COMPASSION in world farming

ANTIBIOTICS IN FARM ANIMAL PRODUCTION

Public health and animal welfare

Revised November 2011

ACKNOWLEDGEMENTS

Dr Jacky Turner for invaluable research, advice and editing on this report.

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1.0 EXECUTIVE SUMMARY

Why non-therapeutic use of antibiotics in farm animals should end

The antibiotic resistance that is developing globally in disease-causing bacteria is one of the major threats to human medicine. It leads to additional burdens on health systems, to treatment failures and, in the worst cases, to untreatable infections or infections treated too late to save life. Although the over-use of antibiotics in human medicine is the major cause of the current crisis of antibiotic resistance, public-health experts are agreed that the over-use and mis-use of antibiotics in intensive animal production is also an important factor – around half of the world's antibiotic production is used in farm animals.

Infectious disease is encouraged by the crowded and stressful conditions in which animals live in factory farms. It is common in the UK and the European Union for animals such as pigs and poultry to be fed antibiotics in their feed and water, not to cure disease (therapeutic use) but to suppress infections that are likely to arise in factory farm conditions (non-therapeutic or preventive use).

When animals are administered an antibiotic that is closely related to an antibiotic used in human medicine, cross-resistance occurs and disease-causing bacteria become resistant to the drug used in human medicine. The consensus of the world's veterinary and medical experts is that it is dangerous and unjustifiable to use antibiotics that are related to drugs of critical importance in human medicine for 'preventive' administration to groups of apparently healthy animals.

The impact on public health

The world's public-health experts, from the European Union, the United States and the World Health Organization, are agreed that drug-resistant bacteria are created in farm animals by antibiotic use and that these resistant bacteria are transmitted to people in food and then spread by person-to-person transmission. In addition, genes for antibiotic resistance are known to be transferable to other bacteria of the same or a different strain or species.

Antibiotic resistance leads to foodborne infections in humans that would not otherwise occur, that are more severe, last longer, are more likely to lead to infections of the bloodstream and to hospitalization, and more likely to lead to death. Severe infections by foodborne bacteria include life-threatening urinary infections and blood poisoning. Children are particularly likely to be infected by drug-resistant foodborne bacteria that have developed in farm animals as a result of over-use of antibiotics.

The use in farm animals of antibiotics that are critically important in human medicine is implicated in the emergence of new forms of multi-resistant bacteria that infect people. These include new strains of multi-resistant foodborne bacteria such as *Salmonella, Campylobacter* and *E. coli* that produce the ESBL and/or AmpC enzymes that inactivate nearly all beta-lactam antibiotics (which include penicillins and the critically important 3rd and 4th generation cephalosporins).

The over-use of antibiotics in intensive pig farming is implicated in the emergence of a new 'pig' strain of the superbug methicillin-resistant *Staphylococcus aureus* (MRSA), first identified in 2004-2005 in the Netherlands. This has spread rapidly among pigs in many European countries, to people who are in contact with the animals, and from these people to the community and to hospitals. The livestock-associated MRSA strain has also colonised chickens, dairy cattle and veal calves and the people who handle them and may also be emerging as a food safety risk.

The current use of antibiotics in EU livestock production

There is as yet no effective centralised data collection of the antibiotic use in every European country and it is not possible for the EU's public health and veterinary authorities to know exactly what doses of each antibiotic are given to farmed animals, for how long and for what reason.
Usage has even increased over the last decade in some of the most intensive sectors such as pig and broiler (meat) chicken production. Antibiotics may be administered for a substantial proportion of an animal's lifetime. Of particular concern, farmers may be increasingly using modern and more potent drugs such as the 3rd and 4th generation cephalosporins and the fluoroquinolones whose use should be strictly limited because they are of critical importance for human medicine.

Preventing disease without prophylactic use of antibiotics

Disease can almost always be prevented by using good husbandry rather than prophylactic use of antibiotics. Positive measures that can reduce disease in farmed animals include: switching to extensive production systems (including high-quality free range and organic systems); reducing stress; avoiding mixing; good weaning practice; keeping stocking densities low and avoiding excessive herd or flock sizes; reducing journey times during live transport of animals; breeding for natural robustness and disease-resistance.

Ending factory farming

Reform of intensive farming is essential, as the most certain and permanent way to reduce and eliminate non-therapeutic uses of antibiotics in European food production. The objective should be to replace the crowded and stressful conditions of factory farms by extensive and free-range systems that respect the animals' welfare and provide conditions in which their health can be maintained without the frequent use of drugs.

Recommendations

- The European Commission and the Member States should develop a more effective strategy to reduce antibiotic use in agriculture in order to ensure that antibiotics remain effective in the fields of both human and animal health. This should include a transparent review into the state of antibiotic use in agriculture and its relationship with patterns of anti-microbial resistance.

- The European Commission should propose new regulations to:
    - Phase out prophylactic use of antibiotics in farm animals other than in very limited, clearly defined situations;
    - Ban all prophylactic and off-label use of 3rd and 4th generation cephalosporin antibiotics in farm animals with immediate effect;
    - Ban all prophylactic and off-label use in farm animals of new antibiotics licensed in the EU.

'Antimicrobials are used in farm animals for growth promotion, prophylaxis, metaphylaxis and therapy. Their use is the principle contributing factor to the emergence and dissemination of antimicrobial resistance among bacterial pathogens and commensals that have food animal reservoirs.' [1]
The Codex Alimentarius Commission's Committee on Food Hygiene, 2001.[i]

'The widespread use of antimicrobials not only for therapeutic purposes but also for prophylactic and growth promotion purposes in livestock production has intensified the risk for the emergence and spread of resistant microorganisms. This raises particular concern since the same classes of antimicrobials are used both in humans and animals. The emergence and spread of antimicrobial resistance in bacteria poses a threat to human health and presents a major financial burden. Moreover, few new antibiotics are being developed to replace those becoming ineffective through resistance.'
World Health Organization, 2007.[ii]

'Drug resistance is becoming more severe and many infections are no longer easily cured, leading to prolonged and expensive treatment and greater risk of death … WHO calls for urgent and concerted action by governments, health professionals, industry and civil society and patients to slow down the spread of drug resistance, limit its impact today and preserve medical advances for future generations.'***World Health Organization, on World Health Day, under the theme 'Combat drug resistance', 7 April, 2011.***[iii]

'[T]he use of antibiotics in food animal production contributes to increased drug resistance. Approximately half of current antibiotic production is used in agriculture, to promote growth and prevent disease as well as to treat sick animals. With such massive use, those drug resistant microbes generated in animals can be later transferred to humans.' ***World Health Organization, on World Health Day, under the theme 'Combat drug resistance', 7 April, 2011.***[iii]

'In Europe as in the world as a whole, antimicrobial resistance is now a real threat to public health, resulting in longer, more complicated courses of treatment, a greater risk of death and extra costs for healthcare systems'.
Eurobarometer report, Antimicrobial Resistance, April 2010.[iv]

1.1 Antibiotic resistance and human medicine

On World Health Day, 7th April 2011, the WHO Director-General, Dr Margaret Chan, warned that 'In the absence of urgent corrective and protective actions, the world is heading towards a post-antibiotic era, in which many common infections will no longer have a cure and, once again, kill unabated' and that 'The responsibility for turning this situation around is entirely in our hands.'[v]

Antibiotics[2] are a precious resource in both human and veterinary medicine. They have saved countless lives since the mid-20th century. All medical experts agree they should be used cautiously, in order to minimise the development of

[1] 'Commensals' are bacteria in animals and people that are harmless within their normal host. 'Metaphylaxis' refers to treatment of a whole flock or herd of animals when only some of them are suffering from disease.
[2] The term 'antibiotic' refers originally to a naturally occurring substance (eg derived from fungi or bacteria) that kills or inhibits the growth of bacteria or other microorganisms. Many antibiotics are now semi-synthetic (ie modifications of

resistance and prolong the useful life of each drug. Yet, in spite of this understanding, we continue to allow them to be used as a tool in the mass, intensive production of farm animals in ways that jeopardise their effectiveness for treating people.

One of the most important threats to modern medicine is the development of bacteria that are resistant to antibiotics, making bacterial infections more difficult or even impossible to treat. While it is recognised that the human use of antibiotics is the largest contributor to antibiotic resistance, the over-use in intensively-produced farm animals is now believed to have played a major role in this global problem.[iii] The use of antibiotics to prevent or treat common production diseases in intensive farming has led to the emergence of antibiotic-resistant bacteria such as *Salmonella*, *Campylobacter* and *Escherichia coli* (*E. coli*) that colonise farm animals and can be transmitted to people in food or through the environment. When these bacteria cause illnesses in people they are more difficult to treat and the resistant bacteria spread further by being transmitted between people. In addition, the genes for resistance can be passed from resistant bacteria to other bacteria that are also potentially disease-causing in people.

The over-use of antibiotics in farm animals has made some food less safe to eat and made resistant bacterial infections more common. Antibiotic resistance has increased rapidly in food-poisoning bacteria, such as *Salmonella* and *Campylobacter*, with the drugs used in farming being the same as, or very similar to, those used as frontline treatments in human medicine. This has contributed to the rise of serious new types of antibiotic resistance that affect humans. Genes for a type of resistance known as extended spectrum beta-lactamase (ESBL) and AmpC beta-lactamase (Section 3.4.2) have spread internationally over the last decade in strains of *E. coli* and *Salmonella* that can cause severe infections including septicaemia (blood poisoning). A new strain of the so-called 'superbug' MRSA has emerged on intensive farms in continental Europe (Section 3.5.2) and has spread from pigs to pig farmers and the community in the Netherlands, and also to other EU countries and to North America. In Dutch hospitals by 2007, about 30% of all MRSA cases were caused by the farm animal strain[vi] and it has been found on 16.0% of Dutch chickenmeat and 10.7% of pork.[vii]

1.2 Antibiotic resistance and intensive animal farming

The fundamental cause of food animal-related antibiotic resistance is factory farming. In intensive pig and poultry production, animals are kept confined in overcrowded conditions, usually with no outdoor access, and they are bred and managed for maximum yield (to grow faster or to produce more meat, milk, eggs, or offspring). These conditions compromise their health and their immune responses and encourage infectious disease to develop and spread easily.[viii,ix] Without the aid of drugs for disease prevention, it would not be possible to keep the animals productive in the intensive conditions in which they are often kept and managed.

Antibiotics should not be used as preventive action to avoid disease that is encouraged by factory-farming methods. The policy-makers of 60 years ago made a serious mistake when they permitted antibiotics to be used for non-therapeutic reasons in animal production, often in spite of scientific misgivings. Sixty years later, while the evidence continues to be disputed by some sections of the industry, the actual and potential damage to public health is acknowledged by scientists and policy-makers in Europe, the US and in most regions of the world. European public-health authorities such as the European Medicines Agency and the European Food Safety Authority are aware that it is essential to curb antibiotic use in farming and that the time has come to take effective action.

This report sets out the evidence that the current level of antibiotic use on Europe's farms is bad for public health, bad for animal health and welfare and bad for the reputation of Europe's farmers and their produce. An essential

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the original naturally-occurring substance) and some are fully synthetic. The term 'antimicrobial' refers to all substances that kill or inhibit the growth of microorganisms.

step to end permanently the over-use of antibiotics is the reform of intensive animal farming, encouraging farmers to move to well-managed extensive and free-range production systems. These systems would enable Europe's farmers to maintain their animals' health with the minimum of drug use and would improve the lives of billions of farmed animals.

2.0 HOW ANTIBIOTICS BECAME PART OF INTENSIVE AGRICULTURE

2.1 How non-therapeutic uses of antibiotics became established in farming

How antibiotics are used in animal production

The therapeutic treatment of individual sick animals with antibiotic drugs is often essential. It relieves suffering and returns them to economic production. But during the 20th century the use of antibiotics in farm animals rapidly expanded to include uses that are, to a greater or lesser degree, non-therapeutic. The non-therapeutic uses enabled the spread of infections on factory farms to be controlled to an extent that had not been possible before, and also unnaturally stimulated growth and productivity. Farm uses of antibiotics are conventionally classified into:

- **For treatment of disease (therapeutic use)**. However, if a few animals are found to be sick, often the whole flock or herd will be treated (known as **metaphylaxis**) to prevent the disease spreading. Thus there is not always a clear distinction between treatment and prevention.[3] Treatment usually occurs at high doses for a relatively short period of time.

- **For prevention of disease (prophylaxis)**. The treatment of animals with low, sub-therapeutic doses of antibiotics in feed or drinking water, when they are not showing signs of disease but there is thought to be a risk of infection. Treatment can be over a period of several weeks, and sometimes longer.

- **For 'growth promotion'** (no longer permitted as such in the EU, but still common in North America and elsewhere). Very low sub-therapeutic doses of antibiotics are given to animals (particularly intensively kept pigs and poultry) in their feed, nominally to increase their growth-rate and productivity. Treatment is continuous and can last for a large part of the animal's life.

Although the 'growth promoting' use of antibiotics is nominally distinct from the 'prophylactic' use of antibiotics, it also has the effect of suppressing infectious diseases that would be encouraged by factory farm conditions. Furthermore, the dosages at which antibiotics are fed for prophylaxis are often sufficiently low to have a growth-promoting effect. Thus there is not always a clear distinction between antibiotic use for 'growth promotion' and for disease prevention.

Antibiotic use for disease prevention and growth promotion is ***'non-therapeutic'***, i.e. the antibiotics are not being used to treat existing disease in a particular animal. The antibiotics are also fed at sub-therapeutic doses. This has always been a matter for particular scientific concern, because the doses used are not sufficiently high to kill off all the target bacteria, leaving the more resistant ones. The fact that in both cases the treatment can be for prolonged periods of time is also very significant. It has been shown that if resistant bacteria are mixed with non-resistant ('sensitive') bacteria in an antibiotic-free environment soon after they have acquired their resistance, they gradually

[3]For example, the American Veterinary Medical Association policy on *Judicious Therapeutic Use of Antimicrobials* (November 2008) classifies 'treatment, control, and prevention of disease' as 'therapeutic'. http://www.avma.org/issues/policy/jtua.asp.

die out. On the other hand, when antibiotics are used for long periods the resistant bacteria eventually become as strong as the original strains.[x] Earlier research also confirmed that in animals fed antibiotics continuously at sub-therapeutic levels, resistance persisted far longer than when antibiotics were administered at therapeutic levels for short periods.[xi] According to the UK's Advisory Committee on the Microbial Safety of Food in 1999, 'The more that bacteria are exposed to antibiotics, the better developed their defence mechanisms become and the more adept they become at developing resistance.'[xii]

Early warnings about non-therapeutic uses of antibiotics

Treatment of infections in people with the then-new wonder drugs penicillin and streptomycin began in the mid-1940s and resistance to penicillin began to emerge in hospitals within a couple of years of its use. In farm animals, penicillin was first used experimentally in 1942, before it was widely available to doctors. Between 1947 and 1954 the Penicillin Act and the Therapeutic Substances (Prevention of Misuse) Acts in the UK restricted the use of antibiotics to therapeutic use on prescription by a doctor, veterinarian or dentist[xiii].

But in parallel with this, trials in the US and UK had shown that pigs and poultry fed low doses of penicillin or tetracycline antibiotics grew faster. This non-therapeutic use of antibiotics was termed 'growth promotion' and later research showed that dosing with antibiotics tended to make farm animals more productive overall, resulting in more eggs from hens, more piglets from sows and more milk from dairy cows – hence cheaper animal products[xiii xiv]. By the mid-1950s certain antibiotics, including penicillin, were permitted to be used as 'growth promoters' in the UK. 'Growth promoting' antibiotics could be bought and used in animal feed without a veterinary prescription, by farmers and feed compounders in the UK, other European countries and the US. A British Minister of Health told Parliament in1953 that, 'I am assured by the Medical Research Council… that there will be no adverse effect whatever upon human beings'.[xv]

It was not until the early 1960s that scientists discovered that antibiotic resistance could be transferred from one bacterial species to another. In the UK, the Netherthorpe Committee in 1962, the Swann Committee in 1969 and the Lamming Committee in 1992 sounded the alarm. According to the Advisory Committee on the Microbiological Safety of Food in 1999, an 'underlying and recurrent theme' of these reports was 'the potential threat of establishing resistant microorganisms in food animal populations and the consequent need to restrict the use of antibiotics in animal husbandry.' [xvi] In 1997 the World Health Organization recommended that the use of any antibiotic for 'growth promotion' in animals should be terminated if that antibiotic is used for human medicine or if its use in animals increases resistance to other antibiotics used in human medicine.[xvi]

The global rise of non-therapeutic antibiotics in animal production

By the mid-1990s the EU had authorised 9 antibiotics, plus the antibacterials carbadox and olaquindox, for use in animal feed as 'growth promoters' and preventive antibiotic use had become a routine aspect of intensive farming. By 1999-2000 it was estimated that in the US around 60% of poultry production units used feed containing antibiotics (compared to over 90% in 1995),[xvii, xviii] and the majority also used antibiotics for the control of gut parasites.[xviii] As of 1999 in the US, 90% of the diets of recently weaned piglets, 70% of the diets of growing pigs and 50% of the diets of 'finishing' pigs approaching their slaughter weight contained some form of antibiotic.[xvii]

During the 20th century therapeutic and non-therapeutic antibiotic treatment of farm animals increased worldwide. By the turn of the 21st century it was estimated that half of the global production of antibiotics was being used in farm animals[iii, xix] and that between 40% and 84% of the total antibiotic use in the USA was inagriculture,with all but a few percent of the US use being for non-therapeutic purposes[xx, xxi]. The Danish monitoring agency DANMAP estimated that in 1997 (after which date there were increasing restrictions on the use of antibiotic 'growth promoters' in Denmark) 'the quantity [of antibiotics] used in humans amounted to about 25% of the total usage in animals'.[xxii] In 2001, the Union of Concerned Scientists in the US estimated that around 70% of all US antibiotic usage

was for non-therapeutic treatment of livestock and that '8 times more antimicrobials are used for non-therapeutic purposes in the three major livestock sectors [ie chickens, pigs and cattle] than in human medicine.'[xxi]

By 2002, scientists at the Carney Hospital, Massachusetts and the Tufts University School of Medicine could conclude that, 'In contrast to use in humans much of the antimicrobial use in farm animals consists of administration to large groups for non-therapeutic applications, such as growth promotion and disease prevention'[xxiii], which would often be in the animals' water or feed.

Since the later 1990s, animal producers and regulators have come under increasing pressure from health experts and informed citizens to monitor and reduce the use of antibiotics in farm animals. But the historical over-use, including the use of antibiotic 'growth promoters', had already made many strains of foodborne bacteria such as *Salmonella, Campylobacter* and *E. Coli* resistant to several of the existing antibiotics simultaneously (see Appendix 1).

2.2 The cross-over between antibiotics used in animals and in people

There are several different classes or families of antibiotics. The antibiotics in one class have a similar chemical structure, mode of action, and range of effectiveness. Bacteria that have a mechanism of resistance to one antibiotic are more likely to develop resistance to a closely related antibiotic. So even if a particular antibiotic is used in animals and not in people, resistance to the animal-use antibiotic can also confer resistance to a related human-use antibiotic. Some of the concerns regarding cross-resistance over recent decades are summarised in Table 1.

Table 1 Examples of how antibiotics used in animals can cause resistance to drugs used in people

ANTIBIOTIC CLASS	ANTIBIOTIC USED FOR FARM ANIMALS (BRAND NAME) AND TYPE OF USE	RELATED ANTIBIOTIC USED FOR HUMANS (BRAND NAME) AND TYPE OF USE	HUMAN HEALTH CONCERNS
Fluoroquinolones	***enrofloxacin (Baytril)*** Treatment of respiratory and alimentary tract infections in pigs and poultry (administered in poultry drinking water)	***ciprofloxacin (Cipro)*** Important for treating severe *Salmonella* and *Campylobacter* infections. Drug of choice for immediate ('empiric') treatment of *Salmonella* in adults	Use of enrofloxacin as prophylactic for chickens implicated in increasing resistance to Cipro
Cephalosporins 3rd generation (belong to beta-lactam class of antibiotics)	***Ceftiofur*** Treatment of bacterial infections by injection in cattle and pigs; in some countries, control of infection and mortality in day-old chicks	***cefotaxime, ceftriaxone*** Drugs of choice for treatment of severe *Salmonella* infections in young children	Use of ceftiofur implicated in development of resistance to 3rd generation cephalosporins
Streptogramins	***virginiamycin*** 'Growth promoter' (banned in EU from 1999)	***quinupristin-dalfopristin (Synercid)*** New antibiotic developed to treat resistant bacteria such as the 'superbug' vancomycin-resistant Enterococci (VRE) and hospital-acquired pneumonia	Use of virginiamycin for growth promotion was banned in the EU because its use could threaten effectiveness of Synercid in treating VRE and other

			dangerous infections
Glycopeptides	***avoparcin*** 'Growth promoter' (banned in EU from 1997)	***vancomycin*** Can be an antibiotic 'of last resort' for resistant *Staphylococcal* infections, including the hospital 'superbug' MRSA	The appearance of vancomycin-resistant *Entero cocci* (VRE) has been linked to use of avoparcin growth promoter. Concern that a vancomycin-resistant MRSA could develop
Macrolides	***spiramycin, tylosin*** 'Growth promotion' in pigs and occasionally in chickens (banned in EU for 'growth promotion' from 1999); tylosin still approved in EU for prevention, control and treatment of infections in pigs	***erythromycin*** Treatment of respiratory infections and food-borne infections such as *Campylobacter*; treatment of people who are allergic to penicillins	Bacteria which develop resistance to tylosin are often cross-resistant to erythromycin

2.3 EU surveillance of antimicrobial resistance in zoonotic bacteria in 2009

In April 2011 EFSA and the European Centre for Disease Prevention and Control (ECDC) reported latest results of tests for antibiotic resistance submitted by EU countries for 2009.[xxiv, 4] Tests found that resistance to antibiotics 'was commonly found' in samples of the common food poisoning bacteria *Salmonella* and *Campylobacter* and in indicator *E. coli* samples from animals and food (such as chickenmeat and pigmeat) in the EU, often at high levels of resistance[xxiv].

Resistance to the older antibiotics (tetracyclines, ampicillin and sulphonamides) was reported as 12% up to 60% in *Salmonella* from meat and animals. The report expressed concern about the high levels of resistance to ciprofloxacin, an important modern fluoroquinolone for human use, in *Salmonella*, *Campylobacter* and *E. coli*. This was up to 22% in *Salmonella* from chickens and chickenmeat, 47% in indicator *E. Coli* from chickens and from 33% to 78% in *Campylobacter* from chickens and chickenmeat, pigs and cattle.[xxiv]

There was also resistance to the important 3rd generation cephalosporins at up to 9% in *Salmonella* and indicator *E. Coli* from chickens, pigs, cattle, chickenmeat and pigmeat. EFSA suggests that 'one of the principal factors' leading to this resistance was the selection pressure caused by the use of 3rd generation cephalosporins and other antibiotics in farm animals, and the transfer of resistance genes between bacteria[xxiv] (see also Section 3.4 below).

According to EFSA there were 'no major changes' in resistance since 2005. The tests showed that if a country had high resistance to a certain antibiotic in a particular bacterium, it was likely to have high resistance to the same antibiotic in other bacteria too. This suggested that 'an important factor accounting for this resistance could be

[4]Reporting varied between member states (MS), which limits the usefulness of the overall results. For example, only 16 member states reported on resistant *Camplyobacter* in animals and food. The report comments that 'It will be evident that, the overall figure for all reporting MSs was highly dependent on which MSs contributed to that overall figure, particularly as different MSs often differ widely in the level of resistance to various antimicrobials.'

antimicrobial usage'[xxiv]. The fact that there was no major reduction in resistance since 2005 indicates that Europe's farmers have not yet succeeded in making the reductions in antibiotic use that are necessary.

3.0 THE IMPACT ON PUBLIC HEALTH

'In animal production systems with high density of animals or poor biosecurity, development and spread of infectious diseases is favoured, which leads more frequently to antimicrobial treatment and prevention of those diseases. This provides favourable conditions for selection, spread and persistence of antimicrobial-resistant bacteria. Some of these bacteria are capable of causing infections in animals and if zoonotic also in humans. Bacteria of animal origin can also be a source for transmission of resistance genes to human and animal pathogens.' *European Medicines Agency, 2006.*[xxv]

3.1 The main areas of risk

The health risks associated with the over-use of antibiotics in farm animals have several related aspects:

- ***Antibiotic-resistant food-borne infections***: Over-use of antibiotics encourages the growth of antibiotic-resistant and multi-resistant foodborne bacteria such as *Campylobacter, Salmonella* and *E. coli*, making it harder to treat food-poisoning or other infections caused by these bacteria when they become serious or life-threatening in people.

- ***New multi-resistant strains of bacteria that have not in the past been food-related***: Antibiotic use in animals has contributed to the emergence of a new strain of the superbug MRSA (Section 3.5) that can be transmitted to the human population through contact with animals or food.

- ***Spread of resistance genes***: The overall burden of antibiotic resistant infections in human medicine is increased, as more types of bacteria are exposed to antibiotics and resistance genes are spread between bacteria and, probably, through the environment.

3.2 How bacteria develop resistance to antibiotics

Resistance to antibiotics has been described as 'the best-known example of rapid adaptation of bacteria to a new ecosystem'.[xxvi] Every time a person or animal receives a dose of antibiotics there is an opportunity for bacteria to develop resistance to that drug. Antibiotic resistance can occur through the multiplication of bacteria that have a particular natural mutation that confers resistance to the antibiotic or by the 'horizontal' transfer of resistance genes between bacteria. Bacteria can develop resistance to several different antibiotics.

Horizontal transmission of resistance genes is now recognised as a major cause of increasing antibiotic resistance. It occurs through natural processes of gene transfer between cells, often via mobile segments of DNA known as transposons ('jumping genes') and plasmids (circles of DNA that can replicate themselves). Plasmids can carry several

resistance genes giving resistance to several different antibiotics at once.[xxvi] These processes of gene transfer are also used by biotechnologists for genetic engineering.

The particular genes that enable some bacteria to resist attack by antibiotics can be transferred to other bacteria of the same or of a different species. Plasmids carrying resistance genes to one or more antibiotics have been found in the *Salmonella* and *E coli* isolated from people in Europe, the US, Asia and Africa, and in farm animals.[ii,xxvi,xxvii,xxviii] Studies of the bacteria in poultry-house litter have found that the same class of antibiotic-resistance genes can be present in different classes of bacteria, suggesting that the resistance genes have spread widely among bacteria.[xxix]

In 2009 scientists from the School of Public Health, University of California, Berkeley, and the University of Pennsylvania, reported that mobile resistance genes found in bacteria in people suffering from *E. coli* urinary tract infections and *Salmonella* infections are widespread in a range of bacteria found in animals, probably as a result of gene transfer. They concluded, 'These data suggest that food-producing animals are a major reservoir for integrons [mobile genetic elements] carrying antimicrobial drug-resistant genes. They may also serve as a source for the transfer of these genes not only to *E. coli* and *Salmonella* but also to other members of *Enterobacteriaceae* and other bacterial species.'[xxx]

3.3 How antibiotic resistance can be transmitted from animals to people

Direct contact with infected animals: farm workers and slaughterers:
Handling pigs and poultry and working in a farm environment puts people at risk of picking up resistant bacteria from the animals' bodies or their faeces. Studies in the Netherlands in 2001-2002 showed the same genetic patterns of resistance in *E. coli* samples from turkeys and broiler chickens and their farmers and slaughterers.[xxxi, xxxii]

Consumption of food contaminated with resistant bacteria (for example, the potentially food-poisoning *Salmonella*, *Campylobacter* and *E coli*)
Contamination of meat generally results from faecal material getting onto the carcase during the slaughter and evisceration process (when the animals' guts are removed). Infected meat can also contaminate other foods in domestic or restaurant/catering kitchens. The European Food Safety Authority (EFSA) concluded in 2010 that live chickens colonised with *Campylobacter* are 30 times more likely to result in contaminated meat than are uninfected birds.[xxxiii]

Antibiotic resistance transferred into the environment
Resistant bacteria can be transferred in water, soil and air. Animals excrete a significant amount of the antibiotics they are administered, making their manure a potential source of both antibiotics and antibiotic-resistant bacteria which can enter soil and groundwater.

In the US, tetracycline-resistance genes have been found in groundwater samples 250 metres downstream from the slurry lagoon of a pig farm and appeared to have spread among the local soil microbes.[xxxiv] Studies show that US intensive farms ('animal feeding operations') can be the 'dominant' cause of the proliferation of antibiotic resistance genes in a river environment, enabling further spread by horizontal gene transfer.[xxxv] In the Netherlands, 14% of people living near turkey farms where the growth-promoter avoparcin was used were found to carry enterococcal bacteria resistant to vancomycin, a closely related and important human drug.[xxxvi] Enterococcal bacteria resistant to three important types of drugs used to treat people (all of which are used in poultry production) have been found on the surfaces of cars driving behind a poultry transport truck and in the air inside the car.[xxxvii]

A study of antibiotic resistance on a US family farm showed that resistant bacteria moved from animal to animal, of the same species or of different species, and that farm workers were colonised for several weeks by *E. coli* bacteria

picked up from a bull. The conclusion was that 'there is no containment of antibiotic or antibiotic resistant bacteria in the farm environment.'[xxxviii,xxxix]

3.4 ESBL- and AmpC-producing *E. coli* and *Salmonella:* a major public health concern

Antibiotics known as the 3rd and 4th generation cephalosporins are important modern drugs developed to replace some of the older antibiotics that bacteria had already become resistant to. Their effectiveness is now threatened by new mechanisms of antibiotic resistance. Types of enzymes known as Extended Spectrum Beta-Lactamases (ESBLs) and AmpC Beta-Lactamases can be carried by bacteria such *as E. coli* and *Salmonella* and make these bacteria resistant to the 3rd generation cephalosporins, as well as to nearly all other beta-lactam antibiotics such as penicillin. ESBLs are also resistance to 4th generation cephalosporins[xl]. Beta-lactams are by far the most used type of antibiotic in human medicine. ESBL and AmpC genes can be transferred horizontally between bacteria and have emerged and spread globally within the last decade.

Infections both in hospital and in the community that are resistant to 3rd and 4th generation cephalosporins include severe urinary tract or kidney infections, blood poisoning and septic shock. The growth of resistance means there are poorer patient outcomes, increased morbidity, mortality, increased length of stay in hospital and increased costs.[xl] The European Medicines Agency has called the emergence of the ESBL type of resistance in people in Europe a 'major public health concern.'[xli]

3.4.1 Consequences for people who are infected

Treatment options are at best 'limited'[xli] when cephalosporins are not effective; 3rd generation cephalosporins (such as ceftriaxone) are drugs of choice for treating children with severe, invasive *Salmonella* infections and for treating *E. coli* blood infections. In addition, ESBL-type resistance is often linked to resistance to other antibiotics, including the fluoroquinolones, which are a first line drug for 'empiric' treatment of adults with severe *Salmonella* infection (that is, when immediate treatment is needed, without waiting for test results).

A 2010 academic review from the Antibiotics Department at the Centro Nacional de Microbiología, Madrid, concluded that ' 'The main significant predictor of mortality caused by ESBL-producing *E. coli* is inadequate initial antimicrobial therapy' (i.e. because of resistance to antibiotics that are tried initially).[xlii] Analysis of records of blood poisoning by *E coli* in France, published in 2010, showed that the ESBL-carrying *E coli* infections were more severe than *E coli* infections that were susceptible to 3rd generation cephalosporins.[xliii]

According to Defra, ESBL-producing *E. coli* have been a 'significant cause of human disease in England and Wales' in recent years and their resistance can 'seriously affect treatment, for example in urinary tract infections'.[xliv] The elderly are most at risk, and the Chief Medical Officer reported in 2006 that people who contract urinary tract infections caused by this type of *E. coli* have a 30% risk of dying.[xlv]

ESBL-type *E. coli* causes an estimated 50,000 cases of urinary tract infection per year in the UK and of these 2,500 cause bacteraemia (blood infection).[xlvi] Because ESBLs usually confer resistance to a range of drugs, 'the choice of agents to treat these infections is diminishing.'[xlvii] An analysis of severe UTI [urinary tract infection] cases with blood

infection in Salford in 2004-2005 found that 48% of the patients who had blood infection caused by ESBL-producing bacteria died within 30 days. The scientists concluded, 'ESBL-producing strains of Enterobacteriaceae [such as *E. coli*] are a significant cause of healthcare-associated blood stream infections. They carry a high risk of mortality.'[xlviii] According to a Health Protection Agency's report in May 2010, 10% of all *E. coli* infections causing blood infection are now resistant to the 3rd generation cephalosporins ceftazidime and cefotaxime.[xlix]

While the majority of infections with ESBL-producing bacteria occur within healthcare settings, farm animals' are now recognised as important carriers of ESBL/AmpC-producing *E. coli* and *Salmonella*.'[xl] According to scientists at the Faculté de Médecine Pierre et Marie Curie in Paris, poultry have been a 'primary food source' for infection with cephalosporin-resistant *Salmonella*.[l]

3.4.2 ESBLs and AmpCs in farm animals in Europe and globally

The most common groups of ESBLs found in farm animals and food are termed CTX-M, TEM, and SHV and the main AmpC group is termed CMY. These have mainly been found in *E. coli* and to a lesser extent in *Salmonella*. ESBLs have been identified in poultry, pigs, cattle and meat in many European countries and beyond, sometimes at high levels.[xl]

The highest prevalence of resistance to 3rd generation cephalosporins and of ESBL-producing bacteria has been found in chickens and chickenmeat[xl].In 2009, resistance to 3rd generation cephalosporinsin *E. Coli* from chickens was found in 3% of tested samples in Austria, Germany and France, 11% in Poland, 18% in the Netherlands and up to 26% in Spain[xl, 5].By 2010, studies had identified ESBL-producing and/or AmpC-producing *E. coli* or *Salmonella* in farmed animals or meat in Spain, Portugal, Ireland, France, UK, Belgium, Netherlands, Italy, Denmark, Czech Republic, Germany, Greece, China, Taiwan, Japan, Korea, USA, Tunisia, Senegal, Canada and Mexico.[xl]

According to studies reviewed by EFSA, ESBL-producing *E.coli* has been found in between 10% and 40% of samples from healthy pigs and poultry in Portugal, the Netherlands and France, and has been found in most of the pig and poultry farms tested in Spain. All of 26 broiler farms tested in the Netherlands in 2010 were positive for ESBL- and/or AmpC-producing *E. coli* and in 85% of these broiler farms 80% or more of the chicken tested positive. ESBL/AmpC-producing *E. coli* have also been found in 92% of chickenmeat imported to Sweden from South America and in 30-36% of samples of chickenmeat imported to Denmark and the UK. [xl] In the Netherlands, microbiologists reported in 2011 having found ESBL-producing *E. Coli* in 94% of retail poultry meat samples tested.[li]

3.4.3 ESBLs in UK farm animals

A conference held in 2010 by the Veterinary Laboratories Agency reported that ESBL-producing *E. coli* now occurred on 37% of dairy farms sampled, a 'completely unexpected' finding. Farms which had used 3rd or 4th generation cephalosporin antibiotics in the previous year were 4 times more likely to have animals carrying ESBL *E. coli*. Some of the CTX-M strains found in farm animals contained the same plasmid (transferable DNA) as those found in CTX-M strains taken from hospital patients.[lii] A 2006 farm study found as many as 65 – 93% of dairy calves carried *E. coli* of the CTX-M type, resistant to a 3rd generation cephalosporin[liii]. CTX-M-type resistant *E. coli* was found in calves for the whole 6 months of this study, although the only use of beta-lactam antibiotics during the study period was cefquinome (a 4th generation cephalosporin) for intramammary treatment of lactating cows for mastitis.[xli,liii]

A survey from the Veterinary Laboratories Agency published in February 2010[liv] found that ESBL–producing *E. coli* were widespread in broiler chickens and in turkeys; 3.6% of individual broiler chickens sampled, over 52.2% of

[5] These were results reported to EFSA by individual European countries.

chicken slaughterhouses, 5.2% of turkey rearing farms and 6.9% of turkey breeding farms tested positive for these bacteria. Broiler chickens testing positive for ESBL-*E.coli* were found from the majority (57.1%) of the 21 broiler production companies surveyed.[liv]

3.4.4 Evidence for transmission from animals to people

The European Medicines Agency (EMA)concluded in 2009 that 'Humans may be exposed to animal bacteria with resistance genes coding for ESBLs or AmpC type enzymes via direct contact, via contaminated food or indirectly through the environment. These genes can be transferred to bacteria with potential to cause infections in humans.' As a result, 'Spread [of ESBL enzymes] from animal reservoirs via food or via the environment may contribute to the dissemination of resistance in the community.'[xli]

Several studies have shown common genetic features of ESBL- and AmpC-producing *E. coli* in both humans and farm animals. EFSA says that these studies provide indirect evidence that ESBL genes, mobile genetic elements and resistant strains are transmitted to people through the food chain.[xl]

Scientists in the Netherlands who found that every one of 26 broiler production farms were positive for ESBL- or AmpC-producing *E. coli* carried out genetic analysis of the plasmids carrying the resistance genes. They concluded in 2010 that poultry had contributed to the transmission of ESBL-carrying plasmids to humans.[lv]

Further strong indications that ESBL-producing genes, plasmids and genetic strains of *E. coli* are transmitted from poultry to people through the food chain came from Dutch microbiologists in 2011. Genetic analysis showed that a substantial proportion (35%) of ESBL-producing *E. coli* taken from people contained ESBL genes detected in *E. coli* from poultry and poultrymeat (termed 'poultry associated' ESBL genes) and 19% of the ESBL-producing *E. coli* samples from people carried ESBL genes on plasmids that were 'genetically indistinguishable from those obtained from poultry meat.'[li] In addition, a substantial proportion (39%) of the ESBL-producing *E. coli* found in poultrymeat samples belonged to genotypes also found in human samples (and 94% of the retail chickenmeat samples contained ESBL-producing *E.coli*). The scientists commented, 'These findings are suggestive for transmission of ESBL-producing *E. coli* from poultry to humans, most likely through the food chain.[li]

The official Danish survey of antibiotic use and resistance for 2009 reported that 11% of pigs at slaughter carried ESBL-producing *E. coli*. Two percent of the positive samples from pigs contained the CTX-M-15 gene which is often found in positive samples from humans.[lvi]

North American public health scientists also believe that bacteria resistant to 3rd generation cephalosporins have been passed from animals to humans. There is a clear association between multi-drug resistant foodborne *Salmonella* infections in humans and the use of ceftiofur in poultry and other farmed animals which occurred over the same time period.[lvii, lviii] The US National Antimicrobial Resistance Monitoring System found that resistance to ceftiofur among *Salmonella* isolated from farm animals rose from 4.0% in 1999 to 18.8% in 2003.[lix] In addition, several US outbreaks of cephalosporin-resistant *Salmonella* infection have been linked to consumption of animal products.[xli] In 2010, the Canadian Integrated Program for Antimicrobial Resistance Surveillance identified a 'strong correlation between ceftiofur-resistant *Salmonella enterica*serovar Heidelberg isolated from retail chicken and incidence of ceftiofur-resistant *Salmonella* serovar Heidelberg infections in humans across Canada'.[lx]

There may also be direct transmission from poultry to farmers and stockpeople. Research published in 2010 showed that people working with poultry have a 6-times higher risk of carrying ESBL-producing bacteria in their intestines, compared to the general population.[xl]

3.4.5 Farm animal ESBLs/AmpCs linked to antibiotic use

3rd and 4th generation cephalosporins are authorised for treatment of disease in farm animals in Europe, although this varies between countries and drug authorisations may be at either national or EU level[xli]. By 2006 the majority of EU countries authorised products containing ceftiofur (3rd generation) and/or cefquinome(4th generation) for systemic treatment and cefquinome for intramammary use (ie infusion into the udder).[xli, 6]

Types of non-therapeutic use of cephalosporins

Ceftiofur and cefquinomeare sometimes prescribed for preventive use, such as for 'dry cow therapy' (to prevent mastitis). The accepted view is that intramammary (local) use in 'dry cow therapy' is less of a risk for developing resistance because the animal's normal bacteria are not exposed to the antibiotic.[xl] However, US research published in 2010 indicated that routine prophylactic use of a 1st generation cephalosporin (cephalothin) for dry cow therapy did increase the resistance of the cows' faecal bacteria to cephalothin, meaning that dry cow therapy should not be ruled out as a possible risk for the transfer of bacterial resistance genes.[lxi]

EFSA is concerned about the 'off-label' use of cephalosporins. These include the use of ceftiofur to prevent various infections in day-old piglets, and the 'unnecessary and off-label use' of ceftiofur worldwide in the poultry industry (such as for treatment of chick embryos in the egg, or by sprays or injection of chicks in hatcheries), which are linked to cephalosporin-resistance.[xl] Ceftiofur has been used for injection into day-old chicks in the UK. [lxii] There are also unregulated/illegal sources of cephalosporins, such as through the internet.[xl]

In 2009, the European Medicines Agency concluded that treatment of farm animals is one likely source of resistance to 3rd generation cephalosporins and that 'the concentrations [of ceftiofur in treated animals] are high enough to select for resistance.'[xli] The rapid growth of resistance to these drugs suggests that, in either authorised or unauthorised ways, they have been over-used in animal production and have contributed to the rise of ESBL-type resistance.

Evidence of 3rd generation cephalosporin use leading to resistance

Scientists in Denmark have shown experimentally that injecting pigs with 3rd or 4th generation cephalosporinsresults in an increase in ESBL-producing *E coli* in the pigs.[lxiii] In a study of 20 pig farms, *E coli* developed resistance to 3rd generation cephalosporins in half of the farms where ceftiofur was used and in only 10% of the farms where it was not used.[lxiv]

The first cases of ESBL-producing *Salmonella* from UK livestock have been reported in pigs[lxv] and were associated with the use of ceftiofur to control and treat illness in piglets.[lxvi] ESBL-type resistance has been found in *Salmonella* samples from a flock of laying hens that had been given ceftiofur at one day old.[**lxvi**] Ceftiofur is not licensed for poultry in the EU.

In Canada, a 'strong correlation' was reported in 2010 between the prevalence of AmpC-producing *Salmonella* and *E. coli* (from both human infections and poultry) and the 'off-label' use of ceftiofur for injection of eggs in poultry hatcheries.[xl]

[6] Systemic treatment involves the drug being circulated through the whole body, rather than applied locally (such as intramammary treatment of the udder)

EFSA's recommendations on ESBLs/AmpCs

In 2011, EFSA reviewed the public health risks from animals and food relating to ESBL/AmpC-type resistance and concluded (emphasis as in original):[xl]

'Cephalosporins (especially 3rd and 4th generation) specifically select for ESBLs. It is considerered that a control option that is likely to be **highly** effective in reducing selection of ESBL/AmpC producing bacteria at an EU level is stopping/reducing the use of cephalosporins in farm animals. Provided adequate compliance, the measure would be more effective the more comprehensive the restrictions. The restrictions could range from **stopping all uses** of cephalosporins/systemically active 3rd /4th generation cephalosporins, to more or less strict **restriction of their use,** allowing use only under specific circumstances.'[xl]

EFSA also emphasised that all use of antibiotics creates selection pressure on bacteria, leading to resistance, and that 'Therefore, generic antimicrobial use is a risk factor for ESBL/AmpC and it is not restricted specifically to the use of cephalosporins.' [xl]

3.5 MRSA in farm animals: a new strain of the superbug

3.5.1 MRSA in people: infections acquired in hospitals and in the community

Staphylococcus aureus (*S. aureus*) bacteria are frequently present on the skin, or in the nose and mouth of people, without causing illness. Danger arises when the bacteria get into wounds (for example following surgery or during other hospital treatment) or damaged skin. Then illnesses may occur that range from minor infections to abscesses, to life-threatening diseases such as pneumonia, meningitis, endocarditis (a heart infection) and bacteraemia (blood poisoning). The highly drug-resistant 'superbug' strain is termed methicillin resistant *Staphylococcus aureus* (MRSA).

Until a few years ago, MRSA was nearly always a hospital-acquired superbug but during the 1990s increasingly caused illness in people who had no contact with hospitals. So-called 'community-acquired' MRSA infections appeared in the US, Britain, Canada, Australia, New Zealand, Finland, Ireland, France, Germany, Switzerland, the Netherlands and Japan.[lxvii] Vancomycin, which is one of the antibiotics most often used to treat MRSA, can only be given intravenously in hospital, so MRSA infections are a burden to health systems as well as potentially disastrous to the infected person.

3.5.2 Emergence and spread of 'pig' MRSA in the Netherlands

In 2004-2005 a new threat from community-acquired MRSA was discovered, when it was found that pigs had developed a previously unknown strain known as MRSA ST398 (or NT-MRSA) and that this was spreading to people in the Netherlands.[lxvii] Netherlands is a major intensive pig producer in Europe which produced nearly 24 million pigs in 2009 and exported 11.2 million live piglets and pigs to other EU countries, particularly to Germany.[lxviii]

The first recorded cases of human colonisation by 'pig' MRSA were in a Dutch baby girl and her parents, who farmed pigs.[lxvii] By 2005, 23% of Dutch pig farmers tested in one region were positive for ST398, making them 760 times more likely to be colonised by MRSA than the general population.[lxvii] In 2008, 5.6% of Dutch pig slaughterhouse workers carried 'livestock-associated' MRSA in their noses.[lxix]

The European Food Safety Authority concluded in 2008, 'It seems likely that MRSA ST398 is widespread in the food animal population, most likely in all Member States with intensive animal production'.[lxx]

In a preliminary EU-wide study of around 4,500 pig breeding farms by the European Food Safety Authority in 2008, an average of 26.9% of farms breeding piglets to be sold on for fattening were assessed as positive for MRSA (and the strain was ST398 in over 92% of cases). The prevalence varied widely between countries, but it was notable that there were a high proportion of MRSA-ST398 infected farms in Germany (37.4% of farms), Belgium (35.9%) and Spain (50.2%), which all import pigs from the Netherlands.[lxxi] In the Netherlands, a study found that 67% of pig breeding farms and 71% of pig finishing farms were positive for livestock-associated MRSA, and that the prevalence more than doubled over the study period (2007-2008).[lxxii] By 2009, MRSA ST398 had also been found in pigs in Switzerland[lxxiii] and in 2010 in Sweden.[lxxiv]

MRSA ST398 also emerged in pigs in North America, and has spread to pig farmers whose pigs are colonized by the bacteria. In Ontario, Canada, 45% of pig farms, 24.9% of pigs and 20% of pig farmers were colonized by MRSA (predominantly ST398) in 2007.[lxxv] In a typical intensive pig breeding farm in the US Midwest, holding 60,000 pigs at any one time, 49% of the pigs and 45% of the farm workers were colonized by MRSA ST398. One hundred per cent of the piglets of around 2-3 months old carried MRSA.[lxxvi]

3.5.3 'Livestock-associated' MRSA in chickens, dairy cattle and workers

'Livestock-associated' MRSA ST398 has also spread among chickens, dairy cattle and veal calves. The farmers and others who handle them are also found to have a much higher prevalence of MRSA ST398 than the general population.[lxxvii, lxxviii, lxxix]

MRSA ST398 has been found in broiler chickens in both the Netherlands and Belgium.[lxxx,lxxxi] The first Belgian samples, dating from 2006, showed that 12.8% of the sampled farms were colonised, suggesting that 'the animal reservoir of MRSA ST398 is broader than previously anticipated.' [lxxx] A Dutch study, published in 2010, tested 40 broiler chicken flocks at 6 slaughterhouses. Thirty five percent of the flocks and 6.9% of the chickens tested positive for MRSA ST398, as did 5.6% of all the slaughterhouse workers, including 20% of the workers who hung the live chickens on the slaughterline.[lxxvii]

Staphylococcus aureus is a common cause of mastitis in dairy cows and MRSA ST398 has been found in mastitic cows or their milk in Switzerland[lxxiii], Germany[lxxxii, lxxxiii] and Belgium[lxxxiv]. In a study of three dairy herds in South West Germany, milk samples from 5% to 17% of the cows and 100% of bulk tank milk samples tested positive for MRSA ST398. In addition, nasal swabs showed that 47% cows, 57% of calves and 78% of the workers carried MRSA.[lxxxiii] Of 102 Dutch veal calf farms studied in 2007-2008, 88% of the farms and 26% of the calves were positive for MRSA, nearly all of these the ST398 strain. At the maximum, 100% of the calves on a farm were positive. Of the people in contact with the calves, 33% of the farmers, 8% of their family members and 26% of their employed workers were also positive for MRSA ST398. The study established that the likelihood of people being colonised by MRSA was 'strongly associated with the intensity of animal contact and with the number of MRSA positive animals on the farm.'[lxxviii] MRSA ST398 has also been found in black rats living on pig or veal farms.[lxxxv]

3.5.4 MRSA transmission from livestock to the community

The Netherlands used to have one of the lowest rates in the world of MRSA among people. By 2007 livestock-related MRSA infections were spreading to the wider population and caused over 20% of MRSA in the Netherlands.[lxxxvi] By 2009 30% of MRSA patients in the Netherlands were infected with the MRSA ST398 strain.[vi]

People or farms colonised by MRSA398 can transmit MRSA ST398 to human contacts in a number of ways:

- Direct contact (with animals or people)
- Preparation of food for others to eat[lxxxvii]
- Airborne micro-organisms in pig sheds and air plumes to neighbouring communities[lxvii]
- Contact with contaminated meat.

Because stockpeople and slaughtermen are more likely to get infected, there is a 'subsequent risk of introduction of MRSA from pig origin, MRSA ST398 or MRSA non-ST398, into the community, i.e. in the human population not in direct contact with pigs or carcasses, and the health-care facilities via those exposed,' according to EFSA.[lxxxviii]

Livestock-related MRSA infections could become considerably more dangerous to people in the future. At present the ST398 strain has relatively low virulence, the ability to cause invasive disease, in comparison to many other MRSA strains infecting humans. This is because it generally lacks several virulence genes, such as those encoding toxins, that are usually present in human MRSA. Scientists believe that the relatively low virulence of MRSA ST398 will change for the worse as the strain acquires more virulence genes by horizontal gene transfer. Researchers at the Department of Medical Microbiology, Utrecht University Medical Centre, concluded in 2010: 'Considering the vast and increasing animal and human reservoirs, we believe it will only be a matter of time before more of these isolates [of MRSA ST398] acquire mobile genetic elements that carry virulence factors which will increase virulence in the human host.'[lxxxix]

3.5.5 Food risks from MRSA: an 'emerging problem'?

If animals are carrying MRSA bacteria in their noses, or on their skin or on tissues such as those of the rectum or cloaca, the bacteria can be accidentally transferred onto their meat during the slaughter process. In 2009 the Dutch Food and Consumer Safety Authority (VWA) reported that MRSA was found in 11.9% of around 2200 raw meat samples for retail sale, including 35.3% of turkeymeat, 10.6% of beef, 15.2% of veal, 16.0% of chickenmeat and 10.7% of pigmeat. Most were the 'pig' type MRSA ST398.[xc]

Scientists believe there is only a low risk of contaminated meat causing cases of MRSA infection in healthy individuals. But it possible that a person whose immune system was not fully functional might be at increased risk of infection from handling contaminated meat,[xci] as immunodeficiency is known to be one of the conditions predisposing people to infections with *S. aureus*.[lxxxvii] Those at a higher risk are likely to include many elderly people, young children and anyone suffering from illnesses such as AIDS, TB and cancer.

Food poisoning due to MRSA has been very rare up to now but MRSA frequently contains the genes associated with enterotoxins, which cause food poisoning. EFSA's Panel on Biological Hazards has concluded that if the prevalence of MRSA increased, this could lead to a higher prevalence of toxinogenic (poison-producing) *S. aureus.* The Panel concluded that, 'Animal-derived products remain a potential source of meticillin-resistant *Staphylococcus aureus* (MRSA). Food associated MRSA, therefore, may be an emerging problem.' [lxx]

3.5.6 The role of antibiotics and intensive farming in the evolution of 'pig' MRSA

Studies of animals from different farms have shown that higher antibiotic usage in animals equals higher antibiotic resistance and that pig and poultry farms that do not routinely use antibiotics tend to have lower levels of resistant bacteria.[xcii, xciii] Pigs, of all farmed animals, receive the largest doses of antibiotics, so it may not be surprising that a new strain of superbug has emerged in intensively farmed pigs. In the Netherlands, both scientists and Government

officials blame the widespread use of antibiotics, such as tetracyclines, for the rise and rapid spread of farm-animal MRSA. [xciv]

The link between antibiotic usage and MRSA has also been confirmed in calves. A study of veal farms in the Netherlands, published in 2010, showed that calves group-treated with antibiotics were more likely to be carriers of MRSA than calves that were not group-treated. The authors commented that, 'Since veal calves were frequently treated with different kinds of antibiotics, even during one treatment, it was not possible to unravel the effects of individual antibiotics or antibiotic classes.'[lxxviii]

It is very likely that the increasing use of powerful modern cephalosporins in pig production has contributed to the spread of MRSA in the European pig industry. This may be one reason why the Danish pig industry in 2010 initiated a 2-year ban on the use of cephalosporins while resistance is further investigated (see also Section 4.2).

MRSA was also linked to larger farms, which are typically more intensive. EFSA reported that large pig breeding farms were twice as likely to be MRSA-positive as smaller farms and that this might reflect 'managerial practices typical of larger holdings' [lxxxviii]; these could include factors such as higher levels of stress among the animals, more transport of animals between farms and countries, more opportunities for transmission of bacteria and more use of antibiotics.[xcv] A Dutch study of 2007-2008 also found that larger pig breeding farms (over 500 sows) were twice as likely to be positive for 'pig' MRSA as were smaller farms (under 250 sows).[lxxii]

When MRSA ST398 also emerged in veal farms, it was found that calves on large farms were 'significantly more often colonised [by MRSA] compared to calves from smaller farms.[lxxviii] As with pigs, farms holding larger numbers of veal calves are more likely to use intensive methods.

3.6 Resistance to fluoroquinolones linked to the global poultry industry

The fluoroquinolones are classified by the WHO as critically important antibiotics for human medicine, and their effectiveness needs to be protected[ii]. One of the main fluoroquinolones in human medicine is ciprofloxacin (brand name Cipro), which is a first line drug for treatment of severe *Salmonella* and *Campylobacter* infections in adults. It is also effective against plague, anthrax, and potential biological weapons.

Poultry are 'a major source of human exposure to fluoroquinolone resistance *via* food', according to EFSA's Panel on Biological Hazards.[lxx] Enrofloxacin (brand name Baytril), a fluoroquinolone drug related to ciprofloxacin, is used worldwide in the poultry industry. Baytril is authorised in the UK for treatment only, for respiratory and digestive system infections in pigs, cattle and poultry, including calves and piglets, and is administered to poultry in drinking water.[xcvi]

There is evidence from nearly every continent that enrofloxacin use in poultry may have damaged, and may still be damaging, the long-term effectiveness of ciprofloxacin in human medicine. Countries where enrofloxacin was approved for use in poultry between the later 1980s and the mid-1990s include Austria, Canada (withdrawn in 1997), Denmark, France, Italy, Japan, the Netherlands, Spain, the UK[xcvii], the USA[xcvii, xcviii], and Turkey.[xcix] Many scientists internationally have pointed to the food animal use of enrofloxacin and growing resistance to it and linked this to the growing resistance to ciprofloxacin in humans (see Appendix 2).

An EU survey of resistance in foodborne disease bacteria transmitted from animals for 2004-2007 found a 'high occurrence' of fluoroquinolone resistance in *Salmonella* from poultry and in *Campylobacter* from poultry, pigs and cattle as well as from meat, in some member states. Depending on the country, resistance varied between 5% and

38% for *Salmonella* and from 20% to 64% for *Campylobacter.*[c] These figures were based on reporting by the individual member states.

In contrast, Australia has never authorised quinolones for use in poultry and fluoroquinolone resistance of *Campylobacter* isolated from people who had locally-acquired infections (as opposed to infections acquired from foreign travel) remained relatively low.[ci,cii]

On the basis of the evidence that the use of enrofloxacin in poultry was contributing to resistance to ciprofloxacin in bacteria infecting humans, the US Food and Drug Administration (FDA) in 2000 decided to ban enrofloxacin in poultry production. The ban was finally achieved in 2005 after years of legal challenges from the veterinary products industry. In March 2004 the Administrative Law Judge in the FDA's case found that that the manufacturer had 'not shown Baytril use in poultry to be safe'.[ciii]

In 2006, the European Medicines Agency came to similar conclusions to the FDA's: that in countries around the world the 'introduction and subsequent use [of fluoroquinolones for animal use] has been followed by the emergence of antimicrobial resistance in bacteria of food-producing animals and subsequently spread of resistant zoonotic bacteria to humans', particularly *Campylobacters*.[xxv] Unlike the US, the EU still permits the use of enrofloxacin in poultry production. As noted above, the use of fluoroquinolones may well also be increasing the spread of MRSA in farm animals.

3.7 Human and economic consequences of drug-resistant infections

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Antibiotic resistance may have serious consequences both for individual people and for society's costs for health care in a number of ways: [civ, cv, cvi, cvii]

- Failure of initial antibiotic treatment
- More limited range of usable antibiotics, infections more difficult to treat
- More severe illnesses, hospitalisations and higher death rate
- Increased likelihood of infection
- Need to use more expensive drugs or drugs with potentially severe side effects or other disadvantages
- Greater impact on children's health care
- Greater impact on people suffering from other illnesses and with weakened immune systems
- Additional costs to health-care system.

The European Commission estimates that 'Each year 25,000 patients die in the EU from an infection caused by resistant micro-organisms with extra healthcare costs and productivity losses of at least 1.5 billion euros per year.' This makes antibiotic resistance 'an important, largely unresolved, issue in public health.' [cviii]

In the US, it is estimated that around 2 million people acquire bacterial infections in hospital per year and around 90,000 people per year die from these infections. Around 70% of these infections are resistant to at least one antibiotic,[cix, cx] meaning that antibiotic resistance may have a role in about 60,000 of these deaths.

Over the last decade public health scientists have argued that antibiotic resistance leads to foodborne infections in humans that would not otherwise occur, that are more severe, last longer, are more likely to lead to infections of the bloodstream and to hospitalization, and more likely to lead to death.[cv]

Antibiotic-resistant strains of *Campylobacter* and *Salmonella* tend to be more virulent than non-resistant strains and cause more severe illness, including bloodstream infection and the need for hospitalization[cxi, cxii]. Studies have found that fluoroquinolone-resistant *Campylobacter* in chickens were overall fitter and outcompeted strains that were

susceptible to the antibiotic.[cxiii] In 32 outbreaks of *Salmonella* infection in the United States between 1984 and 2002, 22% of people infected in antibiotic-resistant outbreaks were hospitalized, compared to 8% of people infected in outbreaks caused by *Salmonella* strains that were susceptible to all antibiotics.[cxiv]

Resistance to fluoroquinolones alone, partly acquired from animals via the food chain, is estimated to result in over 400,000 excess days of diarrhoea in the US in a year.[cxi] People infected with ciprofloxacin-resistant *Salmonella*, who did not take anti-diarrhoea medication, have been found to have twice the number of days of diarrhoea during their illness (12 days) than people with ciprofloxacin-susceptible infections.[cxv]

Similarly, Danish medical scientists found that infection with quinolone-resistant *Salmonella Typhimurium* was associated with a 3.15-fold higher risk of bloodstream infection or death within 90 days of infection, compared to infection with strains that were susceptible to antibiotics.[cxvi] People with erythromycin-resistant *Campylobacter* infections were similarly found to have increased mortality within 90 days.[cv] Antibiotic-resistant infections particularly affect people with compromised immune systems, such as HIV-infected people.[cxvii]

People infected with resistant bacteria appear to have long term effects leading to a reduced lifespan compared to people infected with antibiotic-susceptible bacteria. Danish follow-up studies of people for 2 years after infection showed that people infected with antibiotic-susceptible *SalmonellaTyphimurium* were 2.3 times more likely to die than the general population, people infected with strains resistant to 5 common antibiotics were 4.8 times more likely to die and people infected with quinolone-resistant strains were 10.3 times more likely to die.[cvi, cxviii] The data were adjusted to take account of other illnesses that these people may have had.

Drug resistance of whatever type can result in people being treated with less desirable drugs, for example those that have unpleasant or toxic side effects, or with more expensive drugs. According to the WHO, 'the drugs needed to treat multidrug-resistant forms of tuberculosis are over 100 times more expensive than the first-line drugs used to treat non-resistant forms. In many countries, the high cost of such replacement drugs is prohibitive, with the result that some diseases can no longer be treated in areas where resistance to first-line drugs is widespread'.[cxix]

Studies from Brazil[cxx]and Mexico[cxxi] have shown that young children who have not been treated with antibiotics can acquire antibiotic-resistant foodborne bacteria, probably as a result of the antibiotics fed to poultry. Young children are particularly vulnerable to foodborne infections. Around one third of common *Salmonella* infections and 20% of *Campylobacter* infections are in children under 10 years old. Infants have twice as many *Campylobacter* infections and 10 times as many common *Salmonella* infections than the general population.[xx]

A US hospital paediatrician concerned at the risks created by antibiotics in agriculture for children's health, commented in 2003 that: 'Children, particularly very young children, are at high risk of developing infections with drug-resistant organisms linked directly to the agricultural use of antimicrobials'.[xx] This author emphasises 'the unique vulnerability of infants' from exposure to resistant bacteria around the time of birth.[xx]

Drug-resistance can make it impossible to treat children promptly enough, and the results can be fatal. This is even more likely in poor countries if microbiology laboratory testing facilities are not available. Norwegian scientists in 2004 described an outbreak of *Salmonella* causing fatal meningitis in five babies in a rural hospital in Tanzania, concluding that treatment failure due to antibiotic resistance may have contributed to these deaths.[cxxii]

4.0 THE CURRENT USE OF ANTIBIOTICS IN EU LIVESTOCK PRODUCTION

4.1 Inadequacies in recording antibiotic usage

Up to now, no-one knows adequate details on the uses of antibiotics in farm animals in all EU countries, and this situation has represented a major regulatory failure. According to the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency (EMA) in 2009, 'Information on the consumption of antimicrobial agents for food-producing animals is not readily available for most Member States, although the situation is slowly improving.'[xli] The EMA stated in 2011 that 'the ultimate goal is to collect usage data per animal species and per production category, and to take into account the dosage and the treatment duration for each antimicrobial product'[cxxiii], but this is far from the current situation.

It is now widely accepted that we need Europe-wide monitoring of how much antibiotic use there is in food animal production, broken down by antibiotic type, dose, length of treatment, livestock species and reason for usage. This is essential if we are to:

- relate changes in the rate of usage to the rate of resistance found in bacteria, and so
- produce an effective strategy to reduce antibiotic usage and antibiotic resistance.

Two main ways of reporting antibiotic usage exist: (i) the tonnage of antibiotics (active ingredient) sold for use in farm animals (ii) the calculated number of effective doses of antibiotics received by farm animals. Reporting merely by tonnage sold has major disadvantages, because it gives no indication of the number of active doses the tonnage is equivalent to in the animal species and this varies greatly between antibiotics. Thus in terms of antimicrobial activity, a large tonnage of one antibiotic, such as the tetracyclines, can be equivalent to a much smaller weight of another more potent antibiotic. The EMA says that a typical animal dose for a whole treatment with a tetracycline is 70 times greater (in mg of drug per kg of animal) than it is for treatment with a fluoroquinolone, implying that 'a given weight of active ingredient of fluoroquinolone sold can be used to treat 70 times as many animals as the same weight of active ingredient of tetracycline.'[cxxiii]

In relation to the 3rd and 4th generation cephalosporins, EFSA said in 2011 that 'the number of doses are high in relation to the amount sold as they are given by injection (and not orally) and these are highly potent molecules.'[xl] But, as a result of inadequate reporting, EFSA also admitted that it is 'not possible to compile comparable and relevant data on the use of cephalosporins of different generations in the MSs [member states] at the present time.'[xl]

Up to now the UK's Veterinary Medicines Directorate (VMD) has reported annually on tonnage of antibiotic sales figures provided by the pharmaceutical companies, but in the past has not always found it easy to get accurate figures and has had to make quite major historical revisions to reported data. In 2007 the VMD admitted that 'It is currently impossible to determine how much of a product authorised for use in more than one species has been sold for use in each species.'[cxxiv] In addition, the VMD classifies all antibiotics[7] as 'therapeutic' but also admits that it is unable to quantify or estimate the proportion of these 'therapeutic' antibiotics that are used for prevention and control of disease rather than 'to treat clinical disease manifested in animals.'[cxxv] A further weakness of past reports is that there has been no information on the number of doses the animals receive or the way in which they are used.[8]

Some European countries also calculate average doses of antibiotics received by animals. In Denmark, the monitoring agency DANMAP reports usage by sales and also by Animal Daily Dose (ADD), a method close to that used by the WHO to monitor use in humans.[cxxvi] The Netherlands also produces statistics on Defined Daily Doses per animal year (DDD animal) and on which classes of antibiotics are used in which species.[cxxvii] These measures take into account the different potency and dosage for different antibiotics.

[7] other than the ionophore coccidiostats which are used primarily in poultry production but not in human medicine on account of their toxicity.

[8] From 2011 the VMD intends to additionally report according to new EU guidelines, which will probably include a calculation of the number of antibiotic doses received by animals.

4.2 Trends of antibiotic usage in Europe

Because recording is still inadequate, there is uncertainty about the trends in antibiotic use in the EU as a whole but the indications are that usage remains high and is even possibly increasing in some of the most intensive farming sectors such as pigs and poultry. In October 2011 the Environment Committee of the European Parliament adopted a resolution that stated, 'despite the ban of the use of antibiotics as growth promoters, there seems to be no significant decrease in the consumption of antibiotics in the veterinary sector, which continue to be used systematically for "prophylactic" purposes due to unsustainable agricultural practices.' [cxxviii]

Up to 2009, this lack of 'significant decrease' was confirmed by an analysis by the European Medicines Agency (EMA). In 2011 EMA published estimates of antibiotic usage per kg of animals in each country [9] for 8 EU countries that had kept records: Czech Republic, Denmark, Finland, France, Netherlands, Norway, Sweden, UK, and for Switzerland. Antibiotic usage per kg of animals decreased on average by 8.2% from 2005 to 2009 for these 8 EU countries[cxxiii]. This is a very small reduction compared to the very substantial reduction that is really needed.

However, some countries increased usage. Sales per kg of animals increased in 2009 compared to 2005 for Czech Republic, Denmark, Finland, Netherlands, and decreased by 17% in France, and also decreased slightly in Sweden and UK. Of the 8 countries studied, the highest sales per kg of animals were in the Netherlands, followed by France and the Czech Republic.[cxxiii]

But the apparent decrease in tonnes of antibiotics sold may be misleading, and there may be a much smaller decrease in actual usage of antibiotics. This is because the decrease reported by EMA was mainly in sales of tetracylines, which require a high dose, while the sales of several other antibiotics that require lower doses actually increased[cxxiii].The fluoroquinolones and the 3rd and 4th generation cephalosporins were among the lower-dose antibiotics whose use increased between 2005 and 2009. For the 8 EU countries, the use of 1st and 2nd generation cephalosporins increased 25.5%, the use of 3rd and 4th generation cephalosporins by 18.8% and the use of fluoroquinolones by 31.9% in 2009 compared to 2005[cxxiii].The use of pleuromutilins and penicillins also increased from 2005 to 2009[cxxiii].

In some countries, it is now public and industry policy to reduce antibiotic usage in animals. In the Netherlands, the official monitoring report, MARAN[10], stated that antibiotic sales decreased over 2008-2010 (with a 12% decrease during 2010)[cxxix]. In Denmark there has been a dramatic reduction in the recorded use of fluoroquinolones in broiler chicken production from 2007, in response to official policy, while chicken producers appear to have switched to other antibiotics[cxxiii]. An important development is that in 2010 the Danish pig industry itself responded to the risks to both human and animal health from the use of modern cephalosporins by agreeing a voluntary 2-year ban on their use while a study of possible antibiotic resistance takes place.[cxxx]

4.3 What livestock diseases are antibiotics used for in Europe?

Farmed animals are often exposed to a wide range of infections during their lives. In 2009, a joint report from the European Medicines Agency (EMA) and other European health authorities listed the frequently occurring infections in farmed animals that are treated with antibiotics, variously affecting the animals' intestines, respiratory system and lungs, reproductive tract, blood (septicaemia), skin, feet, brain and joints.[cxxxi]

[9] It is necessary to take account of increase or decrease in the total weight of animals in the country, as well as the increase or decrease in antibiotic sales. A reduction in the number or weight of animals could result in a reduction in antibiotic sales, without this meaning that usage per animal had decreased. This method of comparison is still problematic – for example, the UK has a high proportion of sheep included in its total livestock, and sheep are much more rarely treated with antibiotics than are pigs and poultry.

[10] Monitoring of Antimicrobial Resistance and Antibiotic Usage in the Netherlands (MARAN)

Table 2. Frequently occurring diseases of different farmed species that are likely to be treated with antibiotics. Source: EMA, 2009 [cxxi]

Species	Condition	Flock/herd use of antibiotics?	Individual use of antibiotics?
Dairy cows	mastitis	Yes, when for prevention	Yes
	uterine infections		Yes
Calves	enteritis	Yes	
	pneumonia	Yes	Yes
	diphtheria	Yes	Yes
	umbilical infections		Yes
	septicaemia		Yes
	footrot		Yes
Breeding sows	joint infections		Yes
	footrot		Yes
	mastitis		Yes
	uterine infections		Yes
Weaned piglets	enteritis	Yes	
	septicaemia	Yes	Yes
	meningitis	Yes	
	umbilical infections		Yes (may be injected prophylactically for all piglets)
	skin infections	Yes	
Fattening pigs	enteritis	Yes	
	Pneumonia	Yes	
	tail bite infections	Yes	Yes
Chickens	enteritis	Yes	
	respiratory infections	Yes	
	septicaemia	Yes	
	yolk sac infection (newly hatched chicks)	Yes	

Pigs and poultry are the animals most likely to be reared in factory-farmed conditions, often crowded in large numbers indoors. In 2008, pigs accounted for around 60% of the tonnage of antibiotics (active ingredient) sold in the UK and 80% of the antibiotic doses in Denmark. [cxxv, cxxvi] Poultry account for 36% of the tonnage of antibiotics sold for farm animals in the UK in 2008.[cxxv] In Denmark, the antibiotic dosage per pig increased by as much as 24% between 2001 and 2008 and the Danish monitoring body DANMAP reported that weaning pigs were being prescribed 10 or more courses of tetracycline antibiotics per year and that 'tetracyclines are used systematically in some herds.'[cxxvi]

Between 2004 and 2009, 69-84% of 'therapeutic' antibiotics sold for farm animals in UK were for use in medicated feeds (mostly for pigs and poultry),[cxxxii] a method that allows mass medication. Pigs are often mass-medicated with antibiotics in their feed and water, to prevent or control disease (see Appendix 3). The medicated feed or water can be given for a period of days, weeks or longer for any one prescription (and the prescription can be repeated).

Because the Netherlands monitoring report, MARAN, calculates average doses per animal, it is possible to get a snapshot of the antibiotic doses an average food animal receives. From official Dutch records, the average number of daily doses per animal per year[11] in 2008 was:[cxxxiii]

Broiler chickens (meat chickens): 37
Breeding sows and young piglets: 19 (in practice, nearly all doses would be for the piglets, so this comes to 30 daily doses for a piglet)
Fattening pigs (meat pigs): 17
Veal calves: 34
Dairy cows and calves: 6.6

Depending on the farm, the number of doses could be considerably higher (or lower) than these averages.

The Netherlands report, MARAN 2008[cxxxiii], calculates that the levels of dosage imply that[12]:

- The average **meat pig** living for 191 days in 2008 was exposed to 30 antibiotic daily doses[13] up to 74 days old at the breeding farm and 5 daily doses during the fattening period of 117 days, resulting in exposure for 35-37 days in total, or 18-19% of his or her lifetime.[11]

- An average **broiler (meat) chicken** living 42 days in 2008 was exposed to antibiotic doses for 5 days (12%) of his or her lifetime.[11]

- A **veal calf** in 2008 was exposed to antibiotic doses for at least 23 but more likely 46 days (21%) of his 222-day life. [14, 11]

- Ninety per cent of **dairy cows** in 2008 were treated with antibiotics as 'dry cow treatment'[15] in all 4 quarters of the udder. **Dairy calves** were exposed to antibiotics during 7 days of their 56-day period up to weaning.

[11]Meat pigs, meat chickens and veal calves live on average 6 months, 6 weeks and 7 months, respectively, in the Netherlands,according to MARAN-2008, so each individual animal would receive a corresponding fraction of the annual number of doses.
[12] MARAN's calculations take into account the age and estimated weight of the animals.
[13] MARAN assumes all doses were for the piglets, rather than for the sow.**Error! Bookmark not defined.**
[14]MARAN's calculation takes into account that younger and lighter calves are more likely to be treated with antibiotics than older calves.**Error! Bookmark not defined.**
[15] Antibiotic treatment after lactation to prevent mastitis

4.4 Europe's continuing use of 'preventive' antibiotics

Up to January 2006 low doses of antibiotics were added to animals' feed as 'growth promoters' in the EU. This apparently increased the economic performance of farm animals; in part, this was almost certainly because they kept down low-level infections among animals crowded in intensive farms. The term 'growth promotion' served to disguise the link between antibiotic use and infectious disease and allowed farm animals to be dosed with antibiotics without veterinary oversight, for decades. The practice of feeding 'growth promoters' remains widespread in the US and elsewhere in the world and has been exported from Europe and the US to less industrialised countries.

Concerns were expressed in Europe about 'growth promoters' from the 1960s onward.[xiii,xiv,cxxxiv] From the 1980s and 1990s scientists published increasing evidence showing that the use of low doses of antibiotics in animal feed as 'growth promoters' was linked with increasing antibiotic resistance to related drugs used in human medicine.Between 1999 and January 1st 2006 the EU banned the use for 'growth promotion' of 8 antibiotics: virginiamycin, tylosin phosphate, bacitracin zinc, spiramycin, avilamycin, flavophospholipol, monensin and salinomycin, plus the drugs carbadox and olaquindox.

Research subsequently showed that the ban on antibiotic 'growth promoters' in Europe did reduce some types of antibiotic resistance substantially[cxxxv]. But, according to EFSA's review of the problem of resistance in foodborne zoonoses of 2010, 'the resistance genes still remain present in the bacterial population for a number of years.' [c,cxxxvi]

The ban on 'growth promoters' was intended to limit non-essential uses of antibiotics in animal production and to help safeguard the effectiveness of important human antibiotics. There are several reasons for thinking that this has not happened to the extent that was hoped and that the EU needs to take stronger action to prevent the avoidable over-use of antibiotics as a substitute for good animal husbandry.

- **Antibiotic usage remains high**: The 'growth promoter' ban of 1999-2006 has not substantially reduced the overall use of antibiotics in food animal production, as was intended. On the contrary, there has been an increase in some uses of 'therapeutic' antibiotics and possibly switches to different and more modern antibiotics.

- **Preventive use may be disguised as 'treatment'**: The use of antibiotics specifically licensed as 'growth promoters' was always a small proportion of the total use of antibiotics in farm animals in Europe (about 9% of sales in the UK in 2003 before the ban[cxxxvii]). In fact, much of the use of antibiotics that claims to be 'therapeutic' is intended to control disease in intensive farms and often involves mass medication.

- **Previous 'growth promoters' are still used for 'prevention'**: One of the previous 'growth promoters' is still authorised for use in animal feed for the control of infection. The macrolide antibiotic tylosin is banned as a 'growth promoter' in the EU but is still used in pig feed to prevent and control enteritis for a duration 'until the end of the period of risk.' [xcvi] (see Appendix 3). Tylosin is also used in feed to prevent respiratory infections and necrotic enteritis in broiler chickens and pullets (young hens before they start laying).

- **Antibiotics are still used as coccidiostats**[16]: Some drugs designated as coccidiostats, such as lasalocid, monensin and salinomycin, are in fact antibiotics (known as ionophores, not used in human medicine). They can be added to feed over long periods of the animals' lives and will have a function in suppressing bacterial infections. As such they can also contribute to antibiotic resistance. Monensin and salinomycin are banned as 'growth promoters' in the EU, but are still allowed as coccidiostats.

[16] Drugs used to control disease caused by the intestinal parasite coccidia.

We believe that until significant reform of intensive farming is achieved, farmers will always need artificial chemical means of suppressing infections on factory farms. We urge the EU to conduct an independent, urgent and in-depth review of all antibiotic usage in European farms, related to farming methods, with a view to ending routine preventive antibiotic use.

4.5 'Production' use of antibiotics in the US and the FDA's proposals for reform

'Production' uses of antibiotics for poultry, pigs and cattle are still widespread in the US and elsewhere outside the EU. Many of these drugs can be bought over-the-counter without veterinary supervision or prescription. By 1999, the US Food and Drug Administration (FDA) had authorised the use of 18 antibiotics for 'growth promotion', of which 8 were identical or chemically similar to drugs used in human medicine.[xx] Antibiotics that are classified as 'critically' or 'highly' important in human medicine, including penicillin, tetracyclines and macrolides, are used as 'growth promoters' in the United States.

In 2008, the Animal Drug User Fee Act was passed in the US, which required the FDA to compile and publish data annually on antibiotic sales and distribution for use in farm animals and required pharmaceutical companies to provide sales data to the FDA. At the end of 2010 the FDA published its first report on antibiotic sales for farm animals, as part of its 'ongoing activities in antimicrobial resistance prevention.'[cxxxviii] The reported totals for food-producing animals in 2009 were 13,068 tonnes of antibiotics for domestic use and a further 1,632 tonnes exported.[cxxxix]

In 2010, the FDA raised 'particular concern' about the 'non-therapeutic' use of antibiotics that are important in human medicine but are also 'approved for use in food-producing animals for production or growth-enhancing purposes'.[cix, cxl] The FDA issued new guidelines for the 'judicious use' of antibiotics in animal production, having concluded that 'the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health.'[cxl]

FDA's proposals included (i) limiting the use of medically important drugs to treating, controlling or preventing identified diseases, rather than for 'production' purposes, and (ii) the phase-in of a requirement for veterinary oversight of these drugs (to replace over-the-counter sales).[cxl]

These changes would be a big step in the right direction and would bring US antibiotic policy closer to that current in Europe since the ban on antibiotic 'growth promoters'. But in both the EU and the US it leaves in operation the 'preventive' use of antibiotics for mass medication in intensive farming, with as yet inadequate regulation and monitoring.

5.0 SOME EXPERT VIEWS ON ANTIBIOTIC RESISTANCE AND FARM ANIMALS

The following are a small selection of the conclusions of the many expert bodies that have raised concerns about antibiotic use in farming over the period from 1999 to 2011. They make clear the weight of current veterinary and medical opinion against the irresponsible use of antibiotics in farm animals, based on the risks to public health.

Advisory Committee on the Microbial Safety of Food, 1999.[xvi]
'If the administration of antibiotics to farm animals results in an acceleration in the rate at which antibiotic resistance is emerging in humans, there is clearly a case for restricting the use of antibiotics in animals, particularly as the resistant bacteria would be capable of causing not only gastroenteric infections but other serious illnesses.'

'Antibiotics should never be used as an easy alternative option to good husbandry practice and management, site hygiene or, where it is available, vaccination.'

US Food and Drug Administration Center for Veterinary Medicine, 2000.[cxli]
'After thoroughly analyzing all the data and evidence, the Center has determined that:

1. The primary cause of the emergence of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in humans is the consumption of or contact with contaminated food;
2. Poultry are a predominant source of campylobacteriosis in humans;
3. Poultry carrying fluoroquinolone-resistant *Campylobacter* are the predominant source of fluoroquinolone-resistant campylobacteriosis in humans; and
4. The administration of fluoroquinolones to chickens leads to development of fluoroquinolone-resistant *Campylobacter* in chickens.'

World Health Organization, 2007.[ii]
'[T]here is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials: increased frequency of infections, increased frequency of treatment failures (in some cases death) and increased severity of infections'.

EFSA Panel on Biological Hazards, 2008.[lxx]
'Specific measures to counter the current and developing resistance of known pathogenic bacteria to fluoroquinolones as well as to 3rd and 4th generation cephalosporins found in a variety of foods and in animals in primary production now require to be defined and put in place as a matter of priority.'

United States Department of Agriculture, 2010.[cxlii]
'USDA believes that it is likely that the use of antibiotics in animal agriculture does lead to some cases of antibacterial resistance among humans and in the animals themselves and it is important that these medically important antibiotics be used judiciously.'

United States Food and Drug Administration, 2010.[cix]
'FDA believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes [in farm animals] is not in the interest of protecting and promoting the public health.'

Federal Institute for Risk Assessment (BfR), Ministry of Food, Agriculture and Consumer Protection (BMELV), Berlin, 2010.[cxliii]
'Resistances to pathogens in animals and foods are a serious problem in consumer health protection. Infections with resistant pathogens can prolong or aggravate the course of diseases in humans. They can require hospital treatment and may even become life threatening in certain cases.'

'In order to prevent a further increase in resistances, the use of antibiotics should be limited to the absolutely necessary extent both in human and in veterinary medicine according to BfR.'

World Health Organization, on World Health Day, 2011.[v]
'Irrational and inappropriate use of antimicrobials is by far the biggest driver of drug resistance…. And this includes the massive routine use of antimicrobials, to promote growth and for prophylaxis, in the industrialized production of food. In several parts of the world, more than 50% in tonnage of all antimicrobial production is used in food-producing animals. In addition, veterinarians in some countries earn at least 40% of their income from the sale of drugs, creating a strong disincentive to limit their use. The problem arises when drugs used for food production are medically important for human health, as evidence shows that pathogens that have developed resistance to drugs in animals can be transmitted to humans.'

6.0 PREVENTING DISEASE WITHOUT PROPHYLACTIC USE OF ANTIBIOTICS

Except for the occasional necessary treatment of individual animals, antibiotics are far from being a recipe for animal welfare. The use of antibiotics to suppress infectious disease has allowed animals to be kept in entirely unnatural intensive conditions that make it harder for them to maintain their own health and that frustrate or limit much of their natural behaviour. Crowding and stress provide ideal conditions for the spread of infectious disease.

In many cases, disease can be prevented by good husbandry, good environment and hygiene, rather than by routine prophylactic use of antibiotics. Positive measures that can reduce disease in farmed animals include:

- *Switching to extensive production systems*: High-welfare free-range and organic systems can achieve higher levels of animal health together with lower levels of antibiotic use than intensive production systems. Recent studies in the UK,[cxliv, cxlv] Norway[cxlvi] and Sweden[cxlvii] find that organic dairy farms, where preventive antibiotic treatment of dry cows is less likely to be used, achieve the same level of mastitis control as conventional farms that typically use routine prophylactic antibiotics.

- *Reducing stress:* Stress can lead to animals' immune systems being compromised whereas reducing stress can promote improved immune competence and the ability of animals to fight disease.[viii]

- *Avoiding mixing*: Mixing unfamiliar animals is a well-known source of stress and increases the risk of transmission of infections.[cxlviii]

- *Good weaning practice:* If too early or poorly managed, weaning can cause stress and can lead to disease. Later weaning helps to ensure that animals are more independent of their mother nutritionally, immunologically and psychologically, reduces stress and risk of scouring.[cxlix]

- *Keeping stocking densities low and avoiding excessive herd or flock sizes*: Overcrowding and very large numbers of animals facilitate disease transmission and the mutation of pathogens to become more virulent.[9]

- *Reducing journey times during live transport of animals:* Longer journeys increase stress and result in increased susceptibility to disease and increased shedding of pathogenic agents, including bacteria[viii, cl, cli]. EFSA's Scientific Panel on Animal Health and Welfare concluded in 2004, 'Transport should therefore be avoided wherever possible and journeys should be as short as possible.'[cli]

- *Breeding for natural disease resistance and robustness:* Breeding animals for robustness and health is increasingly recognised as an essential part of sustainable animal farming.[cliii, cliii] In contrast, intensive farming often uses animals bred for levels of production which put them under metabolic or physiological stress and increased risk of compromised immune systems.[cliv]

- *Establishing high welfare animal farming throughout Europe:* Reform of intensive farming is the most certain and permanent way to reduce or eliminate non-therapeutic uses of antibiotics in European food production. The crowded and stressful conditions of factory farms should be replaced by extensive and free-range systems that respect the animals' welfare and provide conditions in which they can maintain their own health without the frequent use of drugs. This would be in the interests of Europe's farmers, by establishing their reputation globally for high-quality standards, and of Europe's citizens who demand higher standards of animal welfare, transparency and quality in food production.[clv, clvi]

7.0 KEY POINTS AND RECOMMENDATIONS

Antibiotic resistance developing globally in disease-causing bacteria is one of the major threats to human medicine throughout the world. It leads to additional burdens on health systems, to treatment failures and, in the worst cases, to untreatable infections or infections treated too late to save life. This report has set out the evidence showing that:

- Although the over-use of antibiotics in human medicine is the major cause of the current crisis of antibiotic resistance, public-health experts are agreed that the over-use and mis-use of antibiotics in intensive animal production is also an important factor – around half the world's antibiotic production is used in farm animals.

- The crowded and stressful conditions that animals are subjected to in intensive farms promote disease, not health. These infectious bacterial diseases are suppressed by the use of 'preventive' doses of antibiotics, often administered to whole herds or flocks of animals in their feed or water.

- Every use of antibiotics can encourage the growth of drug-resistant bacteria. This means that every use of antibiotics should be carefully considered. The therapeutic use of antibiotics to treat an individual sick animal is of course justifiable. The 'preventive' (prophylactic) use of antibiotics, for example in the feed and water of groups of apparently healthy animals, is dangerous and unjustifiable.

- When animals are administered an antibiotic that is closely related to an antibiotic used in human medicine, cross-resistance occurs and disease-causing bacteria become resistant to the drug used in human medicine. It is dangerous and unjustifiable to use antibiotics that are related to drugs of critical importance in human medicine for 'preventive' administration to groups of apparently healthy animals.

- The world's public-health experts, from the European Union, the United States and the World Health Organization, are agreed that drug-resistant bacteria are created in farm animals by antibiotic use and that these resistant bacteria are transmitted to people in food and then spread by person-to-person transmission. In people they can cause severe drug-resistant food poisoning and life-threatening urinary infections and blood poisoning.

- The use of critically important antibiotics in farm animals is implicated in the emergence of new forms of multi-resistant bacteria: these include the emergence of bacteria carrying the ESBL enzymes that inactivate nearly all beta-lactam antibiotics (including penicillins and the 3rd and 4th generation cephalosporins).

- The over-use of antibiotics in pig farming is implicated in the emergence of a new 'pig' strain of the superbug methicillin-resistant *Staphylococcus aureus* (MRSA) which has spread to people and has also been found in chickens and dairy cattle.

- Antibiotic use in animals in the UK and the EU is not being reduced sufficiently rapidly and may still be increasing in some of the most intensive sectors such as pig and broiler (meat) chicken production. Of particular concern, farmers may be increasingly using modern and more potent drugs such as the 3rd and 4th generation cephalosporins and the fluoroquinolones, which are classified as critically important in human medicine.

RECOMMENDATIONS

- The European Commission and the Member States should develop a more effective strategy to reduce antibiotic use in agriculture in order to ensure that antibiotics remain effective in the fields of both human and animal health. This should include a transparent review into the state of antibiotic use in agriculture and its relationship with patterns of anti-microbial resistance.

- The European Commission should propose new regulations to:
    - Phase out prophylactic use of antibiotics in farm animals other than in very limited, clearly defined situations;
    - Ban all prophylactic and off-label use of 3rd and 4th generation cephalosporin antibiotics in farm animals with immediate effect;
    - Ban all prophylactic and off-label use in farm animals of new antibiotics licensed in the EU.

APPENDICES

Appendix 1 Examples of multi-resistant foodborne bacteria in Europe and beyond

Italy (1999-2001): Salmonella strains isolated from humans, food and farm animals showed high rates of resistance to antibiotics tests, except for cefotaxime (3rd generation cephalosporin) and ciprofloxacin (fluoroquinolone). Rates of resistance and multi-resistance were higher in samples from food and farm animals than from humans, confirming the role of livestock as a reservoir of drug-resistant *Salmonella* which can be transmitted to people.[clvii]

France (1992 compared to 2002): Antibiotic resistance of *Campylobacter coli* isolated from skin and faeces of chickens rose substantially between 1992-1996 and 2001-2002; for *C. coli* resistance to ampicillin increased from 2.0% to 36.8%, resistance to nalidixic acid (a quinolone) increased from 2.0% to 45.1%, resistance to enrofloxacin (a fluoroquinolone used for chickens) increased from 2.1% to 38.6%, resistance to tetracycline increased from 56.0% to 83.2% and resistance to erythromycin increased from 36.0% to 61.7%. For *C. coli*, resistance on free-range farms was less prevalent than on standard commercial farms, presumably reflecting differences in antibiotic use.[clviii]

Ireland (2003): 30.7% of *Campylobacter jejuni* strains isolated from a poultry slaughterhouse were resistant to two or more antibiotics. 35.9% of samples were resistant to ampicillin, 20.5 % to tetracycline, 17.9% to ciprofloxacin, 10.2% to erythromycin and 2.5% to streptomycin.[clix]

UK (2007-2008). In official tests of samples of bacteria in fresh retail chicken, 87% of the *Campylobacter* isolates and 41% of the *Salmonella i*solates were resistant to at least one antibiotic, including some strains that were multi-drug resistant. Since 2001, resistance in *Salmonella* had decreased but resistance in *Camplylobacter* had increased.[clx]

France (2002 – 2006) *E. coli* samples from calves with diarrhoea showed simultaneous resistance to between 2 and 10 different antibiotics, and the scientists commented, 'Looking at potential therapeutic implications, the high level of resistance and multiresistance to several antimicrobials observed in *E. coli* makes a critical reassessment of empiric oral antimicrobial therapy in calves highly desirable.'[clxi]

Maryland, USA (2005): 74% of retail chickens tested were contaminated with *Campylobacter* and 44% with *Salmonella*. All *Salmonella Typhimurium* isolates from conventional chickens were resistant to five or more antimicrobials, whereas the large majority of *S. Typhimurium* isolates from organic chickens (79%) were susceptible to all the 17 antimicrobials tested.[clxii]

China (2004-2005): *E. coli* isolated from live chickens in Henan Province were resistant to sulphonamide-metheprim (100%), oxytetracyline (100%), ampicillin (83%), enrofloxacin (83%), ciprofloxacin (81%), chloramphenicol (79%) and florphenicol (29%), indicating that 'prudent use in veterinary medicine' was called for.[clxiii]

Taiwan (2004-2006) All the *Salmonella* samples isolated from chicken meat at markets were multi-resistant and demonstrated high resistance to ampicillin, gentamicin, kanamycin, streptomycin, tetracycline, nalidixic acid, trimethoprim-sulfamethoxazole, and chloramphenicol, indicating some 'abuse of antibiotics' in chicken production.[clxiv]

Appendix 2 Enrofloxacin in poultry production and the rise of fluoroquinolone resistance

Netherlands (1982-1989): During this period quinolone resistance in *E. coli* from poultry products increased from 0% to 14% and in *E. coli* from humans from 0% to 11%, coinciding with the introduction of enrofloxacin. This suggested 'that the resistance observed is mainly due to the use of enrofloxacin in the poultry industry.'[clxv]

Belgium (1998): 'Alarmingly high rates of resistance to ciprofloxacin' were found, including 62.1% of C. coli samples and 44.2% of *C. jejuni* samples from chickens, suggesting that 'the use of fluoroquinolones in poultry has a primary role in increasing resistance to quinolones among *Campylobacter* isolates from humans' .[clxvi]

Austria (2000-2001): 54% of whole broilers at a Styrian slaughterhouse were found to be infected with *Campylobacter jejuni*. High levels of resistance were found, with 62.2% of the samples being resistant to ciprofloxacin. The resistance reflected 'the fact that enrofloxacin is the most frequently used antibiotic in broiler production. [clxvii]

Minnesota, USA (1996 – 1998) A rapid rise in resistance to quinolones in *Campylobacter jejuni* infections in people coincided with the licensing of fluroquinolones for use in poultry. Public health scientists compared the sub-types of resistant *C. jejuni* found in people and in retail chicken and concluded that, 'the use of fluoroquinolones in poultry has had a primary role in increasing resistance to quinolones among *C. jejuni* isolates from humans.'[clxviii]

Brazil (2001): 18.2% of *Campylobacter jejuni* and 25% of C. coli strains isolated from children with diarrhoea were resistant to the fluoroquinolones ciprofloxacin and norfloxacin. Since the young children would probably not have been treated with fluoroquinolones this 'suggests an animal origin of this resistance' related to veterinary use of enrofloxacin.[cxx]

Mexico (2000) In an area of Mexico where the fluoroquinolone enrofloxacin was widely used in poultry production, 18.5% of *E. coli* samples from healthy young children who probably would not have been treated with fluoroquinolones were resistant to the related human antibiotic ciprofloxacin. It was concluded that both the use of fluoroquinolones to treat close relatives in hospital and contaminated food were likely sources of the resistant *E. coli*.[cxxi]

China (1999-2000) Of Salmonella strains isolated from retail chicken and other meats produced in China in 1999-2000, 32% were resistant to nalidixic acid and also showed reduced susceptibility to ciprofloxacin, whereas no isolates from meat imported from the US were resistant to these drugs. The researchers noted that this was probably because quinolones and fluoroquinolones have been used in veterinary medicine in China since the 1980s but only since 1995 in the US. [clxix]

Turkey: (1992-2000): The first fluoroquinolone-resistant *Campylobacter* strain from broiler chickens was found in 1992, around 2 years after the licensing of enrofloxacin for use in farm animals. By 2000 75.5% of Campylobacter isolates were resistant to enrofloxacin and 73% to ciprofloxacin, caused by 'the uncontrolled use of fluoroquinolones in animals in Turkey'.[clxx]

Appendix 3

Antibiotic products used in the UK in the feed and/or water of pigs for the prevention and/or control of infection. Some of these products can also be used for other species, most often poultry. Sources: Nunan and Young, 2007, Table 9.2 [lxvii] ; NOAH, 2010[xcvi]

ANTIBIOTIC NAME	ANTIBIOTIC CLASS	AUTHORISED FOR CONTROL AND/OR PREVENTION OF:	PERIOD OF USE PER PRESCRIPTION
Amoxycillin	beta-lactam	*Streptococcus suis* in weaned piglets (eg	14 days

		meningitis)	
Apramycin	aminoglycoside	bacterial enteritis in young pigs (e.g. *E. coli* infection)	Up to 28 days
Chortetracycline (3 products)	tetracycline	respiratory and systemic infections, including meningitis (*S. suis*), rhinitis, pneumonia	5 to 7 days
Doxycycline	tetracycline	prevention of clinical respiratory disease	5 days
Florfenicol	phenicol	respiratory disease or pneumonia in infected herds	5 days
Lincomycin + spectinomycin	lincosamide / aminoglycoside	enteritis; dysentery; pneumonia	3 weeks or 'until clinical signs disappear'
Phenoxymethylpenicillin	beta-lactam	*S. suis* (meningitis and septicaemia); pathogens causing pneumonia	Up to 6 weeks
Spectinomycin	aminoglycoside	bacterial enteritis caused by *E coli*	3 to 5 days
Tiamulin	pleuromutilin	dysentery, ileitis (inflammation of small intestine), pneumonia	14 days, up to 2 months or 'throughout period of risk'
Tilmicosin	macrolide	respiratory disease, pneumonia	15 to 21 days
Trimethoprim + sulfadiazine	Trimethoprim / sulphonamide	infections in fattening pigs	5 days
Tylavosin (acetylisovaleryltylosin)	macrolide	pneumonia, dysentery	7 to 10 days
Tylosin	macrolide	dysentery, pneumonia	21 days or 'until the end of the period of risk'
Valnemulin	pleuromutilin	dysentery, clinical signs of colitis	up to 4 weeks 'or until signs of disease disappear'

Eleven of the 13 antibiotics listed in the table above are related to drugs that are used in human medicine. Of these antibiotics, only the pleuromutilins (tiamulin and vanemulin in the table) are not used in humans.[clxxi]

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