 1996, the usage fell to nil by 2000.⁴ This was accompanied by a diminution of resistance to avoparcin, macrolides and virginiamycin among enterococci, studied as an 'indicator' species, in food-animal faeces, in Denmark and elsewhere,⁴⁻⁶ although vancomycin-resistant *Enterococcus faecium* has persisted in samples from Danish broilers⁷ and pork.⁸ Nevertheless, the pool of antibiotic resistance genes in animal faecal enterococci appears, overall, to have diminished.

Consequences for human infections

The only attributable effect on humans has been some diminution in vancomycin resistance in enterococci isolated (VRE) from human faecal carriers.^{6,9} However, despite the growth promoter ban and the reduction of carriage of resistant enterococci in animal and human faeces, there has been no diminution in the prevalence of resistant enterococcal infection in humans: little could be expected in Scan-

*Correspondence address. Department of Infectious Diseases, Guy's, King's & St Thomas's School of Medicine (King's College Hospital Campus), Bessemer Road, London SE5 9RS, UK. Fax: +44-20-7346-3404; E-mail: casewell@netcomuk.co.uk

dinavia where VRE infections have rarely been reported,^{10,11} despite the widespread use since 1975 of avoparcin as a growth promoter. Rather, vancomycin resistance appears to be increasing in enterococcal infections in parts of Europe over the period of the ban, probably in relation to the increased prevalence of methicillin-resistant staphylococcal (MRSA) infection¹² necessitating the increased use of glycopeptides and streptogramins—mimicking the conditions found in the USA¹³ where a high incidence of VRE infection has emerged in humans in the absence of the use of avoparcin in animals. The first vancomycin-resistant methicillin-resistant *Staphylococcus aureus* has recently emerged, not in Europe, but in the USA¹⁴ and the most likely explanation is the acquisition of the VanA gene from a strain of vancomycin-resistant *Enterococcus faecalis* that was also present at the site of the patient's chronically infected foot ulcer.¹⁵

The antibiotic susceptibility of salmonellae and campylobacters, responsible for the major zoonoses in Europe, could not have been expected to be affected by the ban to the benefit of human health (except possibly in relation to macrolides in the case of campylobacters) since they are Gram-negative organisms whereas the banned growth promoters had a Gram-positive spectrum of activity. However, human salmonellosis has not responded to control measures in some parts of Europe, and microbiologically confirmed infections actually increased in prevalence in Denmark in 2001⁵ after they had declined for 3 years.¹⁶ Increased antibiotic resistance in salmonella might be expected in response to the increased use of therapeutic antibiotics in animals consequent to the ban, and there is an increase in tetracycline and sulphonamide resistance in *S. typhimurium* isolates from pigs and from human domestic infections in Denmark in 2001.⁵ The case of campylobacter appears to be worse: in Denmark, it has steadily increased in prevalence over the past decade¹⁶ and there is more tetracycline and fluoroquinolone resistance in human than in animal isolates.⁵ One possibility is that the persistence or even increase in prevalence of these two zoonoses might in part be related to the removal of growth-promoting antibiotics but so far as we are aware this hazard has not been explored. For example, the variation in size of broilers not given growth promoters leads to more frequent rupture of the gastrointestinal tract at slaughter, faecal spillage, and potential contamination with salmonella and campylobacter.¹⁷ The possible contribution of increasing international travel to countries with poor food and water hygiene to the increased prevalence of campylobacter and salmonella infections has yet to be defined.

Consequences for animal health

Although originally approved for use as growth promoters, the sudden withdrawal of these antibiotics has revealed animal health promotional effects of growth promoters that are consistent with the prophylaxis of important food-animal infections. Thus, following the bans, the diminution of the resistance pool in animal and human faecal commensal enterococci has been at the cost of a deterioration in animal welfare. In Sweden, 16 years after their ban of growth promoters, the loss in production from pigs has not yet been fully recovered on a national basis.¹ From Denmark, there are reports of increased morbidity and mortality among pigs,¹⁸ mostly associated with enteric infections;¹⁹ 11% of 'finishing' herds (weighing more than 35 kg) experienced permanent problems with increased frequency of diarrhoea or reduced weight gain.²⁰ However, in younger weaning pigs (7–30 kg weight) the problems of post-weaning diarrhoea and chronic infections due to *Lawsonia intracellularis* have persisted in Denmark^{19,20} and in Spain (E. Marco, personal communication) leading to decreased weight gain and an increased mortality

since the removal of growth promoters.^{19,20} In poultry, it had been predicted that if bacitracin was withdrawn, clostridial necrotic enteritis, which is known to be suppressed by this growth promoter,²¹ would emerge as a problem requiring therapy, and this has been reported to be the case in Denmark²² and in France. A recent report from the Danish National Department of Poultry Production points out that since the late 1990s, the broiler industry has been "struggling with leg and skin problems" that may compromise broiler welfare and that, although not previously documented, "the exclusion of animal growth promoters and meat and bone meal from broiler diets has played a major role in the development of leg problems and deteriorated skin health".²³ Modifications in environmental conditions, such as light and feeding programmes, are being tested to improve food safety and customer acceptance of poultry meat.

Increased use of therapeutic antibiotics in food animals

This increase in infections since the ban has driven, at least in part, a substantial increase in the use of therapeutic antibiotics for food animals in Europe.^{24–26} In the UK, the Veterinary Medicines Directorate published in 2002 the sales figures for veterinary antimicrobials up to the year 2000.²⁵ After the EU ban of growth promoters in 1999, there was an increase in sales of therapeutic antimicrobials from 383 tonnes in 1999 to 437 tonnes in 2000. This was due to increases in the sales of tetracyclines (by 36 tonnes), trimethoprim/sulphonamides (by 12 tonnes) and macrolides (by 12 tonnes). There were increases of 7 tonnes in pigs, 13 tonnes in poultry and of 37 tonnes of therapeutics authorized for more than one species. It was thought that in the pig industry, the increase may well be ascribed to the EU ban in 1999 and to the presence of diseases such as porcine dermatitis, nephritis syndrome and post weaning multisystemic wasting syndrome.²⁵ In Denmark, there was an overall increase in therapeutic antibiotics from 48 tonnes in 1996⁴ to 94 tonnes in 2001.⁵ The main antibiotics involved in this increase have been tetracycline, mostly used in pigs,²⁶ whose usage increased from 12.9 to 27.9 tonnes (a 116% increase), macrolides and lincosamides (7.6 to 14.3 tonnes, 88%) and aminoglycosides (7.1 to 11.9 tonnes, 68%).^{4,5} This has occurred despite attempts to improve other critical aspects of animal husbandry²⁷ to make up for the loss of the growth promoters. Experience in Sweden suggests that this may eventually be partially effective but with an increased financial burden;¹ it is far from clear that this will apply to the whole of Europe where farming conditions are different from those of Scandinavia.

Conclusion

The published evidence suggests that the growth-promoter bans have reduced overall antibiotic use in animals. It is increasingly clear, however, that the use of growth promoters was accompanied by other, previously unrecognized, health promotional or prophylactic effects. After the withdrawal of these antibiotics, animal welfare has suffered and despite efforts to improve other aspects of husbandry, the veterinary use of therapeutic antibiotics, which are identical to those used in human medicine, has increased, and this constitutes a theoretical hazard to human health in relation to resistance in salmonellae, campylobacters and zoonotic strains of *E. coli*. The efforts and expenditure involved in the imposition of the ban would have been better spent on achieving rational antibiotic use in humans and animals, and on much greater efforts to understand the complex epidemiology of resistant pathogens and resistance genes, as well as adequate risk assessments of both the ban, the 'precaution', in paral-

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lel with that of the 'threat', i.e. the continued use of growth promoters. The evidence suggests that the remaining growth promoting antibiotics still in use in Europe should not be banned until the relationship between growth promotion and prophylaxis is clarified, and the adverse consequences of the current ban can be remedied in Europe as a whole. The prediction in 1997 that "The elimination of these products will tend to increase the use of therapeutic antimicrobials" and that "animal production is likely to decline in countries which implement a unilateral ban on these products"²⁸ seems thus far to be supported by the evidence.

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