

VMD ADVICE NOTE

The use of antibiotics in animals is not a significant cause of resistance in the majority of organisms creating clinical problems in humans; the clinical problems in humans are primarily the result of antibiotic use in human medicine. The World Health Organisation recognises that the main cause of antimicrobial resistant infections in people is antimicrobial use in human medicine. The Soil Association note that outbreaks of ESBL-producing *E. coli* in humans have led to many deaths. In fact, although these patients died we are advised by the Health Protection Agency (HPA) that the ESBL-producing *E. coli* were not the immediate cause of death in many of the cases you quote. Nevertheless the use of antibiotics in animals is an important factor in the development of resistance in many organisms associated with food-poisoning and can also affect the degree of resistance shown by the normal commensal bacteria and other bacteria which may be carried by animals. Our policy remains, to support precautionary measures such as appropriate antimicrobial use in all sectors and the banning of antibiotic growth promoters in animals from 1 January 2006, to reduce the risk of antibiotic use in animals becoming a significant clinical problem for human health.

Turning to the specific issues in the Soil Association letter, Defra is concerned about the detection of ESBLs in bacteria isolated from farmed animals and is liaising closely with the relevant public health bodies in further investigating these cases and in determining an appropriate course of action. In the UK the animal strains of *Escherichia coli* carrying the ESBL have not so far been shown to be the same as the human strains of *E. coli* carrying ESBLs; the position may change as further cases are investigated, but that is the current position. The PFGE pattern derived from the CTX-M-15 containing *E. coli* was unlike any seen in human *E. coli* isolates carrying CTX-M-15. The *E. coli* isolate from an animal carrying CTX-M-15 was not serotype O25 (the predominant serotype in complex urinary tract infection-related cases found in humans).

The investigations performed on the first farm on which ESBLs have been detected have been published in the Journal of Clinical Microbiology (Liebana, E., et. al. Longitudinal Farm Study of Extended-Spectrum β -Lactamase-Mediated Resistance. J Clin Microbiol (2006), 44, 1630-1634.). This demonstrates Defra's commitment to investigating the occurrence of ESBLs in livestock and in sharing the information with the research community and other interested parties.

The source of the *E. coli* infection on the first farm on which an ESBL was detected has not been determined. Possible sources include imported constituents of animal feed, transfer from human sources to livestock directly or indirectly via environmental routes, contact with other livestock or development on the farm itself. A joint letter on this subject from the Veterinary Laboratories Agency (VLA) and HPA was published in the Veterinary Record on 5 February 2005 (Teale et. al. 2005. Extended-spectrum beta-lactamase detected in *E. coli* recovered from calves in Wales. Vet Rec., 5 Feb, 186-187). Sampling and analysis of samples from the second farm on which ESBLs were detected has not yet finished; a large number of samples are being examined, all aimed to increase knowledge of the on-farm situation.

There is a monitoring scheme in place across the VLA, which was rolled out across the VLA's 14 regional laboratories in 2006 to screen for ESBLs in *E. coli* isolates detected in

clinical material submitted to regional laboratories. This will allow improved surveillance for ESBLs in food producing animals.

Antibiotics are vital to protect the health of farm livestock and are required to be administered under the guidance of a qualified veterinary surgeon. These are prescription only products so farmers are unable to acquire these medicines without veterinary diagnosis and prescription. Defra, the NFU and RUMA all actively encourage and support the responsible use of antibiotics in agricultural to ensure the safe and responsible use of medicines on farms. These bodies also promote positive farm health planning, with farmers and vets working together, to ensure the health of the animals on farm.

The Soil Association note that there are no cephalosporins authorised for use in poultry in the UK, but they believe cephalosporins are being used off-label in poultry. This is not borne out by our consultations with poultry veterinarians. If they have any evidence to support their claim, I would be grateful if they would send this information to Professor Steve Dean, Chief Executive, at the VMD, Woodham Lane, New Haw, Addlestone, Surrey KT15 3LS.

The use of fluoroquinolones and cephalosporins has increased in percentage terms although the total amounts of these antimicrobials used remain comparatively small in comparison with many other antimicrobials.

VMD already publish data which breaks down the sales of veterinary antimicrobials by compound, class and by species where possible, in line with recommendations made by the ACMSF in 1999. Reports of these data have been published for the years 1998 to 2005 inclusive and are available on the VMD website or in hard copy from the VMD free of charge. Publishing more detailed breakdown of the data is not possible because:

1. data cannot be reported if they would breach company confidentiality by revealing annual sales for an individual product; and
2. data are collected on sales of products, not use of products, and authorisations of many products are for more than one species as is the case across much of the EU. Defra is working to collect data on the use of individual antimicrobials, via several methods, but to date has not found a robust statistically valid method to do this.

The proposal to double the withdrawal period for cephalosporins may not have the desired effect of reducing the population of cephalosporin resistant organisms. Although withdrawal of fluoroquinolones may lead to a decrease in the resistant population it may not be possible to extrapolate this phenomenon to other antimicrobials. Fluoroquinolone resistance has, until recently, almost always been due to mutation in one specific chromosomal gene – this often has fitness costs and hence when the drug is withdrawn you may see reversion to fitter, antibiotic sensitive isolates. Cephalosporin resistance is often plasmid-mediated and the genes are frequently found embedded in complex integrons. Although carrying the plasmid may incur a fitness cost, it may be that the plasmid provides the organism with other advantages that balance this out. The maintenance of ESBL producers in the gut (human and animal) in the absence of selective pressure suggests that this is the case. Also expression of these genes is often tightly regulated so the fitness cost may be negligible in the absence of the antimicrobial because the genes are not expressed.

There was considerable debate on how the UK should implement the provision in Directive 2001/8 (as amended) that prohibits the advertising of Prescription only veterinary medicines (POM-V and POM-VPS) to the general public. The "general public" is not defined in the EU legislation and the consensus view from the majority of stakeholders was that it would be beneficial for the professional keepers of animals to be aware of the medicines available for their treatment. We are not aware of any evidence that this has led to an increase in the use of antibiotics. If the Soil Association have any evidence to support their claim, we would be grateful if this information could be sent to Professor Steve Dean.

Finite resources for food surveys only allow screening for a limited number of organisms. Previous retail poultry surveys have concentrated on screening for the known zoonotic pathogens, *Campylobacter* and *Salmonella* and these need to be included in the forthcoming retail survey as they are still the primary causes of bacterial foodborne disease in the UK. This leaves limited resource for screening for other organisms, particularly commensals. Also, inclusion of screening for ESBL producing *E. coli* is problematic as no standardised methodology for isolating these organisms from foodstuffs exists. Underpinning work to optimise such methodology would be required before inclusion in a major food survey and the timeframe for the current survey may not allow for this. However, inclusion of screening for ESBL producing *E. coli* in food surveys is actively under discussion.

Surveys on raw meats and poultry are designed to sample the products available to the consumer at the point of sale. In the current Food Standards Agency (FSA) raw red meat survey and the forthcoming FSA poultry survey, samples will include both home-produced and imported products. Current surveys are designed to allow detection of microbiological contamination in particular products and sample size is calculated on this basis. It may not be possible to analyse the data according to source of the product as the sample size has not been powered to specifically allow this. However, should a significant issue relating to imported foods emerge during a survey further investigation of the problem would ensue. Again as noted above, we would welcome any evidence the Soil Association might have that cephalosporins are being used off-label in UK poultry production.

Finally, we are pleased to report that the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) is being replaced by another advisory Non Departmental Public Body. Recruitment to the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections (ARHAI) is underway and it should be established this spring. The terms of reference include providing scientific advice on maintaining the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections in man and animals. ARHAI will also take into account relevant work of other expert groups in the human and veterinary fields.