



**Soil Association briefing**

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## **MRSA in British cattle. A new farm superbug spreading to humans?**

### **1. Introduction**

A study published today in the medical journal, *The Lancet Infectious Diseases*, reveals the first-ever documented cases of MRSA (methicillin-resistant *Staphylococcus aureus*) in British farm animals [1]. Scientists from Cambridge found 15 cases of a completely new type of MRSA in bulk milk from various dairy farms throughout England.

The study also shows that the new MRSA is already present and causing infections, including some potentially serious blood infections, in humans in England and Scotland. Preliminary evidence suggests that the new type of MRSA is most likely being transmitted from cattle to people. The scientists have said that their discovery is 'potentially of public health importance'.

The new MRSA have novel genetic features which mean that existing 'gold-standard' tests cannot determine whether they are MRSA or not. So as part of their research the scientists had to develop a new MRSA testing method. The significance of this is that the new MRSA may well have developed some time ago and have spread throughout Britain, and even internationally, all the while remaining undetected by gold-standard tests, until now. It is also possible that patients infected with the new MRSA will be misdiagnosed and given incorrect treatment, if the new test is not used to check for MRSA.

### **2. MRSA discovered in British milk after new test developed**

In May 2007, during a project evaluating the spread of mastitis between dairy herds, Cambridge scientists found two isolates of *Staphylococcus aureus*, in a bulk milk sample from a farm in South West England, which they suspected might be MRSA. Confirmatory tests were inconclusive, but after a very detailed genetic analysis, they were able to show that the bacteria were a completely new kind of MRSA.

Using their results, they developed a test which could detect the novel MRSA without the need to carry out a full genetic analysis. They then applied the test to a collection of 940 *S. aureus* bacteria previously collected by the Veterinary Laboratories Agency (VLA) from cows with mastitis infections. VLA testing using existing gold-standard tests had failed to find any MRSA in the collection [2]. However, the Cambridge scientists were able to show that a further 13 of the bacteria were in fact cases of the new MRSA.

### **3. Why a new MRSA test was needed**

Some *S. aureus* bacteria can show a degree of resistance to methicillin-type antibiotics without necessarily being 'true' MRSA. Generally, only bacteria which have a gene called the '*mecA* gene', which enables them to produce a protein giving them resistance to the antibiotic, are considered to be MRSA. On the other hand, bacteria which show some resistance to methicillin in laboratory tests, but lack the gene, are usually 'hyperproducers' of beta-lactamase. This is a type of enzyme which makes them resistant to penicillin, but only results in borderline or low-level resistance to methicillin-type antibiotics. Such resistance can be overcome by treating patients with a chemical known as a 'beta-lactamase inhibitor', in addition to the antibiotic. Consequently, bacteria lacking the *mecA* gene do not present the same treatment difficulties as true MRSA.

So, when the Cambridge scientists found that their bacteria were showing methicillin resistance in laboratory tests, but didn't have a *mecA* gene, it initially appeared that the situation was not as worrisome as it might have been.

However, further tests showed that the bacteria were not hyperproducers of beta-lactamase, and their resistance to methicillin-type antibiotics was higher than would have been expected if they were. They then carried out a full sequencing of the bacteria's genes, and found that they had a 'divergent' *mecA* gene, a gene similar to *mecA*, which is now believed to be responsible for the bacteria's resistance.

People infected with the new MRSA need to be treated in the same way as for conventional MRSA. The complication, however, is that they risk being misdiagnosed if tests do not look for the new gene, and they may then be given incorrect treatment.

### **4. The new bovine-associated MRSA is already causing infections in humans**

Armed with the new test, the scientists turned their attention to the question of whether the new MRSA could already be infecting humans without being identified as MRSA. In collaboration with the Health Protection Agency and the Scottish MRSA Reference Laboratory, 26 suspect *S. aureus* cases were identified in England, and 16 possible cases were found in Scotland. Testing showed that 15 of the English cases and 12 of the Scottish cases had been caused by the new MRSA.

The new MRSA has also already been found abroad. Danish scientists, who published their findings jointly with the British scientists, found that 24 of 32 suspect cases, which had not previously been shown to be MRSA, were in fact MRSA positive when the new test was used. An Irish study, also published today, has found several cases in humans, and German scientists reported at a conference last month that they had found six human cases [3], [4].

The number of cases found so far suggests that the new MRSA already accounts for between 0.2% and 1% of all MRSA in the UK and Denmark [1]. For the UK, this

could well be an underestimate: British MRSA reference laboratories concentrate their MRSA testing primarily on hospitals, and cases which occur in the community

are more likely to go unrecorded. Since the new MRSA is likely to be community-acquired, cases may be under-represented in the laboratories' databases.

Because British MRSA testing is not completely systematic (i.e. not all potential MRSA cases are tested by the reference laboratories, and testing protocols can change over time), it is not yet possible to say whether the incidence of the new MRSA is increasing in the UK. However, in Denmark all MRSA cases in humans are tested so there is a fuller picture, and this shows that the incidence of the new MRSA increased 'substantially between 2007 and 2010' [1].

## **5. The new MRSA is probably spreading from cattle to people**

In theory, it is possible that the new MRSA could have developed separately in people and in cattle; however, the evidence available so far suggests that this is not the case. Instead, there are several pieces of evidence indicating that cattle are the source of the new MRSA infecting humans.

Firstly, there were several strains of MRSA involved in both humans and cattle which showed evidence of a geographical association: different strains were involved in the South West, the East and the North East of England, and the strains in humans and cattle seemed to be largely the same in each region. This suggests that the bacteria were being exchanged between cattle and humans, probably by direct contact, but perhaps also through the environment (when manure is spread on the land, for example). People are very unlikely to acquire MRSA from drinking milk since pasteurisation will kill the bacteria.

Secondly, most of the cases (48 of 66) involved in humans came from a *Staphylococcus aureus* lineage (called CC130) which had previously been detected in cattle in earlier studies [5], [6], and was thought to be unique to animals. This lineage also has certain genetic features which, the German scientists have pointed out, are characteristic of animal-origin *S. aureus* [4]. In addition, none of the other strains found in humans carrying the new MRSA gene came from lineages which had previously been found in humans (although they had not previously been found in cattle either).

Finally, no evidence emerged when the VLA looked for MRSA in cattle milk in 2007 that any previously known human MRSA had transferred from humans to cattle [2].

As a result, the British and Danish scientists conclude that:

*'Such evidence suggests that a bovine reservoir exists, from which  $mecA_{LGA251}$  MRSA [i.e. the new MRSA] is transmitted to people'* [1].

The German scientists reporting on their own findings agree, saying that:

*'Therefore transmission from animal sources and a zoonotic potential with respect to infections in humans seem likely'* [4].

## 6. Antibiotic use and MRSA in dairy cows

Studies in human medicine have shown that the use of antibiotics to which MRSA is resistant have the potential to help the spread of the superbug [7]. All MRSA is resistant, by definition, to the beta-lactam class of antibiotics, the class containing penicillin, methicillin, flucloxacillin (an antibiotic often prescribed by GPs to treat skin infections) and cloxacillin (an antibiotic mostly used in dairy farming) and the cephalosporin antibiotics. The beta-lactams are the most widely used antibiotics in the dairy industry for the treatment, or prevention, of mastitis. Their use undoubtedly is the reason why MRSA is spreading in dairy cows. It now seems likely that MRSA was not previously detected in British cattle because the type of MRSA circulating could not be identified as MRSA by existing gold-standard tests.

There is particularly strong evidence that the use of the most modern cephalosporins (third or fourth generation), antibiotics classified by the World Health Organisation as critically important in human medicine, is associated with the spread of MRSA [8]. The Health Protection Agency, the European Medicines Agency, numerous independent scientists and even a prominent British pig vet have drawn attention to the link between the use of modern cephalosporins and the incidence of MRSA [7], [9], [10], [11].

The excessive use of modern cephalosporins has also been linked to the emergence in farm animals of high levels of resistance in a range of other bacteria, such as *E. coli* and salmonella [10]. The European Medicines Agency has referred to the potential consequences for human health of increasing cephalosporin resistance in farm animals as 'serious', and called for action to reduce their use [10]. Sir Liam Donaldson, the former Chief Medical Officer, believes the situation is so serious that he called for an outright ban on the use of modern cephalosporins in farming. Even Defra's own antibiotic-resistance advisory committee, the DARC committee, has been considering the possibility of restricting their use in agriculture, noting that restrictions had already been implemented in human medicine [12], [13]. Reductions in the use of cephalosporins in human medicine have coincided with a fall in MRSA rates in the UK [14], [15].

On the other hand, despite increasing concern from scientists and regulators about the overuse of these antibiotics, there have been very large increases in the use of cephalosporins, and in particular of modern cephalosporins, in veterinary medicine in the UK over the last decade. Statistics obtained by the Soil Association from the Veterinary Medicines Directorate (VMD) through a Freedom of Information request show that the use of modern cephalosporins has increased more than fourfold over the past decade. Published statistics from the VMD show that the use of all cephalosporins has more than doubled over the same time period [16]. See Table 1.

*Table 1* Use of cephalosporins in UK veterinary medicine (kgs active ingredient)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
<b>Modern cephalosporins</b>	220	220	310	410	410	500	672	739	854	887	976
<b>All cephalosporins</b>	3220	2470	2600	2520	3040	3240	3969	5639	6215	6242	6596

One factor that is likely to have contributed to this sharp increase in consumption is that the modern cephalosporins have been widely advertised in the farming press over the past decade. The VMD has recently accepted that the advertising of antibiotics directly to farmers tends to promote the use of more modern antibiotics, such as the cephalosporins. All advertising of antibiotics to farmers is now banned throughout Europe, with the sole exception of the UK, which has exploited a loophole in an EU directive to allow this to continue.

The Soil Association, and other NGOs like Compassion in World Farming, the Food Ethics Council and Sustain, have consistently campaigned for a ban on the advertising of antibiotics directly to farmers. During a consultation last year, the British Veterinary Association also joined the calls for a ban. After the consultation, the VMD finally advised the Government to implement a ban, partly in order to stem the rise in use of modern antibiotics, which are critically important in human medicine for treating a range of diseases. Unfortunately, their advice was rejected after lobbying by the pharmaceutical industry and the farming press [17]. This is despite the fact that Defra was already aware that MRSA had been found in milk by this time.

## **7. Antibiotic use on conventional versus organic dairy farms**

Intensive dairy farms almost universally rely on the routine use of antibiotics to deal with the health problems associated with the extremely high yields of milk now being produced per cow. In recent years both financial pressure due to very low farmgate milk prices, and UK government policy, has encouraged dairy farms to get larger, with more cows under the management of each herdsman or woman. In addition, farmers have been encouraged to use the highest-yielding cows available, even though it is widely recognised that in many cases this produces health problems including severe and prolonged metabolic stress and hunger – a condition when the cows' genetic ability to produce milk exceeds its metabolic ability to consume adequate energy on a daily basis to replace that used in milk production.

Many studies have found that high-yielding cows are more prone to mastitis infection and lameness. In part this is because the large size of their udder makes it difficult for them to stand squarely on their hoofs. It is also because most ultra high-yielding cows live their entire lives on concrete and are not allowed to graze. This is due to the fact that they need to eat higher energy food than grass and they need to spend as much time as possible eating, not walking to and from the fields.

Scientists from the University of Liverpool, writing in the *Veterinary Record*, have argued that there is 'no welfare case' for the continued use of modern cephalosporins

on dairy farms [18]. They say that the diseases that the antibiotics are used to treat are 'a reflection of suboptimal nutrition and management' and that the reliance on antibiotics 'may actually act as a prop for suboptimal management and welfare'. They conclude that using modern cephalosporins 'may in fact adversely impact on long-term welfare since farmers will use the drug rather than address the underlying conditions'.

There are two principal types of routine antibiotic use which are common on non-organic dairy farms:

- Most dairy cows on intensive farms are given infusions of antibiotics into all four teats at the end of each lactation to prevent mastitis, as a matter of course, whether or not the cow has mastitis. The practice is known as 'dry-cow therapy', and all of the products used contain used are beta lactams, the most widely used class of antibiotics in human medicine. Some of the beta lactams used are cephalosporins, including one modern cephalosporins. MRSA is resistant to all of these antibiotics, so once the bacteria have emerged on a dairy farm, routine dry-cow therapy is likely to promote its spread. The Liverpool scientists have pointed out that the bacteria which cause most of the mastitis infections in cows 'remain supremely sensitive to existing non-cephalosporin antibiotics such as cloxacillin, so it is hard to argue that there are animal welfare grounds for the continued use of cephalosporins in intramammary preparations'. However, one of the reasons the Soil Association is calling for an end to all routine antibiotic use of dairy farms is that even beta-lactams like cloxacillin could increase the spread of MRSA on a dairy farm once it becomes established, because it is very closely related to methicillin and flucloxacillin.
- Antibiotics, including modern cephalosporins, are frequently used to treat lameness in dairy cows.

Three modern cephalosporins are used on dairy farms:

- Cefquinome (a 4th generation cephalosporin) is routinely used on many dairy farms as the treatment of first choice for cases of mastitis in milking cows, and is also used in a very long-acting preparation for dry-cow therapy. The European Medicines Agency has suggested that such long-acting antibiotics have a particular potential to promote MRSA 'as the time when concentrations are close to the minimum inhibitory concentration of intestinal and skin flora can be very long' [10].
- Cefoperazone (a 3rd generation cephalosporin) is also used for the treatment of mastitis.
- Ceftiofur (a 3rd generation cephalosporin) can be given to lactating cows on non-organic farms without any withdrawal period for the treatment of certain respiratory diseases and womb infections after calving, and for a particularly difficult-to-treat type of foot infection called interdigital necrobacillosis, which is increasingly becoming a problem on intensive dairy farms. Although this is more expensive than using other equally effective antibiotics, farmers are not

required to withhold milk from cows during treatment. Selling this milk for human consumption significantly outweighs the extra cost of the drug. As a result there is a strong temptation for dairy farmers, who have been under severe financial pressure, to use ceftiofur, even when (in most cases) the problems could be greatly reduced by management changes, and other antibiotics would in any event be equally effective for all but possibly some cases of interdigital necrobacillosis.

In response to increasing concern about the rise of resistance on farms, in November 2009, the British Veterinary Association (BVA) produced guidelines advising veterinary surgeons on responsible use of antimicrobials. In a special note referring to the modern cephalosporins and fluoroquinolones (another class of antibiotics critically important in human medicine), the BVA said that they should be reserved for clinical conditions that respond poorly to other classes of antimicrobials and where antibiotic sensitivity has been carried out.

However, it is not yet clear to what extent this advice has been taken on board by the veterinary profession and therefore whether it has been effective in reducing the overall use of the drugs. As explained above, there remain commercial reasons why many dairy farmers prefer to use modern cephalosporins in preference to alternatives.

On organic farms, the use of antibiotics is strictly limited. Routine use is not permitted, and dry-cow therapy is not allowed (except occasionally under exceptional circumstances on an individual cow, and with approval). Because of the high level of concern from the WHO and others over the use of modern cephalosporins in farming, the Soil Association has also implemented specific restrictions on this class of antibiotics. Standard 10.09.08 reads, 'From 1 January 2009 you must not use third and fourth generation cephalosporin antibiotics except with our permission and only to treat individual animals. We strongly recommend that you limit your use of these drugs before this date if possible.'

No published research is currently available comparing antibiotic use on British organic and non-organic dairy farms. However, research published by Defra in 2006 compared antibiotic use on 13 organic pig and poultry farms with that on 12 conventional pig and poultry farms. It found that compared with the non-organic farms, usage on the organic farms 'was very low, with many of the farms never using antimicrobials'. Defra also found higher levels of multiple antibiotic resistance on the conventional farms than on the organic farms [19].

## **8. MRSA in other farm animals**

MRSA in British cows is the latest development in the worldwide emergence of MRSA in farm animals. Up until only a few years ago, MRSA was only very rarely detected on farms. However, in the past few years, a new strain of MRSA, called MRSA ST398, has emerged in intensively reared farm animals in many European and North American countries. The new strain is believed to be of pig origin, and is found at very high levels in the pig industries in some countries (such as the Belgium,

Germany, Italy, the Netherlands and Spain), but it is also now being found in poultry and in cattle [20], [21], [22], [23].

MRSA ST398 has not yet been found in British livestock, but several cases of infection have already occurred in humans in Scotland and England [27], [28]. MRSA ST398 has also been isolated from British horses [29].

Although MRSA ST398 has already caused many infections, and even deaths, in humans, it does not appear to pass from human to human as readily as conventional human-origin MRSA [24], [25], [26]. Consequently, the people found to be most at risk of being colonised, or infected by MRSA ST398 are those who are in direct contact with farm animals, i.e. farm workers and vets, or their families.

Although ST398 has become a major MRSA strain in humans in the Netherlands, the total number of human infections throughout Europe has not been as large as was first feared [30]. However, Dutch scientists who carried out a full analysis of the genome of ST398 have found evidence that it has a greater ability than most other *S. aureus* to acquire new genes from other bacteria through 'horizontal gene transfer'. They therefore believe that 'it will only be a matter of time' before it acquires new virulence genes which will increase its ability to cause disease in humans' [31].

More recently, a second major MRSA strain, ST1, has been found in European pigs, primarily in Italy, but also in Spain and Cyprus [19]. Unlike ST398, ST1 is already well adapted to living on, and infecting humans, and it may therefore pose a greater threat to humans. In the UK, it is the most common human MRSA in the community, outside of hospitals, although this is unlikely to be due to transmission from pigs as Italian scientists have shown that there are some differences between most human and porcine ST1 [32],[33]. Nevertheless, in Europe there is already evidence that porcine ST1 is being transferred to humans and causing infections [34]. Furthermore, in a paper published this month, the Italian scientists warn that because of the virulence and antibiotic resistance genes porcine MRSA ST1 already possesses, it '*may represent a serious therapeutic challenge in case of invasive infections in humans*' [33].

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