MRSA in farm animals and meat

A new threat to human health

Soil Association

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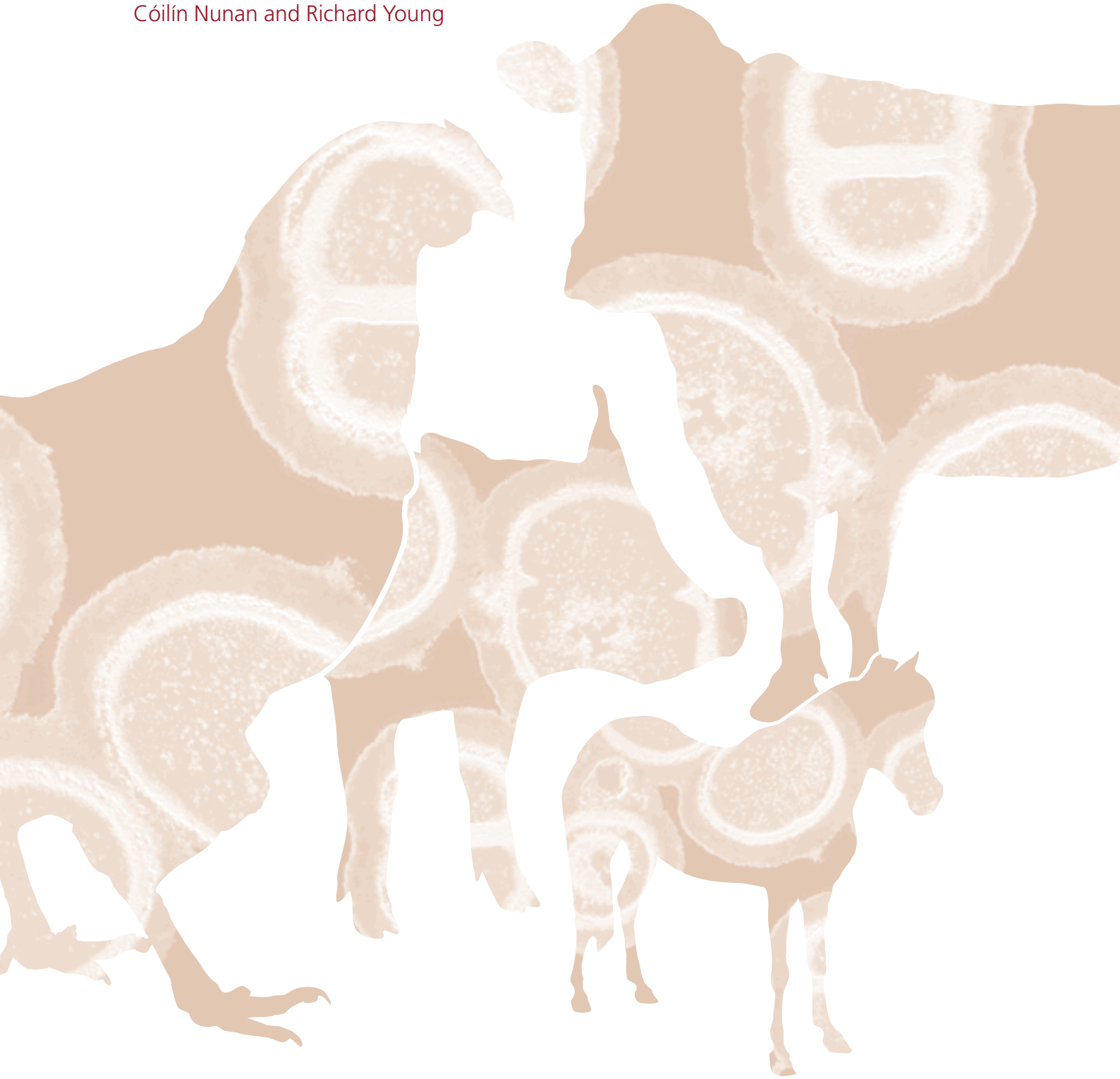
Report five in the series
The use and misuse of antibiotics in UK agriculture
Cóilín Nunan and Richard Young



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Foreword

There is little information about whether MRSA is in British farm animals, but the Soil Association calls on the Government to test both live animals and imported meat as a matter of urgency.

It is already clear, however, that farm-animal MRSA could spread to the UK and that effective measures are needed to prevent this. In addition to biosecurity, it is also necessary to grapple with the routine prophylactic use of antibiotics.

Until now, attention has focused on antibiotics used for growth promotion. The last of these were banned in 2006, but there is no sign of genuine progress; overall antibiotic use is down slightly, but only in line with falling livestock numbers.

For many farmers, the problem is how to get off the antibiotic treadmill. In a global food market, individual producers have limited choice. To be competitive, they are forced to adopt practices such as weaning pigs at an early age when their immune systems are undeveloped and they are vulnerable to infection. This is then used to justify the frequent inclusion of antibiotics in feed.

Organic farming systems are still developing, but already include proven alternatives. The Government acknowledges that organic methods are beneficial for the environment; it is now time it recognised they also reduce the need for antibiotics.

However, it cannot just be left to the market to address a new health threat like this. The Government must set policy in the right direction and make sure it is implemented. When I served on the Policy Commission on the Future of Food and Farming chaired by Sir Don Curry, we urged the Government to ensure that the banned growth-promoters were not simply replaced by increased prophylactic use of prescribed antibiotics. Yet this is what now seems to be happening. In 1992 the Lamming Committee also raised this issue and called for the prophylactic use of antibiotics in farming to be reconsidered.

These important recommendations have been ignored. While action is now needed at a European level, the Government should establish a new independent group to examine the way in which antibiotics are still widely used in the UK to prevent diseases in farm animals that could be avoided by other means.

Helen Browning OBE
Food and Farming Director, Soil Association

Executive summary

'A new monster'

This report focuses on a major new antibiotic-resistance problem in farming, which may have serious consequences for human health. In some countries, methicillin-resistant *Staphylococcus aureus* (MRSA) has been found in a large number of farm animals and in retail meat. The British scientist, Dr Andrew Waller, has described the emergence of MRSA and other methicillin-resistant bacteria in animals as 'a new monster' (see p 11), but according to Defra, there is currently no UK or EU legislation to control it.

Farm-animal MRSA is spreading across Europe

In the Netherlands, where most research has been undertaken to date, a very high proportion of pigs are carrying MRSA. The superbug has also been found at high levels in Dutch calves and on a Dutch chicken farm. A Dutch survey found an alarmingly high proportion of retail meat to be contaminated with MRSA. The Dutch Agriculture, Nature and Food Standards Minister, Dr Cees Veerman, has admitted the situation is 'worrying' (see Appendix). In January 2007, he warned that the international movement of farm animals and the comparable farming methods used in other countries mean that it is 'very unlikely that "animal-farming-related MRSA" only exists in the Netherlands' (see Appendix). Since then, the strain of MRSA found in Dutch farm animals has been discovered in pigs in Belgium, Denmark and Germany, and is strongly suspected in French pigs. The Netherlands is Europe's largest exporter of live pigs, sending almost six million pigs to other EU countries in 2005. This may be contributing to the spread of the superbug.

MRSA has also been found in cattle and chickens and in retail meat in other European and Asian countries, and in a significant number of pigs in Canada.

Farm-animal MRSA is being transmitted to humans

A major concern is that the MRSA bacteria are already transferring from animals to humans. Farmers and their families, farm workers, vets and abattoir workers are at highest risk because of their direct contact with animals. A very high percentage of Dutch pig farmers now carry farm-animal MRSA strains, in a country where, until recently, MRSA infections have remained rare both inside and outside hospitals. In the past year, a high proportion of cases of MRSA detected in the Netherlands have been due to the farm-animal strain, and it has already caused serious infections.

MRSA not yet found in UK farm animals, but the Government not testing pigs, chickens, or imported meat

MRSA has not yet been found in any British farm animals. However, despite being aware of this serious new zoonotic infection in near neighbours and major food-trading partners, Government MRSA testing has been restricted to cattle

and there are no plans to test pigs or chickens. The Food Standards Agency (FSA) has not tested any imported meat for MRSA contamination either. Since 60% of all pig meat consumed in the UK is imported, with most of this coming from countries where MRSA has been confirmed in pigs, British consumers are probably already being exposed to MRSA on meat. Defra recognised last year that 'trade rules might have to be reviewed if MRSA became established in food-producing animals', yet despite clear evidence that this has occurred, it has taken no action to safeguard consumers from contaminated meat.

The UK is fortunate in that it does not import live pigs from any countries known to be affected, and a small Soil Association survey did not detect MRSA in British pigs. The UK does, however, import live chicks and turkey poults from the Netherlands and elsewhere. Since there is evidence that MRSA may be widespread on Dutch chicken farms, there is a high risk that these imports will introduce MRSA to British livestock. The many foreign vets and farm workers who come to work in the UK, and young British farmers who often work abroad to gain experience, could also become colonised and then transmit the resistant bacteria to British farm animals.

Further spread of MRSA will have 'a major public-health impact'

It is not yet clear whether farm-animal MRSA is spreading to people unconnected to farming. Professor Jan Kluytmans, a microbiologist working at one of the worst-affected hospitals in the Netherlands has said: 'The main question is whether this strain will spread from those living on pig farms to other individuals in the community. If so it will have a major public-health impact' (see p 46).

In the UK, between 2000 and 2004, 1,981 MRSA infections were recorded in people who had not recently been in contact with hospitals. These community-acquired cases are typical of a growing global trend, which may be related to farm-animal MRSA. Farm-animal MRSA could spread in the community either by human-to-human contact, or on food. Dr Mark Enright of Imperial College London has recently said that one possibility is that the gene for methicillin resistance is transferring from animal bacteria to human *S. aureus* in the human gut, resulting in new strains of MRSA (see p 45).

High antibiotic use in farming is promoting the spread of MRSA

In the Netherlands, both scientists and Government ministers are blaming MRSA in farm animals on the very high levels of antibiotic use in Dutch intensive farming (see p 51). Dr Veerman refers to insufficient care for individual animals and poor management as factors contributing to high usage levels. He also says that the EU ban on the antibiotic growth-promoters appears to have led some intensive producers to increase their use of prescription antibiotics (see Appendix).

UK Government has failed to cut farm antibiotic use

The British Government committed itself to reducing the overall amount of antibiotics used in UK farming in 1999, but little progress has been made so far. Prompted by an aggressive advertising campaign, controversially permitted by the Government, British pig farmers, like their Dutch counterparts, are switching from the banned growth-promoters to medically important antibiotics obtained with a prescription. Some advertisements even claim that the prescription antibiotics will help the animals grow faster.

MAIN FINDINGS

MRSA in Dutch pigs, calves and chickens (see Chapters 3 and 4)

- A Dutch survey carried out at nine abattoirs accross the country last year found that 209 of 540 pigs (39%) were carriers of MRSA. Another survey found that 20 of 150 calves (13%) were MRSA-positive. MRSA has been found on a Dutch chicken farm but no national survey has yet been undertaken to establish the incidence on other farms.

MRSA on meat (see Chapters 3 and 4)

- A survey by the Dutch Food and Consumer Product Safety Authority in 2006 found very high levels of MRSA in Dutch meat: five of 25 samples of pork (20%), five of 24 samples of chicken (21%) and two of 64 samples of beef (3%) contained MRSA. In a limited number of surveys across the world, MRSA has also been found in pork, beef and chicken.
- Most imported pig meat in the UK comes from the Netherlands, Denmark and Germany, three countries where MRSA has been confirmed in pigs. Despite this, the FSA has tested no imported pig meat for MRSA.

Farm-animal MRSA transferring to humans (see Chapters 3, 5 and 6)

- Nearly 50% of Dutch pig farmers have been found to be carriers of MRSA. This prevalence is 1,500 times higher than in the general Dutch population. Medical authorities in the Netherlands now consider all people living on pig and cattle farms to be at high risk of carrying MRSA, and they are isolated on admission to hospital until screening shows they are clear.
- The rate of detection of the farm-animal MRSA strain in humans has increased sharply in the Netherlands: in the last quarter of 2006, 25% of all MRSA found in humans in the Netherlands was the farm-animal strain. In one Dutch hospital, 80% of the MRSA currently being found is the farm-animal strain.
- Farm-animal MRSA has similarities to community-acquired MRSA in humans and may be a factor in its global rise.

Farm-animal MRSA and human infections (see Chapter 3)

- Dutch patients with pig MRSA have developed skin infections, endocarditis (a heart infection) and osteomyelitis (a bone infection). The same strain of MRSA has caused blood poisoning and other deep-seated infections in Belgium and it has caused infections in Denmark.
- In Germany, this MRSA strain has not only caused has caused skin infections in hospital outpatients, it has also caused pneumonia in seven inpatients. This may be an indication that the strain is now entering and spreading in hospitals.

Excessive use of antibiotics in UK farming (see Chapters 8 and 9)

- Intensively farmed animals are vulnerable to a multitude of diseases which antibiotics are used to control. Overall use is excessively high and, if introduced into the UK, farm-animal MRSA would spread rapidly under these conditions.
- There are no British figures for antibiotic consumption by species, but there are indications that consumption per pig is rising.
- The Government has ignored a requirement in EU Directive 2004/28/EC to prohibit the advertising of antibiotics directly to farmers.

RECOMMENDATIONS

Testing livestock and meat for MRSA

It is imperative that the MRSA status of British farm animals and meat on sale in British retail outlets be officially established as soon as possible. We therefore recommend:

- Immediate surveys of British pigs and poultry, with regular testing of all at-risk food animals for subsequent years.
- Urgent testing of imported live farm animals and pork, chicken and beef from EU countries, and immediate testing by the FSA of imported pig meat and chicken. All future surveys of retail meat should test all detected staphylococci for antibiotic resistance.

Reducing antibiotic use on farms

The 1999 Government commitment to developing a strategy for reducing the use of veterinary antibiotics has never been properly implemented. This should now be given a high priority in order to bring about a substantial and rapid reduction in the farm use of antibiotics.

To assist this process the Government should implement the following important recommendations from independent advisory committees which have not been acted upon:

- prohibit the advertising of prescription-only antibiotics to farmers (Swann Committee 1969)
- review the prophylactic use of antibiotics in livestock production (Lamming Committee 1992)
- ensure that the antibiotic growth-promoters are not replaced by increased prophylactic use of prescribed antibiotics (Curry Commission 2002)
- publish data on the use of antibiotics by species, compound and antibiotic class (ACMSF 1999)

The Government's strategy for reducing veterinary antibiotic use should also:

- encourage farming systems with a low reliance on antibiotics and specifically recognise that organic farming is beneficial because of its lower use of antibiotics

Screening farmers and farm workers

- Farm workers and vets coming to work in the UK from countries which have MRSA in their livestock should be screened for MRSA. If found to be positive they should not work with animals until they have been successfully treated. Young British farmers returning from working abroad should also be screened.
- If MRSA is found in British livestock, British farm workers and vets should be screened.

Enhancing biosecurity and promoting best practice

- The Government should initiate an assessment of all biosecurity measures that could contribute to preventing the spread of MRSA to British farm animals.

Use of critically important antibiotics on farms

Fluoroquinolones and third- and fourth-generation cephalosporin antibiotics are defined by the World Health Organisation as 'critically important' in human medicine. Their use is known to promote the spread of MRSA in humans. We recommend that:

- all prophylactic and off-label use of these antibiotic classes should be prohibited
- any advertising of these drugs to veterinary surgeons (and farmers, until the Government agrees to prohibit this) should make this clear

OTHER FINDINGS

MRSA in pigs (see Chapter 3)

- The strain of MRSA found in Dutch farm animals has recently been discovered in pigs in Belgium, Denmark and Germany and in a pig farmer in France.
- In Canada, a survey of pig farms has found MRSA in a high proportion of pigs on some farms. The MRSA bacteria in Canadian pigs may be different strains to the main strain in European pigs.

MRSA in other animals and in people who work with them (see Chapter 4)

Cattle

- MRSA has been found in cattle, or their milk, in several countries other than the Netherlands in recent years.
- MRSA has been found in cattle from a farm in Hungary. It was being passed between the cattle and the farm workers, although it was not established in which direction the bacteria were transferring.
- A new strain of MRSA has been found in bovine milk in Korea. This strain can produce the Panton-Valentine leukocidin (PVL) toxin, which is often associated with increased virulence in community-acquired MRSA.
- A Dutch study has shown that cattle farmers are far more likely to carry MRSA than members of the general public.

Chickens

- A recent study found MRSA in chicken droppings on a farm in the Netherlands. Five of six adults living on the farm and on two associated poultry farms nearby were also carriers of the same MRSA strain. Dutch Government scientists believe the chickens are likely to have given the MRSA to the farmers.
- The wife of a chicken farmer in the Netherlands developed life-threatening endocarditis caused by farm-animal MRSA. No chickens on their farm or pigs nearby were tested and it is not known for certain how she became infected.

Horses

- In recent years, MRSA has been reported in horses in the UK, Ireland, Austria, Canada, Japan and the US.
- Several studies have found that people who work with horses are colonised by the same strain of MRSA as the horses they handle. One large North American study found MRSA in nearly 5% of horses tested, and on all horse farms with MRSA-positive horses, at least one human was a carrier of the same MRSA strain.
- In some cases, MRSA apparently acquired from horses has caused infections in humans. Some studies have found horses and associated humans to be carrying hospital strains, but others have found them both carrying strains uncommon in humans, suggesting they may have originated in horses.
- The UK Government is allowing the use of a banned antibiotic growth-promoter as a horse-feed additive without reviewing its safety. The product, Founderguard, contains the antibiotic virginiamycin, banned throughout the EU in 1999 because it is closely related to a new drug (Synercid) developed to treat MRSA and other highly antibiotic-resistant infections. The use of Founderguard could result in Synercid-resistant MRSA developing in horses and transferring to humans.

Pets

- MRSA colonisation is increasingly found in pets, including cats and dogs, and is known to cause infections. Although there is good evidence to suggest that

the MRSA in pets is related to hospital strains and comes from contact with humans, pets can form a reservoir of MRSA for reinfecting humans.

Further evidence of MRSA in meat (see Chapters 3 and 4)

- In addition to Dutch Government testing, a private Dutch survey of retail pig meat carried out last year found two of 80 samples (2%) were contaminated with MRSA.
- In Jordan, MRSA was found in three of 317 samples of beef (1%), six of 717 meat samples from sheep (1%) and five of 218 chicken samples (2%).
- In Korea, MRSA was found in one of 69 samples of retail chicken meat (1%).
- MRSA has recently been found in two of 292 samples of retail chicken meat in Japan (1%), although these were believed to have been contaminated by workers handling the meat.

Further aspects of the UK situation (see Chapters 3 and 4)

- MRSA has been found in pets in the UK.
- Defra has tested 425 samples of milk from dairy cows with mastitis, but no MRSA has so far been found.
- A Soil Association survey which tested 92 pigs from eight UK farms (two organic), and 30 samples of Dutch pork bought from retail outlets in the UK did not find MRSA.
- A preliminary and as-yet-unpublished study carried out by scientists from Kingston University in Surrey found that one of 50 samples of retail pig meat and one of 100 chicken-meat samples bought in the UK were contaminated with *S. aureus* which was methicillin-resistant. Genetic tests to identify the strains and show whether the bacteria were true MRSA have yet to be completed.

Farm-animal MRSA can spread in the environment (see Chapter 5)

- MRSA is present in the manure from MRSA-positive farms. Spreading this manure on the land may result in environmental contamination by MRSA and create additional opportunities for the bacteria to pass to humans.
- Recent research has shown that intensive pig farms emit air plumes with very high densities of *S. aureus*. People living near MRSA-positive pig farms may therefore be exposed to MRSA in the air.

Farm-animal and community-acquired MRSA (see Chapter 6)

- Farm-animal MRSA and community-acquired MRSA share certain genetic similarities which distinguish them from hospital-acquired MRSA. This suggests they may be related, or that the resistance genes are being exchanged by horizontal gene transfer.
- The US has very high levels of community-acquired MRSA, but there is no information available on MRSA in US livestock. Since the US imports millions of live pigs each year from Canada, and a significant proportion of Canadian pigs have MRSA, MRSA is probably already present in US livestock. Farm-animal MRSA could therefore have played a role in the emergence of community-acquired MRSA in the US.

Threat to human health from farm-animal MRSA (see Chapter 7)

- Because most farm-animal MRSA and most hospital strains of MRSA are sensitive to different antibiotics, the treatment of MRSA infections may become more complicated if farm-animal MRSA infections become common in humans. Pig MRSA is much more likely to be tetracycline-resistant and much less likely to be fluoroquinolone-resistant than hospital strains.
- Vancomycin is the most widely used antibiotic for treating MRSA infections, but because of the previous use of a growth-promoter very closely related to

vancomycin and the continuing use of certain prescription feed antibiotics, many European farm animals are carriers of vancomycin-resistant bacteria. If these bacteria transfer their resistance gene to MRSA bacteria, this will create a new superbug, vancomycin-resistant MRSA, which will cause major treatment problems and potentially high mortality.

Reducing farm antibiotic use (see Chapters 8 and 9)

- The use of antibiotics to which MRSA is resistant helps it to spread. Four of the five most widely used antibiotic classes in UK farming (tetracyclines, beta-lactams, macrolides and aminoglycosides) increase the spread of MRSA in humans.
- All of the MRSA bacteria in Dutch pigs are resistant to tetracyclines, and some are also resistant to the aminoglycosides and the macrolides. These antibiotics are widely used in pig farming, and will therefore be increasing the farm MRSA problem.
- The Dutch Government is imposing heavy fines of up to £11,400 for vets who prescribe antibiotics for disease prevention. In contrast, the British Government supports the prophylactic use of antibiotics in animal feed.

1. Introduction

This report looks at the problem of methicillin-resistant *Staphylococcus aureus* (MRSA) in farm animals and meat. It investigates the emergence of farm-animal MRSA in a number of countries, how and why it is spreading across continental Europe and looks at the risk of its spreading to the UK if we do not take urgent action to prevent this.

In addition, the report examines two major related issues: first, whether farm-animal MRSA is one of the factors behind the recent global rise of community-acquired MRSA (MRSA in people who have become infected outside a hospital setting), and second, the extent to which the routine use of antibiotics in intensive livestock farming is behind this worrying new twist in the evolution of the infamous MRSA superbug.[1]

There is currently no UK or EU legislation on the control of MRSA in animals (Defra 2006a). Its arrival and spread in European farm animals has been sudden and unexpected. And it is clear that neither the Government nor professional bodies with responsibility in this area have yet recognised the true extent of the problem or its likely consequences.

The British scientist Dr Andrew Waller has called MRSA in farm animals and pets 'the creation of a new monster' (Waller 2005).[2] As this report shows, however, the appearance of MRSA in farm animals is likely to have by far the greater impact on human health.

Twelve months ago the Government's position was that MRSA 'infection in livestock is currently very uncommon' (Defra 2006a). At the time it acknowledged that, 'trade rules might be reviewed if MRSA became established in food-producing animals' (Defra 2006a). Even when this statement was published on the website of the Department for Environment, Food and Rural Affairs (Defra), members of a Defra committee subgroup on antibiotic resistance had known for five months that MRSA had been found in intensively kept pigs in the Netherlands and on 23% of local pig farmers (DARC 2006).

In the last year, animal strains of MRSA have been found in several European countries and there are strong indications that these strains are spreading to others. Pigs are the species most affected, but MRSA has also been found in dairy cows, calves, chickens and horses, as well as in retail pork, chicken and beef. Yet despite the fact that Britain is currently importing large quantities of livestock products from countries where MRSA is present in farm animals, nothing has been done to protect consumers.

What is more, Defra's view that 'humans are likely to be the source of MRSA strains infecting or colonising animals' (DEFRA 2007a) may have to change. Evidence from the Netherlands, Germany and Denmark set out in this report shows that the predominant strain of MRSA in European farm animals is passing from animals to humans, where it easily colonises those in contact with animals and can cause serious infections. In the Netherlands 40% of pigs and nearly 50% of pig farmers are now affected. At no previous point in the history of MRSA have

'The creation of a new monster'

DR ANDREW WALLER (WALLER 2005)

[1] In this report we use the term 'antibiotic' to cover both antibiotics and other antimicrobials.

[2] Dr Waller's comment was also referring to the emergence of methicillin resistance in other bacteria in animals called *Staphylococcus intermedius*

colonisation rates ever been so high in any species. Even in the UK, one of the EU countries with the highest levels of MRSA, carriage in the general population is below 2%. The Dutch Minister for Agriculture, Nature and Food Standards, Dr Cees Veerman has described the situation as 'worrying' (see Appendix).[3]

Scientific understanding of the situation has changed dramatically over the last year and while several important studies have now been published, we are grateful to a number of scientists who have been willing to let us see the preliminary results of research still in progress and in some cases have permitted us to refer to their findings. Although it appears that the highest incidence of MRSA in farm animals is in the Netherlands, it is important to point out that this may only be because this is where most research has been undertaken.

Yet, while a substantial amount of research is now either under way or planned in many other EU countries, Defra appears unwilling to investigate the UK situation properly. A Defra webpage dealing with MRSA in animals, last updated in June 2006, states: 'There have been no reports of infection in livestock species in the UK, but there have been no recent surveys specifically to look for the organism' (Defra 2006a). Since then, Defra has initiated an MRSA survey of milk samples, but has refused to test pigs or any live animals. Similarly, the FSA has tested no meat for MRSA.

Dutch scientists and the Dutch Government are unequivocally blaming excessive antibiotic use in intensive farming for their MRSA problem. In an attempt to reduce antibiotic consumption, the Dutch Government has banned the use of antibiotics for disease prevention in farm animals and recently increased the penalties for those breaking this law (see Appendix).

The British Government, however, continues to support the routine use of antibiotics in animal feed for disease prevention and has even chosen to ignore a requirement in EU Directive 2004/28/EC to prohibit the advertising of antibiotics directly to farmers. As a result, the pharmaceutical industry is actively encouraging farmers to rely on feed antibiotics as management tools and is even advertising the growth-promoting properties of prescription antibiotics licensed only for therapy.

Another disappointing development has been the Government's recent decision to disband the independent Specialist Advisory Committee on Antimicrobial Resistance (SACAR) set up specifically to advise on the important issue of antibiotic resistance in both humans and animals.

An independent committee with a remit like SACAR's has never been needed more than it is now, but instead SACAR's work will be taken over by a committee which focuses primarily on hospital-acquired infections. Lord Soulsby chaired the House of Lords committee which made the recommendation to set up SACAR and has told us, 'I am not happy with the demise of SACAR and believe its merging with the committee mainly dealing with hospital-acquired infections will weaken the important impact SACAR has had'.

We hope this report will alert both the Government and the general public to the urgent need for a series of effective measures which prevent MRSA from spreading to British livestock and deliver reductions in the use of antibiotics as well as improvements in the conditions in which animals are kept. If farm-animal MRSA is allowed to become established in the UK, it may prove both costly and extremely difficult to eradicate.

[3] All quotes from Dr Veerman and from the Zembla television programme (see Chapters 3 and 8) in this report are Soil Association translations.

2. The rise and rise of MRSA

Staphylococcus aureus

Staphylococcus aureus bacteria are frequently present on the skin, in the nose or in the mouth, without causing illness. While one third of the human population is resistant to colonisation, roughly the same proportion are continuous carriers, with the remaining third being intermittent carriers (ISFHH 2006).

Danger arises when the bacteria get into wounds or damaged skin. Then illnesses ranging from minor infections and abscesses, to life-threatening diseases such as pneumonia, meningitis, endocarditis (a heart infection) and bacteraemia (blood poisoning) may occur. *S. aureus* can also cause food poisoning, although this is as a result of toxins produced by the bacteria growing on the food, rather than an infection caused by the bacteria themselves (Defra 2006a).

In the pre-antibiotic era more than eight out every ten patients with *S. aureus* blood poisoning died, but after the introduction of penicillin to human medicine in the 1940s, the death rate was cut dramatically (Lowy 2003).

'All the evolutionary events required for the generation of future animal pandemics may now be in place'

DR ANDREW WALLER (WALLER 2005)

S. aureus develops penicillin resistance

Within a very short time *S. aureus* was showing signs of its remarkable ability to evolve and grow stronger when under attack by antibiotics. By 1942, even before penicillin was available for all doctors to prescribe, penicillin-resistant strains were being found (Rammelkamp and Maxon 1942). The resistant bacteria produced enzymes called beta-lactamases, which destroy not only penicillin but also many more modern antibiotics in the same class (the beta-lactams), such as ampicillin and amoxicillin.

The beta-lactams, including penicillin, were used to treat a wide range of infections. The more they were used, the more the bacteria became resistant, as the sensitive bacteria were killed off and the resistant ones survived. By the end of the 1950s, 90–95% of *S. aureus* involved in clinical infections were penicillin-resistant (DH 2005).

Outside the hospital environment, resistance in *S. aureus* did not develop as quickly, but once it appeared in the 1950s it increased rapidly, and by the 1970s the levels in the community were nearly as high as in hospitals (Chambers 2001).

The first MRSA

The sharp increase in resistance meant there was a need for new antibiotics to treat *S. aureus*, and in 1959 the semi-synthetic antibiotic, methicillin,[1] was introduced into human medicine. Although methicillin was derived from penicillin and is also a beta-lactam antibiotic, it is not normally degraded by the beta-lactamase enzymes and could kill penicillin-resistant *S. aureus*.[2]

Only two years later, however, the UK became the first country in the world to report a case of *S. aureus* that was resistant to methicillin (Jevons 1961, Enright et al. 2002). MRSA remained fairly rare during the 1960s and 1970s, and only increased slightly in the 1980s. But in the 1990s, methicillin resistance in the UK

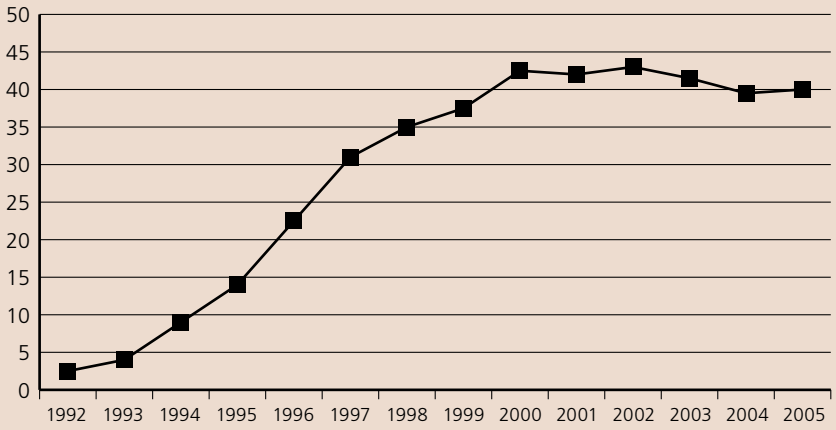
[1] The antibiotic was known as methicillin for many years, but recently the official name has been changed to 'meticillin' in line with international guidelines. We use the term 'methicillin' in this report as it is still the most widely used name outside official or scientific literature.

[2] Vancomycin, a mainstay of MRSA treatment today, was also developed in the late 1950s, but because it was less effective at treating *S. aureus* than methicillin and is also a thick oily solution which needs to be administered slowly and intravenously, it was not widely used at the time.

increased dramatically from very low to very high levels, as shown in Graph 2.1.

Graph 2.1 Methicillin resistance in *S. aureus* from blood-poisoning infections

Figures are for England and Wales



Source: HPA 2006a

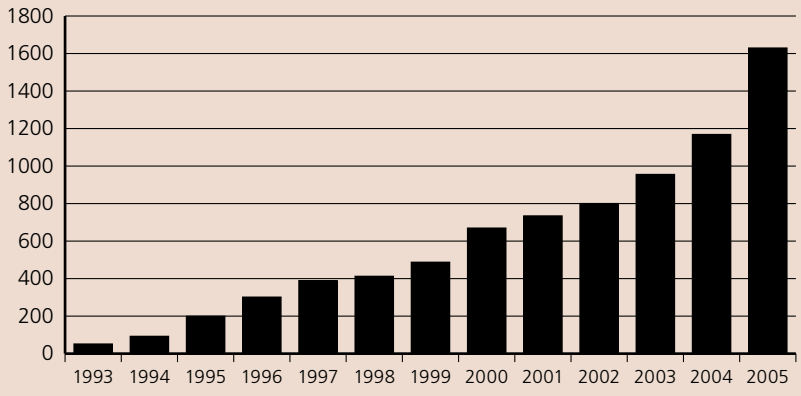
Deaths from MRSA increasing and underestimated

The consequences of methicillin resistance for treatment can be very serious. Once *S. aureus* develops resistance to methicillin, it automatically becomes resistant to nearly all beta-lactams. Since the beta-lactams are the most widely used class of antibiotics in human medicine, this significantly reduces the options for successful antibiotic treatment. Doctors still have a small number of drugs they can use, but some strains of MRSA are resistant to one or more of them. Many of these antibiotics cannot be taken orally at home and/or are less effective than the beta-lactams, meaning that successful treatment can take longer. Most also have side effects, which can lead to complications in some patients.

It is not surprising, therefore, that the spread of methicillin resistance has led to a rapid increase in the number of deaths caused by *S. aureus*. The most recent figures available show that in 2005 there were 1,629 death certificates in England and Wales which mentioned MRSA as a contributing cause (see Graph 2.2), a 39% increase on the 2004 figures.

Graph 2.2 Death certificates with MRSA mentioned as the underlying cause

Figures are for England and Wales



Source: ONS 2007a, ONS 2007b

The Health Minister, Lord Hunt, has argued that the increase in the number of deaths may be due to increased awareness and improved reporting (BBC 2007). However, the National Audit Office has pointed out that the figures from the

Office for National Statistics are 'bound to be a significant underestimate of total deaths from MRSA because doctors need not record MRSA as the cause of death' (Taylor 2005). Furthermore, the accuracy of reporting may be worsening rather than improving: in 2003, a Government report had estimated that nearly half of all death certificates were inaccurate, and promises were made to make improvements, but last year one of the co-authors of the report said the situation had got worse, and that now approximately 55% of certificates were completed improperly (Hill 2006).

The Government emphasises that levels of MRSA blood-poisoning infections have fallen slightly from 7,698 in 2003/04 to 7,087 in 2005/06 (DH 2007, HPA 2007), but in 2005 the Department of Health admitted that some NHS Trusts had broken the rules on reporting and were not including blood-poisoning infections which patients had developed outside hospitals (Revill 2005). As Dr Mark Enright of Imperial College London points out, hospitals can discharge patients with undetected hospital-acquired MRSA. These same patients may subsequently be re-admitted with MRSA blood poisoning, but then go uncounted (Enright 2005).

Enright also says that blood poisoning is not the only MRSA infection that should be reported, since MRSA can cause serious and costly problems like abscesses, bone infections and pneumonia (Enright 2005). A better idea of the full scale of the problem comes from information obtained under the Freedom of Information Act by the Conservative party last year. This suggests that the true extent of the MRSA epidemic was approximately 96,000 cases of infection in hospitals in England in 2004, almost 1,400% more than the figures for MRSA blood poisoning alone (Guardian 2006, Daily Mail 2007).

Box 2.1 Why is it called MRSA?

Cloxacillin, flucloxacillin and oxacillin are semi-synthetic antibiotics closely related to methicillin. MRSA could equally be called CRSA (cloxacillin-resisant *S. aureus),* FRSA (flucloxacillin-resistant *S. aureus*) or ORSA (oxacillin-resistant *S. aureus*) since any *S. aureus* highly resistant to cloxacillin, flucloxacillin or oxacillin will also be highly resistant to methicillin, and vice-versa. However, although methicillin is no longer widely used, the resistant bacteria are still referred to as MRSA because it was the first of these antibiotics to be marketed.

MRSA moves into the community

Until a few years ago, MRSA was viewed exclusively as a hospital superbug, since it was confined to hospitals, long-term care facilities and people who had been in contact with them.

Within the last few years a major change has taken place worldwide. MRSA is now also a serious threat to people who have had no recent contact with hospitals. Some strains of community-acquired MRSA are thought to have originated in hospitals and been taken into the community, but most are generally believed to have developed independently (Coombs et al. 2004, Robinson and Enright 2004) and therefore represent a worrying new development.

A small number of cases of CA-MRSA were noted in the early 1980s (Saravolatz et al. 1982 and Hamoudi et al. 1983 quoted in Buckingham et al. 2004), but it is only since the late 1990s that CA-MRSA strains have become firmly established in the community. This has been most notable in the United States (Boyce 1998, Herold et al. 1998, CDC 1999). One study quoted by the US Government, carried out in 2000 in Minnesota, found that 12% of MRSA infections were community-associated (Naimi et al. 2003, CDC 2005). A more recent study has found an even higher incidence, with 70% of all MRSA infections in some areas of the US being community-acquired (Penn 2005).

CA-MRSA strains have also begun to attract notice in the UK and many other

countries. Cases have been reported in Britain, Canada, Australia, New Zealand, Finland, Ireland, France, Germany, Switzerland, the Netherlands and Japan (Dufour et al. 2002, Ma et al. 2002, Salmenlinna et al. 2002, Vandenesch et al. 2003, O'Brien et al. 2004, Witte et al. 2004, Piao et al. 2005, Rossney et al. 2005, Huijsdens et al. 2006a).

Characteristics of CA-MRSA

Overall, patients with CA-MRSA infections are significantly younger than those with hospital-acquired infections. A study in Minnesota found that patients infected with CA-MRSA had a median age of just 30, compared with 70 for those with hospital-acquired MRSA (Naimi et al. 2003). Infections among children appear to be particularly common. During the first 18 months of a study in children in the Greater Memphis area, 38% of MRSA infections were found to be community-associated. During the last twelve months of the study, this increased to 63% (Buckingham et al. 2004). The incidence among children aged two or younger has also been found to be significantly higher than in those aged two or over (Fridkin et al. 2005).

The kind of infections caused by CA-MRSA also differ from those caused by hospital-acquired strains, with the former much more likely to cause skin and soft-tissue infections (Naimi et al. 2003, Fridkin et al. 2005).

CA-MRSA is often more virulent and can spread even more easily than hospital-acquired MRSA (Rossney et al. 2005). In particular, MRSA which produces the Panton-Valentine leukocidin (PVL) toxin is much more common in community-acquired strains, although in December 2006 PVL MRSA made headline news in Britain because of an outbreak in hospitals (Labandeira-Rey et al. 2007, HPA 2006d). Among other conditions, PVL MRSA is associated with necrotising pneumonia, a life-threatening condition (HPA 2006e). PVL MRSA can also cause a particularly nasty skin infection called necrotising fasciitis, a flesh-eating disease which can require infected tissue to be cut away. Necrotising fasciitis was previously only very rarely caused by *S. aureus*, so the fact that it is now clearly associated with some MRSA is alarming both physicians and scientists (Miller et al. 2005).

A French study published last year also reported on the emergence in the community and hospitals of another virulent MRSA producing a toxin which can cause toxic-shock syndrome (Durand et al. 2006).

Community-acquired MRSA in the UK

The first reported outbreak of CA-MRSA in the UK occurred in a rugby team in the late 1990s (Stacey et al. 1998). No one knows exactly how widespread community-acquired MRSA has become in the UK, but last year the Health Protection Agency (HPA) said that approximately 100 cases had been identified, with one fatality (HPA 2005a, HPA 2006c). A more recent study found that 1,981 CA-MRSA infections were recorded by primary-care institutions between 2000 and 2004 (Scheider-Linder et al. 2007). Furthermore, there is no indication that doctors are required to report cases of CA-MRSA which have been treated successfully without the patient needing to enter hospital. Many websites where MRSA sufferers share their experiences indicate that the origin of MRSA infections is often not established.

The results of an unpublished study by University Hospital Birmingham NHS Trust suggest that the community infection may already be much more common than the HPA's figures suggest. The Trust found that 28% of patients with MRSA had actually picked up their infection before being admitted to hospital. While this suggests that CA-MRSA is spreading very quickly in the UK, the figures may be something of an overestimate, since some of the patients included in the

study came from nursing homes or from other hospitals, rather than the wider community (Mulholland 2005).

MRSA appears in animals

The latest phase in the evolution of MRSA has been its appearance in animals. At first, infections were reported in pets, particularly dogs and cats. The strains involved were usually similar or identical to those infecting humans, and the most obvious explanation for this new veterinary problem was, and still is, that the pets acquired the resistant bacteria from humans. As we shall see in Chapter 4, scientists have found evidence that these human strains of MRSA can also be passed back from animals to humans in what has been described as a 'chicken or egg situation' (Veterinary Record 2005).

The principal subject of this report, however, is the emergence of MRSA in farm animals. Recently MRSA has been found in large numbers of pigs, as well as in chickens, cattle and horses. This development has been sudden and unexpected.

Pigs colonised by MRSA rarely if ever develop infections, although they are able to pass the multi-drug-resistant bacteria on to other species. *S. aureus* is, however, a significant cause of mastitis in dairy cows. It is also a major pathogen of poultry, responsible for a wide variety of conditions including septicaemia, arthritis, yolk sac infections and lameness. Since birds infected with S. aureus are known to carry much higher numbers of bacteria (Devriese 1980), the fact that MRSA has emerged in poultry is especially worrying. MRSA can also cause infection in horses.

3. MRSA in pigs, pig meat and pig farmers

'It transpires that almost 50% of those tested who are in contact with pigs prove to be infected and that is a higher level than ever discovered before. That is previously unheard of.'

PROFESSOR JAN KLUYTMANS (ZEMBLA 2006)

The sudden emergence of MRSA in Dutch pigs

The first ever report of MRSA in pigs came from the Netherlands as recently as December 2005. Initially, scientists thought this an interesting but isolated case. After all, there had been occasional reports of MRSA in animals for several decades without evidence of a widespread problem.

However, since 2005 further studies have revealed that MRSA has spread like wildfire in the Dutch pig herd. It appears that pigs normally display no symptoms of illness. Instead, with MRSA in their noses, on their skin and probably in their intestines, they act as an army of carriers.

The rapid spread of MRSA in pigs is beginning to undermine the long-held scientific consensus that farm animals play no role in the human MRSA epidemic. Already there is clear evidence that pig MRSA is passing to humans, in some cases causing serious infections.

Recent studies, some not yet published, reveal evidence of MRSA in pigs in Germany, France and Belgium. Although Britain does not import any live pigs from the Netherlands, the presence of MRSA in pigs in other EU countries has relevance for British consumers since 60% of pig meat consumed in the UK is imported, and much of it comes from the Netherlands (BPEX 2005). There is also emerging evidence of a significant MRSA problem with pigs in Canada.

The initial discovery

For many years the Netherlands had one of the lowest levels of MRSA in the world. In Dutch hospitals, just 1% of *S. aureus* are methicillin-resistant in comparison with over 40% in the UK (EARSS 2006). Until recently, methicillin resistance in the community in the Netherlands was even rarer – one study found that only 0.03% of people were carriers of MRSA on admission to hospital (Wertheim et al. 2004). In the last three years, however, there have been dramatic developments.

In July 2004, scientists carrying out routine screening of patients for MRSA (Government policy in the Netherlands) were surprised to find the bacteria on a six-month-old baby girl admitted for surgery to a hospital in Nijmegen. For several months the girl remained colonised by MRSA despite repeated attempts to clear the bacteria. Tests revealed that her parents were also positive for MRSA. The family lived on a farm, and raised pigs (Voss et al. 2005).

In early 2005, two new cases of MRSA with an apparent link to pigs were identified – one a pig farmer and one the son of a vet who worked mostly with pigs. Now suspecting that pigs might be the source of the antibiotic-resistant bacteria, scientists screened a selection of pigs from the baby girl's family's farm and from other pig farms in the region. One of 30 pigs was found to be positive for MRSA, and it came from the farm of the baby girl's family (Voss et al. 2005).

Other pig farmers from the same region were also screened in the same study, and six of 26 farmers (23%) tested positive. This was a prevalence rate over 760 times higher than for patients admitted to hospital in the region (Voss et al. 2005).

The scientists attempted to identify the particular strains of MRSA using a 'typing' (i.e. classification) method called pulse-field gel electrophoresis (PFGE). PFGE has long been considered the best method available for identifying MRSA bacteria, but in this case it was unable to type the strains. Using another identification method, random amplification of polymorphic DNA (RAPD) analysis, however, they identified three different strains of MRSA. The MRSA-positive family and the pig from their farm had the same strain of MRSA (*spa*-type t108). The scientists concluded that this was a case of MRSA being passed from pigs to humans (Voss et al. 2005).

Second study finds MRSA in Dutch pigs

A second Dutch paper, entitled 'Community-acquired MRSA and pig farming', and involving scientists from the Dutch National Institute of Public Health and the Environment, reported on the case of a young mother admitted to hospital in October 2004 with mastitis caused by MRSA. Tests showed that the father and baby daughter were also MRSA-positive. Since the father was a pig farmer with 8,000 pigs, the scientists screened ten of his pigs and three of his co-workers. All three workers and eight of the pigs (80%) tested positive for MRSA. Again, all the strains were *spa*-type t108, and using a third strain-identification method known as multi-locus sequence typing (MLST), all cases were classified as sequence type ST398.

The scientists concluded that this was clear evidence of MRSA being transmitted between humans and pigs, but were unsure in which direction the bacteria were moving and said that more research was needed to establish whether pigs were a new source of MRSA (Huijsdens et al. 2006b).

Very high prevalence of MRSA found in Dutch pigs at slaughter

These two initial studies did in fact motivate further research. A much larger-scale study was undertaken by Dutch Government scientists to establish whether the problem was industry-wide.

Between November 2005 and January 2006, pigs were tested in the nine largest Dutch abattoirs, where over 60% of Dutch pigs are slaughtered. In each abattoir six batches of ten pigs were tested, so that 540 pigs were tested in total.

In 44 out of the 54 batches (81%) at least one pig was MRSA-positive and overall 209 of the 540 pigs (39%) were MRSA-positive (see Graph 3.1). The scientists were surprised by the level of MRSA they found, as nothing approaching this high incidence had previously been seen in farm animals. Using MLST, the bacteria were again all classified as ST398 MRSA (de Neeling et al. 2007).

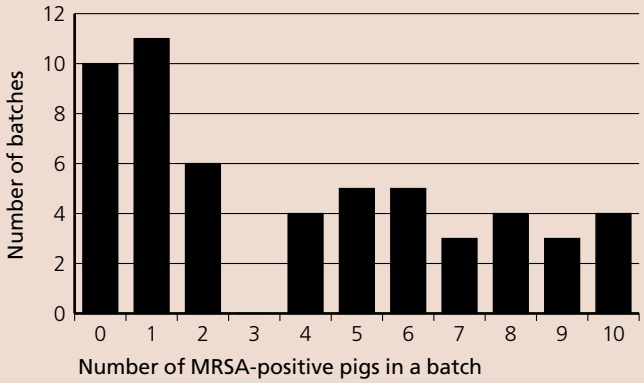
The study also looked at the levels of resistance to other antibiotics. Of 175 MRSA samples tested, all were found to be resistant to tetracyclines, the antibiotic class most widely used in the pig industry in the Netherlands, the UK and elsewhere (Huijsdens et al. 2006c, de Neeling et al. 2007).

Furthermore, of 44 MRSA samples tested, approximately one third were resistant to aminoglycosides and one quarter resistant to macrolides, two other antibiotic classes widely used in the pig industry (de Neeling et al. 2007).

Airborne MRSA in pig sheds

A very recent study published on the website of the Dutch Government's Centre for Infectious Disease Control has shown that airborne MRSA can occur inside pig sheds. An open-culture plate was placed inside a pig shed for just ten minutes, after which more than 50 colonies of MRSA were growing. The Centre's newsletter said this was evidence that the levels of MRSA in the air were high, and expressed concern that farm workers were routinely exposed to MRSA. The pig farmer was also shown to be a carrier of the same strain (RIVM 2007a).

Graph 3.1 Number of MRSA-positive pigs in ten-pig batches in Dutch abattoir survey



Source: de Neeling et al. 2007

Unlike MRSA previously found in Dutch pigs, this MRSA could be analysed by the PFGE method and was identified as strain ST339. This is of concern as it indicates that methicillin resistance is also occurring in other strains of *S. aureus* carried by pigs.

MRSA in pork in the Netherlands

The presence of MRSA in live pigs raises the question of whether or not it can be passed to humans through the food chain. Since MRSA principally lives on the skin, in the nostrils and in faeces, it could be that high hygiene standards at abattoirs will produce uncontaminated meat for human consumption.

As no information about the presence of MRSA on pig meat was available, Professor Jan Kluytmans decided to undertake a testing programme at his own laboratory. Meat samples were bought from 30 local butchers and supermarkets. Out of 80 samples, two (2.5%) were contaminated with MRSA (Zembla 2006). One of the positive samples had MRSA of sequence type ST398, whereas the other was a different strain which has also caused community-acquired infections in humans (Kluytmans 2007). It was, however, revealed in January of this year that the Dutch authorities had carried out a small survey of their own which found much higher levels of contamination (see Box 3.1).

Box 3.1 Dutch authorities find astonishing levels of MRSA on pork

When a representative of the Dutch Food and Consumer Safety Authority (VWA), Dr Oosterom, was asked on a Dutch television programme broadcast in December 2006 why no official testing of retail pig meat had been carried out, he initially said that his organisation did not have sufficient reason for concern and that Professor Kluytmans had not informed them that he had found MRSA in pig meat.

However, Professor Kluytmans had in fact informed the VWA of his findings in June 2006, and Dr Oosterom subsequently admitted that he had had a meeting with Professor Kluytmans at the time to discuss the findings. He said that the authority would undertake a survey in 2007, but was unable to explain why no survey had been undertaken earlier (Zembla 2006).

A month later, it was revealed that the VWA had in fact already carried out a small survey in 2006. A letter from the Dutch Minister for Agriculture, Nature and Food Standards, Dr Veerman, to the Chairman of the Dutch Parliament was published online in January (see Appendix). It said that a survey had found that five of 25 samples of pork (20%) from supermarkets contained MRSA. Extremely high levels of MRSA were also found in retail chicken and some beef samples were positive too (see Chapter 4). Despite the remarkable nature of these findings, which the Minister admitted were 'worrying', the survey was not mentioned by any representatives of the VWA during the television programme. We have since been told by Dr Oosterom that all the isolates found in the survey were the same strain as found in pigs (Oosterom 2007).

Pig MRSA and humans

Evidence that some MRSA in humans comes from pigs

Since nearly all the MRSA found in Dutch pigs is unclassifiable using the PFGE method, the logical next step was to look more closely at all human isolates of MRSA which were also non-typeable by PFGE, to see whether there appeared to be any link with farming. For the remainder of this section, we call strains of MRSA which are non-typeable by PFGE, 'NT-MRSA'.

Humans infected by, or carriers of NT-MRSA were found to be about 12 times more likely to be pig farmers and 18–20 times more likely to be cattle farmers, than those who were infected by, or carriers of, other MRSA strains. The scientists concluded: 'non-typeable MRSA is associated with pig and cattle farming. It causes serious disease and is [also] transmitted between humans' (van Loo et al. 2006a).

A second study examined the microbiological characteristics of human strains of NT-MRSA, and the findings reinforced the farming link.[1] Using MLST, it was shown that 33 of 35 cases examined were of the same sequence type ST398 as had been found in pigs, with the two remaining cases being closely related to it.

Analysis of the antibiotic-resistance profile of the bacteria also showed that NT-MRSA in humans tended to be resistant to the same antibiotics as pig MRSA, rather than to the same antibiotics as other human MRSA. The scientists found that 79% of the human NT-MRSA were resistant to tetracyclines, compared with just 9% of other human MRSA. Moreover, only 6% of the NT-MRSA were resistant to fluoroquinolones, another important class of antibiotics, whereas 51% of other human MRSA proved resistant to these drugs (van Loo et al. 2006b).

Table 3.1 shows how similar the resistance profile of NT-MRSA in humans is to that of pig MRSA. It also shows how different the resistance profile of pig MRSA is to that of normal human MRSA which is typeable by PFGE.

Table 3.1 Resistance of pig and human MRSA to tetracyclines and fluoroquinolones

Antibiotic class	Resistance in MRSA in pigs	Resistance in NT-MRSA in humans	Resistance in typeable MRSA in humans
Tetracyclines	100%	79%	9%
Fluoroquinolones	0%	6%	51%

Sources: Van Loo et al. 2006b, de Neeling et al. 2007

This is not surprising when one considers the different ways in which antibiotics are used in farming and in human medicine. Official Dutch statistics show that in terms of total weight of active ingredient used, tetracyclines make up about 60% of all the antibiotics used in farming. In pigs being fattened for slaughter they make up about 80%. On the other hand, in the Netherlands fluoroquinolones are used in much greater quantities in human medicine than they are in pig farming (FIDIN 2006 and NETHMAP 2006).

Pig-related MRSA is spreading rapidly in the Dutch population

Dutch scientists have also examined the prevalence of NT-MRSA in humans, to see whether these strains are increasing in incidence. This study was possible because since April 2002 the Netherlands has kept a national MRSA database where the PFGE type of all cases is recorded.

Between April 2002 and early 2003, not a single case of human NT-MRSA was found, but between January 2003 and December 2005 NT-MRSA represented 2% of the 4,669 human cases of MRSA (de Neeling et al. 2006).

More recent statistics show that the new pig strain has been spreading rapidly

[1] One microbiological difference found between the pig MRSA and the human NT-MRSA was that 9% of the human NT-MRSA produced the PVL toxin (see Chapter 2), whereas none of the pig MRSA did. Two possible explanations for this are that either some clones of the pig MRSA have subsequently acquired the PVL gene, or that a small proportion of the ST398 MRSA in humans is coming from different sources which have not yet been investigated in detail, e.g. cattle or chickens.

within the human population during the last year or so. Professor Jan Kluytmans, a microbiologist from Amphia Hospital in Breda in the Netherlands, has reported to us that in the last quarter of 2006, 25% of all MRSA found in humans in the Netherlands was ST398 pig MRSA. In his particular hospital, which is in a pig-farming region, the percentage had risen to almost 80%, although he said the rate was now levelling off (Kluytmans 2007).

In December 2006, Professor Kluytmans reported on Dutch television that research had found that nearly 50% of pig farmers were now MRSA carriers (Zembla 2006). This is a notable increase since the original study mentioned above, and is a level 1,500 times higher than for patients admitted to Dutch hospitals. Professor Kluytmans also told the Soil Association that some people associated with pig farms have developed 'serious infections' (Kluytmans 2007).

Dutch MRSA search-and-destroy policy

Although pig-related MRSA in humans has clearly been increasing, some of the increase in detections can be explained by changes in the Dutch strategy for controlling the spread of MRSA.

For many years the Dutch hospital authorities have had a comprehensive approach to surveillance (unlike the situation in the UK), which more recently has been developed into a search-and-destroy policy. This involves the isolation of all high-risk patients on admission to hospital until screening shows that they are not MRSA carriers, or treatment clears any MRSA they are carrying. High-risk patients include those repatriated from hospitals abroad, where MRSA is often much more common, those who were formerly MRSA carriers and those who are in contact with MRSA carriers (Wertheim et al. 2004).

However, because of the reports of MRSA being found in pigs and in those in contact with pigs, people living on pig farms are now also being treated as high-risk patients (WIP 2007). This means that pig farmers are being screened for MRSA much more often, and this has contributed to more pig-related MRSA being found in humans.

Because of the large increase in the number of cases, the search-and-destroy policy is now coming under financial pressure. In February 2007, ten hospitals which account for over 90% of all the pig-MRSA cases in humans in the Netherlands wrote to the Dutch Government requesting greater funding for the policy which, they claimed, was now becoming overstretched because of the spread of the new pig strain (Zibb 2007).

Testing for MRSA in UK pigs and pork

No official testing in British pigs

In September 2005, Defra wrote to the Soil Association, stating: 'the Department agrees that it is important to understand the significance of farmed animals in the spread of MRSA' (Renn 2005). Yet, when in December 2006 Ben Bradshaw, the Defra Minister of State with responsibility for veterinary medicines, was asked about the Government's assessment of the extent of MRSA in pigs in the UK and in imported pork, he said that Defra was undertaking a survey for MRSA in cattle but added that, 'the inclusion of other livestock species, including pigs, in the remit of this project has been considered by the subgroup but has not been taken forward due to little evidence of the occurrence of MRSA in other food-producing animals in the UK, and due to the fact that *S. aureus* is not generally considered to be a major pathogen in livestock species other than cattle, where it is a significant cause of mastitis. There is no current evidence that food-producing animals form a reservoir of MRSA infection in the UK, although the DARC MRSA subgroup will keep the situation under continued review' (Hansard 2006).

This claim of lack of evidence of MRSA in pigs may have been strictly true as far as the UK was concerned, but studies showing that MRSA was present in Dutch pigs were already publicly available: the original paper reporting on MRSA in pigs in the Netherlands had been published one year earlier (Voss et al. 2005), and the minutes of a meeting of the Defra Antimicrobial Resistance Co-ordination Group held on 14 February 2006 record that members were informed of this study. Further studies, including the Dutch abattoir study of which Defra was also aware, had also been published in the scientific literature and on an official Dutch website (de Neeling et al. 2006, Huijsdens et al. 2006c). Furthermore, the fact that *S. aureus* is not a major pathogen in pigs does not alter the fact that pigs can be healthy carriers of MRSA which can pass the bacteria to humans.

In February 2007, Defra's webpage on MRSA in animals was updated to include the fact that MRSA had been found in pigs in other countries. It also stated that the DARC group had discussed the possibility of extending its MRSA surveillance work in cattle to other species, but decided not to do this unless it received a recommendation from colleagues in public health. The group described the possibility of carrying out surveillance for MRSA in other animal species, including pigs, as 'speculative' (Defra 2007b).

Soil Association testing of British pigs

Because of the lack of Government action, the Soil Association collected 97 nasal swabs from pigs from a range of farms including organic, free-range and intensive enterprises and sent these for analysis. The samples were analysed by Dr Scott Weese of Guelph University in Canada and by NationWide Laboratories in Blackpool. All of the samples were negative.[2]

Our view is that Defra should nonetheless reconsider its position on testing pigs. Since there is solid evidence of a major problem in pigs in the Netherlands, it is important to undertake a widespread survey of UK pigs to establish whether or not MRSA has already emerged in the British pig herd. Defra also has access to laboratories that can use a range of techniques to test samples. This, is significant because the Dutch strains of MRSA are unlike those normally identified in the UK.

Survey finds methicillin resistance in *S. aureus* from retail pork in UK

Scientists from Kingston University in Surrey recently carried out a survey of retail pork and chicken meat. Out of 50 samples of pork and 100 samples of chicken meat tested, the scientists found one sample of pork and one sample of chicken meat contaminated with *S. aureus* which was resistant to methicillin (Fielder 2007a, Fielder 2007b). As explained in Box 3.2, some *S. aureus* can show resistance to methicillin without having the *mec*A gene which is present in 'true' MRSA. These *S. aureus* are not as great a threat to human health as true MRSA, so it is important to determine if the methicillin resistance is due to the presence of the *mec*A gene. Dr Mark Fielder, one of the scientists involved in the study, has told us that work to establish this is still in progress (Fielder 2007b).

Soil Association testing for pig MRSA in Dutch pork imported into the UK

In December 2006, Defra Minister Ben Bradshaw also indicated in a written Parliamentary answer that no testing for MRSA in imported produce was being carried out. He said: 'The Food Standards Agency (FSA) is not aware of any UK surveillance of imported pork or other meats for the presence of MRSA. An FSA-funded survey to determine the prevalence of various pathogens and indicator organisms on raw red meat on retail sale is currently being undertaken across the UK. Both UK-produced and imported pork is included in this survey and, while enumeration of S. aureus is being undertaken, isolates are not being screened for antimicrobial resistance' (Hansard 2006).

[2] The first batch of ten samples sent to the laboratory were tested using a method unlikely to identify pig MRSA. It emerged that the laboratory used the fluoroquinolone antibiotic ciprofloxacin in the testing process on the basis that most hospital strains of MRSA in the UK are now also resistant to ciprofloxacin. But since the strain of MRSA identified in Dutch pigs is sensitive to ciprofloxacin this method would have been very unlikely to identify MRSA of pig origin. After discussion, the laboratory changed to using oxacillin for subsequent samples.

So when the Soil Association wrote to the FSA about a highly resistant strain of *E. coli* (ESBL *E. coli*) in January 2007, we also suggested that the FSA survey be extended to include examination of resistance in *S. aureus* (Young 2007). In reply, Dame Deirdre Hutton, Chair of the FSA, did not address the issue directly but stated 'Should a significant issue relating to imported food emerge during a survey, then further investigation of the problem would ensue' (Hutton 2007).

BOX 3.2 Methicillin-resistant, but is it actually MRSA?

MRSA has been found in animals from time to time since the 1970s, but it has been pointed out that some of the early cases may not in fact have been 'true' MRSA (Teale 2004). True MRSA bacteria have a '*mec*A' gene which enables them to produce a protein which makes the bacteria resistant to methicillin/oxacillin.

However, it is also possible for the bacteria to show resistance to methicillin without having the *mec*A gene. This can happen if they are 'hyperproducers' of beta-lactamase, a type of enzyme which makes bacteria resistant to penicillin and most other beta-lactam antibiotics (De Oliveira et al. 2000). These hyperproducers of beta-lactamase usually only have low-level or borderline methicillin resistance, which can be overcome by using a chemical which is a beta-lactamase inhibitor at the same time as the antibiotic. (Turutoglu et al. 2006). As a result, they do not present the same treatment difficulties as real MRSA. Modern molecular techniques mean that distinguishing between true MRSA and hyperproducers of beta-lactamase is now possible (Teale 2004).

In an attempt to see whether there is an issue with the safety of imported Dutch pork, the Soil Association purchased 28 samples of Dutch pork, and sausages containing pork 'of EU origin' during February and March. Samples came from Tesco, ASDA, Morrisons and Iceland and were sent to Nationwide Laboratories for testing. No MRSA was found. Our survey was particularly limited because these were the only supermarket chains we found to have Dutch pork (as opposed to bacon)[3] on sale at the time and each had only one line of product. For meat used in processed meat products, there is no requirement to identify the country of origin, we were not able to ensure that the sausages tested did in fact contain Dutch pork.

Although we did not find any MRSA in our small survey, the fact that both the Dutch Food and Consumer Safety Authority and Professor Kluytmans did find positive samples in their surveys shows that MRSA-contaminated meat is almost certainly being imported. Since there is now evidence of 'a significant issue relating to imported food' which Dame Deirdre Hutton suggested would motivate research to be carried out in the UK, the FSA should carry out a statistically valid survey of imported Dutch pork, to establish to what extent British consumers are being put at risk.

Pig MRSA in other countries

Along with the recent Dutch findings on MRSA in pigs, evidence is emerging (some of it very recent and not yet published) of MRSA occurring in pigs in countries other than the Netherlands. There is also evidence that the bacteria carried by these animals are passing to humans.

In some European countries this MRSA is the same ST398 strain as found in Dutch pigs. One explanation for this spread is that, in addition to producing large quantities of pork and bacon for export, the Netherlands is also Europe's largest exporter of live pigs, having exported nearly six million in 2005 (Pig Progress 2007a). Young Dutch 'weaner' pigs are exported to Italy, Spain, Belgium, Hungary, Croatia, Romania and Poland, but not the UK (Pig World 2007a). In addition, about three million Dutch pigs are exported to Germany each year (Pig World 2007b), but most of these go directly to be slaughtered. Older pigs are also exported for slaughter to Belgium (Pig World 2007a).

[3] We assumed (without scientific confirmation) that there would be less likelihood of finding MRSA on bacon than on pork because of the curing process.

Canada

The reporting of high levels of MRSA in Dutch pigs motivated a similar survey of Canadian pigs. The survey involves 30 farms in Ontario, from which 450 pigs are due to be tested (Weese 2007a).

The results are preliminary and as yet unpublished, but suggest that MRSA is also prevalent in pigs in Ontario. No precise figures are yet available from the study, but it is already known that a significant percentage of the farms proved to have MRSA-positive pigs, and on some of these farms a high percentage of the animals tested positive. Some of the pig farmers also tested positive for MRSA. It appears that more strains may be involved than in the Netherlands, but there is no definite information yet about which these are (Weese 2007b, 2007c).

The finding of potentially high levels of MRSA in some Canadian pigs may have implications for the United States where it appears that no surveillance for MRSA in pigs has yet been carried out. Since the US imports live pigs from Canada in increasingly large quantities, MRSA may be being introduced on a significant scale. It was forecast last year that in 2006 the US would import nearly nine million live pigs from Canada (Pig International 2006).

Denmark

A recent study has found the first confirmed case of MRSA in a Danish pig (Guardabassi et al. 2007). The strain involved was the same ST398 found in Dutch pigs. In an earlier study the scientists had tested 100 pigs from three farms in Denmark, and found no MRSA (Bagcigil et al. 2007). However, they found *S. aureus* which was not classifiable by PFGE from ten pigs from two of the three farms. Aware that the MRSA found in the Netherlands was also not classifiable by PFGE, they decided to re-examine the ten samples and this time found that one was positive for MRSA (Guardabassi et al. 2007). The scientists referred to unpublished research in Denmark and to published research in the Netherlands (Huijsdens et al. 2006b) and Germany (Witte et al. 2007) showing that ST398 can cause infections in humans and said that 'MRSA ST398 represents an important public health issue'. They concluded that 'the detection of ST398 in Danish pigs suggests that this new emerging zoonotic pathogen is rapidly spreading in the pig population in Europe'.

Danish Government scientists had previously noted a statistical association between human infections with the Dutch pig MRSA and contact with food-producing animals, which led them to suspect that MRSA might be present in Danish pigs. Professor Henrik Wegener from the National Food Institute in Denmark told us in December 2006 that 'We've seen an association between contact with food-producing animals and infection with CA-MRSA of the Dutch "swine-phagetype" in humans. I think it is likely that we will find it in the contact farms of the infected individuals, when we begin looking properly' (Wegener 2006). Professor Wegener also told us his laboratory had not isolated any MRSA from pigs through randomly checking submissions to the laboratory, which he said indicated that it may still be at a low level. He said that a larger survey of Danish pigs is now under way.

Belgium

The Soil Association has been told by Dr Marc Struelens, Professor of Clinical Microbiology at the Université Libre de Bruxelles, that preliminary research has found ST398 MRSA in pigs in Belgium. There is no information yet available on the number or proportion of pigs affected, but a national survey coordinated by the Belgian Antibiotic Policy Coordination Committee (BAPCOC), which advises the Ministry of Public Health, is now underway. The results of this investigation are due this summer (Struelens 2007).

'The detection of ST398 in Danish pigs suggests that this new emerging zoonotic pathogen is rapidly spreading in the pig population in Europe'

(GUARDABASSI ET AL. 2007)

There is already evidence in Belgium of ST398 MRSA causing infections in humans. Since 2003, there have been eight cases of human colonisation or infection (this represents less than 0.5% of strains from hospitalised patients surveyed in 2003-2005). Some of the infections were deep-seated, and there was one case of blood poisoning. Whether or not the patients had contacts with livestock is now being investigated (Struelens 2007).

In January 2007 it was reported in the Belgian press that an abattoir worker in Flanders had been infected by MRSA from a pig he had been handling (Agri Press 2007). Dr Bart Gordt of the St Jan hospital in Bruges warned of the possibility of people who handle or work with pigs becoming infected with MRSA. The case has not yet been published in the scientific literature, but a paper is currently in preparation.

Germany

In January 2007, a group of German and Austrian scientists led by Professor Wolfgang Witte reported finding ST398 MRSA in a pig, a dog, a foal, and 15 humans, nine of whom had infections, with the other six being carriers. In addition, two horses similarly infected were detected in Austria. All of the MRSA bacteria were resistant to tetracyclines, and the MRSA from the pig, the dog and 13 of the humans were also resistant to macrolide antibiotics (Witte et al. 2007).

Witte and co-authors argued that the ST398 strain of MRSA, which they noted was the same strain as found in Dutch pigs, appeared to have arisen only recently in humans. They explained that a characteristic of ST398 MRSA is that it cannot be successfully analysed by a method known as *Sma*I macrorestriction analysis and pointed out that between 1992 and 2003, of 11,250 human isolates of MRSA taken from hospitals and from within the community in Germany, all could be analysed by *Sma*I macrorestriction analysis. In addition, they said, a British study published in 2002 and another unpublished German study did not detect any ST398 in human MRSA carriers.

Witte and colleagues say that ST398 MRSA is clearly capable of causing disease in humans, and they are particularly concerned because they had already detected the MRSA not just in outpatients but also in seven inpatients with ventilator-associated pneumonia (Witte et al. 2007, Cuny et al. 2006a). The presence of ST398 in inpatients may be an indication that we are already seeing this pig-associated MRSA entering, and spreading in hospitals.

France

Scientists in France report evidence, albeit inconclusive, of the same ST398 strain of MRSA being passed from pigs to humans. In their study, they compared bacteria isolated from pig farmers with those from non-farmers, and found that pig farmers were significantly more likely to have *S. aureus* in their nose or pharynx: as Table 3.2 shows, 50 out of 112 pig farmers (45%) tested positive for *S. aureus* compared to 27 out 112 non-farmers (24%). Levels of resistance to antibiotics, in particular resistance to macrolide antibiotics, were also higher in the bacteria isolated from pig farmers.

The authors of the study explained that since the pig farmers and non-farmers used similar amounts of antibiotics for their own medication, they did not think this could explain the differences in the levels of antibiotic resistance. They concluded that the most likely explanation was that resistant *S. aureus* bacteria were being transferred from the pigs to the farmers (Aubry-Damon et al. 2004).

MRSA was also isolated from five pig farmers (10%), but no MRSA was isolated from any of the non-farmers (see Table 3.2). This difference, however, was not considered to be statistically significant (Aubry-Damon et al. 2004).

Table 3.2 *S. aureus* from pig farmers and non-farmers, and their antibiotic resistance

	Pig farmers	Non-farmers
Number with *S. aureus*	50 out of 112 (44.6%)	27 out of 112 (24.1%)
Resistant to methicillin (MRSA)	5 out 50 (10%)	0 out of 27 (0%)
Resistant to macrolides	36 out of 50 (72%)	2 out of 27 (7.4%)
Resistant to gentamicin	10 out 50 (20%)	0 out of 27 (0%)
Resistant to pefloxacin	8 out of 50 (16%)	1 out of 27 (3.7%)

Source: Aubry-Damon et al. 2004

In a follow-up study, the scientists analysed the sequence type of the *S. aureus* bacteria (including the MRSA) taken from the pig farmers and the non-farmers, as well as some isolates from the pigs: they looked at 44 of the *S. aureus* isolated from pig farmers, 21 of the *S. aureus* from non-farmers and 14 *S. aureus* from pigs, using the MLST method. They found that 25 of the 44 isolates (57%) taken from the pig farmers had sequence types found in the bacteria from the pigs but these were not present in the non-farmers. They also found that 13 of the 14 isolates (93%) from the pigs were found in the pig farmers, but not in the non-farmers. The scientists concluded that 'The high risk for nasal *S. aureus* colonisation that we previously reported in pig farmers was due to strains exchanged with swine' (Armand-Lefevre et al. 2005).

Three sequence types were shared by the *S. aureus* from pigs and pig farmers. One of these three sequence types was ST398,[4] the same sequence type found in the Dutch and German pigs. Furthermore, one of the five MRSA isolates previously found on the pig farmers was also sequence type ST398. The scientists concluded that: 'Animal MRSA have been suggested as a source of infection for humans. Our results suggest that such transmission may be frequent, particularly since virtually no barrier precautions were used by the pig farmers in our previous investigation' (Armand-Lefevre et al. 2005).

Ireland

Large numbers of live pigs are imported each year from the Republic of Ireland into Northern Ireland, for slaughter. In 2004, 402,000 pigs were imported (BPEX 2005), so the MRSA status of Irish pigs is significant for the British consumer.

Some preliminary investigations have been carried out. Dr Nola Leonard of University College Dublin has told us that she has tested a few samples collected from the perineum (the area between the genitals and the rectum) of pigs at abattoirs. She isolated *S. aureus*, but no MRSA (Leonard 2007). The Food Standards Agency of Ireland is also planning an MRSA survey, to include pigs.

[4] The other strains were ST9 and ST433.

4. MRSA in other animals, meat and farmers

'To our knowledge, this finding indicates the first documented case of direct transmission of MRSA between cows and humans'

DR ÉVA JUHÁSZ-KASZANYITZKY AND OTHERS (JUHÁSZ-KASZANYITZKY ET AL. 2007)

MRSA in cattle

The first report of MRSA in farm animals was published in the early 1970s when the bacteria were isolated from the milk of dairy cows with mastitis in Belgium (Devriese et al. 1972, Devriese and Hommez 1975). In the past few years, MRSA has been isolated from cows (or their milk) in Korea, Hungary, Mexico and the Netherlands (Lee 2003, Kaszanyitsky et al. 2004, Bernabé et al. 2005, Kwon et al. 2005, Juhász-Kaszanyitzky et al. 2007, Veerman 2007).

There have also been numerous reports of oxacillin/methicillin-resistant *S. aureus* from cows or their milk in Brazil, Italy, Pakistan, Nigeria, Turkey and the US. However, in these reports, it is not clear whether these were cases of 'true' MRSA (see Box 3.2) (Umoh et al. 1990, Costa et al. 2000, Cuteri et al. 2002, Erskine et al. 2002, Farzana et al. 2004, Turutoglu et al. 2006). The early Belgian report, in contrast, was very probably a case of MRSA as the scientists were able to show that the bacteria shared important characteristics with human MRSA.

In the UK, no MRSA has so far been found in cattle, but the cases in other countries motivated Defra to look for MRSA in milk from cows with mastitis. To date, 425 samples have been analysed and no MRSA found (Defra 2007b).

The Dutch Minister, Dr Cees Veerman, revealed earlier this year that a study in 2006 by the Dutch Food and Consumer Safety Authority had found a very high incidence of MRSA in the faeces of Dutch calves: 20 of 150 samples tested (13%) were MRSA-positive. Furthermore, Dr Veerman said that MRSA had also been found in Dutch dairy cows from four farms. This was detected during routine testing for mastitis in 2006. Several raw milk samples from the MRSA-positive farms also contained MRSA (see Appendix). All isolates were the same Dutch pig strain (Oosterom 2007).

In the past, when *S. aureus* causing mastitis in dairy cows have been compared with *S. aureus* which cause infections in humans, they have generally been found to be different strains (Teale 2002). Nevertheless, a number of studies have considered whether bovine MRSA is related to human MRSA and whether contact with cows, or consumption of food from cattle, can result in human infections. A Korean study by Dr John Lee, published in 2003, found 12 samples of MRSA in 894 milk samples from dairy cows. The MRSA bacteria were analysed using the random amplification polymorphic DNA (RAPD) method, and Lee found that the RAPD patterns were identical to patterns from human MRSA. He concluded that MRSA in animals was a 'possible source of human infections caused by consuming contaminated food products' (Lee 2003).

Using different analytical methods, however, other scientists have since reached a different conclusion. Dr Kwon and colleagues isolated 14 samples of MRSA in bovine milk and analysed these using the MLST and PFGE methods, which are considered to be more reliable than the RAPD method used by Lee. They found that all the MRSA produced the Panton-Valentine leukocidin toxin, and had 'community-acquired characteristics', but the MLST method showed that they

were unrelated to the community-acquired MRSA causing infection in Korea at the time. The researchers suggested that the MRSA might have evolved in cattle, perhaps due to the excessive use of antibiotics to treat chronic mastitis problems. They recommended that 'the prudent use of antibiotics and rapid and continuous screening for resistant microorganisms should be more focused to prevent the emergence and spread of new types of MRSA' (Kwon et al. 2005).

However, a recent Hungarian study has found clear evidence that certain MRSA strains can be passed between cattle and humans in one direction or the other. The study examined 595 milk samples from a dairy farm over a three-year period, 27 of which (4.5%) were found to contain MRSA. Tonsil swabs were also collected from 12 of the workers on the farm (vets, milkmen and attendants) who were in close contact with the animals. Of the 12 samples, three contained *S. aureus*; one of these was MRSA.

The genetic make-up of the bovine and human MRSA bacteria were analysed by a number of different methods including PFGE typing, *spa* typing and MLST typing, and all were found to be identical by all methods. The scientists concluded that the use of antibiotics may have contributed to the emergence of MRSA on the farm and suggested that people in close contact with MRSA-infected cattle, such as vets, farmers, herdsmen and abattoir workers may become colonised. They were not able to say definitively whether the MRSA had passed from the animals to humans or from humans to animals (Juhász-Kaszanyitzky et al. 2007).

MRSA has also been found in retail beef. A study by the Dutch Food and Consumer Safety Authority carried out in 2006 found the same strain of MRSA as found on live pigs and cattle, on two out of 64 samples of raw beef (3%) from supermarkets (Oosterom 2007, Veerman 2007). A Jordanian study found that three samples of beef out of 317 (0.9%) bought in the Amman area were contaminated with MRSA. The authors of the research warned that consuming meat products, meat processing or direct contact with the animals could be a source of MRSA infections (Quddoumi et al. 2006).

MRSA in chickens

The findings of a recent study from the Netherlands suggest that poultry may also be a source of MRSA which can pass to humans. The study, carried out by microbiologist Sander Leenders and published by the National Institute of Public Health and the Environment (Dutch acronym RIVM), describes the case of a patient who lives on a poultry farm and who was screened on entrance to a Dutch hospital because he was returning from abroad and was therefore considered to be in a high-risk category. When he was found to be an MRSA carrier, his daughter-in-law, who happened to work as a nurse in the same hospital but who was not caring for him, asked to also be screened for MRSA. Tests showed that she was also MRSA-positive.

It was then decided to screen the three families living on the poultry farm and on two related poultry farms nearby. Five of the six adults were found to be MRSA carriers, but none of the three children were. Chicken droppings from the farms were also tested for MRSA, and one of 16 samples was positive, for the same strain as found in the humans.

All the MRSA isolates were of the same strain, which was unclassifiable by the PFGE method, just like most of the MRSA which has been found in Dutch pigs (see Chapter 3) (RIVM 2007b). We were told by a spokesperson for the RIVM that it was not possible to conclude from the study whether or not the chickens were an MRSA source for the humans, or vice versa, but that their feeling is that it is most likely that the chickens gave MRSA to the humans (Tiemersma 2007).

The Director of the RIVM's Centre for Infectious Disease Control, Professor Roel Coutinho, has said that there is no evidence yet that chickens are a

'structural' source of MRSA for humans, but he has warned that there is a real danger that MRSA in chickens could cause 'big problems' in the future (Kok 2007)

Dr Leenders said that the results of the study showed the need for more research to establish the prevalence of MRSA in all farm animals, instead of only focusing on pigs and cattle (Pig Progress 2007b). The RIVM has now decided to carry out a 'quick scan' of poultry abattoirs in 2008 (Tiemersma 2007).

The finding of MRSA on a chicken farm, which was apparently the same as the MRSA previously found on pig farms in the Netherlands, gives a new perspective on a report, published in November 2006, of a serious MRSA ST398 infection in a Dutch woman (Ekkelenkamp et al. 2006). This case concerned a 63-year-old woman who developed a life-threatening heart infection called endocarditis. Although the Dutch authorities have recognised that pig farmers, abattoir workers and vets are at high risk of acquiring ST398, she was not in any of these risk groups. However she and her husband did have a chicken farm and lived close to a pig farm. It remains unclear how she acquired the infection since the chickens on her farm and the pigs on the neighbouring farm were not tested.

MRSA has also been detected in chickens in Korea. Samples were collected from 15 abattoirs, and two of 119 joint samples were positive. No MRSA was found in faeces or in throat samples (Lee 2003).

Several studies have found MRSA in retail chicken meat. In 2006, the Dutch Food Safety Authority found MRSA in a remarkably high percentage of chicken-meat samples from supermarkets: five of the 24 samples (21%) were MRSA positive. All were the main Dutch farm-animal strain. This is a much higher percentage than found in other studies around the world. The Korean study mentioned above found MRSA on one of 69 samples (1%) (Lee 2003). A study in Japan found the bacteria on two out 292 samples (1%). The strain in this case was a type found in humans and the scientists felt it likely that workers handling the meat had contaminated it (Kitai et al. 2005). The Jordanian study previously cited also found MRSA on five samples out of 218 (4%) (Quddoumi et al. 2006).

BOX 4.1 A possible case of MRSA in British chicken?

In the UK, scientists from Kingston University recently tested 100 samples of retail chicken for MRSA, and found one sample of *S. aureus* which showed resistance to methicillin. However, it has not yet been established whether the resistant bacteria have the *mec*A gene, which characterises true MRSA (see Box 3.2). The research is very recent and is still ongoing (Fielder 2007a, 2007b).

In a survey of retail chicken, researchers in Korea found 'pre-MRSA' (that is, *S. aureus* which is not fully resistant to methicillin despite having the *mec*A gene, but which quickly evolves into MRSA when treated with methicillin) in three out of 190 samples (1%) (Kwon et al. 2006).

MRSA in sheep

Very few studies have reported on the prevalence of MRSA in sheep. Overall antibiotic use tends to be much lower in sheep than in pigs, poultry or dairy cows, which may result in a low prevalence of MRSA. However, antibiotics are liable to be used in greater quantities in herds of dairy sheep, particularly for the treatment or prevention of mastitis, and in some flocks lambed indoors where antibiotics are used routinely in young lambs to prevent both *E. coli* infections and navel ill.[1]

A Spanish study examined 38 samples of *S. aureus* taken from dairy-sheep flocks and found that one sample showed methicillin resistance. However, the bacteria were not tested for the presence of the *mec*A gene (Goni et al. 2004).

Meat samples from sheep were also tested in the Jordanian study. Out of

[1] Navel ill is a bacterial infection of the navel, occurring soon after birth in lambs born in unhygienic conditions indoors. It can rapidly spread to the joints and cause deformity or death.

717 samples collected in the Amman area, six (0.8%) were positive for MRSA (Quddoumi et al. 2006).

MRSA in horses

Horses are kept on many farms and their meat is consumed in some European countries. In recent years, studies from the UK, Ireland, Austria, Canada, the US and Japan have found MRSA in horses (Hartmann et al. 1997, Shimizu et al. 1997, Baptiste et al. 2005, Middleton et al. 2005, O'Mahony et al. 2005, Weese et al. 2005a, Cuny et al. 2006b, Moodley et al. 2006). Evidence has also emerged that MRSA from horses can be transmitted to humans and even cause infections.

A cross-border study in North America conducted by Dr Scott Weese and colleagues, published in 2005, examined the prevalence of MRSA in horses and people who work with horses. A total of 972 horses and 107 personnel from 42 equine farms in Ontario, Canada, and from two equine farms in New York State were examined. MRSA was isolated from 46 horses (4.7%) and 14 humans (13%) (from farms in both Ontario and New York State). Only one strain was found, called Canadian MRSA-5, a strain which is uncommon in humans. On every farm where MRSA was found in a horse at least one person was also colonised with the same strain of MRSA (Weese et al. 2005a).

Although we have found no data on levels on MRSA colonisation of the general population in Canada, the level found in people working with horses in this study is much higher than published community-acquired MRSA colonisation rates for the general population in other countries (see Table 4.1).

Table 4.1 MRSA carriage levels in different populations in the community

Canadians working with horses[a]	13%
UK population in Birmingham[b]	1.5%
UK elderly[c]	0.8%
Overall international level until 2002[d]	1.3%
International level until 2002 for those with no healthcare contact[d]	0.2%
Switzerland at hospital admission[e]	0.1%

Sources: (a) Weese et al. 2005a, (b) Abudu et al. 2001, (c) Maudsley et al. 2004, (d) Salgado et al. 2003, (e) Harbarth et al. 2005, (f) Wertheim et al. 2004

In a second paper, Dr Weese and colleagues reported further cases in Ontario of MRSA in horses and people who work with them. They also found the first reported case of an MRSA infection in a human working with horses. The researchers were unsure of the origin of the equine MRSA and said that it might have come from humans, but that it could also be due to 'the increasing use of antimicrobial drugs in veterinary medicine'. They warned that 'equine MRSA infection may be an important emerging zoonotic and veterinary disease' (Weese et al. 2005b).

A later study by Dr Weese and colleagues found several further cases of human infection with MRSA apparently acquired from horses. Three individuals working in a veterinary hospital, and who were in contact with a foal which was colonised by MRSA, developed skin infections. The MRSA strain was the same strain as previously found in horses and people who work with horses (Weese et al. 2006a).

Further evidence that MRSA may have evolved in horses, rather than merely being passed from humans to horses, comes in an Austrian study. Scientists examined 768 samples taken from horse wounds and found MRSA in 24 of them. The bacteria were analysed using molecular methods, including MLST, and were all found to be similar. They were also all different from almost 3,700 human MRSA isolates examined by the same scientists. They concluded that the MRSA had emerged in horses independently. They also found that two vets working with

'These results imply that MRSA is present in the general horse population and may represent a reservoir of new or rare MRSA strains that could be transmitted to humans'

(BAPTISTE ET AL. 2005)

horses had nasal colonisation by this equine MRSA strain (Cuny et al. 2006b).

MRSA has also been found in eight horses in Ireland, where the pattern of isolates were said to be 'unlike any patterns previously reported in Irish studies of human isolates'. While one of two isolated strains may have come from hospitals, the source of the other strain could not be identified (O'Mahony et al. 2005).

MRSA has also been found in 11 of 67 horses (16%) sampled at the Philip Leverhume Equine Hospital. Three horses had MRSA-associated infections, the others were MRSA carriers with no signs of infection. In contrast to other studies of MRSA in horses, there was no evidence that MRSA had transferred between horses and staff in either direction. However, the study only screened staff at the veterinary hospital, and not those who had worked with the horses over longer periods. Five different strains of MRSA were identified, none related to hospital strains. The scientists concluded that 'these results imply that MRSA is present in the general horse population and may represent a reservoir of new or rare MRSA strains that could be transmitted to humans' (Baptiste et al. 2005). Table 4.2 summarises these recent studies comparing MRSA in horses and humans.

Table 4.2 MRSA studies in horses and people who work with horses

	Related to common human MRSA	Same MRSA found in people working with the horses
Austria[a]	No	Yes
Canada[b]	No	Yes
Ireland[c]	One yes, one unsure	Yes
UK[d]	No	No

Sources: (a) Cuny et al. 2006b, (b) Weese et al. 2005a, Weese et al. 2005b, Weese et al. 2006a (c) O'Mahony et al. 2005, (d) Baptiste et al. 2005

The case of Founderguard use in horse feed

Founderguard is an imported feed additive given to horses to prevent a condition known as laminitis, which occurs in horses fed a high-energy diet.[2] The active ingredient is the antibiotic virginiamycin, which was banned throughout the European Union in 1999 amid concerns that it could cause resistance to a closely related new drug, Synercid, used to treat MRSA and other serious infections caused by highly antibiotic-resistant bacteria.[3] Founderguard enables higher-energy diets to be fed to the animals without inducing laminitis.

However, Founderguard is not an officially approved medicine and has undergone no British or EU assessment for safety. The VMD has even acknowledged that 'There is an unknown element of risk associated with its use in so far as the UK licensing authorities are aware' (MAVIS 2005). Nevertheless, the VMD has been issuing Special Treatment Authorisations (STAs)[4] allowing vets to import Founderguard for use in horse feed. In discussions with the Soil Association and other consumer groups, the VMD defended this by emphasising 'the distressing nature' of laminitis (VMD 2001). The Soil Association remains concerned over this issue and has attempted to establish the extent of Founderguard usage (see Box 4.2)

Understandably, vets are being put under pressure by horse owners who have found Founderguard to be effective. Equine internet chat rooms describe frustration at veterinary control of Founderguard. Alarmingly, contributors to these chat rooms also discuss numerous ways round the restrictions. For example, Founderguard is for sale on the US website eBay, 'shipped worldwide'. Internet adverts for 'opened buckets of Founderguard' for sale to any buyer can also be found. Evidently, the use of Founderguard is not fully traceable.

[2] Laminitis (also known as founder) is a painful and debilitating condition causing lameness in horses. Most cases are caused by allowing the horses to ingest lush grass rich in carbohydrates, or by feeding them high-energy grains. The acidity caused by this diet can release toxic substances from the gut into the bloodstream and this disrupts blood supply to the feet. While laminitis can be prevented by good management, a horse which has become affected is subsequently more prone to repeat attacks.

[3] Synercid is a combination of the two streptogramin antibiotics quinupristin and dalfopristin, which have been shown to be cross–resistant with the streptogramin antibiotic virginiamycin. Despite the ban on virginiamycin in the EU, strong industry opposition to a similar ban in the US and some other countries means that it continues to be used outside the EU as a feed additive in chicken and cattle.

[4] Special Treatment Authorisations are issued in certain circumstances to permit the use of non-approved drugs.

BOX 4.2 Protection of corporate interests

In 2001, after a meeting with consumer representatives where the issue of Founderguard had been raised, the VMD provided John Verrall, of the charity the Food Ethics Council, with sales figures for Founderguard between September 2000 and March 2001 (Lewsey 2001). Mr Verrall made a copy of this letter available to the Soil Association which had also been represented at the meeting. During this winter period when laminitis is not usually a problem, there had been 379 STAs to authorise the use of 2,500 kg of Founderguard.

Mr Verrall later became a member of the Veterinary Products Committee and drew to its attention the problem with Founderguard at meetings in 2004 and 2005. Eventually the VMD tightened its procedures and reported a 65% reduction in the quantity of Founderguard imported between January and June 2005 compared with the same period in 2004. During that same period, however, the VMD published a warning to vets stating: 'We are aware that increasing amounts of Founderguard are being imported from Australia into the UK' (MAVIS 2005).

To clarify whether imports of Founderguard were in fact increasing or decreasing, in June 2005 the Soil Association asked the VMD to provide import figures of Founderguard along with the number of Special Treatment Authorisations issued. In July 2005 it explained that, in line with the Freedom of Information Act, it felt unable to release this information because it would be to the 'obvious commercial detriment of the company' which sells Founderguard. The Soil Association questioned the legitimacy of this excuse on the basis that the company, Virbac Limited of Bury St Edmonds, has a monopoly on Founderguard, and so releasing sales information would not hinder its competitive edge. Furthermore, we felt that public interests were best served by the full disclosure of information in order to increase awareness of the scale of usage and the potential dangers from the use of the drug.

The Soil Association's appeal led to an internal review by the VMD that included an undisclosed discussion with the Department for Constitutional Affairs (DCA) but produced the same conclusion, namely that commercial interests outweigh public interest in this case. We then appealed to the Information Commissioner in November 2005 setting out detailed reasons why the information should be released, but despite regular holding letters and many phone calls to the Commissioner's office, our case, now understood to be the oldest unresolved case on their files, has still not been decided.

The use of Founderguard in horses could, however, impair our future ability to keep pace with the development of multi-drug resistance in MRSA. Already, only a small number of antibiotics are still effective against MRSA infections, and most of these have side effects. The latest Government guidelines recommend that Synercid should be kept as a 'reserve drug', to be used for MRSA infections which have developed resistance to the current drug of choice, vancomycin (Gemmel et al. 2006). If equine strains of MRSA develop resistance to virginiamycin and Synercid, and then pass to humans, our future ability to treat infections in humans could be limited. While there is currently no evidence to demonstrate that resistance to virginiamycin or Synercid has already developed in horses with MRSA, the possibility that this will eventually happen must be high (if it has not already happened and gone undetected), and we already know that MRSA can pass readily from horses to humans.

Horses which have been treated with non-approved drugs like Founderguard are not permitted to enter the human food chain, and a horse-passport system exists to enforce this legislation. However, those working in the pet-food industry, either slaughtering horses or handling raw meat before processing, could still be at risk of becoming carriers of Synercid-resistant strains of MRSA. Also, because of the relative heat resistance of MRSA (Defra 2006a), practices within the pet food industry should be scrutinised to ensure that MRSA does not pass from horses to pets via pet food.

MRSA in pets

MRSA is being reported with increased frequency in pets. The bacteria have been found in dogs in the UK, Ireland, Holland, South Korea, the US and Germany (Pak et al. 1999, Tomlin et al. 1999, van Duijkeren et al. 2004a, Baptiste et al. 2005,

Loeffler et al. 2005, Middleton et al. 2005, O'Mahony et al. 2005, Kwon et al. 2006, Leonard et al. 2006, Moodley et al. 2006, Rich and Roberts 2006, Strommenger et al. 2006). MRSA has also been found in cats in the UK, Ireland, Canada, the US and Germany (Middleton et al. 2005, O'Mahony et al. 2005, Rankin et al. 2005, Moodley et al. 2006, Morris et al. 2006, Rich and Roberts 2006, Strommenger et al. 2006, Vitale et al. 2006, Weese et al. 2006b).

MRSA is not just carried by pets but can cause disease too. In the UK, one laboratory has reported finding over 600 clinical cases of MRSA infections in pets, from veterinary clinics across the country (Rich et al. 2007). MRSA infections have been found in the UK in pet birds, rodents and lagomorphs (mammals such as hares and rabbits), as well as in cats and dogs (Rich and Roberts 2006).

MRSA in pets is attributed to their close contact with humans (Manian 2003, Duquette and Nuttall 2004, Guardabassi et al. 2004, Weese et al. 2006b). Several studies have examined the strains of MRSA in pets and have found that they are indistinguishable from, or closely related to, human strains (Loeffler et al. 2005, Strommenger et al. 2006, Weese et al. 2006b). Scientists also now generally accept that pet-to-human transmission of MRSA can occur.

A number of studies have provided evidence of MRSA passing between humans and pets. In 1988 the removal of a cat colonised with MRSA from a geriatric ward led to the rapid resolution of an MRSA outbreak. The cat was believed to have acquired the resistant bacteria from the hospital environment (Scott et al. 1988 quoted in Duquette and Nuttall 2004). Similarly, recurrent MRSA infections in a man and his wife were only cured when the bacteria were eradicated from the nostrils of the family's dog (Manian 2003).

In the UK, very high levels of MRSA (17.9%) were found in staff working in a small-animal hospital. The same strains were found in 9% of dogs tested in the hospital; further evidence of inter-species spread (Loeffler et al. 2005).

A Canadian study found MRSA in dogs and cats, and in humans who came into contact with them. An indistinguishable MRSA was found on at least one human in contact with each MRSA-positive animal. The scientists suspected MRSA movement in both directions between humans and animals. They said that 'investigation of community-acquired MRSA should involve consideration of animals as sources of infection, and animals as potential reservoirs of infection should they acquire MRSA in the household' (Weese et al. 2006b).

Scientists have emphasised that virtually the same antibiotics are used in pets as in humans, and that there are fewer restrictions on their use than in food-producing animals (Guardabassi et al. 2004). Since the close contact that pets have with humans enables the transmission of any resistant bacteria, scientists have recommended that the use of antibiotics in pets should be as responsible and prudent as possible (Duquette and Nuttall 2004, Guardabassi et al. 2004).

5. The spread of farm-animal MRSA

The risk that farm-animal MRSA will spread to the UK

Despite the emergence of the MRSA strain ST398 in the Netherlands, it is still too early to judge whether this is in fact where it originated. The Dutch have a history of great care and attention when it comes to the early identification of new MRSA problems and action to deal with them effectively. In most other countries there has still been little or no research even to establish whether MRSA is present in farm animals.

Nevertheless, it is now clear that MRSA is well-established in Dutch pigs and the fact that the Netherlands exports approximately six million live pigs a year to other EU countries is a major cause for concern. The international live-pig trade may explain why the same strain of MRSA has already been found in pigs in Belgium, Denmark and Germany, and is suspected to be French pigs too. It also strongly suggests that MRSA will already be present, undetected, in pigs in other countries that import Dutch pigs, such as Italy, Spain and Poland.

The UK is fortunate in that it imports no live pigs from the Netherlands, or any country in which pig MRSA has so far been found or suspected. It does, however, import millions of live chicks and turkey poults each year from continental Europe, including the Netherlands, and from the United States (Defra 2007b, 2007c). With MRSA having been found on a Dutch poultry farm and on 21% of Dutch retail chicken-meat samples (see pp. 29–30), there is a clear risk of MRSA-positive birds being imported into the UK.

There are also less obvious ways by which MRSA could spread to British pigs. The most likely mode of transmission would be via foreign farm workers or vets who become carriers while working with pigs or other animals carrying MRSA in one of the countries where MRSA is now present, and then come to work on UK farms. There has been a long tradition in western Europe of young farmers and farm workers gaining experience in other countries, and since the enlargement of the EU in May 2004, nationals from the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia and Slovenia have also come to work in Britain. Government figures show that over 50,000 such workers have taken up jobs in British agriculture (Home Office et al. 2006).

In addition the Home Office runs the Seasonal Agricultural Workers Scheme (SAWS) which this year permits 16,250 migrant workers from outside the European Economic Area to work in UK agriculture for up to six months at a time (Home Office 2007). While the majority of these will be involved in seasonal field work, the scheme also permits workers to be employed for handling livestock (Dench et al. 2006).

Similarly, agricultural students and others from the UK who get work experience in other countries on livestock farms could become carriers and bring new strains of MRSA back with them on their return.

Out of the 15,461 vets working in the UK, approximately 4,000 come from abroad (RCVS 2006, RCVS 2007). Since 45% of British veterinary practices are

'The overall Dutch approach and the new information about MRSA in pigs […] have implications for other countries beyond the Netherlands'

DR ROBERT SPENCER (MOYER 2006)

mixed-animal practices, with a further 1% specialising in farm animals only, many of these vets will be working with farm animals. Some vets from other EU countries are employed by the Meat Hygiene Service to inspect abattoirs and have to be present all the time that slaughtering is taking place. In addition, British farmers and their families travel to other EU countries on business or on holiday, just as other Europeans come to Britain where they may have direct contact with farm animals at agricultural shows and farms open to the public.

How MRSA can be transmitted from farm animals to humans

There are a number of recognised ways by which animal MRSA can be transmitted to humans:

- by direct contact with the animals
- through environmental contamination
- by eating or handling contaminated meat

Direct contact: farmers, abattoir workers and vets at risk

As when MRSA spreads between humans, direct contact is an important way by which animal MRSA can be transmitted. As a result, those who have direct contact with farm animals which carry MRSA have the highest risk of acquiring farm-animal MRSA.

The evidence presented in Chapter 3 showed that Dutch pig farmers have a high risk of becoming carriers of pig MRSA: the most recent study found that approximately 50% of those living on Dutch pig farms were carriers, and some of these people develop serious infections (Zembla 2006, Kluytmans 2007). A Belgian abattoir worker also became infected with pig MRSA (Agri Press 2007).

In Chapter 4 we saw that there was also evidence of MRSA being transmitted between cattle and farmers, and chickens and farmers, although it has not yet been firmly established that these animals are passing the bacteria to humans (Juhász-Kaszanyitzky et al. 2007, RIVM 2007b). On the other hand, there is convincing evidence that most equine strains of MRSA are being transmitted to people who work with horses, and are causing infection in some cases (O'Mahony et al. 2005, Weese et al. 2005b, Cuny et al. 2006b, Weese et al. 2006a).

Vets are also at risk if the animals they are handling are infected with MRSA. In a Dutch study published in December 2006, vets and veterinary students attending a conference in the Netherlands were screened for MRSA colonisation. Of 179 vets and students who had had contact with animals, seven (4.6%) were colonised with MRSA (Wulf et al. 2006). This was a prevalence rate 150 times higher than found in an earlier study for the general Dutch population (Wertheim et al. 2004). None of the 27 students who had not been in contact with animals were colonised with MRSA. All of the seven individuals who were MRSA-positive had been in contact with pigs and cattle, whereas only two of them had been in contact with pets. The scientists concluded that contact with pigs and cattle presented the highest risk factor for MRSA colonisation and that people working with farm animals should be screened for MRSA on admission to hospital (Wulf et al. 2006).

Attendees at a veterinary conference in the United States were found to have high rates of MRSA colonisation. Nasal swabs were taken from 417 attendees, and MRSA was found in 27 samples (6.5%). Those most likely to be colonised were vets working with large animals (in this case mainly horses but also cattle): 15 of 96 vets (15.6%) working with large animals were colonised, 12 of 271 of those working with small animals (4.4%), compared with none of 50 people working in industry or research. The scientists warned that MRSA colonisation might be an occupational risk for vets (Hanselman et al. 2006).

Of note in this study was the particularly high rate of MRSA colonisation for

attendees from the UK: two of 12 British attendees (17%) were MRSA carriers, and both worked with large animals. A similarly high MRSA rate was found in British vets working in a small-animal referral hospital in London: 14 of 78 staff (17.9%) and 4 of 45 dogs (8.9%) were colonised with MRSA. The majority of the MRSA were indistinguishable from (56%) or closely related to (26%) a strain known as EMRSA-15, one of the two dominant epidemic strains in UK hospitals (Loeffler et al. 2005).

A recent Danish study also found high levels of MRSA in vets. In total, 6% of the vets tested were MRSA-positive (Guardabassi and Skov 2006). None of the MRSA carriers had received antibiotics or been hospitalised in the previous six months, but all had worked with cattle and some with other animals. This study was carried out before MRSA had been found in a Danish pig, and the authors pointed to the low levels of MRSA in the Danish population and in animals in Denmark. They suggested that one possible explanation for relatively high levels of MRSA in Danish vets might be that vets frequently handle antibiotics without gloves.

BOX 5.1 Defra and animal MRSA

A subgroup of Defra's internal advisory and policy coordination committee, the Defra Antimicrobial Resistance Coordination (DARC) Group, currently advises the Department on MRSA in animals. The DARC committee's minutes are publicly available and a webpage based on the subgroup's advice provides information about the appearance of MRSA in livestock and other animals.

While Defra's open approach is welcome, its assessment of the dangers associated with farm-animal MRSA over-emphasises the unknowns and fails to give adequate weight to what is already known. The webpage, most recently updated in March 2007, states that 'the overall significance of the detection of MRSA in animals in relation to public health is not known'. Although Defra has recently acknowledged that MRSA has been found in pigs in some countries, it makes no mention of the evidence that this strain is already being transmitted to humans and causing serious infections.

DARC also still supports the long-held view that the movement of MRSA is most likely to be one-way – from humans to animals. Another Defra webpage, updated in February 2007 states that 'the available evidence suggests that humans are likely to be the source of MRSA strains infecting or colonising animals', although it concedes that 'animals colonised or infected with MRSA form a potential reservoir that could re-infect human contacts' (Defra 2007a). Again, the developments in the Netherlands are not mentioned.

Some of the uncertainties surrounding the significance of MRSA in farm animals are also due to Defra's reluctance to investigate. The Department has decided not to carry out a survey of pigs in the UK saying that such a survey would be 'speculative' (see Chapter 3).

Environmental contamination through manure and air

There are two main ways by which antibiotic-resistant bacteria from farm animals can escape into the environment: through manure, and by being carried in the air.

Studies in humans have shown that MRSA colonisation of the gastrointestinal tract is as common as nasal colonisation (Rimland and Roberson 1986, Campillo et al. 2001, Boyce et al. 2005). It is reasonable to expect that the same will apply for animals, and the available evidence suggests that this is the case. Although the Dutch abattoir survey which found that 39% of pigs were MRSA carriers only tested nasal swabs and did not examine whether pigs excreted MRSA in their faeces (de Neeling et al. 2007), the first study to find MRSA in a pig actually found the bacteria by testing samples from the perineum of pigs (the area between the genitals and the rectum), having previously failed to find MRSA from the same farm through testing nasal samples (Voss et al. 2005). MRSA has also been found in chicken droppings, and in cattle faeces in the Netherlands (RIVM 2007b).

Since manure from farm animals gets spread on the land, there is real danger of MRSA being spread with it, contaminating the water supply and crops. British consumers may be exposed to MRSA on imported vegetables which have been

grown in fields fertilised with contaminated manure.

A recent American study suggests that people living near an MRSA-positive intensive pig farm may also be exposed to high concentrations of MRSA in the air. The study examined the levels of antibiotic-resistant bacteria in bioaerosols (that is, airborne micro-organisms) within, upwind and downwind of an intensive pig farm, at various distances of up to 150m. Significantly, *S. aureus* was the organism most frequently found: within the pig shed it accounted for 76% of all the organisms recovered (Gibbs et al. 2006).

All recovered organisms were tested for resistance to tetracycline, beta-lactam, macrolide and lincosamide antibiotics. No testing for methicillin resistance was carried out, so we do not know whether any of the *S. aureus* recovered were MRSA. As Table 5.1 shows, much higher concentrations of organisms were found inside the shed and downwind of it than were found upwind. The concentration of organisms resistant to at least two antibiotic classes was over 600 times higher inside the shed than upwind of it, and was still four times higher 150m downwind of the shed than it was 25m upwind. Bacterial concentrations in the air at distances greater than 150m were not tested. The scientists concluded that the high concentrations of multi-resistant bacteria in the air at distances of (at least) 150m 'could pose a potential human health effect for those who work within or live in close proximity to these facilities' (Gibbs et al. 2006).

Table 5.1 Organisms from near an intensive pig farm and their antibiotic resistance

	25m upwind	Inside pig shed	25m downwind	50m downwind	100m downwind	150m downwind
No of organisms recovered	63	18,132	1,295	970	414	141
% resistant to at least two antibiotic classes	44	94	93	80	82	81
% resistant to all four antibiotic classes	14	45	16	14	24	10
No of organisms resistant to at least two antibiotic classes	27	17,044	1,230	776	339	114
No of organisms resistant to all four antibiotic classes	9	8,159	207	136	99	14

Source: Gibbs et al. 2006

As reported in Chapter 3, high levels of MRSA have also been found in the air on a Dutch pig farm (RIVM 2007a). This finding, in the light of the American research by Gibbs et al., suggests that MRSA is probably being emitted into the air from MRSA-positive pig farms and could be transferred to those living in proximity to them.

MRSA on meat

MRSA has been found on meat from pigs, cattle, chickens and sheep (Lee 2003, Kitai et al. 2005, Quddoumi et al. 2006, Zembla 2006, Veerman 2007). Preliminary work has also found *S. aureus* resistant to methicillin in a pork sample and a chicken-meat sample from British shops, although tests to verify that these are fully methicillin-resistant MRSA have not yet been carried out (Fielder 2007a, Fielder 2007b) (see Chapters 3 and 4).

While MRSA will resist a temperature of 60°C for 30 minutes, thorough cooking will kill it. But thorough cooking will also kill food-poisoning bacteria such as

salmonella, *E. coli* and campylobacter, and yet tens of thousands of people in the UK are infected by these bacteria each year, often through eating meat.

Handling raw meat with bare hands potentially allows MRSA to bypass cooking; the phenomenon is well-attested with salmonella and other food-poisoning bacteria. However, in the case of MRSA it is additionally significant since MRSA lives very easily on skin and can be readily transferred by direct contact. Butchers, cooks and all those working in meat-processing plants can expect to be at particularly high risk of MRSA colonisation if the meat they are handling is contaminated with the bacteria.

Cases of MRSA food poisoning have also been recorded in the scientific literature. An outbreak of food poisoning in the United States was traced to pork contaminated with MRSA (Jones et al. 2002). Food is also thought to have played a role in disseminating MRSA during an outbreak in a Dutch hospital in the 1990s (Kluytmans et al. 1995). In both these cases, however, the strain is likely to have been of human, not animal, origin.

Unfortunately, very little work has been done to establish how common MRSA might be on retail meat and what dangers this might pose to the general population. Dr Mark Fielder from Kingston University in Surrey recently wrote: 'The dearth of data from Europe and the US points towards the requirement for a co-ordinated surveillance programme to be carried out to determine the epidemiology of *S. aureus* and MRSA in the food chain […] to ascertain the importance of this versatile pathogen in a potentially new role' (Fielder 2007a).

Although the presence of MRSA has not yet been confirmed on British meat, British consumers could nonetheless be exposed to MRSA on imported meat. It is estimated that around 60% of all the pig meat consumed in the UK is now imported, and with MRSA having being confirmed to be present in pigs in the Netherlands, Denmark and Germany, it is significant from the point of view of the British consumer that these three countries supply the overwhelming majority of imports: 87% of imported bacon comes from the Netherlands or Denmark, while 63% of imported pork and 57% of imported processed pig meat comes from Denmark, the Netherlands or Germany (see Table 5.2).

'The dearth of data from Europe and the US points towards the requirement for a co-ordinated surveillance programme to be carried out to determine the epidemiology of *S. aureus* and MRSA in the food chain'

(FIELDER 2007A)

Table 5.2 Main exporters of pig meat into UK in 2004

	Pork	Bacon	Processed pig meat
Denmark	37%	33%	18%
Germany	11%		18%
Netherlands	15%	53%	21%
Other	37%	14%	43%

Source: BPEX 2005

Imported organic produce

As far as we are aware, no MRSA has ever been reported from animals farmed organically. However, under limited circumstances, some organic farmers and horticulturalists are permitted to use manures from intensive farming systems. This cannot be applied directly to growing crops and Soil Association standards require that it must be properly composted or stacked for 12 months before use, to reduce the level of pathogens (Soil Association 2005b). No similar restrictions apply to the use of manures in the production of non-organic crops. We are not aware of any information on the extent to which MRSA may survive in animal manures under different management regimes, but the issue requires consideration, especially in countries where MRSA has been found in farm animals.

6. Farm-animal and community-acquired MRSA

'The source of many important antibiotic resistance genes is unknown. For example, the *mec*A gene that makes an MRSA an MRSA has come from an as yet undiscovered source. It is perfectly plausible that the gut or stomach could be an important locus where important gene transfer events occur'

DR MARK ENRIGHT (HIGHFIELD 2007)

Has farm-animal MRSA spread in the community?

Both community-acquired MRSA (CA-MRSA) in humans and MRSA in animals have greatly increased in incidence in recent years, but are these developments related? Is farm-animal MRSA an as-yet-unrecognised cause of the emergence of CA-MRSA, or did the emergence of MRSA in humans in the community result in these strains being transmitted to animals? Or is it a coincidence that these two developments have occurred at roughly the same time?

In the case of pets infected with MRSA, scientists agree that they probably acquired their MRSA through close contact with humans, and it seems likely that the rise of both hospital and CA-MRSA will have been factors in the increased occurrence of MRSA in pets. While pets can pass MRSA back to humans, there is no evidence that the emergence of MRSA in pets is a primary cause of MRSA in the community.

The situation with MRSA in farm animals is different. We saw compelling evidence in Chapters 3 and 4 that MRSA has spread from animals to farmers and other people who work with or live close to farm animals. For these people, pigs, cattle, chicken and horses may therefore all be a source of CA-MRSA infections.

What is not yet known is whether these strains of farm-animal MRSA can, or already have, spread more widely in the community. Little is known about how long MRSA has been present in farm animals and whether it played a role in the initial emergence of CA-MRSA. In the United States, for example, where CA-MRSA was first noted and has now become very widespread, it appears there have been no surveys for MRSA in farm animals whatsoever, but because the extensive importation of live pigs from Canada (see p 25), it is likely that MRSA is already present in US livestock.

Penicillin and tetracyclines in animal feed and the emergence of resistant *S. aureus* in the community

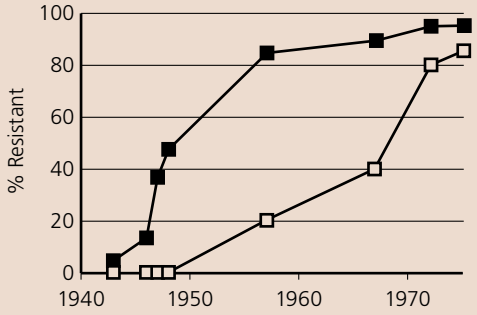
We briefly turn our attention away from MRSA, to consider the evolution of penicillin resistance in *S. aureus*, as this shows similarities with the current spread of methicillin resistance: in both cases, resistance in *S. aureus* to the antibiotic in question appears to have emerged in the community just when it was spreading in animals, which could suggest that they are linked.

As mentioned in Chapter 2, penicillin resistance in hospitals became a problem very soon after the drug's introduction in the 1940s, but resistance in community-acquired *S. aureus* infections did not begin to emerge until the1950s. This development coincided with a large increase in use of penicillin in farm animals (and therefore, most likely, a large increase in penicillin resistance in farm-animal *S. aureus*). In the US, farmers had begun adding small amounts of penicillin (5–10 g per ton) or tetracycline (10–20g per ton) antibiotics to animal feed in 1949 to promote faster growth, and this practice was legalised in 1951 (Swann et al. 1969, National Research Council 1999). The UK soon followed, with trials on several

Government research farms and the practice approved by Parliament in 1953 (Gordon and Taylor 1953, Hansard 1953). Data from the US shows that by the 1970s the level of resistance in the community was nearly as high as in hospitals (see Graph 6.1).

Graph 6.1 Approximate prevalence of penicillin-resistant strains of *S. aureus* in the US

Hospitals (closed symbols), in the community (open symbols)



Source: Chambers 2001

A British study carried out in 1960 found evidence suggesting that antibiotic-resistant *S. aureus* bacteria were being transferred between intensively farmed animals and farm workers, which could explain the steep increase in pencillin-resistant *S. aureus* in the community in the early 1950s. The study showed that pigs and poultry given penicillin and/or tetracyclines in feed had much higher levels of *S. aureus* resistant to the antibiotics they were being fed in comparison to control animals on antibiotic-free diets (Smith and Crabb 1960). It also showed that *S. aureus* from the noses or skin of the human attendants of the antibiotic-fed animals were much more penicillin- and/or tetracycline-resistant than those from the attendants of animals in a control not fed with antibiotics. Using a method for classifying bacteria called phage-typing, the scientists showed that the dominant strain on seven out of eight pig or chicken farms was found to be the same type as that on the corresponding human attendants, and that the strain involved was different on each farm.

This study was partly responsible for the UK ban in 1971 on the use of penicillin and tetracyclines as growth-promoters (Swann et al. 1969), although at the time it was seen by some as slender evidence for justifying the ban (BMJ 1969).

Despite this early British study and Swann's conclusions, many scientists have remained unconvinced that the use of antibiotics in animal feed made any contribution to the rise of pencillin resistance in *S. aureus* infecting humans. This claim has been supported by scientific evidence showing that staphylococci in general tend to be host-adapted (Kiser 1980, Lacey 1984, Teale 2004, van Duijkeren et al. 2004), which means they tend to live well on only one animal species. It appeared to follow from this that antibiotic resistance in animal *S. aureus* was not of much relevance for human medicine. In the 1980s, Professor Richard Lacey of the University of Leeds concluded that 'it is possible to account entirely for the emergence of the multiresistant staphylococci by antibiotic use in man' (Lacey 1984).

A possible explanation for this apparently contradictory evidence and conflicting conclusions is that many of the studies showing that *S. aureus* tend to be host-adapted have focussed primarily on human hospital-acquired infections, whereas farm-animal *S. aureus* is more likely to have contributed to community-acquired infections. With hindsight, it may be that the fact that the emergence of penicillin resistance in community-acquired *S. aureus* occurred just after the introduction of the growth-promoters was not just a coincidence, since the spread

of methicillin resistance is showing a similar pattern.

Similarities and differences between CA-MRSA and farm-animal MRSA

When MRSA first appeared in the community, it was unclear whether it was an overspill from hospitals, or whether methicillin-sensitive *S. aureus* had acquired resistance in the community resulting in new strains of MRSA. Scientific studies have since shown that most community strains share few of the characteristics of most hospital-acquired MRSA, whereas they do share important features with methicillin-sensitive strains in the community.[1] This has led some scientists to argue that the new resistant strains may have acquired their resistance in the community, not in hospitals (Naimi et al. 2003, Robinson and Enright 2004), and it is worth comparing some the genetic features of farm-animal MRSA with those of human CA-MRSA.

Toxins in farm-animal-associated *S. aureus*

While one of the most striking characteristics of CA-MRSA is the high percentage of strains which produce the Panton-Valentine leukocidin (PVL) toxin (see Chapter 2), there is at present only limited evidence of the presence of PVL MRSA in farm animals. The ST398 MRSA found in Dutch pigs has been shown not to produce the PVL toxin, but 9% of the ST398 MRSA bacteria in humans in the Netherlands were found to have the PVL genes (van Loo et al. 2006b). This suggests that ST398 MRSA in pigs could still acquire this trait, or it may even suggest that some of the ST398 MRSA bacteria in cattle or chickens are already PVL MRSA. There is no information yet on whether the MRSA found in Canadian pigs is PVL-positive.

In Korea, however, 14 MRSA samples collected from cattle over a number of years and from different regions all had the PVL gene. This particular PVL strain is believed to have developed in cattle rather than to have been acquired from humans (Kwon et al. 2005).

Another condition sometimes associated with CA-MRSA is toxic-shock syndrome (Gosbell 2005, Durand et al. 2006), a rare but potentially fatal illness. Until recently, toxic-shock syndrome in humans caused by MRSA had been found extensively in Japan, rarely in the US, and not at all in Europe (Jamart et al. 2005). However, in France in 2003 scientists reported a case of neonatal toxic-shock-like syndrome in a newborn baby, which was caused by MRSA carrying the toxic-shock syndrome gene (van der Mee-Marquet et al. 2003). In 2005, scientists in Belgium reported a case of toxic-shock syndrome caused by MRSA, and Belgian scientists warned of the increasing risk of MRSA outside Japan causing the syndrome (Jamart et al. 2005). In 2006, toxic-shock syndrome caused by MRSA was also reported in Russia and the US (Dmitrenko et al. 2006, Haddadin et al. 2006).

This rise in the incidence of toxic-shock syndrome associated with MRSA may indicate a farm-animal link, as the gene which enables MRSA to produce the toxin which causes toxic-shock syndrome has been found to be particularly common in *S. aureus* from farm animals. A Dutch study published in 2005 compared the genetics and virulence traits of *S. aureus* from humans with those of *S. aureus* from animals, including farm animals. In addition to finding that many of the bacteria fell within the same 'genomic classes', the scientists discovered that the distribution of eight of the ten genes was similar for both human and animal isolates across each class. Two virulence genes were more prevalent in veterinary isolates, including the gene encoding the toxic-shock syndrome toxin, which was found to be much more common in farm-animal mastitis infections than in human infections (van Leeuwen et al. 2005). Most studies which have found MRSA in farm animals have not looked into whether the bacteria were carrying

[1] Methicillin-sensitive *Staphylococcus aureus* (MSSA) is the general description of *S. aureus* strains which can be treated successfully with methicillin. These are nevertheless still capable of causing serious infections and can harbour some of the genes which can make MRSA so deadly

the toxic-shock syndrome gene. The MRSA found on two chicken-meat samples in Japan did contain the gene, but scientists believed the MRSA were probably transferred to the meat by humans handling it (Kitai et al. 2005).

CA-MRSA and farm-animal MRSA have similar antibiotic resistance elements

Most CA-MRSA and most MRSA from animals share one significant characteristic which distinguishes them from most hospital-acquired MRSA: the type of antibiotic-resistance element which they carry.

As mentioned in previous chapters, the gene which makes *S. aureus* bacteria resistant to methicillin in all true MRSA is called *mec*A. This gene is part of a larger genetic grouping, or 'cassette', which is found in the *S. aureus* chromosome. This cassette is called a staphylococcal chromosomal cassette *mec* (SCC*mec*), and can vary in size and in the range of genes it contains.

Until a few years ago, only three different kinds of SCC*mec*, referred to as SCC*mec* I, II and III, were known in hospital-acquired MRSA. However, two new cassettes, SCC*mec* IV and SCC*mec* V have been found in community-acquired MRSA in recent years (Baba et al. 2002, Daum et al. 2002, Ito et al. 2004).[2] Studies have also confirmed that most community-acquired MRSA have these new SCC*mec* IV and V (Fey et al. 2003, Baggett et al. 2004, Buckingham et al. 2004, Liassine et al. 2004, O'Brien et al. 2004, Caddick et al. 2005).

While the SCC*mec* IV genetic cassette has now been shown to be present in some hospital-acquired MRSA (Naimi et al. 2003, Caddick et al. 2005), the scientific consensus is that CA-MRSA probably acquired the SCC*mec* IV cassette in the community (Fey et al. 2003, Naimi et al. 2003).

Similarly, although the type of SCC*mec* has not always been determined for MRSA from farm animals, when it has, the SCC*mec* identified has usually been type IV or V (see Table 6.1).

Table 6.1 Studies where the SCC*mec* cassette types in farm-animal MRSA is identified

Species/product	Country	SCC*mec* I, II and III	SCC*mec* IV and V
10 pigs and workers [a]	Netherlands		V
209 pigs [b]	Netherlands	III (3%)	V (57%), IVa (39%)
1 pig [c]	Germany		V
14 milk samples [d]	Korea		IVg
1 cow [e]	Hungary		IVa
22 horses and 1 vet [f]	Canada		IV
5 horses and 43 vets and animal keepers [g]	Austria		IVd
2 chicken-meat samples [h]	Korea	III[3]	

Sources: (a) Huijsdens et al. 2006b, (b) de Neeling et al. 2007, (c) Witte et al. 2007, (d) Kwon et al. 2005, (e) Juhász-Kaszanyitzky et al. 2007, (f) Weese et al. 2005b, (g) Cuny et al. 2006b, (h) Kwon et al. 2006

The SCC*mec* types IV and V are significantly smaller than types I, II and III, and unlike types II and III, they do not usually carry any antibiotic resistance genes other than the *mec*A gene (Ito et al. 2004, Grundmann et al. 2006). One consequence of this is that CA-MRSA appear to be less resistant to other antibiotics than many hospital-acquired MRSA (Fey et al. 2003, Naimi et al. 2003), and this may also turn out to be the case for farm-animal MRSA.

Another issue is whether, in the absence of antibiotics, the type of SCC*mec*

[2] A further cassette, SCC*mec* VI, was discovered in late 2006 (Oliveira et al. 2006).

[3] According to the scientists, these MRSA were probably transferred to the meat by human handling.

carried gives resistant bacteria a 'fitness'[4] disadvantage in comparison to antibiotic-sensitive *S. aureus* which have no SCC*mec*. In this case they will tend to die out and be replaced by the antibiotic-sensitive *S. aureus* if antibiotic use ceases.

Evidence suggests that the SCC*mec* carried by farm-animal MRSA and CA-MRSA do not reduce fitness as much as those in hospital-acquired MRSA, and thus are more resilient where antibiotics are not being used. One study showed that MRSA carrying SCC*mec* IV multiply faster than hospital-acquired MRSA (Okuma et al. 2002). Another recent study has shown that MRSA carrying SCC*mec* I have increased energy consumption (thus reducing their fitness in the absence of antibiotics) in comparison to antibiotic-sensitive *S. aureus*, whereas MRSA with an SCC*mec* of type IV do not (Lee et al. 2007). It has also been argued that since SCC*mec* V is of similar size to SCC*mec* IV and significantly smaller than SCC*mec* II and III, it also should not compromise fitness (Grundmann et al. 2006).[5]

These findings appear to explain why CA-MRSA, which usually carry SCC*mec* IV and V, are adapted to survive better in the community where antibiotic use is relatively low, whereas MRSA carrying SCC*mec* I, II and III tend to be restricted to hospitals only, where the use of antibiotics better enables them to remain competitive with non-resistant *S. aureus*. However, they also suggest that if MRSA carrying SCC*mec* IV and V are allowed to become widespread in farm animals, subsequently reducing antibiotic consumption in an attempt to lower their incidence may not be as effective as might be hoped. A better strategy would be to reduce consumption now in order to prevent the problem occurring.

Transfer of methicillin resistance between bacteria

As with other antibiotic-resistance genes, the *mec*A gene which gives rise to methicillin resistance can be transferred horizontally between bacteria, that is directly between bacteria rather than vertically by reproduction. When the receiving bacterium which was antibiotic-sensitive becomes antibiotic-resistant (the donor bacterium retains a copy of the gene and also remains resistant). Horizontal transfer (which also occurs between bacteria of different species) can significantly accelerate the spread of resistance. This therefore suggests a possible indirect way by which farm-animal MRSA could be contributing to the emergence of CA-MRSA: if human *S. aureus* acquire the *mec*A gene from animal MRSA, then new strains of human MRSA will emerge.

Some scientists, however, have claimed that animal *S. aureus* are not in general a significant source of antibiotic resistance genes in human *S. aureus*. Based on experiments with other antibiotic resistance genes, Professor Richard Lacey has claimed that the rate of transfer of antibiotic resistance genes between animal and human *S. aureus* is low (Lacey 1984). Other scientists, though, have pointed out that bacterial numbers in the human gut are extremely high, so even the low rate of transfer which Professor Lacey found might lead to many transfers occurring in practice (SOU 1997 p. 108). They also point out that the transfer of antibiotic resistance from animal to human bacteria does not have to be frequent to have an effect: once the resistance gene is present in recipient bacteria, then the subsequent human use of antibiotics will provide a selective pressure which will allow these resistant bacteria to multiply (SOU 1997 p 101 and p 308).

The SCC*mec* cassettes which contain the *mec*A gene are also believed to be transferable by horizontal gene transfer, although little is known about the mechanism at work (Hanssen and Ericson Sollid 2006). The fact that most farm-animal MRSA and most CA-MRSA have similar types of SCC*mec* may indicate that these transfers have been occurring. Scientists also believe that, perhaps due to their smaller size, SCC*mec* IV and V are more likely to be transferred by horizontal gene transfer than SCC*mec* I, II and III (Grundmann et al. 2006, Nimmo et al. 2006). This may mean that most farm-animal MRSA and CA-MRSA are more likely

[4] 'Fitness' is the capability of a member of a species to reproduce in relation to others of the same species. If genetic differences between individuals in the same species affect fitness, then the frequencies of their genes will change over generations, with the genes associated with higher fitness becoming gradually more common in the species (the process known as natural selection).

[5] This is because genes contain information necessary to make proteins, and when these genes are expressed, energy is consumed to produce the proteins. So since SCC*mec* V contains fewer genes than SCC*mec* I, II or III, it is probable that less energy will be spent producing the corresponding smaller number of proteins.

to transfer methicillin resistance to other *S. aureus* than most hospital MRSA.

The presence of these mobile genetic elements carrying the *mec*A resistance gene in *S. aureus* in farm animals and on food could, therefore, impact on human health in two ways: either through farm-animal MRSA directly infecting humans or through the horizonal transfer of the SCC*mec* element from farm-animal MRSA to human methicillin-sensitive *S. aureus*, which then become MRSA.

We have seen that people working with, or living close to farm animals which are carriers of MRSA are frequently colonised by these animal MRSA strains. The SCC*mec* elements IV and V in these animal strains may then transfer to other human *S. aureus* living on these people, leading to the emergence of new human strains of MRSA. Such MRSA could then spread further within the community, just as other community-acquired strains already spread from person to person. Although, in cases of infection the link with farming would be difficult to prove, the possibility of this occurring is widely recognised by scientists. Defra's Chris Teale, for instance, has warned that 'Even though different subtypes of bacterial "species" may affect man and animals, the ability of bacterial strains to transfer genes between each other means that either population may act as a reservoir of resistance genes' (Teale 2002).

Dr Mark Enright of Imperial College has also suggested that the presence of methicillin-resistant bacteria on food could result in the *mec*A gene being transferred to human *S. aureus*. He said, 'The source of many important antibiotic resistance genes is unknown. For example, the *mec*A gene that makes an MRSA an MRSA has come from an as yet undiscovered source. It is perfectly plausible that the gut or stomach could be an important locus where important gene transfer events occur' (Highfield 2007).

7. The threat to human health from farm-animal MRSA

'The main question is whether this strain will spread from those living on pig farms to other individuals in the community. If so it will have a major public-health impact.'

PROFESSOR JAN KLUYTMANS (KLUYTMANS 2007)

The extent of the threat is uncertain

The full scale of the threat to human health from MRSA on farms is clearly not yet known. Those in direct contact with farm animals are certainly at high risk of acquiring the bacteria, but for the general population there remains uncertainty about the scale of the danger, although Dutch scientists, including Government scientists, have said that pig-MRSA can also be transmitted between humans (van Loo et al. 2006a).

Speaking about the significance of MRSA in pigs and pork, Professor Jan Kluytmans has said: 'At present, people living on pig farms [in the Netherlands] have carriage rates approaching 50% and we do see some people from these farms with serious infections. The main question is whether this strain will spread from those living on pig farms to other individuals in the community. If so it will have a major public-health impact' (Kluytmans 2007).

Although it is yet to be proven that ST398 MRSA has spread from the farming community to those outside it, one possibly worrying development is that in Germany, where ST398 MRSA has been found in a pig and in other animals, it has already been reported that this strain of MRSA has caused infections in seven hospital inpatients with ventilator-associated pneumonia (Witte et al. 2007). This could be an indication that MRSA ST398 is moving into hospitals. Also worth noting is that MRSA ST398 has been reported as a cause of blood poisoning in two patients in hospitals in Hong Kong (Ip et al. 2005). No connection with pig farming was reported, although the scientists did say that the MRSA may have originated in the community.

Animal and human MRSA are resistant to different antibiotics

Although animal MRSA may not be resistant to as many antibiotics as hospital-acquired MRSA, the different ways in which antibiotics are used in farming and in human medicine mean that they can each be more resistant to particular antibiotics. Predicting which antibiotics are likely to be successful in treating an MRSA infection in humans may become even more difficult than it already is if farm animals become a significant source of MRSA infections.

As detailed in Chapter 3, all MRSA bacteria from pigs in the Netherlands and Germany are resistant to tetracycline antibiotics (de Neeling et al. 2007, Witte et al. 2007). Also, most MRSA bacteria in humans of apparent porcine origin are much more tetracycline-resistant than other human MRSA strains, despite generally being sensitive to fluoroquinolones (van Loo et al. 2006b).

Tetracyclines are an old class of drugs and are one of a number currently being reassessed as potential treatments for MRSA, because resistance to vancomycin, the current drug of choice for MRSA infections, is on the increase (Drew 2007). Draft guidelines for the treatment of MRSA infections in humans in the UK recommend that tetracyclines should be more widely used for skin and soft-

tissue infections and should be used as first-line treatments for urinary infections (Gemmell et al. 2006).

A survey carried out in UK hospitals in 2004 found that 95% of MRSA bacteria from 309 patients were susceptible to tetracycline antibiotics (Gemmell et al. 2006). The emergence and spread of new tetracycline-resistant strains of MRSA of animal origin could therefore potentially have very serious human-health consequences.

Possibility for more MRSA with greater genetic diversity

An important characteristic of hospital-acquired MRSA is its clonality, that is, its lack of genetic diversity. In the UK, it has been estimated that over 95% of hospital MRSA infections are caused by just two epidemic strains (Johnson et al. 2001). Worldwide, five major strains account for the vast majority of MRSA infections (Robinson and Enright 2003).

However, CA-MRSA are not restricted to just a few clones, and are derived from many different genetic backgrounds (Okuma et al. 2002, Said-Salim et al. 2003, Vandenesch et al. 2003, Coombs et al. 2004, O'Brien et al. 2004). This genetic diversity has been ascribed to the greater mobility of the SCC*mec* IV and V which are often found in CA-MRSA (Robinson and Enright 2003, Coombs et al. 2004, Grundmann et al. 2006). Australian scientists have said that the increasing number of strains of MRSA which have mobile SCC*mec* cassettes is of great concern since 'the transmission of SCC*mec* ... raises the prospect of widespread acquisition of methicillin resistance in *S. aureus*, similar to the spread of penicillin resistance seen in the latter half of the 20th century, which led to penicillin resistance levels greater than 80%' (Nimmo et al. 2006).

Since farm-animal MRSA also generally have these mobile SCC*mec* cassettes, it is reasonable to expect that a similar spread will occur, and that in time more animal *S. aureus* will become methicillin-resistant. This may result in farm-animal MRSA with a wider variety of toxin genes, such as the PVL gene or the toxic-shock gene, and also more complicated and unpredictable resistance profiles.

MRSA is already a hugely challenging problem in British hospitals, but with the current dominance of a very small number of strains, it is at least predictable and readily understandable. At present, doctors can generally choose an effective antibiotic of last resort and start treatment immediately, without having to wait 24 hours for the results of an antibiotic-sensitivity test. If, on the other hand, a wide variety of new strains from animals were added to the mix because a significant number of people are being hospitalised for treatment for farm-animal MRSA strains, it is likely that we would start to see the emergence of some further new hospital strains of MRSA, which could significantly complicate the problems facing doctors.

Vancomycin-resistant MRSA, the ultimate superbug?

Vancomycin is the preferred antibiotic for treating MRSA infections. It is also very closely related to avoparcin, an antibiotic which was used as a growth-promoter in pigs, poultry and cattle in most European countries until, in April 1997, it became the first growth-promoter in recent years to be banned by the EU. The widespread use of avoparcin led to the emergence of vancomycin-resistant enterococci (VRE) in farm animals, and evidence that these bacteria were being passed to humans was a major factor in motivating scientists to push for the avoparcin ban, against industry and some veterinary opposition.

Enterococci are natural inhabitants of the human gut, but some strains can cause serious disease such as blood poisoning, particularly in those who are immuno-compromised or who have had previous treatment with antibiotics (HPA 2006e). A particular problem with enterococci is that they can be naturally

resistant to a large range of antibiotics, so when they acquire resistance to vancomycin, they become superbugs which are particularly difficult to treat (NPHSW 2006).

Is the use of avoparcin related to the emergence of vancomycin-resistant *S. aureus*?
For a number of years a major concern about VRE has been that the *van*A gene, one of the genes which make the bacteria resistant to vancomcyin, could transfer from enterococci to MRSA, rendering MRSA also vancomycin-resistant and virtually untreatable. This is now believed to have occurred in two cases reported in 2002 in human patients in the United States (MMWR 2002a, MMWR 2002b, Witte 2004).

Scientists from Canada and the US have shown that bacteria contaminating animal feed containing avoparcin had a genetic cluster which was related to a genetic cluster, the 'van cluster', which is required by bacteria for high-level resistance to vancomycin. They proposed that the use of avoparcin in farming had both created vancomycin-resistance in bacteria and selected for this resistance. They also suggested that 'the emergence of vancomycin-resistance in *Staphylococcus aureus* (VRSA) is a recent sequela to this train of events involving the van gene clusters' (Lu et al. 2004).

This conclusion is liable to be controversial, however. This is because in the United States, the only country where VRSA has yet been found, avoparcin was never licensed as a growth-promoter. Representatives of the medicated animal-feed industry have argued that the higher prevalence of VRE in the US in comparison to Europe proves that avoparcin is not an important contributory factor to the emergence and spread of VRE (Cervantes 2005). Professor Wegener of the Danish Zoonoses Center has disagreed with this analysis, pointing out that it is only in hospitals that there is a higher prevalence of VRE in the US than in Europe, whereas outside of hospitals VRE is more common in Europe (Wegener 1998). He also suggested that VRE may first have emerged in the US through tourism and imported food, and that the high level of vancomycin use in US hospitals may then have helped its spread. Reports of illegal use of avoparcin in US agriculture in the US are also worth noting (FDA 1996).

MRSA in farm animals may hasten the spread of vancomycin-resistant *S. aureus*
The emergence of MRSA in farm animals could, however, greatly increase the chances of resistance gene transfers between enterococci and staphylococci in animals occurring in the future. This is because, despite the avoparcin ban, high levels of VRE are still found in poultry, and VRE is also sometimes found in pigs. While the British Government has failed to undertake any systematic antimicrobial-sensitivity testing of enterococci in UK poultry for over a decade, a study by Garcia-Migura et al (2005) took faecal samples from UK broiler farms between January 2002 and February 2003 and found at least one VRE-positive sample from 20 of 27 farms (74%). Studies in Denmark, Norway and Austria have also found high levels of VRE in poultry (Heuer et al. 2002, Eisner et al. 2005, Sorum et al. 2006). Levels of VRE in pigs appear to be lower, but nonetheless the study by Garcia-Migura and co-authors found VRE on four of 14 British pig farms investigated (29%) and another study found VRE in 34% of pig-manure samples from 11 Spanish farms (Kuhn et al. 2005).

It has been suggested that the persistence of VRE in pigs could be linked to the continued use of macrolide antibiotics, as evidence exists that macrolide-resistance genes can be linked to vancomycin-resistance genes in porcine VRE (Aarestrup 2000). The linkage of vancomcyin resistance to macrolide resistance has also been observed in human VRE (Leclercq et al. 1989, Uttley et al. 1989 cited in Aarestrup 2000), and it is possible that this is also the case for VRE from

poultry. The available evidence suggests that the use of macrolides has increased in poultry production since the growth-promoter ban, and it is therefore plausible that this might be a factor behing the continuing high levels of VRE in chickens.

The finding of potentially high levels of MRSA in Canada, discussed in Chapter 3, may be particularly significant. This is because, although as in the United States avoparcin was not approved as a growth-promoter in Canada, it is legal for Canadian farmers to import unapproved growth promoters for use in their livestock, so long as the farmer only imports the antibiotic for use on his own farm (Health Canada 2004). A website of the Ontario Ministry of Agriculture, Food and Rural Affairs states: 'Avoparcin and some other drugs used elsewhere in the world to improve growth are not currently approved for use in animals in Canada. However, unapproved antibiotics may be imported and used by producers for their "own use" on their livestock' (MAFRA 2005). Furthermore, a recent scientific paper has suggested that avoparcin is still in use in some countries, including Malaysia (Shah-Majid et al. 2007), and if this is true, then it is potentially still being used by some farmers in Canada.

A recent British laboratory experiment has found that certain bovine *S. aureus* are 500 times more likely to receive vancomycin-resistance genes from enterococci than *S. aureus* from humans with which they were compared (Sung and Lindsay 2007). They also found that one equine *S. aureus* they tested was very susceptible to this transfer and concluded that 'the high incidence of antibiotic-resistance gene transfer into animal strains strongly supports the decision to ban glycopeptide antibiotics, such as avoparcin, for agricultural use'.The significance of their finding is increased now that it is known that MRSA has emerged in farm animals, including cattle and horses.

The European Commission pushed ahead with the ban on avoparcin despite initial resistance from the British Government at the time and strong industry opposition. While the European move was welcome progress, levels of antibiotic use in British and European farming remain unacceptably high. With VRE still present on farms and farm-animal MRSA having appeared, the ideal conditions for the creation of vancomycin-resistant MRSA may now exist on some EU farms. If vancomcyin-resistant MRSA does emerge in farm animals it could turn out to be a lasting legacy of years of abuse of antibiotics in intensive farming, which could have dire consequences for human health and society.

8. Intensive farming, 'an MRSA paradise'

'We have to question the role of antibiotic usage among animal farmers'

PROFESSOR ROEL COUTINHO (COUTINHO 2006)

The Dutch paradox: MRSA is widespread in pigs despite being rare in humans

On the surface, it is surprising that the Netherlands has become the first country in the world to report a major MRSA problem in its farm animals. After all, the human population in the Netherlands has one of the lowest MRSA rates in the world. In the UK, for instance, over 40% of *S. aureus* from hospital infections are methicillin-resistant, but in the Netherlands just 1% are resistant (EARSS 2006).

So why, in a country where MRSA rates have been kept so impressively low in humans, has it become such a major problem in pigs?

Two main reasons have been put forward for the very low level of MRSA in Dutch hospitals:

- the high levels of hygiene and the 'search-and-destroy' policy (see Chapter 3), which involves routine screening of patients on admission to hospital, and the isolation of all MRSA-positive and high-risk patients (Wertheim et al. 2004, Moyer 2006)
- the particularly low level of antibiotic use in Dutch hospitals and outpatients (Monnet and Frimodt-Moller 2001, Wertheim et al. 2004)

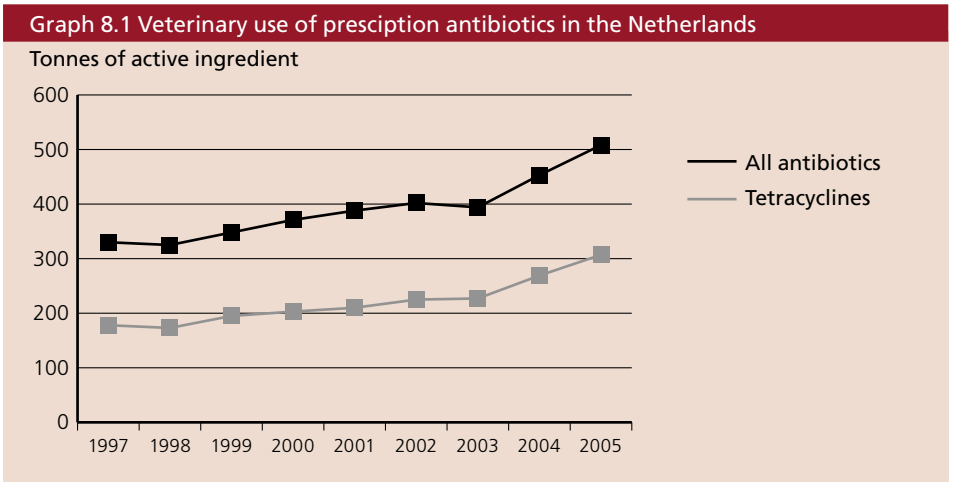
In sharp contrast, the Netherlands has one of the most intensive pig industries in the world, with all the implications for antibiotic use that this entails. Furthermore, as in other countries, the high number of pigs kept indoors in close proximity to each other ensures that bacteria can easily pass from animal to animal.

So, while the level of antibiotic use in humans is low in comparison to many other countries, the use of antibiotics in farm animals in the Netherlands is high. In human medicine, Dutch antibiotic use is the lowest in Western Europe, at least for outpatients (Ferech et al. 2006).[1] However, total farm antibiotic use in 2004 was 508 tonnes of active ingredient (exclusive of growth-promoter use and the use of antibiotics to control the disease coccidiosis) (FIDIN 2006). This compares with 446 tonnes in UK agriculture in 2005. While the Netherlands has over twice as many pigs as the UK, it has little more than half the number of chickens, around a quarter of the number of cattle and nearly 30 times fewer sheep (MARAN 2005, Goodyear 2006). In addition, the Dutch veterinary-antibiotic sales statistics show that the consumption of antibiotics has been on an upward trend since 1998, and increased by a remarkable 29% between 2003 and 2005 (see Graph 8.1).

This increase in antibiotic usage is occurring despite the Dutch authorities having taken the progressive step of prohibiting the feeding of antibiotics to farm animals for disease prevention (Zembla 2006), something which has not yet been done in the UK. In practice the use of antibiotics for routine disease prevention continues despite the legislation, since without the aid of these drugs, the animals could not be reared successfully in the conditions in which they are kept. On a recent Dutch television programme, one vet was asked if farmers use antibiotics

[1] We have been unable to find data on all aspects of antibiotic use in hospitals and have had to rely instead on claims by Dutch scientists that the overall use in the Netherlands is low and figures showing that outpatient use is very low.

Graph 8.1 Veterinary use of presciption antibiotics in the Netherlands



Sources: Fidin 2006, MARAN 2003, 2004, 2005

'The high usage of antibiotics in livestock farming is the most important factor in the development of antibiotic resistance, a consequence of which is the spread of resistant microorganisms (MRSA included) in animal populations'

(VEERMAN 2007)

for disease prevention. He said: 'They do and I'm ashamed on behalf of my profession, which is forced to do it, to admit it. It is done under economic pressure and the fear that if you don't do it you run the risk that the pigs become sick' (Zembla 2006).

The role that high antibiotic usage has played in the spread of MRSA on Dutch pig farms has already been accepted by the Dutch authorities. A representative of the Government's National Institute for Public Health and the Environment, Professor Roel Coutinho said: 'We have to question the role of antibiotic usage among livestock farmers. Officially, antibiotics may not be used as a preventative measure, but they are widely used as treatment and the suggestion is that this [MRSA problem] could be a side effect of this. A large pig farm cannot survive without using antibiotics. The animals live in a sickness inducing environment – too many too close together. One sick animal and the whole sty joins in' (Zembla 2006).

The Dutch Government itself has also been clear that high antibiotic usage is to blame. The Minister, Dr Cees Veerman, said earlier this year: 'the high usage of antibiotics in livestock farming is the most important factor in the development of antibiotic resistance, a consequence of which is the spread of resistant microorganisms (MRSA included) in animal populations' (see Appendix).

This official recognition of the role being played by excessive antibiotic usage in the spread of the superbug reflects a recent shift in the understanding of the MRSA epidemic. As we shall see, until recently conventional wisdom had not considered high antibiotic use to be a significant contributory factor in the spread of MRSA.

Antibiotic use – an overlooked risk factor for MRSA?

Within a year of the first widespread use of penicillin in British hospitals in 1943, antibiotic-resistant strains, including resistant *S. aureus* were being found (Todd et al. 1945). By 1948 the British Medical Journal was beginning to address itself to 'the magnitude of this change' (which had been found with streptomycin as well as penicillin), and an editorial in the Veterinary Record was asking 'what are the causes of this waning power of penicillin?'. It concluded: 'The present enormous consumption of the drug can be accounted for only by a good deal of indiscriminate use and it is generally considered that widespread use particularly of inadequate doses is a potent factor in breeding resistant strains of bacteria' (Veterinary Record 1948). As a general rule, this conclusion still holds today: widespread use of antibiotics, particularly at 'inadequate doses' (i.e. doses which are insufficiently high to kill off partly resistant bacteria), encourages the

emergence and subsequent spread of antibiotic resistance.

It is therefore surprising to find that, in discussions of MRSA in hospitals, excessive antibiotic use has often been overlooked as a factor in the spread of the superbug. Instead, strategies to prevent and control MRSA have focused primarily on improving hygiene and the ability to isolate carriers.

For instance, when listing important MRSA risk factors, the HPA refers to 'patient transfers within and between hospitals', 'the difficulty in isolating some patients with MRSA', 'the increasing complexity of healthcare and medical intervention', and high workloads which mean that 'the more the required number of hand hygiene measures needed per hour the less the compliance'. The Agency makes no mention of antibiotic use (HPA 2006b).

Since MRSA is frequently spread from person to person by skin contact, or through objects like towels or clothes, there is no doubt that hygiene is important. Hospital cleanliness, patient isolation, good personal hygiene including, in particular, regular hand-washing, are all ways by which the spread of the bug can be minimised. But attempting to control MRSA by these means alone will inevitably be complicated if a key issue such as antibiotic usage is ignored.

Why, then, has antibiotic use been ignored as an important risk factor in the spread of MRSA?

In 1999, American scientist Louis Rice explained some of the key arguments against the idea that antibiotics play a role in the spread of MRSA. He focused on specific differences between MRSA and other bacteria, such as *Enterococci* or *Acinetobacter* which acquire resistance as a result of antibiotic pressure, saying that: 'The determinant that confers methicillin resistance in staphylococci, the *mec* region, is chromosomally determined and has never been shown to be transferable between staphylococci. As a result, the spread of these strains is almost entirely clonal and is due to person-to-person transmission. Second, the primary sites of staphylococcal colonization are not the gastrointestinal and urinary tracts but the anterior nares, the skin, the axillae, and open wounds. In contrast to the levels of antibiotic achievable in the gastrointestinal and urinary tracts, concentrations of antimicrobials achievable in these areas are often negligible' (Rice 1999).

By referring to the fact that the spread of MRSA is 'clonal', i.e. that there are only a small number of strains involved in the vast majority of hospital-acquired MRSA, Rice is saying that antibiotic use cannot be 'creating' MRSA by causing sensitive *S. aureus* to mutate to become resistant, since if this were occurring we would expect a far greater variety of MRSA strains, whereas in the UK for instance, it has been estimated that over 95% of hospital MRSA infections are caused by just two epidemic strains (Johnson et al. 2001).

However, this argument ignores the fact that in the presence of an antibiotic, resistant MRSA bacteria can benefit by having sensitive bacteria killed off, as this reduces natural bacterial competition. Even if there are initially only a few resistant bacteria, the additional space and opportunity for expansion means that the resistant strains will quickly replace the original *S. aureus* (Hill et al. 1998, Wilcox 2005).

In addition, Rice's belief that the *mec* region, containing the *mec*A gene which makes the bacteria resistant to methicillin is not transferable between bacteria has been questioned by many scientists who believe there is now evidence that the *mec*A gene is transferable between staphylococci, particularly when contained in the genetic elements SCC*mec* IV and V, as in community-acquired MRSA and farm-animal MRSA (see pp. 44–45).

Another aspect of Rice's case, that antibiotics taken orally remain in the gut and will therefore not cause resistance in bacteria on the skin or in the nose, where most MRSA is found, has been challenged by the French scientist Dr

Dominique Monnet, head of the Danish Antimicrobial Resistance Surveillance Unit at the National Center for Antimicrobials and Infection Control in Copenhagen (Monnet 2006). He points out that several studies have shown that gastrointestinal MRSA colonisation is as common as nasal colonisation, and claims that this may represent an underestimated source of transmission (Rimland and Roberson 1986, Campillo et al. 2001, Boyce et al. 2005).

Dr Monnet also disagrees with Rice's assumption that antibiotics taken orally cannot have an effect on bacteria on skin: Monnet points out that certain antibiotics like the fluoroquinolones and the beta-lactams are excreted in sweat (Hoiby et al. 1997, Hoiby et al. 2000). Other antibiotic classes which can achieve high skin concentrations include tetracyclines, macrolides and lincosamides (Gemmell et al. 2006).

If antibiotic use in hospitals is a factor in the spread of MRSA, it is also likely that the use of antibiotics on farms is a factor in the spread of MRSA among farm animals. As such, it is worth examining the evidence in more detail.

Use of certain antibiotics can promote MRSA

Unsurprisingly, most of the evidence for the effects of various classes of antibiotics on MRSA incidence comes from studies in humans, since the organism has only begun to emerge as a significant problem in animals in the past few years.

Demonstrating that antibiotic use can promote the spread of MRSA is complicated by the influence of other factors. For instance, hospital patients receiving more antibiotics may be more likely to be colonised by MRSA, but this could, in some cases, also be due to the fact that such patients have spent a longer time in hospital where MRSA is more widespread.

Nonetheless, a number of scientists such as Dr Monnet now believe there is accumulating evidence to support the role of certain types of antibiotic in the spread of MRSA. They feel that greater attempts should therefore be made to restrict the prescribing of some antibiotics used in human medicine (Monnet et al. 2004, Monnet et al. 2005, Wilcox 2005).

A recently published review of the scientific literature examining the effect of antibiotic prescribing on MRSA incidence found that while many of studies had drawbacks, the evidence suggests that overall, certain classes of antibiotics 'almost certainly' promote the spread of MRSA (Wilcox 2005).

Unsurprisingly, the use of all beta-lactam antibiotics (including cephalosporins), to which MRSA is by definition resistant, have been found to promote MRSA in a number of studies (Fukatsu et al. 1997 quoted in Wilcox 2005, Hill et al. 1998, Crowcroft et al. 1999, Graffunder and Venezia 2002, Muller et al. 2003, Monnet 2005).

More generally, though, where MRSA has developed resistance to a particular antibiotic class then the use of that antibiotic is likely to promote the spread of MRSA because by definition these antibiotics do not kill MRSA, but do kill many other bacteria with which MRSA would normally have to compete (Monnet et al. 2004).

An example of this is the case of the fluoroquinolones, which were introduced to human medicine in the late 1980s and to veterinary medicine in the UK in 1993. One early study, completed before 1994, found that fluoroquinolones could be successfully used to treat or prevent MRSA infections (Cagni et al. 1995). However, resistance in MRSA developed rapidly and today, whereas most methicillin-sensitive *S. aureus* (MSSA) are still fluoroquinolone-sensitive, the overwhelming majority of hospital-acquired MRSA are fluoroquinolone-resistant: in one study 92% and 3% of MRSA and MSSA respectively were found to be fluoroquinolone-resistant (Weber et al. 2003).

It is to be expected, therefore, that the use of fluoroquinolones will favour MRSA over MSSA and other sensitive bacteria. This is confirmed by the significant

number of studies which have found that fluoroquinolone consumption is a risk factor for the development of an MRSA infection (Hill et al. 1998, Harbarth et al. 2000, Graffunder and Venezia 2002, Charbonneau et al. 2003 quoted in Monnet 2005, Muller et al. 2003, Weber et al. 2003, Monnet et al. 2004, Wilcox 2005).

Fluoroquinolones can favour MRSA colonisation in two principal ways: as already mentioned, they can be excreted in sweat, thus killing sensitive bacteria on the skin and allowing the MRSA to fill the vacated space (Hoiby et al. 1997 quoted in Hill et al. 1998). They can also have an effect on the MRSA bacteria themselves, inducing them to produce greater quantities of proteins which enhance their ability to attach to their host. This increased adherence makes it easier for the bacteria to survive on skin and spread (Bisognano et al. 2000, Weber et al. 2003).

Other classes of antibiotics which appear to be associated with the spread of MRSA are the macrolides and the aminoglycosides, both important classes of antibiotics used in human and veterinary medicine (Graffunder and Venezia 2002, Muller et al. 2003, Monnet et al. 2004).

A study funded by the European Commission has confirmed the growing evidence that high levels of antibiotic use are associated with high levels of MRSA. According to the HPA, the study found that out of approximately 300 hospitals studied throughout the EU, those with the highest MRSA levels also had the highest antibiotic use. Professor Barry Cookson, an MRSA expert at the HPA, said: 'In addition to the strong association between total antibiotic use and MRSA prevalence, the work also shows that the use of specific classes of antibiotics such as macrolides and third generation cephalosporins is also associated with higher MRSA prevalence' (HPA 2005b).

Countries with low antibiotic use often have low MRSA rates

A striking feature of the international MRSA epidemic is the very wide disparity in the MRSA rate from one country to another: in some EU countries the percentage of *S. aureus* infections which are MRSA exceeds 40%, whereas in others the rate is just 1 or 2%, or even lower (EARSS 2006).

A variety of factors contribute to these large differences, such as hygiene procedures and the availability of isolation units, but it is interesting to note that many of the countries which appear to have the lowest levels of antibiotic consumption also have low MRSA rates. We have been unable to find reliable data for the overall medical use of antibiotics in all European countries, but since 1997 the European Surveillance of Antimicrobial Consumption (ESAC) project has gathered antibiotic-usage data for outpatients for 24 European countries and Israel.

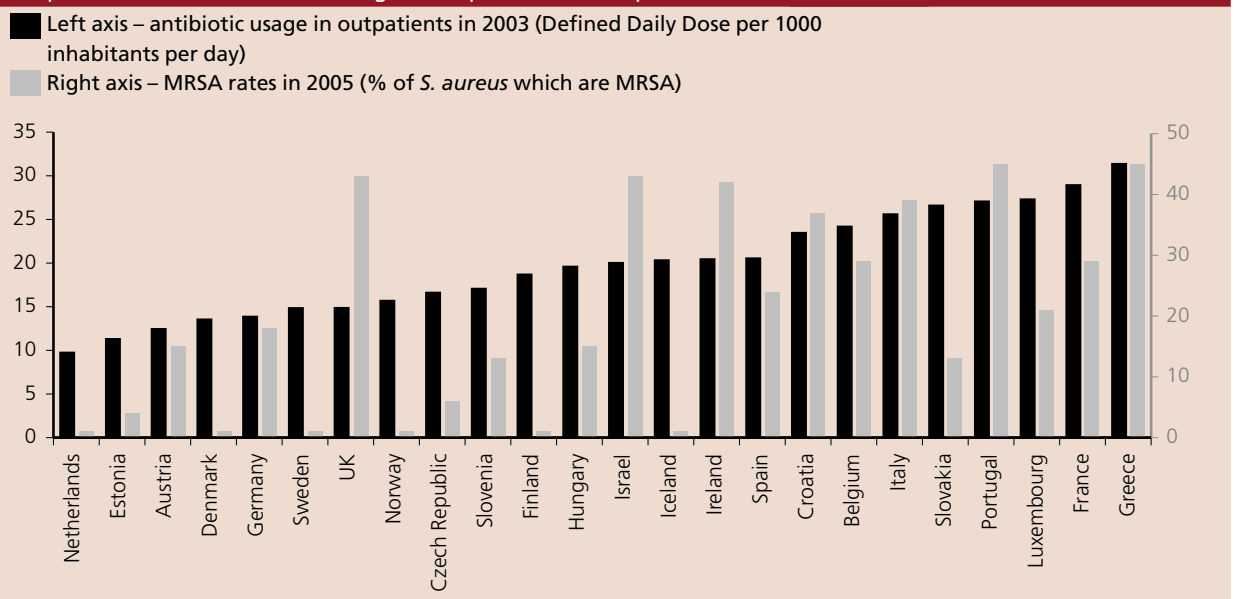
Among the countries with the lowest antibiotic consumption are the Netherlands, Estonia, Denmark and Sweden, all of which have MRSA rates at 2% or lower. On the other hand, many of the highest-consuming countries, such as Greece, France, Portugal, Belgium and Italy, have MRSA rates between 30 and 40% (see Graph 8.2). Though not shown on this graph, Romania, Malta and Cyprus have rates in excess of 50%.

How Denmark reduced its incidence of MRSA

The low MRSA rate in Denmark is particularly noteworthy. The rate peaked in Denmark at 18% at the end of the 1960s, and then steadily decreased over the next 10 years. Since the early 1980s it has remained at very low levels (Monnet and Frimodt-Moller 2001).

So how did Denmark manage to put the genie back in the bottle? The decrease followed efforts to improve hospital hygiene and the establishment of a National Center for Hospital Hygiene, but it has also been argued that an information campaign teaching 'rational' antibiotic use also probably played a key role, by

Graph 8.2 MRSA and antibiotic usage in outpatients in European countries

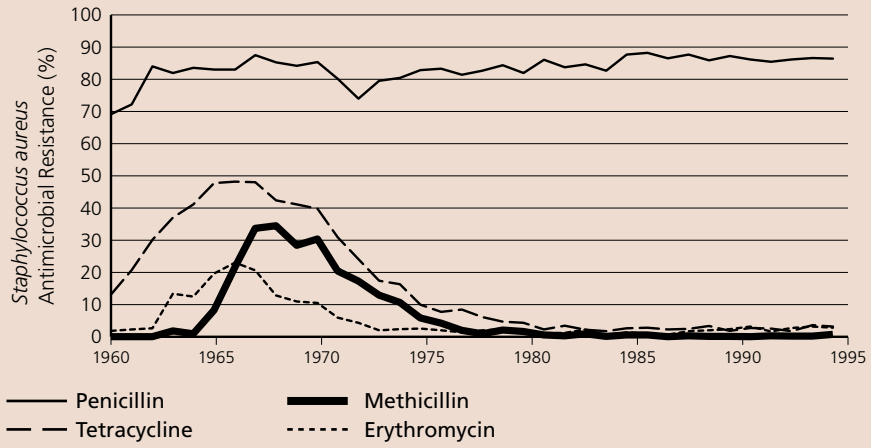


Sources: EARSS 2006, Ferech et al. 2006

helping bring about significant decreases in the consumption of antibiotics.

This is illustrated by the fact that one strain of MRSA which was resistant to tetracyclines and streptomycin had been dominant, but declined dramatically during the 1970s as Denmark reduced the consumption of these antibiotics. Between 1976 and 1980 consumption of tetracyclines per person fell by just under 40% (Rosendal et al. 1977, Monnet and Frimodt-Moller 2001, Monnet 2006). The reduced selective pressure from tetracycline use probably contributed to the decline of the tetracycline-resistant MRSA strain (see Graph 8.3).

Graph 8.3 MRSA in humans and use of antibiotics in human medicine in Denmark



Source: Monnet 2006

Lessons for the pig industry

The rise and fall of MRSA in Denmark may have important lessons for the present time in relation to the emergence of MRSA in pigs. In the intensive pig industry in the UK, the Netherlands and elsewhere, the most widely used antibiotics are the tetracyclines, and the strain of MRSA which is spreading in pigs is known to be tetracycline-resistant, just like the previously widespread strain of MRSA in Danish hospitals. Since high levels of tetracycline consumption in Denmark in the 1960s

‘If it can spread so easily in hospitals where containing measures are taken, you can imagine the effect in a pig sty where there is complete body contact – that is an MRSA paradise!’

PROFESSOR JAN KLUYTMANS

appeared to have helped spread this strain, there is good reason to anticipate that the even higher levels of tetracycline consumption in the pig industry may well be doing the same.

Conditions of intensive farming promote MRSA spread

Whereas in hospitals efforts are made to minimise the spread of MRSA from person to person, through hand-washing, cleaning, or the use of isolation wards, the high density in which animals are kept on an intensive pig or poultry farm ensures that once MRSA appears it can quickly spread to a large number of animals. The Dutch microbiologist Professor Jan Kluytmans has said: ‘If it can spread so easily in hospitals where containing measures are taken, you can imagine the effect in a pig sty where there is complete body contact – that is an MRSA paradise!’ (Zembla 2006).

MRSA and flu

Recent research from the US has shown that there is a strong link between influenza and the risk of people falling victim to certain strains of community-acquired MRSA. During the flu season in 2003–04, scientists reported 17 cases of community-acquired pneumonia caused by *S. aureus*, of which 15 were caused by MRSA. Of the 17 patients, 12 (71%) had evidence of flu infection.

Referring to scientific evidence that *S. aureus* can interact synergistically with the flu virus to increase the chances of co-infection, the researchers concluded that the infections in these cases were probably associated with the flu (Hageman 2006). The scientists pointed out that it is already known that:

- infection of mammalian cells by the flu virus increases bacterial adherence of *S. aureus* specifically (Davison and Sanford 1981, Sanford and Ramsay 1987)
- the flu virus inhibits the ability of the immune system, and cells such as white blood cells, to kill *S. aureus* (Abramson et al. 1983). Even mild flu infections have been shown to inhibit immune defences against *S. aureus* infections (Nickerson and Jakab 1990)
- *S. aureus* secretes enzymes which enable the flu virus to increase its rate of replication and its infectivity (Tashiro et al. 1987a, Tashiro et al. 1987b)

Speaking about this work, Professor Richard James of Nottingham’s Centre for Biomolecular Sciences has warned: ‘The real doomsday scenario now is that you have an increasing number of young fit people with Community MRSA, you have a flu epidemic that makes the lungs more susceptible to infection and then the MRSA will actually kill people very quickly’ (Tzabar 2006).

The evidence for a synergistic relationship between flu and *S. aureus* (including MRSA) does not, however, only have implications for MRSA infections in humans. It may also help explain the spread of MRSA in pigs. This is because various strains of influenza A, the group of flu strains causing infection in humans which scientists have shown to have a synergistic relationship with *S. aureus*, are also known to infect pigs. The most endemic strains in the pig industry are the H3N2 (which causes most flu outbreaks in humans), the H1N1 and the H1N2 influenza A viruses (Brown 2000, CDC 2006, NIMR 2007). Experiments have shown that both the H3N2 and H1N1 strains increase the adherence of and reduce immune defences to *S. aureus* (Davison and Sanford 1981, Abramson et al. 1983, Nickerson and Jakab 1990).

If pig flu does have a synergistic relationship with MRSA in pigs, as it appears to have in humans, this would be a major concern, since the conditions in which pigs are kept in the modern intensive pig industry almost guarantee that the herd will be carrying a flu infection virtually all the time. Maes et al. (2000), Myers et al. (2006) and Saenz et al. (2006) have all recognised that large numbers of animals kept in confined spaces, combined with the frequent introduction of susceptible

young animals, contribute to the high levels of pig flu in the modern pig industry. Pig flu, like the human flu, used to be seasonal, but it can now occur all year round (Myers et al. 2006). A website for the intensive pig industry even admits that 'it is virtually impossible to maintain a population of pigs that is influenza free' and that in large herds it 'may become endemic' (ThePigSite 2007).

The intensive conditions in which the pigs are kept may, therefore, not only increase the opportunities for MRSA to spread by pig-to-pig contact, but also help the superbug by weakening the pigs' resistance to MRSA colonisation.

Animals' defences against MRSA infection may help its spread

Fortunately for the welfare of the pigs, the animals themselves do not appear to develop sickness as a result of becoming MRSA carriers. This may be in part due to the fact that they produce higher levels than humans of chemicals called cathelicidins, which have antibacterial properties. These have been shown to protect humans from skin infections and may have a similar effect in pigs, protecting them from infections such as MRSA. Horses and cattle also produce higher levels of cathelicidins than humans. (BBC 2005, Lee et al 2005)

Whatever the reason for pigs' apparent immunity to MRSA infection, the fact that they do not develop disease means that carrier animals will not be diagnosed and treated. This will inevitably increase the opportunities for MRSA to spread in the environment and on pig meat, ultimately leading to greater dangers to human health.

9. Antibiotic use in UK farming and the MRSA threat

'Because many of the antimicrobials used in animals are also used in human medicine, the use of antimicrobials in animals is part of the global problem of antimicrobial resistance'

(UNION OF CONCERNED SCIENTISTS 2001)

Intensive conditions create need for high antibiotic use

Intensive pig and poultry production systems rely heavily on the use of antibiotics in feed and water to control or treat the multitude of often interlinked diseases which farm animals kept in crowded indoor conditions are prone to develop. The Dutch Minister, Dr Cees Veerman, has said that pig vets in the Netherlands believe that insufficient care for individual animals and poor management are factors contributing to high antibiotic usage (see Appendix).

Enzootic pneumonia is a typical disease of intensive systems, and according to the drug company Schering-Plough, 'the organism is spread from pig to pig by aerosol droplet, hence the condition is worse where there is poor ventilation, overcrowding and mixed ages of growing pigs' (Schering-Plough 2005). Intensive pig production has also seen the emergence of serious viral syndromes over the past decade which have created a new range of problems (see Box 9.1).

Box 9.1 The changing face of pig disease, according to Schering-Plough

'Over the last decade ... on-farm disease has changed significantly with the introduction of both porcine reproductive and respiratory syndrome virus (PRRSv), which ... damages the immune system and destroys lung macrophages and also the advent of post-weaning multi-systemic wasting syndrome (P.M.W.S.) associated with porcine circovirus type 2, which further damages the pig's immune system. Both viruses permit other viruses such as swine influenza virus (SIV) and porcine respiratory coronavirus (PRCV) to become endemic in herds as well as increase the susceptibility of pigs to further bacteria including salmonella. This has led to the term the porcine respiratory disease complex (PRDC) being used to refer to this mix of respiratory diseases which has had a significant impact on pig production and mortality rates across Europe.'

Source: (Schering-Plough 2005)

Most of the antibiotics used on intensive farms are the same as those described in Chapter 8 which promote the spread of MRSA. If MRSA were to emerge in British farm animals, intensive conditions and high levels of antibiotic use would foster the rapid spread of the superbug, as has occurred in the Netherlands.

Government strategy for reducing antibiotic use in farming

While the rapid spread of MRSA raises new questions about the wisdom of food-production systems that rely so fundamentally on antibiotic feed additives, the need to reduce antibiotic usage in livestock has been understood for some time. In 1998, a report by the Science and Technology Select Committee of the House of Lords drew attention to the excessive use of antibiotics in both human and veterinary medicine. In the press release to launch the report the Chairman, Lord Soulsby, said: 'Misuse and overuse of antibiotics are now threatening to undo their early promises and success in curing disease' (House of Lords 1998).

In 1999 the Government's Advisory Committee on the Microbiological Safety of Food (ACMSF) also published a review of the scientific literature on antibiotic

resistance and food safety. It found that 'humans can acquire antibiotic-resistant pathogenic and non-pathogenic microorganisms via food, direct contact with animals, or faecally contaminated environments' (ACMSF 1999). In common with the House of Lords, it called for some of the growth-promoting antibiotics (AGPs) to be banned, but it also recommended that the Government should develop 'a coherent strategy aimed at reducing the veterinary use of antibiotics', a recommendation the Government accepted (ACMSF 1999, MAFF 2000).

At first there appeared to be substance to the commitment. After initial reluctance, the British Government joined forces with other EU countries in pushing through a ban on all AGPs, despite strong industry opposition. Codes of practice were drawn up and the Government commissioned research into production systems with low antibiotic use. In 2001, the House of Lords committee concluded: 'There is good news about this problem from the agricultural sector. Sales of antibiotics for use in animals … have fallen' (House of Lords 2001).

Despite these initial encouraging signs, there has been no conviction to the Government's strategy. While the ban on the AGPs was a move in the right direction, nothing has been done to stop farmers from switching to using prescription antibiotics in animal feed for 'disease prevention'. For intensive pig and poultry production, obtaining a prescription is usually just a formality, since producers have gravitated towards veterinary surgeons most willing to make these available (Clark 1999).

An earlier advisory committee, chaired by Professor Eric Lamming, recognised that the use of antibiotics for disease prevention could have consequences for human health, and said: 'We recommend that not only should antibiotics giving cross-resistance to those used in human medicine not be used as growth-promoters but that their prophylactic use in animals be reconsidered' (Lamming et al. 1992). Successive administrations have, however, ignored this recommendation, and no formal consideration has ever been given to the subject.

While the Government claims to take the problem of antimicrobial resistance in farm animals 'very seriously' (Bradshaw 2007), a sign of the low priority it is actually given comes from the reply to a written Parliamentary Question in 2005, in which the Minister responsible for this area, Ben Bradshaw, stated: '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' (Hansard 2006).

Furthermore, the VMD, which is responsible for providing advice to the Government on all aspects of the authorisation and use of antibiotics on farms, has refused to take responsibility for advising the Government on how a strategy for reducing antibiotic use might be implemented. In response to a Soil Association question, it said that the veterinary use of antibiotics is under the control of vets and that reducing the use on farms is not the VMD's role.

'We recommend that not only should antibiotics giving cross-resistance to those used in human medicine not be used as growth-promoters but that their prophylactic use in animals be reconsidered'

(LAMMING ET AL. 1992)

Indications that antibiotic consumption per pig has increased

Government statistics on the sales of veterinary antimicrobials have been subject to several major historical revisions. As such, it is difficult to have total confidence in their accuracy at any given point. In addition, all the data so far has been gathered from manufacturers on a voluntary basis. Taken at face value, however, the figures show that the total veterinary use of growth-promoting and 'therapeutic' (including disease prevention) antibiotics fell from 502 tonnes of active ingredient in 1999 to 460 tonnes in 2005. This 8% fall may seem like welcome, albeit slow, progress, but closer examination of the statistics suggests that the use per pig has actually increased. Since 1999 there has been a 33% fall in pig numbers (see Box 9.2).

BOX 9.2 Improving pig welfare undermined by allowing cheap imports

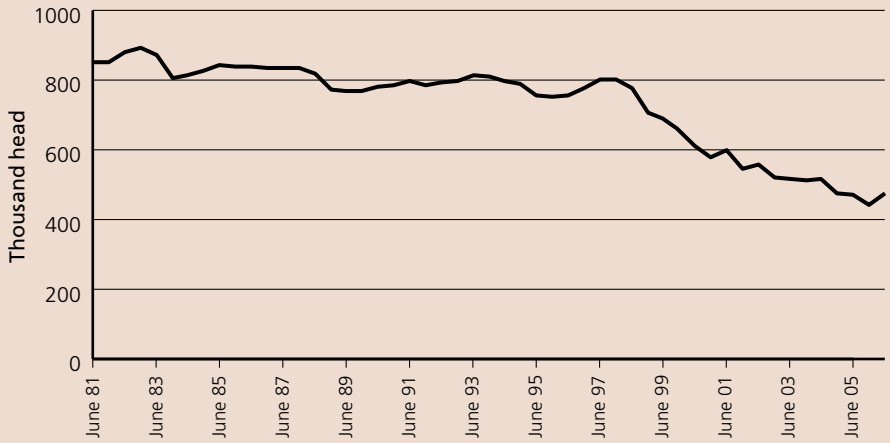
Throughout most of Europe and the US, intensively farmed breeding pigs are housed for long periods in small sow stalls with bare concrete and slatted floors in which they cannot turn round or lie down comfortably. This can cause joint problems and lameness. In some non-EU countries, sows can also be tethered. This was banned in the EU in January 2006.[1]

The UK followed Sweden in banning both sow stalls and tethering in 1999. Indoor sows are now usually kept in free-moving groups on straw bedding, although the use of farrowing crates is still permitted for several weeks at a time. Sow stalls will also be banned in the Netherlands next year and throughout the EU from 2013 (CIWF 2000).

While some multiple retailers have pigs reared on contract in other EU countries and impose their own welfare standards, there is no UK national requirement that imported pork and bacon be from pigs reared to the same welfare standards as those which apply to UK farmers. It is believed that a significant quantity of low-welfare imported pork and bacon ends up in the catering trade and other outlets, where it can be sold without any requirement to declare the country of origin. As a result, British pig farmers have suffered from cheaper imports produced under lower welfare requirements. Set against this, however, it is necessary to note that some aspects of welfare, such as space allowances, are higher in the Netherlands than the legal minimums in the UK (Clarke 2005).

As the graph below shows, a sharp fall in the size of the UK pig breeding herd occurred after the introduction of the new British pig-welfare laws.

UK pig breeding herd (June 1981 to June 2006)



Source: Defra 2006b

The resulting fall in production has been made up by increaed imports. According to the British Pig Executive, 60% of pig meat consumed in the UK in 2004 was imported, and only 20% of this was produced to UK welfare standards. The Netherlands provided 53% of bacon and 15% of pork imports, and Denmark provided 33% of bacon and 37% of pork imports (BPEX 2005).

Sheep and cattle numbers are also down by 21% and 9% respectively, while chicken numbers have increased by just 4% (Goodyear 2006). In the UK, over 90% of veterinary antibiotics are used in pig or poultry production (Goodyear 2006), and despite the lack of a species breakdown, there are indications that the total use in pigs is greater than in total poultry (SACAR 2005). This suggests that antibiotic consumption per pig has increased since 1999, otherwise there would have been a much larger fall in total veterinary consumption.

Switching from AGPs to therapeutic antibiotics

To compound the issue, the veterinary use of therapeutic antibiotics in food animals has actually increased by 3.5%, from 405 tonnes of active ingredient in 1999 to 419 tonnes in 2005 (Goodyear 2006) (see Table 9.1), despite the fall in livestock numbers. This is hard evidence of producers switching

[1] Council Directive 2001/88/EC of 23 October 2001

between antibiotics. With the exception of just one minor class of drugs, the pleuromutilins, therapeutic antibiotics are all closely related to antibiotics used in human medicine and the development of resistance to them could have serious consequences for human health. The increase in the use of therapeutic antibiotics has occurred despite a warning from the Policy Commission on the Future of Farming and Food, which guides the Government's policy on sustainable food and farming, that 'progress made through the reduction of licensed antibiotic growth-promoters [should not] be eroded by the use of other antibiotics also cross-resistant with important medical drugs' (Curry et al. 2002).

'Progress made through the reduction of licensed antibiotic growth-promoters [should not] be eroded by the use of other antibiotics also cross-resistant with important medical drugs'

(CURRY ET AL. 2002)

Table 9.1 Tonnes of therapeutic antimicrobials by active ingredient, sold for farm use

1999	2000	2001	2002	2003	2004	2005
405	425	400	416	405	425	419

Source: Goodyear 2006

However, this appears to be exactly what has been happening. No figures are available yet for antibiotic use since the final stage of the growth-promoter ban came into force on 1 January 2006, but according to David Burch, a vet who advises the pharmaceutical industry, the earlier bans on some of the growth-promoters led to substantial levels of switching to therapeutic antibiotics (Burch 2005). Other scientists who opposed the ban on the growth-promoters claimed in 2003 that the initial bans had led to animals becoming sick more often and that 'a directly attributable effect of these infections is the increase in usage of therapeutic antibiotics in food animals, including that of tetracycline, aminoglycosides, trimethoprim/sulphonamide, macrolides and lincosamides, all of which are of direct importance in human medicine' (Casewell et al. 2003).

The Dutch Minister, Dr Veerman, has indicated that drug switching has also occurred in the Netherlands. He said that: 'Because AGPs, in part, had a preventative effect for a number of animal diseases, the use of antibiotics registered for therapeutic use increased in some businesses (in particular in businesses with shortcomings in housing and hygiene)' (see Appendix).

Government fails to promote real management changes

Increasing levels of infection would not be surprising since the growth-promoter bans have not been accompanied by any fundamental changes to the nature of intensive systems. This is the key area where the Government has failed to encourage effective action. Rather than put any serious effort into promoting the widespread adoption of management systems with lower antibiotic requirements, it has looked the other way and left it to farmers and vets to continue as before with the drugs still available.

Furthermore, while the Government supports and encourages organic farming because of its environmental benefits, it does not acknowledge that organic livestock production should additionally be encouraged because of its lower antibiotic usage. Organic systems are still not perfect, but one of their primary aims is to keep farm animals in conditions where they are naturally healthy and antibiotics are needed only rarely.

Government permits direct advertising to farmers of prescription-only antibiotics

The lack of commitment from the Government on reducing farm antibiotic use became clearer still when, under pressure from the pharmaceutical industry, the UK decided not to implement an EU-wide ban on the advertising of prescription-only medicines, including antibiotics, directly to farmers.

EU Directive 2004/28/EC, implemented in the UK in October 2005, required that member states ban the advertising of prescription-only medicines to 'members of the general public', bringing veterinary medicines into line with human medicines. The VMD initially interpreted this to mean that advertising to farmers could no longer be permitted, since farmers are not qualified to write veterinary prescriptions and the Directive only made exceptions to the prohibition for veterinary surgeons and pharmacists. The proposals were put out to consultation in January 2005, but circulated almost exclusively to industry parties. The Soil Association and two other consumer groups expressed their support of the proposed ban on advertising to farmers, but the National Office of Animal Health (NOAH), the body which represents the pharmaceutical industry, strongly opposed it and made its feelings known to the VMD (NOAH 2004).

Two months into the consultation, the VMD took the unusual step of producing revised proposals under which limited 'informative and educational' advertising to farmers would be permitted. This move was welcomed by NOAH as 'going a long way to answer our concerns'. Nevertheless, NOAH said it still did not go far enough, and called on the VMD to avoid introducing any new restrictions at all on advertising to farmers and to rely instead on voluntary self-regulation by the pharmaceutical industry (NOAH 2005). On the basis of written legal advice that 'it is impossible to reconcile this proposal with the clear prohibitions included in the Directive and such a Regulation would therefore fail to be in conformity with the Directive' (Burton 2005), the Soil Association strongly opposed the move to water down the original proposal (Soil Association 2005a).

The possibility of permitting limited advertising to farmers was discussed at a meeting betwen the VMD and consumer groups on 8 August 2005. The consumer groups, including the Soil Association, argued that the original interpretation of the European Directive should be retained, whereas the VMD defended its revised proposals.

At the meeting the VMD did not indicate that its compromise proposal of educational advertising had also been dropped and that it was about to abandon the proposed restrictions on advertising entirely. Yet when the new Veterinary Medicines Regulations 2005 were laid before Parliament in early October, advertising to farmers was allowed to continue as before, with no new restrictions at all, exactly as NOAH had requested (The Veterinary Medicines Regulations 2005).

In the following sections on prescription-only medicines used in the pig, poultry and dairy sectors, we provide examples of how these antibiotics are still being promoted to pig and dairy farmers in the farming press.

The use in pig and poultry farming of antibiotics which promote the spread of MRSA

Of all the farmed animal species, pigs and poultry receive the highest amounts of antibiotics. In addition to the disease problems associated with intensive indoor conditions, the practice in pig farming of weaning piglets as early as three weeks of age, when it is known that their immune systems do not develop properly until seven or eight weeks, makes the animals especially susceptible to diseases such as streptococcal or *E. coli* infections.

Unfortunately, the full antibiotic usage picture is hard to discern, since a proper breakdown of antibiotic use by species and antibiotic class is still not available in the UK, despite a Government commitment to produce such statistics in 2000 (MAFF 2000). Nonetheless, the partial breakdown provided in the UK's annual antimicrobial sales reports suggests that well over 90% of all antibiotics used in farming in the UK are used in pig or poultry production (Goodyear 2006). Table 9.2 provides a full list of the antibiotics permitted in pig feed for disease prevention. Some of these are also among the antibiotics licensed to treat disease.

Table 9.2 Antibiotics used orally in pigs for disease prevention or control in the UK

Antibiotic class	Antibiotic	Product	Maximum period of use
Aminoglycoside	Apramycin	Apralan G 200 Premix	Up to 28 days
Aminoglycoside	Neomycin	Neobiotic Soluble Powder 70%, Neomycin Premix	Up to 7 days
Aminoglycoside	Spectinomycin	Spectam Scour Halt	Up to 5 days
Beta-lactam	Amoxicillin	Stabox 5% Premix	Up to 14 days
Beta-lactam	Phenoxymethyl-penicillin	Potencil	Up to 6 weeks
Lincosamide / aminoglycoside	Lincomycin + spectinomycin	Lincocin Premix, Linco-Spectin Premix,	Up to 3 weeks or 'throughout period of risk' or 'until clinical signs disappear'
Macrolide	Acetylisovaleryl-tylosin	Aivlosin Premix	Up to 10 days
Macrolide	Tilmicosin	Pulmotil G100 & G200 Premix[a]	15 days
Macrolide	Tylosin	Tylan G20, Tylan Premix	Up to 21 days or 'until end of period of risk'
Pleuromutilin	Tiamulin[b]	Tiamutin Premix, Tiamutin 12.5% Solution[b]	Up to 2 months or 'throughout period of risk'
Pleuromutilin	Valnemulin[b]	Econor Premix	Up to 28 days or 'until clinical signs disappear'
Tetracycline	Chlortetracycline	Aurofac 100, Aurogran 500, Chlorsal 50	Up to 7 days
Tetracycline	Oxytetracycline	Tetramin 200 Powder, Tetroxy L.A.	Up to 15 days
Trimethoprim / sulphonamide	Trimethoprim + sulfadiazine	Synutrim Fortesol, Synutrim Granular	Up to 7 days

Source: NOAH 2007

Notes: (a) Pulmotil G100 and G200 are licensed for treatment only and not for disease control or prevention. However, we include them here because of the long treatment period (15 days). Furthermore, although these products are only authorised for use at the full therapeutic dose, Elanco Animal Health advertises them as an alternative to the antibiotic growth-promoters for 'management', and in practice they are also used for the 'control of chronic outbreaks' of pneumonia, seemingly with Elanco's approval (White 2007). (b) Tiamulin and Valnemulin are not related to any currently licensed medical drugs.

Official Dutch statistics, on the other hand, do provide information on species breakdown on Dutch farms, and since it is not unreasonable to expect that antibiotics will be used in a similar way on British farms, we give details of Dutch use in the sections on specific antibiotics below.

Tetracyclines, beta-lactams, macrolides and aminoglycosides are four of the five most widely used antibiotic classes in pig and poultry farming, and we saw in Chapter 8 that the use of these antibiotics promotes the spread of MRSA if the strain is already resistant to them. In the next sections, we look at how these antibiotics are used in more detail, and at how they are advertised to farmers.

Tetracyclines

By weight of active ingredient, the most widely used antibiotics in UK farming are the tetracyclines. They accounted for 53% of total usage in 2005 (Goodyear 2006). This is despite the fact that tetracyclines were banned as growth-promoters in 1971 because it was recognised that their use was leading to antibiotic resistance in bacteria in farm animals, which could be transmitted to humans. Products such as Aurofac and Aurogran, which both contain chlortetracycline, are added to pig and poultry feed for the treatment or prevention of various respiratory infections, *E. coli*, salmonella and any other tetracycline-sensitive infections.

In the Netherlands, tetracyclines account for a similarly high proportion of total antibiotic use: in 2005, 60% of all antibiotics used in Dutch animals were tetracyclines (FIDIN 2006). In pig production in the Netherlands in 2004, tetracyclines accounted for between 39% of usage (in breeding facilities) and 79% (in fattening facilities), measured in daily doses per animal per year (a method which takes into account differences in the potency of each active ingredient). The total usage of tetracyclines in Dutch farming increased by 14% between 2004 and 2005, and this was the seventh annual increase in a row (MARAN 2005, FIDIN 2006).

Given the high levels of tetracyclines used in the Dutch pig industry, it is not surprising to find that the MRSA found in Dutch pigs is tetracycline-resistant (Huijsdens et al. 2006b, de Neeling et al. 2007). The tetracycline-resistance of the MRSA is significant as it suggests that tetracycline use in pig feed will be helping the MRSA to spread, by selecting for *S. aureus* strains, including MRSA, that are resistant to these antibiotics.

Box 9.3 Tetracyclines and beta-lactams

Dutch use of tetracyclines in poultry farming is also very high, accounting for about one third of antibiotic use in broilers (chickens raised for their meat) and approximately 70% in turkeys (MARAN 2005).

Beta-lactams

Beta-lactam antibiotics, to which MRSA is by definition resistant, are the third most widely used antibiotic class in UK farming by weight of active ingredient,[2] and various beta-lactam feed additives are used in pig and poultry farming. Penicillin can still be added to pig feed for periods of up to six weeks for the control of respiratory diseases and various streptococcal infections, despite having being banned in the UK as a growth-promoter over 30 years ago. Amoxicillin is also used as a feed additive in pigs and poultry for the treatment or prophylactic control of a variety of diseases such as salmonellosis, pasteurella, colibacillosis or streptococcal infections.

More recently, ceftiofur, a modern beta-lactam known as a third-generation cephalosporin, has also been licensed for the treatment of a limited range of diseases in pig production and is available in two products, Excenel and Naxcel. Concern already exists about the use of ceftiofur since it has been implicated in the possible spread though food of highly resistant strains of *E. coli*, known as extended-spectrum beta-lactamases. However, ceftiofur could also encourage the spread of MRSA in pigs: studies show that humans treated with third-generation cephalosporins are at increased risk of MRSA infection (Crowcroft et al. 1999, Weber et al. 2003). In Denmark ceftiofur is only licensed for the treatment of respiratory infections, but an analysis of the data by Danish scientists 'strongly indicates that off-label[3] use is widespread' (Jørgensen et al. 2007). In the absence of a prohibition of off-label use, it is likely that a similar situation exists in the UK.

Macrolides

Macrolide antibiotics are the fourth most widely used antibiotic class in UK farming (Goodyear 2006). Until a few years ago, the use of two macrolides (tylosin and spiramycin) was permitted in pig farming for growth promotion, but the EU imposed a ban on them in 1999 because of concerns that their excessive use in veterinary medicine was leading to more antibiotic-resistant bacteria in pigs which could then infect humans – macrolide antibiotics are also important in human medicine for the treatment of, for example, children with campylobacter infections and anyone allergic to penicillin-type antibiotics.

Box 9.4 The growth-promoter that won't go away

The ban on tylosin for growth promotion in 1999 came 30 years after the Swann Committee recommended that tyosin should not be used for growth promotion. At the time, the Government accepted this and a prohibition was introduced in the UK in 1971.

However, industry and pro-industy scientists lobbied the Department of Health and fought a persistent campaign to get it reinstated, including the publication of many papers claiming that tylosin-resistant bacteria posed no risk to humans. As a result, it was added to Annex 1 of the EEC feed-additive Directive 70/524/EEC in 1978, effectively overturning the British ban. Now tylosin feed additives, available on prescription, are advertised for their growth-promoting effects.

Sources: Mackinnon 1981, Lacey 1981

However, many pig producers appear to have compensated for the ban by increasing the overall use of macrolides for disease prevention and control, something they are clearly being urged to do by the pharmaceutical companies that market these drugs. In the UK, in the three years after the ban, macrolide use on prescription increased by nearly 90% from 23 tonnes of active ingredient in

[2] The second most widely used antibiotic class in UK farming is the trimethoprim/sulphonamides, but we do not describe these drugs in detail in this report as they have not been linked to the spread of MRSA.

[3] 'Off-label' use allows antibiotics to be used under certain circumstances in species or for purposes for which they have not been authorised.

Box 9.5 Macrolides

1999 to 37 tonnes in 2005 (Goodyear 2006). Dutch figures show that significant quantities of macrolides are still used in both the pig and poultry industries (MARAN 2005).

In the UK, the macrolide product Tylan is licensed for the prevention or control of swine dysentery and pneumonia, and the treatment of other diseases. Its active ingredient, tylosin phosphate, was previously used as a growth-promoter in a product called Tylamix, but now, in flagrant contravention of the spirit of the 1999 ban, Tylan is being advertised as an alternative to the growth-promoters. It clearly has similar effects since it is the same chemical, and although it is generally pointed out that Tylan is used at higher dosage rates than Tylamix was, it can still be used legally at the previous growth-promoting level of 40g per tonne. The dosage instructions for Tylan use show that after being used at 100g of tylosin per tonne of feed for 21 days, it can then be used at 40g per tonne 'until the end of the period of risk' (NOAH 2007). The previous dosage range at which tylosin was used as a growth-promoter was 20–40g per tonne (Mounsey 1998).

The tylosin derivatives Pulmotil (tilmicosin) and Aivlosin (acetylisovaleryltylosin) are also promoted as alternatives to the banned growth-promoters and used as feed additives in pigs for the treatment or control of pneumonia.

In poultry, tylosin is used to control necrotic enteritis (a common disease in intensively farmed birds, previously controlled by growth-promoting antibiotics) and infections caused by bacteria called mycoplasma. Erythromycin, an important macrolide antibiotic in human medicine, is used to treat respiratory infections.

Of 44 strains of pig MRSA tested in the Netherlands, ten (23%) were resistant to macrolide antibiotics (de Neeling et al. 2007). The MRSA found in a pig in Germany was also macrolide-resistant (Witte et al. 2007). The macrolide resistance of some strains of pig MRSA combined with high levels of macrolide use in pigs may encourage the spread of MRSA.

Lincosamides and aminoglycosides

Lincomycin is a lincosamide, an antibiotic class closely related to and partially cross-resistant with both the macrolides and the banned antibiotic growth-promoter virginiamycin. It is available on its own as Lincocin, or in combination with the aminoglycoside spectinomycin as Linco-Spectin. It is licensed as an antibiotic growth-promoter in some non-EU countries. According to the specialist pig and poultry vet David Burch, the use of lincomycin in the pig industry has increased since the ban in 1999 on two growth-promoters, carbadox and olaquindox, which had helped control swine dysentery (Burch 2005). He also describes lincomycin as an alternative to salinomycin, another growth-promoter banned in January 2006, so despite being more expensive than salinomycin, its use may increase further still.

Aminoglycosides are the fifth most widely used class of antibiotics in British farm animals (Goodyear 2006). The aminoglycosides neomycin, apramycin and spectinomycin are used as additives in pig and poultry feed. In the Netherlands, however, aminoglycosides do not appear to be used in significant quantities in the pig industry (MARAN 2005).

Box 9.6 Lincosamides and aminoglycosides

BOX 9.7 Advertising antibiotics – how much has changed in 35 years?

In 1970, Dr H. Williams Smith, a highly respected British scientist whose research partly prompted the formation of the Swann Committee, wrote: 'The diagnosis and treatment of disease is becoming increasingly complex and I suggest that it is economically beneficial for a farmer to pay a veterinary surgeon for advice regarding treatment of his animals rather than to base his disease-controlling policies on what he reads in the advertising colums of the farming papers' (Williams Smith 1970).

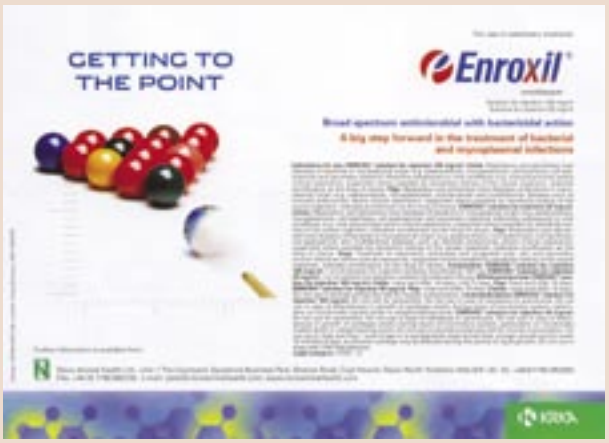
The advertisment on the left is from this period. How much has since changed? Cyfac is no longer listed as a permitted product in the UK. It contained three antibiotics: chlortetracyline, penicillin and sulphadimidine. The first two can both still be used for extended periods in animal feed. The third is no longer available, having been replaced by other similar sulphonamide drugs, which may only be used now for a maximum of seven days. Cyfac was available without veterinary prescription, whereas all antibiotics today have to be approved by a vet. Nevertheless, the use of tetracyclines, penicillins and sulphonamides in animal feed have all greatly increased over the past 35 years.

Fluoroquinolones

Fluoroquinolones are used in pigs and cattle to treat individual animals by injection. In poultry they can still be legally added to the drinking water of entire flocks.

The US has recently banned the use of the fluoroquinolone enrofloxacin in poultry farming, because fluoroquinolones are the antibiotics of choice for treating salmonella and campylobacter infections in humans, and enrofloxacin use in poultry was leading to fluoroquinolone-resistant campylobacter multiplying in the intestines of chickens and subsequently contaminating chicken meat at the slaughter plant (FDA 2005). The Soil Association has also effectively banned the use of fluoroquinolones in organic poultry production certified to its standards. The standards state: 'You must not use fluoroquinolone antibiotics without our permission and only to treat individual animals' (Soil Association 2005). In the UK, however, fluoroquinolone usage increased in 2005 to the highest level since 1999 (Goodyear 2006).

Box 9.8 Fluoroquinolones



While the veterinary use of fluoroquinolones is significantly higher in some European countries than others, in general their use in farm animals remains at a lower level than in humans. This is the case in the UK and also in the Netherlands, which probably explains why the MRSA found in Dutch pigs is not yet fluoroquinolone-resistant, while most human MRSA strains already are (de Neeling et al. 2007).

One reason for the relatively low level of fluoroquinolone use in animals has been the high price of the drugs. In Hungary, fluoroquinolone use in agriculture is extremely high – it has been estimated to account for 25% of all antibiotic use in farm animals, in comparison to just 1% in the UK (Hellmann 2006, Goodyear 2006). This high usage has been attributed to the fact that cheaper generic fluoroquinolone products have been available for some time in Hungary as alternatives to the more expensive branded products (Hellman 2006). Generic fluoroquinolone products are now also beginning to be introduced into the UK and advertised directly to pig and poultry farmers in the trade publications Pig World and Poultry World. For example, the drug Enroxil is a new generic fluoroquinolone only recently put on sale in the UK. Further generic versions are expected on the market over the next few years, and the drug industry is expected to try compensate for the inevitable price fall by increasing overall sales.[4]

Dairy cows, dry-cow therapy and MRSA

After the pig and poultry industry, dairying uses the most antibiotics. Beta-lactam antibiotics, in particular, are widely used in dairy cows for the treatment and prevention of mastitis.

Dry-cow therapy is routinely used in non-organic dairy herds after the final milking of a lactation. A beta-lactam antibiotic, such as cloxacillin (an antibiotic very closely related to methicillin), ampicillin, cephalonium or cefquinome (a fourth-generation cephalosporin), is infused into each teat. This is done in an attempt to provide protection against summer mastitis, which can occur during the period when the cow is not giving milk, and to reduce the chances of mastitis at the beginning of the next lactation.

The practice is strongly discouraged in organic farming, although special permission is given under certain circumstances for individual cows with a history of recurrent mastitis. Cloxacillin and other antibiotics are also used to treat lactating cows with mastitis.

Cloxacillin is not licensed for any other livestock apart from sheep (NOAH 2007). Although no precise figures are available, it is clear that use in dairy cows is very much higher than in sheep, because of its use in dry-cow therapy.

S. aureus is a cause of mastitis in dairy cows and, as long as the bacteria have not developed resistance, the infection can be treated with beta-lactams. Methicillin resistance in bovine mastitis appears to be rare, but where it does occur the continued use of cloxacillin will favour its spread, leading also to the potential for contaminated milk to enter the food chain (Lee 2003).

The presence of *S. aureus* in cows' udders and the routine use of beta-lactam antibiotics create conditions highly conducive to the spread of MRSA and it is not surprising that there have been reports of MRSA in dairy cows or their milk from around the world, although no cases have yet been found in the UK (see Chapter 4). Direct contact with a farmer who is an MRSA carrier may explain some of these cases, but evidence from Korea suggests that specific bovine MRSA strains have developed too (Kwon et al. 2005).

[4] During a meeting held in London, on the 12 October 2006, by the European Agency for the Evaluation of Medicinal Products, as part of its consultation on the use of fluoroquinolone antibiotics in farming, a pharmaceutical industry representative indicated that the industry would seek to increase sales if the introduction of generic drugs led to a price fall.

Box 9.9 Dry-cow therapy

Appendix. Letter from Dutch Minister to Dutch Parliament

De Voorzitter van de Tweede Kamer
der Staten-Generaal
Postbus 20018
2500 EA 's-GRAVENHAGE

18 December 2006

Dear Chairman,
Following your request for further information on the situation concerning the methicillin-resistant *S. aureus* (MRSA) problem and the relationship to and the consequences for public health and animal farming in general, here is my reply. I can state that I find, on behalf of the Minister for Public Health, Welfare and Sport, that the discovery of MRSA in various agricultural animals and animal products is a worrying development which motivates me to come up with several new measures. Here below I set out the facts known to me so far, the actions being undertaken and my policy proposals.

MRSA in humans
There are 3 types of MRSA bacteria. Besides the 'classic hospital MRSA' and a type of MRSA that is found amongst the population, there is yet another type of MRSA that, in 2005, was found in pigs in the Netherlands. All three types have in common that they have become less sensitive to penicillin, methicillin and antibiotics that work in a similar way. The first two types of MRSA occur with very low frequency amongst the Dutch population (altogether less than 0.1%) and, so far as is known, have nothing to do with Dutch pig farming or other forms of animal farming.

The MRSA which is found in pigs and that we, for simplicity, refer to as 'animal-farming-related MRSA' is confirmed at a much higher frequency in Dutch pig farmers. During a limited investigation in 2006, 23% of this group were found to be 'carriers'. Also, the co-habiting family members of pig farmers could be carriers of the 'animal-farming-related MRSA'. Since 2003 there is also evidence of an increased presence of 'animal-farming-related MRSA' in calf breeders, according to the findings of a retrospective study by the Royal Institute for Public Health and Environment (RIVM) carried out in 2006 on material found in MRSA cases in hospitals which was stored by the RIVM.

The presence of 'animal-farming-related MRSA' in persons in close contact with pigs or in the immediate surroundings of them creates a problem with the admittance to hospital and nursing homes, as with all other types of MRSA, and brings with it risks to public health. In patients with (temporary) lowered resistance because, for example, of an operation or specific medication, all forms of MRSA, of which a patient is normally an unsuspecting carrier, can cause an

infection. MRSA infections carry greater risks for patients than antibiotic-sensitive infections because, fewer antibiotics are appropriate for the treatment of MRSA, and because the limited number of appropriate antibiotics show more negative side effects.

The low frequency of the presence of human infections with the first two types of MRSA in the Netherlands are due, according to experts, to successful Dutch policy in the area of infection prevention measures in Dutch hospitals on the basis of national guidelines by the 'Working Party for Prevention of Infection' (WIP) and a restricted use of antibiotics. As well as the extent of the use of antibiotics in health care, the presence of resistant micro-organisms is, in general, among the lowest in Europe. Therefore, there is a much larger margin of safety for hospital patients. Hospital infections are not totally preventable but the number and seriousness of hospital infections is limited by precautionary measures and limited antibiotic resistance.

MRSA in animals and animal products

As mentioned before, in 2005 wholesale 'animal-farming-related MRSA' was found in pigs (about 40%). In the course of 2006, MRSA was found by the Food Safety Authority (VWA) in calves that were examined within the framework of Zoonoses guidelines (faeces examination). Here 13% of the calf samples tested positive (20 of the 150 samples). Added to that, during the regular mastitis test in 2006, it was found that this type of MRSA was present in dairy cows (on 4 premises) and in some samples of raw milk from these premises.

'Animal-farming-related MRSA' has also shown up in a small-scale investigation by the VWA in 2006 into a small number of samples of meat. It was found in 5 of 25 samples (20%) of raw pork, 2 of 64 samples (3%) raw beef and 5 of 24 samples (21%) raw chicken. The samples were drawn from supermarkets. The VWA has, after consultation with the RIVM in mid-2006, concluded that the consumption of these animal products poses no significant public-health problem. Because it is difficult to draw further conclusions on the basis of these findings, it has been decided to repeat this investigation on a larger scale. Within the framework of the MRSA investigative programme which was started on 1 December 2006, the prevention of 'animal-farming-related MRSA' in pigs, calves, cattle (among which are calves and dairy cows) poultry and other intensively reared animals is being closely examined and furthermore in raw meat from pigs, calves, cattle, poultry, milk and other relevant animal products. The results of this can be expected in the second half of 2007.

Causes – increased veterinary use of antibiotics and 'animal-farming-related MRSA'

As previously mentioned, I find the established facts regarding 'animal-farming-related MRSA' worrying. This type of MRSA is not only found in pigs but also in other animals although it is not clear to what extent. As to the causes of this development, I mention the following.

There are even stronger indications that the high usage of antibiotics in livestock farming is the most important factor in the development of antibiotic resistance, a consequence of which is the spread of resistant micro-organisms (MRSA included) in animal populations. The use of antibiotics in agricultural animals has increased since 1998 while, at the same time, resistance levels are tending to increase (see Maran report from the CIDC – Central Institute for Animal Disease Control in Lelystad during 2004 and the agri-monitor of the LEI Agriculture Economy Institute of December 2006 about the use of veterinary antibiotics in the Netherlands in 2005). According to FIDIN, the branch organisation for the pharmaceutical industry in the Netherlands, there was an increase in the use of veterinary antibiotics of approx. 12% in 2005 compared

with the previous year.

The causes are not completely clear but many suggest a connection with the banning of the use of so-called 'antimicrobial growth-promoters' (AGPs) on 1 January 2006. This ban was introduced to counteract antibiotic resistance. AGPs are antibiotics which are administered constantly, via animal feed, in low concentration as a preventative measure. I included this in my reply to the parliamentary question from Mr Ormel. The AGPs have an inhibiting effect on certain unwelcome bacteria in the intestinal canal of the stomach in animals and probably encourage growth in agricultural animals. This ban, which started with a ban on the antibiotic avoparcin as an AGP in the second half of the nineties, was gradually carried through in Europe with the ban on other AGPs leading to a total ban. Because AGPs in part had a preventative effect for a number of animal diseases, the use of antibiotics registered for therapeutic use increased in some businesses (in particular businesses with shortcomings in housing and hygiene measures). Also, there was talk of preventative use.

This is evident from the recent FIDIN initiated survey amongst vets. The majority of the 164 polled pig vets is of the opinion that the ban on AGPs is the most important cause of the increase in the use of antibiotics in the pig industry. In addition, the pig vets refer to the increase in the size of businesses (less care for the individual animal) as another factor in the increased use of antibiotics and also to the increasing infection rate and insufficiently good management. The vets in the calf and poultry industry were less outspoken about the increase in the use of antibiotics. It was noticeable that about a third of the calf vets were of the opinion that there was pressure from the farmers and/or feed adviser to use more antibiotics (see results of the FIDIN survey in the 'Tijdschrift voor Diergeneeskunde' [Magazine for Veterinary Medicine] of 16 November 2006). The extent to which increasing usage is a direct consequence of existing antibiotic resistance is being further investigated.

Improper use

In my reply to the question by Mr Ormel of 24 October, I declared that the Ministry of Agriculture, Nature and Food Standards (LNV) had already received various signs of improper use of antibiotics in the intensive Dutch animal farming industry. From a recent report by the General Inspectorate (AID) and VWA of 7 November 2006, it appears that in 22% of the legally compulsory prescriptions from vets for medicated animal feed, irregularities were found. This led to 62 prosecutions and 32 warnings to vets. The irregularities were incorrect dosage duration, no notification of waiting period and incorrect dosage. Also, animal keepers were found who, without consulting a vet, had in their possession antibiotics or antibiotic-containing feedstuffs probably to use preventatively or for growth promotion. This is expressly forbidden. It was also found that antibiotics are advertised to farmers on the internet and, after ordering, are delivered with no further diagnosis with or without a prescription from a vet. The AID will, in 2007, pay more attention to enforcing the animal-medication ruling. Further to this, I want to mention that the impression exists that the majority of vets do follow the rules and are aware of their responsibility in the use of antibiotics.

MRSA in an international context

It is very unlikely that 'animal-farming-related MRSA' only exists in the Netherlands, considering the animal types where MRSA is found and the many animal movements and comparable livestock farming methods in other EU member states. So far, there are no hard facts about this. It is important, for these reasons, that all Member States examine their animals. 'Animal-farming-related MRSA' was on the agenda of the Task Force on Zoonose Data Collection of the

EFSA (European Food Safety Authority) in October 2006. Sweden has announced that it is soon to start an enquiry into 'animal-farming-related MRSA' and there are also plans to do this in Belgium. In 2004, the French carried out an enquiry into MRSA with pig farmers. Although it is not known if this concerned exactly the same 'animal-farming-related MRSA'. The conclusion was that there was talk of a significant connection between pig farming and resistant bacteria, of which Staphylococcus aureus was one. In Canada, the veterinary faculty of Ontario is to undertake an enquiry into MRSA in pigs and pig farmers. It probably involves a different type of MRSA to that found in the Netherlands. The bacteria were previously found in varying quantities in horses and people working with horses. In vets working with horses an infection percentage (probably carriers) was found of 10–14%.

Investigation

The implementation of the MRSA research programme, as was announced in the reply to the parliamentary question by Mr Ormel on 24 October last about antibiotic use, is now under way. The veterinary investigation is aimed at, amongst other things, at the original connection between the veterinary use of antibiotics and the presence of 'animal-farming-related MRSA' in agricultural animals and the meat from these animals, at the role played by the characteristics of the industry and at the manner in which MRSA is transferred into and among the product chain. For the veterinary part of the investigation, I have made available a budget of over 1.3Million euros over 2 years. The pig sector has initiated its own enquiry to gain more insight into the background of antibiotic use, and to promote discussion and awareness of the risks of antibiotic use.

The part of this programme which is aimed at public health is directed towards the specific properties of 'animal-farming-related MRSA', the possible risks to public health of 'animal-farming-related MRSA', the spread of 'animal-farming-related MRSA' from animals to humans and from human to human, and possible means of intervention.

From contacts with representative organisations of the primary livestock businesses, I know that this is taken very seriously there. In the coming consultation (see the following) I hope to reach agreement on joint action.

Concrete steps towards the reduction of the veterinary use of antibiotics, with respect to the presence of 'animal-farming-related MRSA' in the Netherlands.

A number of campaigns were already started in 2006, partly prompted by the European ruling (see appendix). Added to this, I shall, in anticipation of the results of the current investigative programme, shortly take the following steps. It concerns here the 'no-regret' measures which I, regardless of the results of the current process, consider useful.

1. I shall shortly enter into discussion with representatives of various animal sectors and the vets' organisation, the Royal Dutch Society for Veterinary Medicine (KNMvD), about antibiotic resistance in general and MRSA in particular, probably as a consequence of the high veterinary use of antibiotics. Obviously, measures to curb the use of veterinary antibiotics, resistance and MRSA will be discussed.
2. In the framework of further awareness, the ministers for LNV and VWS will see to it that measures are put in place to pass this information on to the relevant animal keepers, their co-habiting family members and all others who, professionally, are in close contact with the relevant live animal types and fresh animal products, about the risks of antibiotic use, antibiotic resistance (including 'animal-farming-related MRSA') and inappropriate antibiotic usage in the intensive Dutch livestock industry.

3. In addition to the existing MRSA investigative programme, I shall ensure that, at short notice, an enquiry is made into alternatives to AGPs, in particular animal feed additives which improve intestinal bacteria.
4. In the interests of better control of inappropriate antibiotic use, there will shortly be an investigation into whether new legal requirements for veterinary prescriptions should be made. Among other things, earlier suggestions made by the vets' organisation, the KNMvD, in this framework will be included in this investigation (the KNMvD is intensively involved in the discussion about the 'pushing back' of 'animal farming related MRSA' and antibiotic resistance).
5. In anticipation of the European ruling on the hygiene package, I want to encourage the producers of primary animal products to speed up the voluntary sending of the European compulsory details on the use of antibiotics to slaughterhouses so that management of the use of medicines in a data file becomes possible sooner. (Europe has determined that this compulsion applies for pigs from 1 January 2008, for calves and horses from 1 January 2009 and for other livestock from 1 January 2010). For poultry this is already compulsory.
6. Within the framework of the Codex Task Force AMR and the working party which will co-ordinate the problems in the area of antibiotic resistance worldwide, the Netherlands will suggest that other countries also start investigations into the presence of 'animal-farming-related MRSA' in agricultural animals. The meeting will take place from 23–26 October 2007 in Seoul.
7. The European Commission will be asked to implement a ruling for member states to provide an annual statement of veterinary antibiotic usage per food-producing animal type as well as the already existing obligation for 'monitoring the antibiotic resistance development and antimicrobial substances' within the framework of the Zoonoses guidelines 2003/99/EG. Such a statement will clarify the trend in veterinary use of antibiotics in the various animal sectors, facilitate an analysis of the differences between member states and possibly offer negotiating points for the reduction of antibiotic use.

The Minister for Agriculture, Nature and Food Standards

Dr. C.P.Veerman

Appendix

Measures already taken to limit antibiotic use and farm-animal MRSA

1. By the beginning of 2006, the requirement for vets and traders of in-and-outgoing regulated medicines, including antibiotics, to keep records is becomes Dutch law.
2. It is agreed with the General Inspectorate (AID) that in 2007, special attention will be paid to the correct prescribing and administration of antibiotics by vets, and also for medicated feedstuffs and, furthermore, attention will be paid to the use of antibiotics by animal keepers according to regulations and to the illegal presence of antimicrobial raw materials, antibiotic-containing animal feed and to non-registered antimicrobial animal medicines at animal holding businesses. In 2006 it was proposed that AID would pay more attention to the use of tetracyclines and the correct use of medicated feedstuffs. This lead to the action called 'inappropriate use' in this letter.
3. To reach a good maintenance strategy, the ministry of LNV, in conjunction with the ministry of Justice, has, from September 2006, started with a project 'programmed maintenance of animal medicines and growth-promoters'. This is expected to help in the search for efficient methods to control the use of

antibiotics in intensive animal keeping.

4. In the interests of maintaining the code of practice for vets, the cabinet approved my proposal at the end of December 2006 to uphold the maximum punishment which veterinary disciplinary colleges can impose for transgressions, e.g. the preventative administration of antibiotics, to be doubled to 6.700 euros (and in special cases, when there has been great economic gain, to a maximum of 16,754 euros). In combination with financial fines, other sanctions are imposed, such as the suspension or withdrawal of authority to perform animal medical care. The veterinary disciplinary colleges make their own independent statement.
5. Since 1 January 2007, it is prohibited in Europe and so also in the Netherlands, to use antibiotics to control salmonella infections in certain breeding poultry couples (there are exceptions). This ruling will be extended in the coming years throughout Europe with similar measures for slaughter chickens, turkey and pork. These hygiene regulations are also intended to combat the antibiotic resistance of various salmonella types.
6. The European Commission is asked to put the subject of MRSA on the agenda in its own right.
7. By the beginning of December 2006, an extensive programme was started to put the relationship between antibiotic use and MRSA in pigs as well as the spread and means of transferring the 'animal-farming-related MRSA' in animals and humans in the frame.

This letter was translated by Marion Biles for the Soil Association.
The original letter in Dutch can be downloaded from the Dutch Ministry's website at: http://www.minlnv.nl/cdlpub/servlet/CDLServlet?p_file_id=16653

Abbreviations

ACMSF – Advisory Committee on the Microbiological Safety of Food
AGP – Antibiotic growth-promoter
CA-MRSA – Community-acquired MRSA
ESBL *E. coli* – Extended-spectrum beta-lactamase *E. coli*
***mec*A gene –** The gene conferring methicillin resistance
MLST – Multilocus sequence typing
MRSA – Methicillin-resistant Staphylococcus aureus
NOAH – National Office of Animal Health.
NT-MRSA – MRSA which cannot be analysed by PFGE
PFGE – Pulse-field gel electrophoresis
PVL – Panton-Valentine leukocidin
RAPD – Random amplification of polymorphic DNA. A method used for distinguishing between different strains of bacteria
RIVM – National Institute of Public Health and Environment of the Netherlands
SCC*mec* – Staphylococcal chromosomal cassette *mec*. The genetic element of the bacterial chromosome which contains the *mec*A gene in MRSA.
VMD – Veterinary Medicines Directorate
VRE – Vancomycin-resistant enterococci
VRSA – Vancomycin-resistant *Staphyylococcus aureus*
VWA – Food and Consumer Safety Authority of the Netherlands

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