Soil Association

Waste milk and the spread of ESBL *E. coli* on dairy farms

ESBL *E. coli* in humans and in farm animals

Some *E. coli* and other bacteria can produce enzymes called 'extended-spectrum beta-lactamases' which enable them to destroy and become resistant to many penicillin-type antibiotics, including the modern (3rd and 4th generation) cephalosporins. ESBL *E. coli* were first found in the 1980s, but remained rare until the past decade. Since 2003, a new, more virulent type of ESBL *E. coli*, which is often resistant to many other classes of antibiotics, has become the most common form of ESBL *E. coli* in the UK.

Unlike earlier ESBL *E. coli* which were almost exclusively restricted to hospitals, CTX-M ESBL *E. coli* mainly affect community patients. This is surprising because the modern cephalosporins, the antibiotics which most strongly select for and promote the spread of ESBL *E. coli*, are usually only prescribed by hospital doctors treating serious cases of infection, not by GPs seeing patients in their surgeries.

One explanation for part of this community epidemic is that some *E. coli* acquire their resistance in farm animals, which are increasingly treated with modern cephalosporins. These ESBL strains are then transmitted to humans via food, where the strains can persist for a period of time and then cause infection, or transmit their ESBL resistance genes to other *E. coli* in the human gut, which subsequently infect humans.

The extent of the farm contribution to the problem is now a major area of investigation. In some countries, such as the Netherlands, there is already strong evidence that farm animals, particularly poultry, are a significant source of ESBL resistance in humans.

In the UK, the main epidemic strain, which accounts for about 45% of all infections appears to be circulating among humans, although a farm-animal link cannot yet be ruled out entirely because it has now been found once in cattle.

However, the most common CTX-M resistance genes found in humans, CTX-M-14 and CTX-M-15, are also the most common CTX-M genes found in cattle. These resistance genes are on 'plasmids', small loops of DNA which can often readily be transmitted between bacteria. The same CTX-M plasmids have been found in ESBL *E. coli* from cattle and humans in the UK. [1]

The first case of ESBL E. coli in British farm animals was found by the Veterinary Laboratories Agency in the autumn of 2004, in scouring calves from a dairy farm

in Wales. Testing showed that 56% (27 of 48) calves and 3% (2 of 60) cows were positive for the bacteria. [2]

Further research carried out in 2008/2009 and first published in 2010, found that 37.5% of randomly selected dairy herds in the North-West of England were found to have CTX-M ESBLs, and farms which had used modern cephalosporins in the previous year were four times more likely to be positive. A study carried out on a single positive farm showed that nearly all the calves were positive at 2 days of age, but that there appeared to be a window between 53 and 177 days where the probability of a calf testing positive fell from 90% to 10%. [3][4]

Waste milk: calves being dosed with antibiotic residues and antibiotic resistance

It is very likely that the extremely high numbers of young calves positive for ESBL *E. coli* compared with older animals can be explained by the practice on many dairy farms of feeding calves waste milk with antibiotic residues. This is milk taken from cows being treated with injectable or intramammary antibiotics, during the treatment period when residues in milk will be high, and during the statutory withdrawal period, during which time they will progressively decline. Waste milk cannot be sold for human consumption.

A Defra survey published last year found that 81% of British dairy farms feed waste milk to calves. [5] Soil Association organic standards do not permit the feeding of waste milk to calves during the statutory withdrawal period and only permit milk to be sold for humans after an extended period of three times the statutory withdrawal period.

In April 2012, at a conference in London, Defra scientists presented the results from tests on waste milk samples from 103 dairy farms, for residues of cephalosporin antibiotics. They found that 21% of samples contained residues of cefquinome, a modern (4^{th} generation) cephalosporin, which is the second most widely used antibiotic on UK farms for treating mastitis in milking cows. [6] Cefquinome is also licensed for 'dry-cow therapy', when antibiotics are infused into the cow's udder at the end of each lactation as a matter of course, whether or not the cow has mastitis. However, cefquinome is not as widely used for this purpose as many other antibiotics. [5]

A further 16% of samples contained residues of older cephalosporin antibiotics, which can also select for ESBL *E. coli*, but not as strongly as modern cephalosporins. The 1^{st} generation cephalosporin, cefalonium, which is the most widely used antibiotic for dry-cow therapy on British dairy farms, was the most frequently found antibiotic after cefquinome, being found in 8% of samples. [5][6]

The recent Defra research also found that 6% of waste milk samples contained bacteria producing CTX-M ESBL enzymes, of which two thirds (i.e. 4% of all samples) were *E. coli*. Furthermore, 99% of all waste milk samples contained

bacteria believed to be *E. coli*. The scientists said 'The results indicate that feeding untreated waste milk to calves can lead to exposure to antibiotic resistant bacteria, including bacteria containing CTX-M enzymes'. [7]

The Defra survey of British dairy farms found that 96% of them use antibiotic dry-cow therapy at the end of lactations. [5] This means that many calves will be getting antibiotic residues, often cephalosporins, in their colostrum, the essential first milk which contains nutrients and antibodies to protect the calf against disease.

In their latest research, the Defra scientists have shown that incubating milk at 18°C for 72 hours, or at 37°C for 24 hours, can effectively decrease the concentration of cefquinome in spiked unpasteurised milk. [6] However, the effect of this incubation on the resistant *E. coli* bacteria and on other antibiotic residues found in the milk was not evaluated. Nor do we yet know what the effect would be of this treatment on the health-giving qualities of the colostrum or subsequent milk.

The problems associated with waste milk are not likely to be restricted to just cephalosporins and ESBL *E. coli*, but will involve other antibiotics and resistant *E. coli* too. In 2003, research from Edinburgh University with penicillin G residues in milk found that resistance in calves' gut bacteria increases with increasing concentrations of the antibiotic in the milk they are being fed. [8]

Previous Veterinary Laboratories Agency research, published in 1990, which examined waste milk containing various antibiotics, found that 'ambient conditions in the United Kingdom inhibited natural fermentation, which would degrade the antibiotics and make it an acceptable feed'. [9] This also found that 'antibiotic-containing milk had a poor palatability' and the growth rate of calves fed this milk was poor, although earlier research by US scientists had found no impact on calf growth rate or health. [10][11]

Increasing farm use of modern cephalosporins

According to the Health Protection Agency, modern cephalosporins are 'workhorse hospital antibiotics, given as first-line agents to many severely-ill patients'. They have been classified by the WHO as 'critically important in human medicine' and are used for complicated urinary-tract infections, meningitis, blood-poisoning infections, hospital-acquired pneumonia and intra-abdominal infections.

Because of their importance in human medicine, there are increasing concerns about their excessive use in farming. Sir Liam Donaldson, the former Chief Medical Officer, was so concerned about the irresponsible use of these antibiotics in farming that, in 2009, he called for an outright ban on their in animals. [12]

The Soil Association has implemented restrictions on their use on the farms it certifies, so that they can only be used in individual animals, and even then only

with the permission of the organisation, in cases where other antibiotics are likely to be ineffective.

In 2009, the British Veterinary Association adopted an antibiotics policy which placed similar restrictions on the use of these antibiotics. This, however, is a voluntary move by the BVA which does not yet seem to have been effective, as in 2010 the use of modern cephalosporins increased by over 40% compared with 2009. As Table 1 shows, their farm use has now increased in 9 of the last 10 years, and by over sixfold in total.

Table 1 Use of modern cephalosporins in UK farming (kg of active ingredient)

1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
220	220	310	410	410	500	672	739	854	887	976	1,400

As patents for some modern cephalosporin antibiotics have expired in recent years, many new generic products have come on the market. This may have depressed the wholesale price and led to increased use. The Veterinary Medicines Directorate has included a statement on some of the datasheets of these new products saying that use of the product 'selects for resistant strains such as bacteria carrying extended spectrum beta-lactamases (ESBL) and may constitute a risk to human health if these strains disseminate to humans e.g. via food' and so 'should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment'. The Soil Association wants this statement and restriction on use included on all modern cephalosporin datasheets as a matter of urgency.

Recommendations

The latest research findings mean that action must be taken to prevent calves being fed milk with high levels of antibiotic residues and resistant bacteria. The Soil Association recommends:

- a ban on feeding calves waste milk from cows receiving antibiotics or from cows during the withdrawal period after having recently received antibiotics, unless and until it can be shown that the milk can be treated so that antibiotic residues are destroyed, resistant bacteria are killed and that the resulting milk remains sufficiently wholesome to be fed to calves
- veterinary datasheets for all modern cephalosporins be amended so that these antibiotics are only prescribed when other antibiotics are likely to be ineffective. If these restrictions do not greatly reduce their farm use, regulators should implement a complete ban on farm use.

References

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