



20 December 2006

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Soil Association

Dear Minister

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As you will be aware, the emergence and spread of extended-spectrum-beta-lactamase (ESBL) -producing E.coli, with CTX-M genes in farm animals is of increasing concern to scientists. According to Defra, these antibiotic-resistant bacteria have now been identified on 11 cattle farms in the UK, and resistant bacteria from several other cattle and pig farms are currently being analysed.¹ ESBL E.coli have also been reported in recent years from farm animals in Denmark, France, Japan and Spain.^{2,3,4,5}

We welcome the way this problem, and the complex issues associated with it, have been openly detailed, discussed and updated on the Defra website. We also recognise the excellent quality of the research being produced by Government scientists working in this area, but are concerned that the Government is not taking enough action as a result of scientific findings.

You will also be aware that infections in humans with ESBL-producing E.coli, with CTX-M genes, have increased at an alarming rate over the last three years in the UK and in many other countries.^{6,7} An outbreak in Shropshire in 2002-2004 led to 28 deaths out of 105 patients, and another outbreak in Southampton in 2003-4 led to 29 deaths.^{6,8} The Chief Medical Officer reported that community-acquired urinary tract infections caused by ESBL E.coli have approximately a 30% fatality rate.⁹

Only two of the bovine ESBL E.coli isolates which Government scientists have identified have been fully analysed so far, and slight differences between these and the strains causing most human infections have been found (although one of the two isolates does have the CTX-M 15 gene which is widespread in human cases in the UK).

Despite this, many scientists, including some British government scientists, believe that food may be implicated in the spread of ESBL genes. As the authors of a recent paper suggest, 'It may be that low-level gut colonization occurs in the community, via the food chain, perhaps with plasmid transfer to resident E.coli, and that the

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proportion of resistant E.coli with CTX-M enzymes tends to be enriched during healthcare contacts, owing to frequent antimicrobial exposure.’⁷

The use of both cephalosporin and fluoroquinolone antibiotics are recognised risk factors for acquiring ESBL infections.^{10,11} For this reason, we are concerned about the increase in sales of cephalosporins and fluoroquinolones used on farms which were recently reported by the Veterinary Medicines Directorate: in 2005, sales of cephalosporins increased for the third year in succession. At 3,969 kg of active ingredient, total use was 23% higher than in 2004 and 58% higher than in 2002. At the same time the sales of fluoroquinolones, which had shown a welcome fall in recent years, increased by 39% between 2004 and 2005 from 1,044 kg to 1,451kg.¹²

Upward trends in the farm use of such drugs, which has coincided with the rapid emergence of the ESBL problem, are very unwelcome. The World Health Organisation has described the fluoroquinolones and the 3rd and 4th generation cephalosporins as ‘critically important for human medicine’ and, in the context of the increasing ESBL problem, scientists from the Health Protection Agency and the Veterinary Laboratories Agency have argued that, ‘Where possible, the use of newer generation cephalosporins should be limited in veterinary medicine.’^{13,14}

We recognise that research is still ongoing and that you may be reluctant to take policy decisions on an issue like this while the science is still not fully understood. We should remind you, however, that the history of antibiotic resistance teaches us that if one waits until the problems are fully understood before taking action, then resistance genes become widely disseminated and, even after remedial action has been taken, it may be decades before the situation begins to improve. Several scientists have told us that, even though there may be slight differences between the CTX-M genes and even the serotypes in the strains found in farm animals and the most widespread human strain, the spread of these resistance genes in E.coli in farm animals is a serious concern as the genes are usually on ‘plasmids’ (genetic elements which can transfer from one bacterium to another).

It is also important to note that in the UK and elsewhere there is evidence of the emergence of salmonella carrying ESBLs.¹⁵ This is very significant since, as the HPA has commented, salmonella is a ‘classical zoonotic pathogen’.¹⁵ In some other countries, there have already been reports of ESBL salmonella isolated from farm animals.^{16,17}

In a written question to the Veterinary Medicines Directorate (VMD) before its open meeting in November, we referred to the Government’s previously stated intention to ‘develop a coherent strategy aimed at reducing the veterinary use of antimicrobials’ and asked whether the VMD wanted to see the farm use of antibiotics reduced. In reply we were told that while the VMD supported the responsible use of antimicrobials, the ‘amounts of antimicrobials prescribed for use in veterinary health care are... under the control of the professional veterinarian, not the Government.’

As we see it, the problem with this situation is that the veterinary profession understandably tends to consider resistance issues first and foremost from the perspective of success in veterinary treatment. If Defra does not provide clear

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advice to veterinary professionals about how to minimize the development of antibiotic-resistant strains with potential human health implications, then no one else is likely to do so either.

In our experience vets are increasingly prescribing modern cephalosporins because they are highly effective drugs, and they have no concerns about doing this since there is a widespread belief within the veterinary profession, based on publicity material produced by one or more manufacturers, that there are no significant resistance issues associated with them. The manufacturer's claims in this respect, however have been challenged by the Food and Drug Administration in the US.¹⁸

We are unsure of your precise position on the likely threat to human health from the development of highly antibiotic-resistant bacteria on farms, but wonder whether your apparent reluctance to accept that resistance in farm animals does pose a threat to humans might explain your reticence to take a more pro-active role over the ESBL problem on farms?

We say this because, in May 2005 you replied to a written Parliamentary Question on the use of farm antibiotics and said, 'There is increasing scientific support for the view that the increase in antimicrobial resistance affecting human health is primarily the result of the use of antibiotics in human rather than veterinary medicines.' We recognise that several serious forms of multi-antibiotic resistance infections affecting humans have little or no connection with the use of antimicrobials on farms, but the evidence suggests to us that in certain cases, most particularly with the food-poisoning bacteria, that a significant part of the problem has an agricultural dimension.

We note from the Defra webpage setting out Defra's position on ESBLs on farms, that Defra is considering assisting 'with the control of endemic disease to minimize the use of antimicrobials on the farms' and advising, 'in conjunction with the PVS [private veterinary surgeon], on appropriate antimicrobial usage to treat the endemic disease problems currently affecting the herds.'¹

Defra acknowledges that it 'cannot be confident that all farms that are currently affected have been identified'. We would therefore ask you to give serious consideration to extending the advice you intend to provide to affected farms to all livestock farmers in the country, including organic farmers, who also use antibiotics, albeit generally less often than non-organic farmers.

In addition, we urge you to give consideration to taking a number of further actions on a precautionary basis. In particular, we believe the Government should:

- establish the extent to which 3rd and 4th generation cephalosporins are prescribed in the UK 'off-label' in poultry production, and consider whether further restrictions would be prudent
- collect antimicrobial sales and usage data in such a way that it is possible to detail the amounts of antibiotics given to food animals by compound, antibiotic class and target species
- ask the Veterinary Products Committee to consider doubling the withdrawal periods for cephalosporins for meat animals to allow resistant bacteria to decline before slaughter

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- introduce minimum withdrawal periods on cephalosporin products which have low or zero withdrawal periods, to allow resistant bacteria to decline before livestock products enter the food chain
- ban the advertising of 3rd and 4th generation cephalosporins and of fluoroquinolones to farmers
- introduce surveillance for ESBLs and other 3rd- or 4th- generation- cephalosporin resistance in salmonella and E.coli from poultry, pigs and cattle in live animals at abattoirs and in carcasses at retail outlets

Our reasons for making these recommendations are set out below:

Off-label use of cephalosporins

Cephalosporins are licensed for use in cattle and pigs, but not in poultry. However, under certain circumstances, except where there is a specific prohibition on an individual drug, veterinary surgeons are permitted to use the provisions of the 'prescribing cascade' and make available a drug to a species for which it is not authorised. As far as we are aware, no cephalosporins are licensed for use in UK poultry production, but at least one cephalosporin product licensed in the UK is permitted in poultry in some countries for the treatment of E.coli infections in young chicks. We believe it is likely that they are also being used in British poultry farming.

Given the current concerns about ESBL resistance, we feel it is important to quantify such use, consider the implications of this and any further regulations that might be needed to prevent the development of cephalosporin resistance in E.coli in UK poultry.

Breakdown of usage by species

In order to increase scientific understanding of the issues, and in particular whether changing patterns of antimicrobial use on farms leads to changing patterns of antimicrobial resistance with implications for human health, it is important to have accurate antibiotic usage data, providing a full breakdown by compound, antibiotic class and species.

Unfortunately, despite the Advisory Committee on the Microbiological Safety of Food recommending in 1999 that such data should be collected, and despite the Government accepting the recommendation, it has still not been fully implemented.

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The sales data published by the VMD are not broken down by compound, because they claim this would breach 'commercial confidentiality', and they also provide no useful species breakdown. As such, we feel that the data gathered by the VMD over the last eight years has very limited value as a tool for fine-tuning drug-licensing policy, with a view to addressing and preventing antimicrobial resistance problems.

One example of this problem relates specifically to the cephalosporins. The VMD has told us that of the almost 4 tonnes of cephalosporins sold in the UK, 887kg were for use in cattle. They add, 'but these sold products did not all have a single species authorisation. As a result some of this amount may also have been used in animal species other than cattle. Unfortunately we have no way of determining how much

was used only in cattle.’ Because of the way the data is gathered, the VMD would have a similar problem if asked to quantify the amounts used in pigs, poultry, or even companion animals.

Withdrawal periods for cephalosporin and fluoroquinolone antibiotics

A Defra-commissioned study with fluoroquinolone antibiotics found that the , withdrawal period, which like all withdrawal periods was calculated with the sole purpose of ensuring that drug residues in food were below the legally enforceable Maximum Residue Limits, was not long enough to allow resistant bacteria to decline before animals were slaughtered. In the study, a relatively small increase in the withdrawal period brought significant reductions in the populations of resistant bacteria in animals at slaughter.²⁰

Organic farmers already apply longer withdrawal periods than those required by veterinary medicines legislation for just such reasons. We would, therefore, ask you to ensure that this issue is reviewed for all farm antibiotics, but focusing first on the cephalosporins and fluoroquinolones, with a view to extending withdrawal periods if this might lead to lower levels of potentially dangerous resistant bacteria entering the food chain.

Advertising of antibiotics

As you are aware, in 2005 the Veterinary Medicines Directorate (VMD) carried out a major review of veterinary medicines regulations, timed to coincide with the implementation of an important new EU directive in this area. The EU directive covered all aspects of regulation, including advertising, and required the UK Government to ‘prohibit advertising to the general public’ of prescription-only medicines. Initially, the VMD interpreted this to mean that the advertising of prescription-only medicines, including antibiotics, directly to farmers should be banned.

However, under pressure from the pharmaceutical industry, the stance was subsequently altered, and despite the Soil Association and other consumer organisations arguing that such advertising should be restricted, the new veterinary medicines legislation permits the advertising of all licensed veterinary antibiotics directly to farmers.

In view of the serious concerns which now exist about antibiotic resistance related to the use of cephalosporins and fluoroquinolones, we would urge you to consider reviewing your decision at the time, and implementing, at the very least, a specific ban on the advertising of these antibiotics to farmers.

Surveillance

We welcome the fact that Defra intends to undertake increased surveillance for ESBLs in farm animals, but are seriously concerned that it appears to have undertaken no surveillance at all of live poultry since the ACMSF report was published in 1999.

Can we urge you to undertake an abattoir survey of poultry as soon as possible, and can we also suggest that you discuss with your colleagues in the Food Standards Agency the possibility of screening samples for antimicrobial resistance in both

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commensal E.coli and ESBL E.coli, in addition to salmonella and campylobacter, in their forthcoming survey of retail poultry?

Imported meat

There is little available information on the levels of ESBL and other cephalosporin-resistant bacteria in imported meat. However a survey commissioned by the BBC and carried out by the Health Protection Agency in 2005 found that 2 (5%) of chickens from other EU member states which were tested contained E.coli that were resistant to cefotaxime and 2 (5%) were resistant to ceftazidime, both 3rd generation cephalosporins.

We are told by a microbiologist that this resistance is likely to have resulted from the use of ceftiofur, the 3rd generation cephalosporin used in chicken hatcheries in some countries to reduce chick mortality. Furthermore, as mentioned above, we suspect this drug may still be used off-label in poultry in the UK. It is not clear from the survey whether resistance to both these modern cephalosporins was found in the same or different chickens.

The HPA did not identify these strains as ESBLs, though we are not sure how closely these isolates were examined. In any event we are advised that the presence of 3rd-generation-cephalosporin resistance in E.coli from chickens is a serious development and one that needs to be addressed. We urge you to consider extending surveillance to include imported beef, pork and poultry.

Finally, I would like to say how very disappointed I am to learn that SACAR, the Government's Specialist Advisory Committee on Antimicrobial Resistance is to be disbanded. This was established following a carefully argued recommendation in a report, published in 1998, by a House of Lords' committee. The recommendation was based on a case originally set out in the Swann Report in 1969. The SACAR committee was an over-arching committee, with specialists from both human and veterinary medicine. It was therefore ideally placed to be able to assess the scientific evidence for a link between the ESBL problem on farms and that in humans, which was precisely the kind of activity for which the creation of such a committee was originally envisaged.

In view of the potential interest in these issues we intend to make this letter publicly available.

Yours sincerely
Richard Young

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