Introduction
The occurrence of antimicrobial resistance in bacteria harboured by animals is likely to become an increasingly important threat to sustainable methods of agriculture in future. Resistant bacteria which are animal pathogens may be refractory to treatment, with important consequences for animal health, welfare and the spread of disease, as well as significant economic consequences. Where zoonotic bacteria carried by animals (for example Campylobacter and Salmonella) have acquired resistance, then treatment of human infections may be compromised. There is also concern that the commensal flora of animals may act as a reservoir of resistance genes that can be transferred to other more significant bacteria in both animals and man. In future, the degree and scale of resistance amongst bacteria in food derived from animals and in livestock may be compromised. There is also concern that the commensal flora of animals may act as a reservoir of resistance genes that can be transferred to other more significant bacteria in both animals and man. In future, the degree and scale of resistance amongst bacteria in food derived from animals and in livestock may have implications for international trade. It has also been suggested that a low prevalence and degree of resistance in commensal bacteria from food-producing animals may in future be recognised as a distinguishing food quality and safety mark. However, antimicrobial usage in animals has brought many benefits to both animal health and welfare. The treatment of animal diseases can result in an improvement in food quality and help to prevent the transmission of zoonotic diseases from animals to man.

A global problem
Antimicrobials have been used in veterinary medicine for both growth promotion purposes and as therapeutic and prophylactic agents, although within the EU all antimicrobial growth promoters are currently due to be phased out in 2006. The most important factor in the development of antimicrobial resistance is generally considered to be the level of usage of antimicrobials and there is usually a close relationship between the quantity of antimicrobial used and the rate of emergence of resistance to that antimicrobial (Aarestrup and Seyfarth 2000). The increasingly global nature of trade and the international movement of both animals and man provide a means for widespread dissemination of organisms. A good example of this is provided by Salmonella enterica subspecies enterica serotype Typhimurium determinative type (DT) 104, which has been reported in many countries throughout the world. Strains of DT 104 are typically resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines. Analysis of the resistance genes carried by the organism revealed that the gene for resistance to ampicillin is bla_pse-1 which was first identified in Pseudomonas aeruginosa and which encodes resistance to carbenicillin (it is interesting to note at this point that carbenicillin has reportedly never been used in agriculture). Two of the other resistance genes carried by this organism (conferring resistance to chloramphenicol and tetracyclines) are genetically very similar to genes previously described in fish pathogens and it has been postulated that the initial selective pressure for emergence of these resistance genes may have occurred in aquaculture (Chaslus-Dancla et al 2000). It may also be of significance in relation to the evolution of DT 104 that Pseudomonas aeruginosa commonly inhabits aqueous environments.

The relevance of antimicrobial resistance to veterinary practice
The problems in human medicine of drug resistant strains of Mycobacterium tuberculosis and methicillin-resistant Staphylococcus aureus (MRSA) are related to the use of antimicrobials in human medicine and have not emerged as the result of usage of antibiotics in animals or agriculture. Cases of bovine tuberculosis in food-producing animals are slaughtered rather than treated and although there have been reports of MRSA affecting canine surgical patients and cattle (mastitis), in many cases the source of infection appears to have been man. Problems on a similar scale to those caused in hospitals by MRSA have not so far emerged in veterinary practice. A number of reasons have been put forward to explain this, including the shorter length of stay of most animal patients, less invasive surgical procedures, the lower average degree of immuno-suppression in veterinary patients,
euthanasia, the shorter lifespan of animals and the options for periodic depopulation of animal accommodation (Normand et al 2000). An additional, extremely important factor, is the species difference between animals and man; in hospitals medical staff can be colonised by MRSA and transfer it between patients, whereas in veterinary medicine the organisms colonising man as commensals are in general different from the strains of commensal bacteria colonising animals. Therefore the potential for the dissemination of epidemic strains between patients is reduced, since man can transfer these strains mechanically but is less likely to be colonised by them. The term ‘hot-bedding’ has been used in human medicine to refer to the rapid turn-round of hospital bed places. There is a direct parallel in veterinary medicine, in that farms in which all cows calve through a single calving box sooner or later run into problems with calf morbidity and mortality as a result of the emergence of bacteria with either exalted virulence or multiple antimicrobial resistance (or both). Similar parallels can be observed in lambing pens, farrowing houses and hatcheries.

Adequate terminal hygiene and disinfection is one of the key control points for minimising the build-up and emergence of resistant bacteria on farms, and should be combined with biosecurity measures to prevent the introduction of resistant organisms. In future, these aspects are likely to increase in importance, particularly in cases where effective vaccines are not available for disease control.

The maintenance of high health status of herds and flocks by purchase of high health status animals is already important and is likely to have an increasing role in future.

The main threats to sustainable agriculture in the UK

Resistance to tylosin and lincomycin in cases of swine dysentery (as judged by lack of clinical response) was reported in 1993 in the UK, although tiamulin remained effective (MacKinnon 1993). Since then, swine dysentery strains have emerged, both in the UK and elsewhere in Europe, that are resistant in vitro to all available antimicrobials used for treatment, including tiamulin, though these resistant strains do not appear to have persisted in the UK. It is of critical...
importance to the pig industry that the spread of any strains with such emergent resistance is limited. Widespread dissemination of bacterial clones compounds the problems caused by resistant bacteria and emphasises the important roles that quarantine and isolation of incoming stock, thorough terminal hygiene, and adequate biosecurity all play in modern farming.

The global spread of *Salmonella typhimurium* DT 104 has already been mentioned. This organism has caused significant and widespread disease in cattle, with periparturient animals particularly affected. The degree of resistance shown by DT 104 has limited the therapeutic options for treatment, with trimethoprim/sulphonamide combinations and fluoroquinolones proving most effective in the author's experience, although strains resistant to trimethoprim/sulphonamides do occur. Decreased susceptibility to fluoroquinolones has been reported in DT 104 and usually correlates well with resistance to nalidixic acid. There is some evidence that human infections with such strains have a worse outcome than infections with fully-susceptible strains. Fortunately however, there appears to be counter-selection of highly-resistant fluoroquinolone *Salmonella* strains in the field in the absence of selective pressure (Giraud *et al* 1999). Prudent use of fluoroquinolones to ensure that this selective pressure is minimised as far as possible will be important. The evolutionary prowess of bacteria is such that if a sufficient selective pressure is maintained then one might predict that compensatory mechanisms are likely to occur within the organism to allow it to persist and overcome this counter-selection. This would severely limit the therapeutic options for treatment of animals affected with salmonellosis and also have important public health implications.

A further emerging resistance, which has been reported in both *Salmonella typhimurium* and *Salmonella newport* in the United States, is resistance to third-generation cephalosporins, such as ceftriaxone. These compounds are often regarded as one of the drugs of choice for the treatment of *Salmonella* infections in human infants and so there are significant public health implications relating to this development. Currently, published data indicates that resistance to third-generation cephalosporins in *Salmonellas* recovered from both animals and man is relatively rare in Europe. Resistance in organisms such as *Campylobacter* may have limited clinical relevance on farm for the livestock carrying them, but may have significant implications for public health and consumers. This situation arises because *Campylobacter* are often commensals in the intestinal flora of animals, but are a major cause of food-poisoning in man. In future, it is likely that considerations such as these will increasingly impinge on farming practices.

**Physiological cost and the fitness of organisms**

Resistant bacterial strains may initially be less well-adapted or ‘fit’ than their wild-type counterparts and unable to compete with them in other than optimal environments. This decreased fitness is thought to result from the physiological cost of carrying extra genes conferring antimicrobial resistance. The early studies on resistance of the commensal intestinal flora tended to show that within a couple of years of the introduction of antimicrobials the normal enteric flora had often become resistant, demonstrating that compensatory mechanisms had been developed or acquired to allow them to compete successfully with the susceptible flora, even in the absence of any selective antimicrobial pressure.

The biological cost to an organism of possession of a resistance gene has been considered to be a factor that would favour its decline once a selective pressure was removed. However, this biological cost to the organism can be minimised by various mechanisms, such as those that switch on the resistance only when it is needed in the presence of antimicrobial. Other mechanisms have also been discovered, including the excision of the resistance gene from the chromosome or plasmid bearing it so that it can lie ‘inert’ within the cell cytoplasm, and arranging the genes in their order of importance within a ‘cassette’ of resistance genes so that only that required most frequently is produced most effectively.
Where resistance genes are closely linked to other genes encoding resistance (or possibly other characteristics), then use of an antimicrobial or substance that selects for a particular resistance gene will also select for the linked gene (co-selection). Co-selection has been shown to be important in the veterinary field and may partly explain why resistance to compounds such as chloramphenicol and furazolidone, which were banned from use in food-producing animals some years ago, may still be detected.

**An ecological view**

A bacterial ecosystem exists with simple and complex routes of transfer of resistance genes between the bacterial populations in animals, man and their environments. In addition to the transfer of organisms from animals to man there is also evidence of resistance genes spilling back from humans into the animal population. This is important because of the amplification that can occur in animal populations through faecal-oral recycling (Teale 2002). Transfer of resistance genes rather than actual organisms can also be important; therefore the flora that co-habit a niche in an animal can have important consequences for the potential to develop resistance. For example, *Pasteurella aerogenes* is generally considered a normal commensal of the oropharynx and intestinal tract of pigs, though it has been reportedly associated with some cases of porcine stillbirth and abortion. Horizontal transfer of tetracycline resistance plasmids has recently been described between *Pasteurella multocida* and isolates of *P. aerogenes* from pigs (Kehrenberg and Schwarz 2000). Organisms causing mastitis, particularly those with a restricted distribution outside the udder, have in most countries developed far less resistance than organisms inhabiting sites such as the intestinal tract and it has been suggested that this relates, at least in part, to the reduced diversity of bacterial flora within the udder and consequently reduced potential for exchange of genetic material. This does not mean that development of resistance is not possible however, and experiences in human medicine may prove a useful forecast of what may potentially happen in veterinary medicine. A number of pathogens (for example *Streptococcus pneumoniae* and *Neisseria gonorrhoea*) in human medicine remained susceptible to many antimicrobials for many years, though they have now developed extensive and significant resistance.

**Conclusions**

This paper gives an overview of some of the challenges which antimicrobial resistance is likely to pose for UK agriculture over the coming decades. These challenges may be severe and it will be important for veterinarians to assist the industry in minimising the development of antimicrobial resistance, solving any problems which develop and ensuring that husbandry methods are sustainable. Adherence to the various prudent use guidelines that have been produced, attention to thorough terminal hygiene and disinfection, maintenance of biosecurity, vaccination and good husbandry (such as ensuring adequate colostrum intake) are all likely to be key factors in minimising the threat to UK agriculture. Clinical and laboratory surveillance will help to ensure that emerging problems can be tackled at an early stage whilst their occurrence remains sporadic.

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Full references available from the author on request.