Antimicrobial resistance – why the irresponsible use of antibiotics in agriculture must stop

A briefing from the Alliance to Save Our Antibiotics

"Antimicrobial resistance poses a catastrophic threat. If we don't act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can't be treated by antibiotics"

Chief Medical Officer,
Professor Dame Sally Davies

The Alliance to Save Our Antibiotics is an alliance of health, medical, environmental and animal welfare groups working to stop the over-use of antibiotics in animal farming. It was founded by the Soil Association, Compassion in World Farming, and Sustain in 2009 and is supported by the Jeremy Coller Foundation. Its vision is a world in which human and animal health and well-being are protected by food and farming systems that do not rely routinely on antibiotics and related drugs.

June 2014

‘The WHO’s first global report on antimicrobial resistance, with a focus on antibiotic resistance, reveals that it is no longer a prediction for the future. Antibiotic resistance - when bacteria change and antibiotics fail - is happening right now, across the world... without urgent action we are heading for a post antibiotic era in which common infections and minor injuries can once again kill’

World Health Organisation, April 2014

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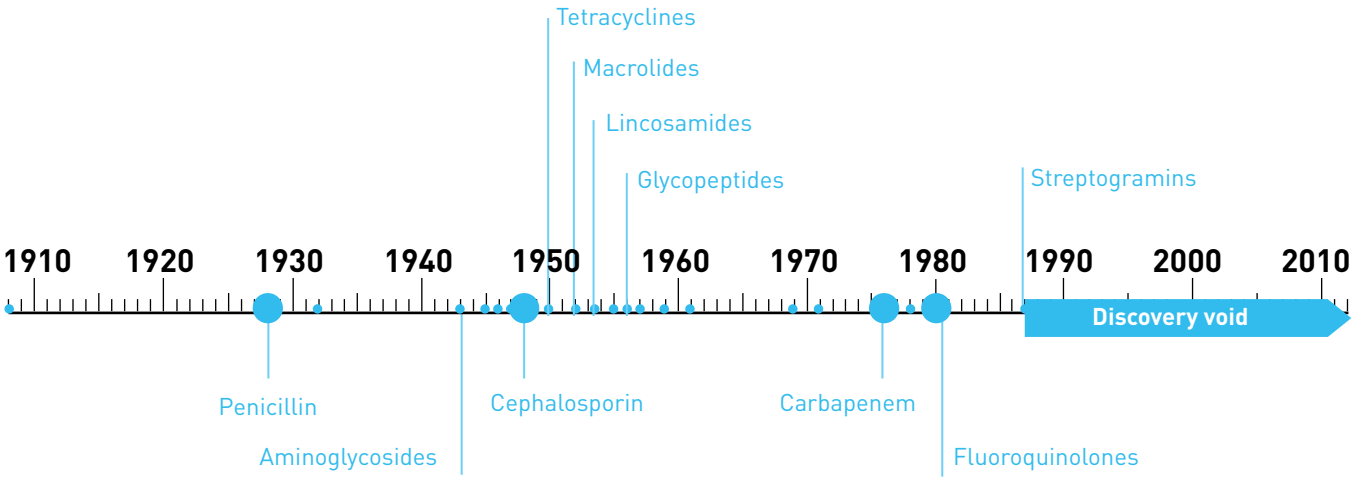
Executive summary

In April this year (2014) the World Health Organisation (WHO) published a report about rising antibiotic resistance around the globe, in which it said that a post-antibiotic era is not an apocalyptic fantasy, but a real possibility for the 21st century. The WHO warns that resistance is becoming a problem so serious that it threatens the achievements of modern medicine.

Minor injuries, routine surgical procedures and natural processes such as childbirth are set to kill us again, or cause protracted illness. Antibiotic resistance is developing faster than new antibiotics are being developed, and finding new antibiotics is becoming increasingly difficult and expensive.

Over the last 30 years, no major new types of antibiotics have been developed



We over-use and abuse antibiotics. Surveys have shown that many doctors still prescribe antibiotics far more often than necessary and a significant number of patients fail to complete a full course of antibiotics, sometimes saving tablets for later self-medication. A high proportion of patients still believe that antibiotics are effective against viruses. Strenuous efforts are being made in medicine to reduce such profligacy, and whole batteries of guidelines have been produced for both doctors and patients.

Medicine is only a part of the picture, however. This briefing sets out why healthcare professionals, policy-makers, and the public should be concerned about farm antibiotic use.

In livestock production, especially pigs and poultry, many antibiotics are used routinely for disease prevention or for the treatment of avoidable outbreaks of disease. This is because in intensive production, typically thousands of the animals are kept together indoors, in confined spaces, on their own faeces, where disease outbreaks are inevitable. Farmers are even permitted to use antibiotics which are critically important in human medicine (CIAs) on animals, and this use is actually increasing.

It is estimated that just under half the total of all antibiotics used in the UK are given to farm animals [1]. It is only an estimate, because although farm antibiotic use - as in medicine - is prescription-only, no prescription records are collected. So nobody yet knows for sure how many antibiotics are used, in which species, or by farm. But what is clear is that antimicrobial resistance from farm animals is a significant threat to human health.

Although resistance in human infections is mainly caused by human antibiotic use, for a range of bacteria, farm animal use contributes significantly, and for some infections it is the main source of resistance. This fact has been established by decades of research and is acknowledged by organisations like the WHO and the European Food Safety Authority: this briefing summarises some of the most important findings.

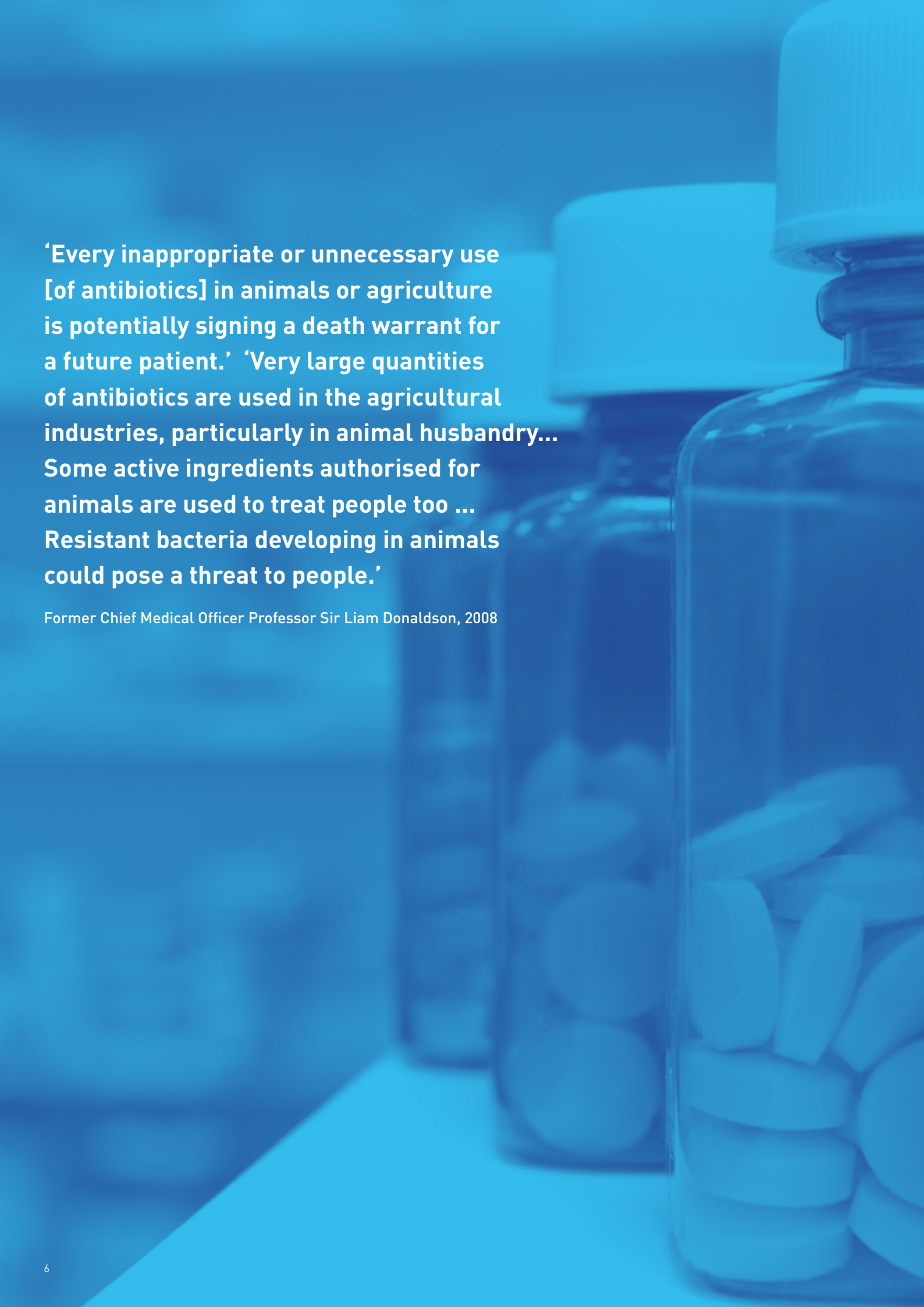
Antibiotic-resistant bacteria pass between humans, between animals and between humans and animals in both directions much more frequently than once realised. Copies of antibiotic-resistance genes can also move between bacteria, and this exchange can occur in the human gut, so in some cases the bacteria causing a human infection will not be of farm-animal origin, but the resistance will be. This complexity means there are few completely conclusive results in antibiotic-resistance science.

Economic concerns can also further muddy the debate. Those representing the interests of the pharmaceutical industry and intensive livestock producers are keen to avoid increased regulation of farm antibiotics, perhaps concerned by the prospect of falling drug sales or increased farm production costs. Therefore they generally argue that farm use of antibiotics does not contribute to the problem of antibiotic resistance in humans to any appreciable extent.

Nevertheless, the overall weight of scientific research has led to a consensus amongst many scientists that:

- for some bacterial infections, such as *Campylobacter* and *Salmonella*, farm antibiotic use is the principal cause of resistance in human infections.
- for other infections, like E. coli and enterococcal infections, farm antibiotic use contributes, or has contributed, significantly to the human resistance problem.
- the emergence of resistance to critically important antibiotics, in particular of ESBL resistance in E. coli and *Salmonella*, is a major development which has occurred in recent years, which has been driven by inappropriate use of these antibiotics in both human and veterinary medicine.
- livestock-associated strains of MRSA infecting humans are also a developing problem, which results from the high use of certain antibiotics in farm animals.
- some other emerging antibiotic-resistant infections in humans may in part be due to farm antibiotic use, but while research is ongoing, there is currently insufficient evidence to draw clear conclusions.

We are reaching a crisis point at which the costs to the health service of increasing antibiotic resistance are unaffordable. Lack of success in developing new antibiotics means that it has become ever more important that we preserve the antibiotics that we have. Profligate farm antibiotic use can no longer be afforded.



‘Every inappropriate or unnecessary use [of antibiotics] in animals or agriculture is potentially signing a death warrant for a future patient.’ ‘Very large quantities of antibiotics are used in the agricultural industries, particularly in animal husbandry... Some active ingredients authorised for animals are used to treat people too ... Resistant bacteria developing in animals could pose a threat to people.’

Former Chief Medical Officer Professor Sir Liam Donaldson, 2008

1

The threat of antimicrobial resistance

In 2013, the Chief Medical Officer in the United Kingdom, Professor Dame Sally Davies, warned Parliament that the rise of antibiotic resistance could cause a national emergency comparable to a catastrophic terrorist attack, pandemic flu or major coastal flooding. She told MPs of an 'apocalyptic scenario' where people going for simple operations in 20 years' time die of routine infections because 'we have run out of antibiotics'. The Cabinet Office is adding antibiotic resistance to the national strategic risk register.

The rise of antibiotic resistance is becoming a major problem for treating many serious infections, and threatens to also have unforeseen impacts on a wide range of medical procedures.

Doctors frequently need to start antibiotic treatment blind, or 'empirically', because determining the bacteria which are causing the illness, and the antibiotics to which they are sensitive, can take two or three days. As resistance becomes more commonplace, the chances that the initial antibiotic chosen will be ineffective increases. Numerous studies have shown that with blood-poisoning infections caused by E. coli or some other bacteria, failure to select an effective initial antibiotic doubles the likelihood that the patient will die [2]. The EU estimates that at least 25,000 people die in Europe each year from an antibiotic-resistant infection [3].

This creates a pressure to use the last few effective antibiotics which in turn is increasing the rate at which resistance develops to these too. Resistance to last-resort antibiotics, the carbapenems, increased from about 5 hospital patients in England in 2006 to over 600 in 2013 [4].

As well as increased mortality, antibiotic resistance results in more severe illness, longer duration of illness, more bloodstream infections and more hospitalisation [5]. The additional cost per patient of antibiotic resistance varies significantly, but has been put as high as £30,000 [6].

However, all of this fails to fully grasp the effect that losing antibiotics would have on human medicine. Achievements in modern medicine, such as major surgery, organ transplantation, treatment of preterm babies, and cancer chemotherapy, which we today take for granted, would not be possible without access to effective treatment for bacterial infections [7].

As an example, of the wider impact of resistance, British scientists have examined the estimate of having no antibiotics on patients having a total hip replacement. Antibiotics are at present used preventatively in such operations, and for treatment if an infection occurs. Infection rates are currently about 0.5-2%, and nearly all infected patients recover after treatment. Without antibiotics, the infection rate is estimated to be 40-50%, and 30% of infected patients will die. The scientists use this example to show that the increasing resistance may have 'consequences in terms of health service costs and human health which may be unimaginable' [6].

‘Bacteria that we are creating through widespread use of antibiotics in agriculture are increasingly now impacting on human health. There is a link between antibiotic use in farming and increases in resistance in pathogens present in humans. There is a need for greater antibiotic stewardship in agriculture, and for rationalisation of farm use of antibiotics which are particularly prone to causing increased resistance - quinolones and cephalosporins.

My intensive care unit has a footprint of over 10k square meters. Within that unit, we look after 12 patients treated in isolation. These patients all have bacteria. If we changed our system to look after 50 or 100 patients within that same footprint then all those patients would start to share their bacteria and we would find the spread of resistant and abnormal bacteria between those patients very quickly. It’s clear that’s analogous to intensive farming. Such systems are at risk of increasing the problem of antibiotic resistance among animals and humans, which in turn will cost human lives.’

Dr Ron Daniels, Consultant in Critical Care at the Heart of England NHS Foundation Trust; Chair: UK Sepsis Trust; CEO: Global Sepsis Alliance

2

The contribution of farm antibiotic use to antimicrobial resistance

The rise of antibiotic resistance is widely seen by organisations like the European Food Safety Authority, the World Health Organization and the Lancet Infectious Diseases Commission as a consequence of the use and overuse of antibiotics in both human and veterinary medicine [7][8][9][10].

Despite this shared responsibility, attention understandably tends to focus on the continuing overuse of antibiotics in human medicine, where considerable improvements could still be made in many countries. Research in the UK shows that almost half the people who visit their GPs with coughs and colds still expect to be given antibiotics, and that GPs can be concerned that a refusal to prescribe antibiotics will harm the doctor-patient relationship [11] [12]. A Health Protection Agency survey found that a quarter of people who are prescribed antibiotics don't finish them, and a Welsh study concluded that approximately 1.6 million unnecessary prescriptions were made each year in the UK [11][13]. Infections in people who have taken antibiotics in the last six months are twice as likely to be resistant, so reducing unnecessary antibiotic use would have major benefits [11].

The situation in some developing countries is even more alarming. Antibiotics, including those which should be reserved for second- or third-line treatment of serious infections are on general sale, sometimes produced illegally and not full strength. Often the poor cannot afford to pay for a complete course, so they buy just a few tablets which are insufficient to kill off all the infectious bacteria, leaving the more resistant ones to proliferate. Then, due to the high level of international travel today, new types of antibiotic resistance in one country can spread worldwide within just a few years [14].

For a wide range of human diseases it is clear that the use and overuse of antibiotics in human medicine, and not farm animals or companion animals, is the cause of increasing resistance. This includes, for example, the spread of multi-resistant tuberculosis and the emergence of resistance to the antibiotics of last resort, the carbapenems (as these are not licensed for use in farm animals).

Because of this, however, there is a tendency amongst some sections of the intensive livestock industry and even some governments, to dismiss the contribution from veterinary use almost entirely. In the UK, a Defra advisory committee has considered how cross-departmental government action could be used to counter media stories suggesting that farm antibiotic use could cause problems for people [15].

'A way forward would be to acknowledge that human health, animal health, and the environment are all interlinked, and that the responsibility for dealing with the problems of resistance is shared by all stakeholders.'

Lancet Infectious Diseases Commission [7].

In a Parliamentary debate in the UK in 2013 on the link between farm antibiotic use and resistance in human medicine, initiated by Zac Goldsmith MP, the then Parliamentary Undersecretary for Health, Anna Soubry MP remarked: 'As individuals and parents, we all should be concerned... about what we eat and what we feed our children and loved ones. This is as much a public health issue as an animal welfare issue.' She acknowledged that 'there are a number of areas that require attention and more radical thinking' by the government. She then correctly stated that:

'There is scientific consensus that the use of antimicrobials[1] in human medicine is the main driving force for antimicrobial-resistant human infections' [16].

However, this is not the whole story. While antibiotic use in animals may not be the main driver of resistance in humans, use in farm animals (and to a lesser extent use in companion animals) is a very important contributor. For some human diseases it is actually the main cause of resistance. Despite this, the Minister continued by saying:

'There is no conclusive scientific evidence that food-producing animals form a reservoir of infection in the UK. Food is not considered to be a major source of infections resistant to antibiotics.'

The Minister made it clear that her notes were in part provided by Defra, where the Veterinary Medicines Directorate (VMD), a largely industry-funded executive agency of Defra, is responsible for antimicrobial resistance. The statement was clearly a reflection of VMD's position statement on antibiotic resistance which fails to recognise explicitly that farm antibiotic use contributes to resistance problems in humans [17].

George Eustice MP, the Under-Secretary of State for Farming, Food and Marine Environment, repeated a similar message to the Science and Technology Committee's enquiry into antimicrobial resistance, saying during oral evidence that 'We think the evidence suggests that actually antimicrobial resistance on antibiotics used in humans tends to be distinct from those used in veterinary practice. While there is a potential for crossover, the evidence so far is that there is not a huge amount of crossover' [18].

In this respect, Defra's position is increasingly out of step with a broader European perspective as reflected by reports from the European Food Safety Authority (EFSA) and the World health Organisation (WHO) [8][9].

Although absolute proof of cause and effect in this field can be extremely difficult to establish because so many of the same antibiotics are used in both veterinary and human medicine, scientists have established a clear link between antibiotic use in farm animals and resistance in humans.

[1] Antimicrobials are substances which kill or inhibit the growth of micro-organisms such as bacteria, fungi or protists. Antimicrobials can be synthetic or naturally produced by other micro-organisms.

In particular, the scientific evidence shows that:

1. For some major human bacterial infections, such as *Salmonella* and *Campylobacter*, farm animals are the most important source of antimicrobial resistance.
2. For certain other human infections, such as E. coli and enterococci, there is strong evidence that farm animals are an important source of antibiotic resistance.
3. For some infections, like MRSA, there is evidence that in the UK the farm use of antibiotics currently makes a small contribution to treatment problems in human medicine. But based on the experiences in some other countries, this contribution may increase significantly unless we take decisive action very quickly.
4. For a further small number of antimicrobial-resistant infections, such as *Neisseria gonorrhoeae*, there is as yet no evidence of any link with farm antimicrobial use at all, yet there is a solid theoretical case that the horizontal transmission of resistance genes of farm-animal origin could contribute to the rise of potentially untreatable cases in humans. This would be such a serious and quite possibly irreversible development that precautionary action without waiting for evidence would be wise, even if the probability of the worst-case scenario is only moderate.
5. For many other infections, such as multi-drug resistant tuberculosis and the wide range of infections caused by antibiotic-resistant strains of *Streptococcus pneumoniae*, the use of antibiotics on farms plays no part in the resistance problem in human medicine.

Antibiotic-resistant bacteria of farm-animal origin can pass to humans in a number of ways, principally on food, but also by direct contact and through the environment. Resistant bacteria can and also pass from humans to farm animals. Here they can multiply and acquire additional resistance genes, then pass back to humans.

In each case, the resistant farm-animal bacteria can contribute to higher levels of resistance in human infections in two main ways:

- they can directly cause an infection in humans, and this infection will be antibiotic-resistant.
- they can colonise the human gut (and potentially other sites such as the nares) without causing an infection, and pass on copies of their resistance genes ('horizontally') to bacteria already living in the human gut. The human-adapted bacteria receiving the resistance genes may subsequently, possibly at a much later date, cause an infection, if they get into the wrong part of the body (e.g. a urinary-tract infection). In this case, the pathogen will be of human origin, but its resistance will originate (either wholly or partly) from the farm use of antibiotics.

Tracing the origin of the resistance tends to be much easier in the first scenario, as when foodborne bacteria cause immediate outbreaks of infection in a significant number of people at once, scientists can frequently trace the source of the infection to a particular food, often meat.

In the second scenario, establishing the origin of the resistance tends to be more difficult and can involve molecular studies examining resistance genes and associated genes such as plasmids[2], rather than just comparing bacterial strains. The Minister said in the Parliamentary debate that 'The majority of resistant strains affecting humans are different from those affecting animals', but differences in strains does not always mean that the resistance is not of farm-animal origin, due to horizontal gene transmission.

[2] A plasmid is a small loop of DNA, which is separate from the bacterium's chromosome, and which can carry antibiotic-resistance genes. Copies of resistance plasmids, sometimes with more than one resistance gene can be transferred between bacteria, making the recipient bacteria resistant to all the corresponding antibiotics.

[3] The resistance profile is the list of antibiotics to which a bacterium is resistant.

A factor complicating the detective work is that human antibiotic use can add to the resistance profile of some bacteria, which may already be resistant to certain antibiotics due to earlier farm antibiotic use. The fact that some of the resistance in this case will be due to human use does not detract from the fact that a possibly large amount of resistance to vitally important medical antimicrobials in these bacteria may initially come from the use of similar, or identical, drugs in livestock production.

Companion animals can also be a source of resistant bacteria which infect humans, and there is a significant amount of resistance which can be transmitted from humans to animals as well. Transmission is often by direct contact, and this is a particular problem with MRSA which can be easily passed on in this way [19]. Although overall antibiotic use is much lower in companion animals than in the high-consuming farm species like pigs and poultry [20], efforts should nevertheless be made to ensure that unnecessary use is avoided.

The WHO has summarised the situation by saying:

'Since this resistance has no ecological, sectoral or geographical borders, its appearance in one sector or country affects resistance in other sectors and countries. National authorities, veterinarians, physicians, patients and farmers all have key roles in preserving the power of antibiotics. The prevention and containment of antibiotic resistance therefore requires addressing all risk factors for the development and spread of antibiotic resistance across the full spectrum of conditions, sectors, settings (from health care to use in food-animal production) and countries' [9].

In addition to the genuine scientific difficulties in establishing certainty on the origin of some antibiotic resistance, it is important to recognise that commercial interests may influence the debate. In the UK, the Responsible Use of Medicines in Agriculture Alliance (RUMA), an alliance representing the interests of the pharmaceutical and intensive-farming industries which is opposing attempts to ban the routine preventative use of antibiotics in farming, has dismissed the claim that the overuse of antibiotics in intensive farming adds to the serious public-health threat from antibiotic resistance as a 'myth', despite the wealth of evidence to the contrary [21].

Furthermore, although government scientists have produced many high-quality studies over the past decades examining the farm resistance issue, government officials recognise that implementing significant restrictions on antibiotic use in farming could increase costs. A report published last year by Defra and Department of Health scientific advisors and officials argued against taking too many measures at an EU level, saying this could put EU farmers at a commercial disadvantage leading to more imports [22].

They warned that costs might increase because, they claimed, fewer animals might survive, but also because 'livestock have to be kept more extensively or in better buildings to minimise risks of becoming infected, such as avoiding pneumonia by building better designed, well-ventilated buildings'. The report concluded that 'Unless consumers are prepared to pay a premium for food produced by means designed to lower the risk of transmitting antimicrobial resistance (while not compromising animal welfare) the potential for unintended consequences of certain measures that may be used to control antimicrobial resistance is high'.

As a result, despite accepting that improving the conditions in which animals are reared can result in significant improvements in antibiotic use, Defra officials largely continue to support the status quo.

‘The common goal should be to preserve the effect of antimicrobials for future generations of human beings, but also for animals. Antimicrobials should only be used when needed. In the case of animals, this means that growth promotion and routine prevention with antimicrobials also used for treatment should be phased out, as recommended by the Swann Committee.’

Lancet Infectious Diseases Commission [7].

3

A history of government failure to reduce farm antibiotic use

In September 2013 the government published its UK Five Year Antimicrobial Resistance Strategy (2013 to 2018). Although the new strategy takes a "'One-Health' approach, which spans people, animals, agriculture and the wider environment", it fails to include any specific recommendations for reducing farm antibiotic use [23]. The strategy contains only general advice that farmers and vets should use antimicrobials responsibly, but is leaving it to the industry to decide what is, and what is not, responsible.

The Strategy does recognise that 'use of antibiotics in animals is an important factor in contributing to the wider pool of resistance', but it sets no targets for reducing overall antibiotic use or the use of antibiotics classified as critically important in human medicine (the fluoroquinolones and the modern cephalosporins). Critically, it does not include any proposals for phasing out the routine preventative use of antibiotics which frequently occurs in intensive livestock farming.

This distinct lack of ambition means that the strategy is in danger of repeating a pattern failing government strategies which has held since the Swann Committee published its influential report in 1969 [24]. The Committee was established by the then government after serious outbreaks of multi-drug resistant *salmonella* food poisoning were linked to the use of antibiotics in livestock production. It recommended that all antibiotics which were important in human medicine should be banned as growth promoters in farming.

As a result, in the early 1970s the use of penicillin and tetracyclines were banned as growth promoters. The same antibiotics, however, could still be added for routine disease prevention or treatment to animal feed or water, frequently at the same doses as used for growth promotion, and for long periods of time, so long as a veterinary prescription was obtained. This loophole meant that the use of these antibiotics in animal feed continued to increase, despite the Committee's intentions. By 2012, the farm use of penicillin-type antibiotics (beta-lactams) had increased five-fold since the growth-promoter ban, and the use of tetracyclines had increased ten-fold. See Table 1.

Table 1

UK Farm use of beta-lactams and tetracyclines before and after the ban on using these antibiotics as growth promoters (tonnes active ingredient)

	Beta-lactams	Tetracyclines
1966	16.8	19.6
2012	82	187

Source: Swann report and VMD statistics [20][24].

Similarly, in 1999 the then government's Advisory Committee on the Microbiological Safety of Food (ACMSF) published a report which recommended that the government develop 'a coherent strategy aimed at reducing the veterinary use of antibiotics', a recommendation that was accepted [25]. However, other than implementing the EU ban on all remaining antibiotic growth promoters, no significant new policies were developed which might have reduced usage levels.

As a result, in the early years of the 21st century, although total farm antibiotic use did fall (from 494 tonnes of active ingredient in 1999 to 384 tonnes in 2008), this was overwhelmingly due to a 35% fall in the pig population (pigs are the species which consumes most antibiotics), rather than any significant improvement in use per animal. In more recent years, falls in livestock numbers have been much smaller and there have been no further falls in antibiotic use. See Table 2.

Table 2

UK Total veterinary antibiotic use (tonnes of active ingredient)

2008	2009	2010	2011	2012
384	402	447	346	409

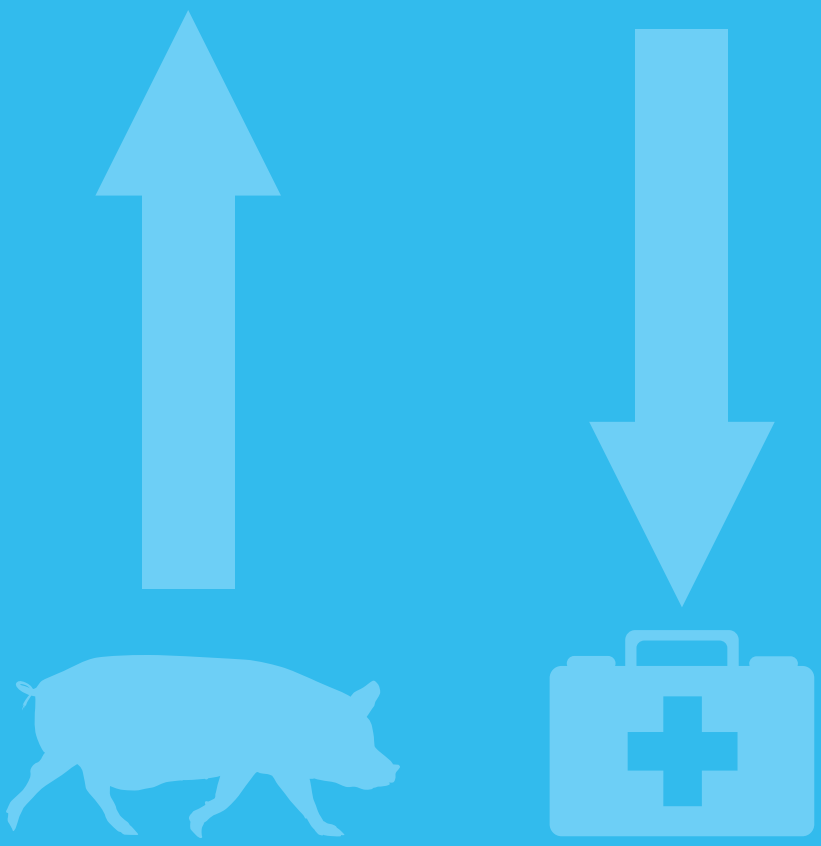
If this latest government strategy is not to also fail, the key issue which will need to be tackled is the routine preventative use of antibiotics, particularly in pig and poultry farming, but also in dairy farming.

It might appear encouraging, therefore, that the government, the VMD, and even the industry representatives RUMA, have all declared their opposition to using antibiotics for routine prevention [18][26][27][28]. However, at present the government has refused to legislate, and has merely committed itself to strengthening guidance on preventative use [27].

Despite this lack of effective action, George Eustice, the Under-Secretary of State for Farming, Food and Marine Environment, has claimed regarding the preventative use of antibiotics in animal feed, that 'some progress is being made in reducing that', even though the statistics show that no significant progress is being made [18].

During an evidence session to the Science and Technology Select Committee Inquiry on antimicrobial resistance, on 12th March 2014, he said that antibiotics 'tend to be used, I think, more sparingly in the veterinary world than in the medical world'. From the data that are available, this is untrue.

The Government's position is in line with RUMA's opposition to any ban on routine preventative use. Despite issuing guidelines which state that routine prevention should not occur, RUMA strongly criticised an Early Day Motion which was aimed at phasing out routine preventative use [29].



Farm use of critically important antibiotics is rising while medical use is reducing

4

Farm use of critically important antibiotics is rising while medical use is reducing

Modern cephalosporins (3rd and 4th generation cephalosporins) and fluoroquinolones are two of the most important classes of antibiotics used in human medicine, and have been classified by the WHO as critically important in human medicine.

The increasing use of these antibiotics in agriculture over the past decade is widely recognised to have contributed to the emergence of a range of highly resistant bacteria in farm animals, such as ESBL *E. coli*, ESBL *Salmonella*, fluoroquinolone-resistant *Campylobacter* and MRSA.

Statistics in the UK from the Veterinary Medicines Directorate show that, after fluoroquinolone use was cut significantly in 2000 following warnings in a report by the House of Lords Committee on Science and Technology in 1998 and a report by the Advisory Committee on the Microbiological Safety of Food in 1999, the use of both fluoroquinolones and modern cephalosporins has increased in most years since then.

In 2009, the British Veterinary Association issued an 8-point plan for limiting the development of antibiotic resistance in farm animals. One of its recommendations was that vets should keep the fluoroquinolones and modern cephalosporins in reserve and only use them in very limited situations. The Summary of Product Characteristics of many of these antibiotic products have also been amended to discourage overuse. Unfortunately, the government has refused to introduce more restrictive legislation, as has been done in some other countries, and use continues to rise.

In contrast, in human medicine the use of these antibiotics has fallen sharply in recent years. This appears to have occurred as a result of the Health Act 2006 which introduced a requirement for all NHS Trusts to have antibiotic-prescribing policies. The Act put a particular emphasis on reducing the use of certain antibiotics, including the fluoroquinolones and modern cephalosporins, which are known to promote and exacerbate *C. difficile* infections. The focus on better antibiotic prescribing as a means for reducing these infections was re-enforced in the Health and Social Care Act 2008.

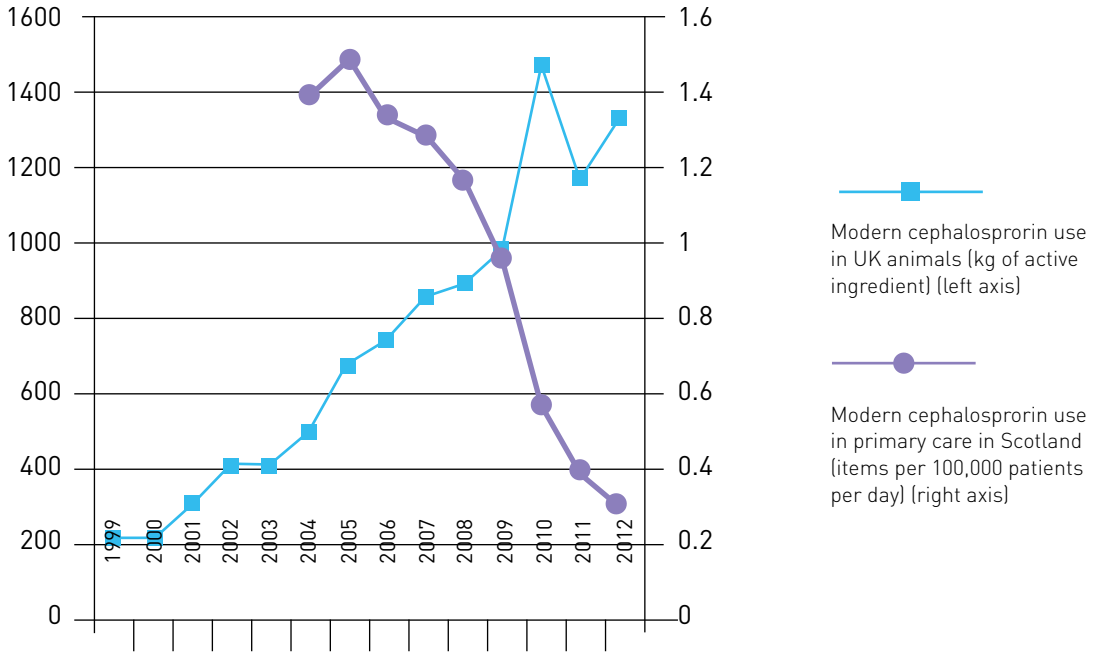
Graphs 1 and 2 illustrate how farm use of these antibiotics has continued to soar even while human medical use is being cut back[4].

'Resistance [in the foodborne zoonotic bacteria *salmonella* and *campylobacter*] is clearly linked to antibiotic use in food animals, and foodborne diseases caused by such resistant bacteria are well documented in people. Of special concern is resistance to so-called critically important antibiotics for human medicine. ... Antibiotic resistance ... has been associated with more frequent and longer hospitalization, longer illness, a higher risk of invasive infection and a twofold increase in the risk of death ...'

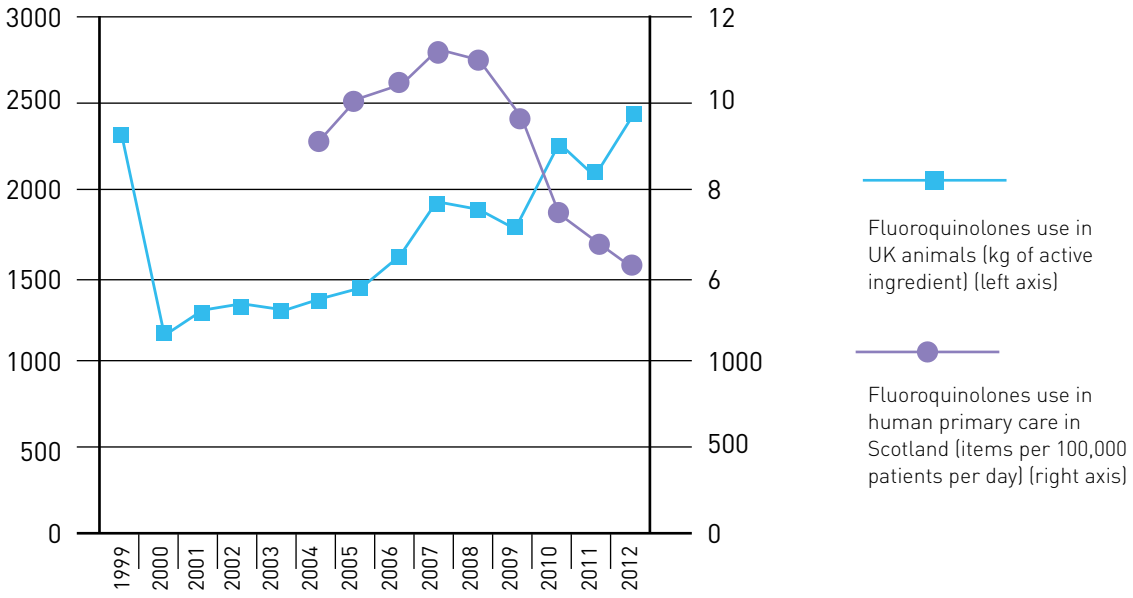
World Health Organisation, 2011

[4]For human medicine, Scottish statistics are used as only Scotland publishes annual statistics on human use of these antibiotics, but similar trends apply throughout the UK.

Graph 1 Human and veterinary use of modern cephalosporins



Graph 2 Human and veterinary use of fluoroquinolones



‘People are getting seriously ill and are dying as a result of skin infections and diarrhoea. Common surgeries like knee replacement will become potential killers because of secondary infections that are untreatable. This is a global problem on par with, if not more serious than, nuclear security, international terrorism and climate change.’

Minister of Health of the Netherlands Edith Schippers, World Health Assembly, 20 May 2014

5

The evidence for a farm animal reservoir of antimicrobial resistance

Human infections where farm antibiotic use is the main source of resistance: *Salmonella* and *Campylobacter*

Salmonella is a food-poisoning infection which often causes outbreaks where a number of people are infected at the same time. Because of this it is generally easy to establish the cause, and there is now a large scientific consensus that most antibiotic resistance in human infections is of farm-animal origin.

Campylobacter infections tend to be more sporadic, making it more difficult to trace their origin precisely. Nevertheless meat, particularly poultry, is known to be a major source of infection, and the emergence of resistance in human infections to certain particularly important antibiotics, such as the fluoroquinolones, followed the introduction of these antibiotics to farming, providing strong evidence of a link [8].

EFSA concluded in its 2008 report, which reviewed the evidence on foodborne antimicrobial resistance, that: 'Resistant *Salmonella* and *Campylobacter* involved in human disease are mostly spread through foods' [8].

The WHO similarly said in its 2011 report on foodborne antibiotic resistance: 'Resistance in the foodborne zoonotic bacteria *Salmonella* and *Campylobacter* is clearly linked to antibiotic use in food animals, and foodborne diseases caused by such resistant bacteria are well documented in people. Of special concern is resistance to so-called critically important antibiotics for human medicine. For example, the use of fluoroquinolones in food animals has led to a corresponding antibiotic resistance in *Salmonella* and *Campylobacter* species, thus causing infections in people. Also, antibiotic resistance in *Salmonella* has been associated with more frequent and longer hospitalization, longer illness, a higher risk of invasive infection and a twofold increase in the risk of death in the two years after infection' [9].

Human infections where farm antibiotic use is an important source of resistance: *E coli* and enterococci

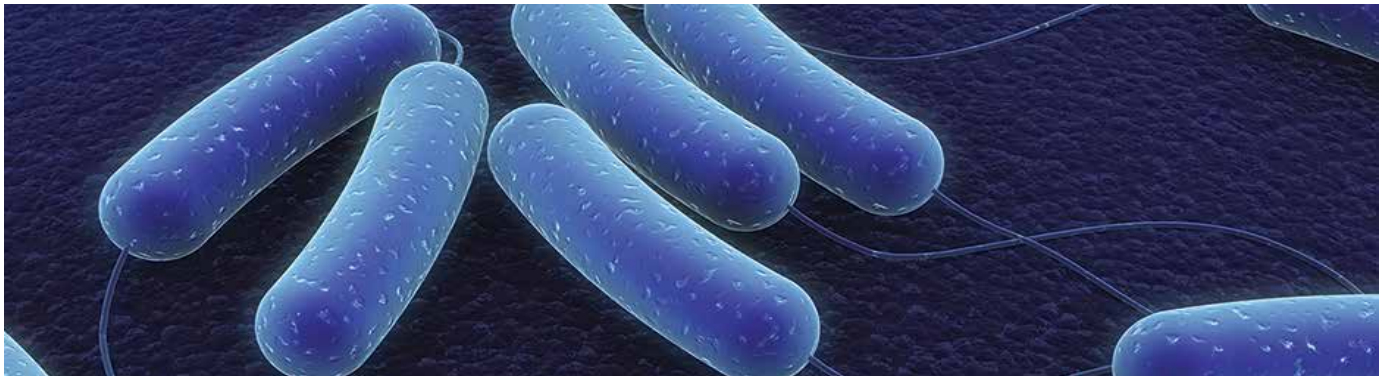
With infections caused by *E. coli* which cause extra-intestinal infections (such as urinary-tract and blood-poisoning infections) and by enterococci which cause kidney and wound infections, the situation is more complicated than for *Salmonella* and *Campylobacter* because farm-animal strains can frequently contribute to resistance in human infections by transferring copies of resistance genes to human-adapted *E. coli* and enterococci in the human gut, rather than by directly causing infections.

In the case of *E. coli*, farm-animal strains, especially those originating with poultry, can also cause infections directly. This may also occur for enterococci, but there is less evidence of this happening.

However, despite the greater scientific difficulties in establishing the source of resistance for these two types of bacteria, in both cases, there is now clear evidence that farm-animal antibiotic use does contribute significantly to levels of antibiotic resistance in human infections.

'Resistant [bacteria] involved in human disease are mostly spread through foods. With regards to *salmonella*, contaminated poultry meat, eggs, pork and beef are prominent in this regard. For *campylobacter*, contaminated poultry meat is prominent. Cattle are a major reservoir for *E coli* [verotoxigenic Escherichia coli] and resistant strains may colonize humans via contaminated meat of bovine origin more commonly than from other foods. Animal-derived products remain a potential source of methicillin-resistant *staphylococcus aureus* (MRSA). Food-associated MRSA, therefore, may be an emerging problem.'

European Food Safety Authority,
9 July 2008



E. coli

Headline coverage of antibiotic resistance in *E. coli* infections inevitably focuses on the most serious emerging forms resistance: extended-spectrum beta lactamase (ESBL) resistance which renders the bacteria resistant to modern cephalosporins, which have for many years been the most important antibiotics for treating cases of blood poisoning, and resistance to carbapenems, drugs of last resort which doctors had until recently managed to hold in reserve, but are now often forced to use in life-threatening cases, because of the growing risk that modern cephalosporins will not be effective.

Resistance to other antibiotics may sometimes be seen as less important because these resistances have been around for longer, however, we have only reached the current critical situation where we are already seeing some untreatable *E. coli* infections because we have allowed a large number of antibiotics over the years to be used far too freely in both human and veterinary medicine, in the latter case most frequently on a routine basis at sub-therapeutic levels over prolonged periods, the very conditions most likely to cause resistance to become a problem. It is important, therefore, to examine the evidence that a significant proportion of the resistance to these earlier antibiotics in human infections has been caused by the farm use of antibiotics, before we look at the particular case of ESBL resistance.

Certain scientists, including some funded by the pharmaceutical industry, have used the fact that some studies have found differences in the strains of *E. coli* which colonise the intestines of farm animals and those which infect humans, to argue that resistance in farm-animal *E. coli* is largely irrelevant to human health [30].

However, this view is now disputed by many scientists, as evidence mounts that a very significant proportion of the resistance in *E. coli* causing urinary-tract and blood-poisoning infections in humans is of farm-animal origin [31][32][33]. There is now compelling evidence that food animals are a reservoir for antibiotic-resistant *E. coli*, colonising or infecting humans, and also a reservoir for resistance genes which can transfer to *E. coli* which can cause infections in humans. This accumulating evidence has led one leading Australian scientist to warn that, with resistant *E. coli*, 'We are what we eat' [31].

The transfer of antibiotic resistance genes from farm-animal *E. coli* to human *E. coli* in the human gut was shown to occur in a study published in 1969 [34]. Since then a number of studies have confirmed the finding, including a study carried out on a Danish pig farm which found that while the *E. coli* from the pigs, the pig farmers and the environment were all genetically different they carried the same resistance plasmid [35].

Danish government scientists believe that taken together, these studies show that: 'The transfer of resistance genes between *E. coli* of animal and human origin in the intestine of humans is very likely' [32].

Some of the strongest evidence that resistance genes in human *E. coli* can originate in farm animals comes from occasions when an antibiotic has been used in veterinary medicine but not in human medicine. The antibiotic nourseothricin was used in pigs in the former East Germany in the 1980s, but no equivalent antibiotic was used in humans during the same period.

Resistance to the antibiotic was first detected in porcine *E. coli*, two years after the introduction of the antibiotic, and later resistance was found in *E. coli* from pig farmers. In subsequent years, resistance was found in *E. coli* and other pathogens, such as *Salmonella* and *Shigella* (the cause of dysentery in humans), from people in the wider community. One scientist from the UK's Veterinary Laboratories Agency commented that: 'These observations strongly support the premise that resistance genes present in the commensal flora of animals can spread to bacteria which can colonize or infect humans' [36].

EFSA has come to a similar conclusion, saying: 'Some categories of food may often be contaminated with *E. coli*, including resistant isolates, and these bacteria reside long enough in the intestines of humans to be able to transfer resistance genes to the residential flora. It is

therefore highly probable that food is a vehicle for spread of resistance genes between different ecosystems' [8].

While most scientists have refrained from claiming their research provides conclusive proof, this is largely because it is not possible to observe under experimental conditions all components of resistance gene transfer and subsequent infection at one time. As such, conclusions have to be based on deduction. The small element of uncertainty introduced by words like 'highly probable' should not be taken to indicate that the incidence of such gene transfer is not frequent or that the implications of this are not significant.

Although there are differences from country to country it is important to note that many of the findings from research in other countries are relevant to the situation in the UK. Some British research has also found evidence of resistance to important antibiotics in human *E. coli* infections originating in farm animals.

In the 1980s and 1990s, for example, government scientists working for the Public Health Laboratory Service (PHLS) produced some strong evidence that resistance to aminoglycoside antibiotics, which have been important for treating *E. coli* infections, was passing from farm animals to humans. By 1994, they said that their findings: 'support the view that resistance to gentamicin and apramycin in clinical isolates of *E. coli* results from the spread of resistant organisms from animals to man, with subsequent inter-strain or inter-species spread, or both, of resistance genes on transferable plasmids' [37].

Given this, and other similar statements by scientists from the Health Protection Agency and the Veterinary Laboratories Agency over the years, it is disappointing that the British Government appears to be so reluctant to acknowledge the significance of farm-animal-to-human transmission of antimicrobial resistance, or to take effective action to limit it.

In addition to the mounting evidence that resistance genes from farm animal *E. coli* can spread to human-adapted *E. coli*, there is also evidence that farm-animal *E. coli*, particularly *E. coli* from poultry, can directly cause infection in humans [31][32]. Two studies carried out in Spain and the United States, for example, have found strong evidence that poultry are a source of antibiotic-resistant human *E. coli* infections [38][39]. The scientists used genetic methods to compare human and poultry *E. coli* and found that human resistant *E. coli* were genetically similar to resistant poultry *E. coli* and that resistant poultry *E. coli* were also genetically similar to sensitive poultry *E. coli*. However, the human resistant *E. coli* were genetically unrelated to the human sensitive *E. coli*.

Both sets of scientists concluded that it appeared that the *E. coli* had evolved to become resistant in poultry, before being transferred to humans. The scientists working in the United States said: 'Many drug-resistant human fecal *E. coli* isolates may originate from poultry, whereas drug-resistant poultry-source *E. coli* isolates likely originate from susceptible poultry-source precursors' [39].

The WHO, commenting on the evidence, has concluded: 'Resistant *E. coli* can spread from animals to people through the food-chain' [9].

Direct evidence of the effect of food on levels of antibiotic-resistant *E. coli* in humans has been provided by a French study. This involved feeding six volunteers a near-sterile diet for an average of 17 days, after an earlier control period of 21 days. During the control period, they were fed their usual diet, and for the sterile-diet period their food was heated to 105º C for one hour, which was shown to be sufficient to destroy any *E. coli* bacteria on the food. The day after the sterile diet began, the number of *E. coli* in the volunteers which were resistant to ampicillin, streptomycin, and tetracycline fell significantly, and it reached a minimum in just three days. For the antibiotic tetracycline, for example, the number of resistant bacteria fell by an average factor of 500. On the other hand, there was a much smaller fall in the number of sensitive *E. coli* (average factor of 3), which was not statistically significant. The scientist concluded that most resistant *E. coli* in the human gut come from food [40].

Although estimating the size of the precise contribution of farm-animal antibiotic use to resistance in human *E. coli* infections has proved more difficult than for *Salmonella* and *Campylobacter* for the reasons detailed above, evidence gathered in recent years has suggested that it is likely to be very significant.

An international study by Australian, Canadian and Danish scientists used data from 11 European countries on levels of antibiotic resistance in human and farm-animal *E. coli*, and antibiotic use in humans. They found strong and statistically significant correlations between resistance to several antibiotics, including critically important antibiotics such as fluoroquinolones and modern cephalosporins, in human *E. coli*, and resistance to the same antibiotics in poultry and pig *E. coli*. They also found that antibiotic use in humans was only correlated with antibiotic resistance in humans for two of the four classes of antibiotics examined.

They concluded that: 'In addition to the contribution of antimicrobial usage in people, a large proportion of resistant *E. coli* isolates causing blood stream infections in people are likely derived from food animal sources' [33].

ESBL *E. coli*

A major cause for concern regarding resistance in *E. coli* has been the emergence over the past decade, in both humans and farm animals, of extended-spectrum beta-lactamases (ESBL) resistance. This is caused by a large family of enzymes which render the bacteria resistant to modern cephalosporins, which are very important treatments for patients who have to be hospitalised with resistant *E. coli* infections. Defra and HPA scientists, and many others, believe that the emergence of these bacteria in farm animals, in the UK and throughout Europe, is partly linked to the increasing use of modern cephalosporins and fluoroquinolones in farming, two antibiotic classes classified as critically important in human medicine by the WHO [41].

A review of the scientific evidence by Defra and Department of Health scientists in the UK, which was published last year recognised only a minor role for farm animals in the emergence of this, but did conclude: 'It is thought that emergence of ESBL bacteria in food producing animals may present a risk of resistant strains being transmitted to humans through the food chain' [41].

In view of the potential importance to human health of the emergence of ESBL *E. coli* in farm animals, it is welcome news that a three-year collaborative research project is to be undertaken by four universities, the AHVLA, Health Protection Scotland and the HPA to provide further evidence of 'the risk to public health posed by ESBLs in bacteria from non-human sources, including the food chain' [42]. However, based on the existing evidence, it would not be justifiable to delay taking effective action to limit the rise of ESBLs in farm animals until this project has been completed.

Many of the ESBL resistant infections in humans are nowadays acquired in the community. According to the Defra/DH ESBL report published last year:

'Whilst initially confined to enterobacteriaceae causing hospital acquired infection, the emergence and spread particularly in the community of Escherichia coli (*E. coli*) strains producing CTX-M ESBLs is a very serious challenge to effective therapy of infections caused by all Gram negative bacteria' [41].

All bacteria are classified as Gram-positive or Gram-negative. *E. coli*, like *Salmonella* and *Campylobacter*, are Gram-negative, whereas *Staphylococcus aureus* and enterococci are Gram-positive.

Not only is the emergence of these bacteria in the community a serious development regarding therapy, it may also be important evidence of a farming connection. In 2005, the HPA published a report on the spread of ESBL *E. coli*, and the author of the report, Dr Georgina Duckworth said:

'The findings in our report show evidence of people carrying these bacteria in their gut. If this is found to be commonplace in the general population this may point towards the food chain being a potential source' [43][44].

At the time of the publication of the HPA report, one study had found that 1.4% (8 of 565) of community-based patients had ESBL *E. coli* bacteria in their faeces, whereas just 0.25% (1 of 394) of hospital-based patients had the bacteria [45]. More recent research, carried out in Birmingham, found that 11.3% of community patients (GP patients or outpatients) had ESBL *E. coli* in their faecal matter [45]. This is a very large increase over earlier findings, and perhaps pointing towards the food chain as a possible source, as Dr Duckworth had suggested. However, it has to be recognized that the Birmingham study may not accurately reflect the national situation and that further more comprehensive surveys are needed.

A key point to note here is that modern cephalosporins are not normally prescribed by GPs, not least because, with only one exception, they are not available in tablet form. They are also not prescribed by veterinary surgeons for companion animals, so where ESBL carriage is found in members of the public who have not been treated with these antibiotics in hospitals, food or farm animals are likely to be the source of the resistance in a significant proportion of cases.

While the evidence for ESBL resistance coming from animals is a major cause for concern, it should also be pointed out that the main epidemic strain of ESBL *E. coli* in humans in the UK, called ST131, is not thought to have a significant farm-animal link. There is, nevertheless, evidence that farm animals may be a source for some of the other ESBL *E. coli* strains causing infection in humans, as well as of various ESBL plasmids.

In the Netherlands, where more research has been carried into ESBL *E. coli* in farm animals than has been the case in the UK (and where levels of ESBL *E. coli* in farm animals are also higher than in the UK), the evidence is even stronger. Scientists there, including Dutch government scientists, found that a very high proportion

(94%) of retail poultry was contaminated with ESBL *E. coli*, and that 39% of these bacteria belonged to strains causing human infections. They said that:

'These findings are suggestive for transmission of ESBL producing *E. coli* from poultry to humans, most likely through the food chain' [47].

Other Dutch scientists also found a proportion (80%) of retail poultry had ESBL bacteria and that the predominant ESBL genes in poultry meat and in human rectal samples were identical. They said:

'These findings suggest that the abundant presence of ESBL genes in the food chain may have a profound effect on future treatment options for a wide range of infections caused by gram-negative bacteria' [48].

Further Dutch research published confirmed that 40% of human ESBL *E. coli* were 'chicken-meat isolates'. The scientists said that:

'Therefore, chicken meat is a likely contributor to the recent emergence of ESBL *E. coli* in human infections in the study region. This raises serious food safety questions regarding the abundant presence of ESBL *E. coli* in chicken meat' [49].

A more recent, study, however, has challenged some of these findings. Using a more sensitive method of comparing bacteria (whole genome sequencing), Dutch scientists found that contrary to what had been found in earlier studies, the human and poultry *E. coli* strains were different. The plasmids, however, are frequently the identical, and the scientists acknowledged that horizontal gene transfer of these plasmids between the strains was likely to be occurring .

EFSA has also concluded that genetic similarities between certain ESBL plasmids found in farm animals and in humans 'strongly suggests an animal reservoir for this ESBL gene variant' [59]. These particular ESBL plasmids are very common in human infections in some countries, but less common in the UK.

Enterococci

For enterococci, there is less evidence that farm-animal strains cause infection directly in humans, but they can transfer their resistance genes to human enterococci. EFSA says: 'While the direct clinical infection in humans by VRE [vancomycin-resistant enterococci] from food sources apparently is rare although not totally excluded as a possibility, the reservoir of VRE in food-producing animals presents a definite risk of resistance genes being transferred to virulent human strains through food and other routes' [8].

Avoparcin was an antibiotic growth promoter, widely used in pigs, poultry and cattle in the UK and throughout Europe. It is chemically very closely related to vancomycin, an extremely important hospital antibiotic for treating MRSA and enterococcal infections.

The first evidence that the widespread use of this antibiotic on farms was leading to resistance problems was produced by British scientists working at the University of Oxford: they isolated vancomycin-resistant enterococci (VRE) from pig herds and from uncooked chickens [51]. Soon after, German scientists found that VRE could be isolated from pigs, poultry and from humans in the community [52][53]. In contrast, in the United States, where avoparcin had never been licensed as a growth promoter, VRE was not found in people in the community, nor in farm animals [53][54][55].

Concerns about VRE being transmitted from farm animals to humans were a major reason for the EU ban on the growth promoters. Avoparcin was the first growth promoter to be banned throughout Europe in 1997, after first having been banned in Sweden in the 1980s, in Denmark in 1995 and then in Germany in 1996.

In hindsight, the ban appears to have had the desired effect, according to data collected in some countries (the UK and many other countries did not collect the data which would have enabled the ban's effect to be evaluated). In Germany, the incidence of VRE on poultry meat fell from 100% in 1994 to 25% in 1997, and in faecal samples taken from people in the community it fell from 12% in 1994 to just 3% in 1997 [53][56]. In Denmark, VRE prevalence in poultry fell from 82% in 1995 to less than 5% in 1998 [57], and in the Netherlands VRE prevalence fell sharply between 1997 and 1999: from 80% to 31% for broilers, from 34% to 17% for pigs and from 12% to 6% for humans [58].

Referring to some of these findings, the WHO said in their 2011 report that: 'Data have shown that this intervention resulted in reduction of vancomycin-resistant enterococci in food animals and the general population' [9].

Human infections where there is compelling evidence that farm antibiotic use in the UK contributes to a small, but likely increasing, proportion of resistance

MRSA are strains of *Staphylococcus aureus* with resistance to beta-lactam antibiotics, and often resistance to other antibiotics as well. Strains of MRSA have emerged in farm animals in recent years, and unlike many strains of *Staphylococcus aureus* of farm-animal origin, these livestock-associated MRSA strains can colonise and multiply on most species, including humans. The most common of these, MRSA ST398, was first detected in the Netherlands in 2005 [60].

The spread of MRSA ST398 throughout Europe's pig population in particular (it is also present in poultry and cattle), is recognised to have led to a growing number of these infections in humans. This strain now accounts for approximately 39% of human cases of MRSA in the Netherlands [61]. Although farmers and those in direct contact with livestock are those most at risk, MRSA ST398 can also sometimes pass from human to human. Consumers of meat contaminated with MRSA are not thought to be at great risk, but further research is needed to clarify this.

Most MRSA infections in humans in the UK currently have nothing to do with agriculture, but the recent detection of a small number of cases of MRSA ST398 and other types of MRSA in British cattle is cause for concern [62]. Livestock-associated MRSA have already caused infections in humans in the UK, and experience from abroad suggests that, for MRSA ST398 in particular, there is a real danger that it will spread widely in livestock unless changes in farm antimicrobial use are introduced urgently.

Several further types of MRSA are now emerging in pigs in Europe, North and South America, and Asia, and some of these are epidemic human strains which are thought to have transferred initially from humans to animals [63][64][65]. If these strains become widespread on farms, there is a real danger that livestock will become a very important reservoir of human MRSA infections.

It is worth noting how quickly the livestock-associated MRSA problem has emerged. Less than ten years ago, MRSA had never been detected in pigs, and the very small number of cases found in other farm animals were believed to have been incidental transfers from humans.

More recently, MRSA has been found in abattoir studies in 61% of Spanish pigs, in 60% of Germany pigs and 39% of Dutch pigs [66][67][68]. The emergence of this problem, like the emergence of the highly resistant ESBL *E. coli*, is believed by scientists to be particularly linked to the increased use in farming of modern cephalosporins, which are classified by the WHO as critically important antibiotics in human medicine [69][70].

Human infections for which there is currently no evidence that the farm use of antibiotic is contributing to resistance but where theoretical considerations suggest this could happen

Modern cephalosporins are first-line treatments for gonorrhoea, and Health Protection Agency scientists have warned that any emergence of resistance to these antibiotics would be a 'catastrophic development' [71].

As mentioned above, resistance to modern cephalosporins, in the form of ESBL resistance, already occurs in *E. coli* from humans and farm animals, and HPA scientists are worried that this resistance could transfer in the genitourinary tract from *E. coli* to *Neisseria gonorrhoeae*. They say that at the moment, in the UK, most cases of ESBL *E. coli* occur in older patients in the community. However, they point out that studies from abroad, in Canada and Hong Kong, are finding significant levels of ESBL *E. coli* in women of all ages.

The scientists say: 'Rising rates of *E. coli* with CTX-M ESBLs [a type of ESBL resistance]in the genitourinary tracts of sexually active women raise the alarming possibility that these enzymes might "escape" into sexually transmitted bacterial pathogens, specifically *Neisseria gonorrhoeae*' [71].

Since it is known that the presence of ESBL *E. coli* in farm animals and on food is contributing to the presence of these bacteria in the human gut, the use of these antibiotics on farms is increasing the risk that ESBL genes will eventually spread from *E. coli* to *Neisseria gonorrhoeae*.

‘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.’

European Medicines Agency, 2006

Recommendations

In addition to action on inappropriate antibiotic use, overall farm antibiotic use must be reduced. This is widely recognised as the most likely strategy which will slow, or even reverse, the growth of antibiotic resistance.

The European Union has already taken some welcome action aimed at reducing the veterinary use of critically important antibiotics, particularly the modern cephalosporins. However, much more remains to be done [73]. Industry initiatives tend to promote 'biosecurity' and hygiene, which can have some benefits. However, British research has shown that disinfectants can also 'co-select' for antibiotic resistance [74].

Some of the most important elements of a truly effective strategy would be:

1. A legally binding timetable to phase out routine prophylactic use of antibiotics.

Some European countries, like the Netherlands and Denmark, have already banned routine preventative use, but in the UK it remains legal to administer antibiotics to groups of animals even when no disease has been diagnosed in any of the animals. In particular, the use of antibiotics in hatcheries (in ovo and on day-old chicks) is clearly routine prophylactic use, and a ban on it should be imposed without delay.

2. All veterinary antibiotics should be classified as first, second and third choice, according to their importance for treating antibiotic-resistant infections in humans and animals.

Only first-choice antibiotics should be permitted for empirical treatment. Second-choice antibiotics should only be prescribed if susceptibility testing or information previously gathered about on-farm resistance profiles demonstrates that first-choice antibiotics would not work. Similarly, third-choice antibiotics should only be permitted if it is shown that first or second-choice antibiotics would not work. A system like this is currently in operation in the Netherlands [75].

3. A ban on the use of modern cephalosporins in pigs and for dry-cow therapy should be introduced.

Danish, Dutch and French pig producers have already introduced voluntary bans on the use of modern cephalosporins [76]. Dutch dairy farmers have also already introduced a voluntary ban on the use of modern cephalosporins for dry-cow therapy. According to the Dutch Chief Veterinary Officer, these voluntary bans have contributed to a 92% reduction in the Dutch farm use of these antibiotics between 2009 and 2012 [77].

4. A ban on all off-label farm use of modern cephalosporins should be introduced.

The risk of ESBL resistance and MRSA transferring from farm animals to humans is too great to permit use of these antibiotics in animals which is not fully regulated. A number of highly important human medicines, such as carbapenems, tigeclycline, daptomycin, oxazolidones, mupirocin and vancomycin should also be banned from all veterinary off-label use, whether in farm animals or companion animals.

The important element which I think gets lost in discussions about a post-antibiotic era, is that antibiotics allow modern medicine. So only because we can treat infections, can we treat cancer - because the treatments we give people to treat cancer cause them to get infections. Major surgery relies on antibiotic prophylaxis to prevent post-operative infections.'

Dr Robin Howe, Head of the Welsh Antimicrobial Resistance Programme, 24 Oct 2013

5. A ban on the use of fluoroquinolones in poultry should be introduced.

Fluoroquinolones are critically important antibiotics in human medicine because of their importance for treating infections such as *Campylobacter*, *Salmonella* and E. coli. Poultry are recognised as an important source of these infections in humans, and in the case of *Campylobacter* are by far the most important source. The United States banned the use of these antibiotics in poultry for that reason [78].

6. New legislation should be introduced as part of an EU-wide antimicrobials strategy aimed at improving animal health and welfare and ensuring that farm animals are kept in less-intensive conditions with, wherever possible, access to the outdoors.

It is essential that a farm-animal health and welfare strategy should be recognised as a key tool in helping to address the rise of antibiotic resistance. Improving animal health through increased animal welfare, better system design and the selection of breeds that are less susceptible to disease can dramatically reduce the need for antibiotics. There are a number of studies finding significantly lower use of antibiotics and correspondingly lower levels of antibiotic-resistant bacteria in organically farmed animals, and both the Belgian and Danish governments are beginning to require reductions in livestock stocking density in order to reduce the use of antibiotics [76] [79].

7. Improved surveillance of antibiotic use and antibiotic resistance is needed.

Prescription data should be collected so that statistics can be published on the use of each antibiotic class in each animal species and so that high users and prescribers can be identified. Mandatory surveillance for livestock MRSA should be introduced.

What you can do

To support our campaign, your organisation can join the Alliance to Save Our Antibiotics. To become a Supporter Member of the Alliance is completely free of charge. Your organisation's name would appear in a list supporting our aims and campaign demands (see Recommendations above), and you would be contacted with key news about four times a year, or when campaign developments are critical. You would also receive invitations to meetings for our Supporter Members. Contact: acraig@saveourantibiotics.eu

For the history of the campaign and all other documents see:

www.soilassociation.org/antibiotics

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Glossary 1 - technical terms

Antimicrobials	Drugs, chemicals, or other substances - synthetic or naturally produced by other micro-organisms - that either kill or slow the growth of microbes. They are most commonly used to prevent or treat disease and infections due to micro-organisms. Antimicrobial agents include antibacterials, antibiotics, antivirals, antifungals, and antiparasitic drugs.
Antibiotics	Antibiotics were originally defined as antimicrobials which are naturally produced, although the two terms are often now used interchangeably. The majority of antibiotics are used to kill or inhibit the growth of bacteria. Antibiotics which are effective against Gram-positive bacteria are called Gram-positive, and antibiotics effective against Gram-negative bacteria are called Gram-negative. Those which are effective against both Gram-positive and Gram-negative bacteria are called broad spectrum. Narrow-spectrum antibiotics are effective against a more limited range of bacteria. The best-known antibiotic is penicillin, produced from the Penicillium fungi. Tetracyclines, modern cephalosporins and fluoroquinolones are examples of broad-spectrum antibiotics. Antibiotics are not effective against infections caused by viruses.
Bacteria	Bacteria are microscopic, single-celled organisms that are present nearly everywhere, including on our skin and in our gut. In fact there are more bacterial cells inside us, and on us, than human cells: bacterial cells are estimated to outnumber our own cells by 3 to 1. Bacteria make up about 1 to 3 kilos of an adult human's weight, and there are around 10,000 different bacterial species in the human ecosystem. Bacteria in the gastro-intestinal tract allow humans to digest foods and absorb nutrients that otherwise would be unavailable. However, some bacteria are harmful to humans and can cause life-threatening infections and death.
Carbapenems	Carbapenems are a class of beta-lactam antibiotics with a broad spectrum of antibacterial activity. Carbapenems are one of the antibiotics of last resort for many bacterial infections, such as Escherichia coli (*E. coli*) and *Klebsiella* pneumoniae.
Modern Cephalosporins	Modern cephalosporins are Critically Important Antibiotics which are important in the treatment of infections caused by *E. coli*, *Salmonella* or Gonorrhoea.
Critically Important Antibiotics	Antimicrobials are Critically Important if they are: (i) sole therapies or one of few alternatives to treat serious human disease, and (ii) used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources (World Health Organisation, 2007)
Dry cow therapy	Dry-cow therapy is a antibiotic treatment infused up the teats into the udder of dairy cows in order to prevent the occurrence of mastitis. These preventative treatment is given routinely on many dairy farms during the 'dry' period, when dairy cows are 'dried off' to provide a rest period between the end of one lactation (cycle of milk production) and the start of the next.
ESBL *E coli*	Extended-spectrum beta lactamase (ESBL) resistance which renders the *E coli* bacteria resistant to modern cephalosporins.
Fluoroquinolones	Fluoroquinolones are Critically Important Antibiotics. They are broad-spectrum, and effective for both gram-negative and gram-positive bacteria.
Gene	A segment of deoxyribonucleic acid (DNA), inside every cell of every living thing, whether animal or plant, containing the information to build and maintain an organism's cells and pass on traits to offspring.
Gram positive/ negative bacteria	Almost all bacteria can be classified as Gram-positive or Gram-negative. Common Gram-positive bacteria include Streptococcus and *Staphylococcus*. Gram-negative bacteria include *Campylobacter*, *Salmonella*, and those that cause syphilis and gonorrhoea.

Horizontal transfer or transmission	A major cause of increasing antibiotic resistance, whereby genes are transferred between two bacteria by a process which does not involve reproduction, i.e. the genetic information is not passed on by the usual process of descent from a parent.
Last resort, antibiotics of	A drug of last resort is a common name for a pharmaceutical agent that is tried after all other treatment options have failed to produce an adequate response in the patient.
Macrolides	Macrolides are Critically Important Antibiotics. Antibiotic macrolides are used to treat infections caused by Gram-positive bacteria (e.g., *Streptococcus pneumoniae*) and Haemophilus influenzae infections such as respiratory tract and soft-tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and, therefore, macrolides are a common substitute for patients with a penicillin allergy.
Micro-organisms	Any form of microscopic life from algae (plant), bacteria, fungi, to plankton (animal), protozoa (single-cell life forms) and viruses (although some scientists question whether viruses can truly be described as 'living').
MRSA	Multi-resistant Staphylococccus aureus. MRSA are strains of S. aureus with resistance to beta-lactam antibiotics, and often resistance to other antibiotics as well. Strains of MRSA have emerged in farm animals in recent years, and unlike many strains of S. aureus of farm-animal origin, these Livestock-Associated MRSA strains can colonise and multiply on most species, including humans. the most common of these, MRSA ST398, was first detected in the Netherlands in 2005.
Pathogenic	Capable of causing disease.
Plasmid	A small loop of genetic material, not part of the bacterium's chromosome, which can carry antibiotic resistance genes. Copies of resistance plasmids, sometimes with more than one resistance gene, can easily be transferred between bacteria, making the recipient bacteria resistant to all the corresponding antibiotics.
Prophylactic	From the Greek to guard or 'prevent beforehand'. Where drugs are administered to animals or people before they are showing any symptoms of the disease. In the context of antibiotic use in animals, the term preventive is often used synonymously with prophylactic.
Resistance	The ability of bacteria or other microorganisms to survive and reproduce in the presence of antibiotic drugs that were previously effective against them.
Resistance profile	The resistance profile is the list of antibiotics to which the bacterium is resistant.
'Super-bugs'	Strains of bacteria resistant to a number of antibiotics (multi-resistant) and ultimately to nearly all known antibiotics. Examples include: MRSA – resistant to both methicillin and vancomycin; Multi-drug resistant Tuberculosis – which causes TB; VRE – vancomycin resistant *Enterococcus faecalis* – which can infect the digestive system. A recently identified strain of the sexually transmitted disease, gonorrhoea, H041 has been found to be resistant to over 30 antimicrobials, including the cephalosporins.
Viruses	Unlike bacteria, viruses cannot live independently, but require a host organism to reproduce within. Antibiotics are ineffective against viruses. Anti-viral drugs either boost the host organism/person's immunity to viruses or affect the virus's ability to reproduce. HIV and the common cold are viruses.
Zoonotic	Diseases and infections that can be transferred between animals and humans. *Campylobacter*, *E. coli*, MRSA and *Salmonella* are all bacterial infections that can be passed between animals and humans.

Glossary 2 - organisations/acronyms

ACMSF	Advisory Committee on the Microbiological Safety of Food www.acmsf.food.gov.uk	Set up in 1990, this non-statutory committee provides expert advice to government on questions relating to microbiological issues and food
ARHAI	Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection www.gov.uk/government/groups/advisory-committee-on-antimicrobial-resistance-and-healthcare-associated-infection	Scientific committee that provides advice to the government on minimising the risk of healthcare associated infections
DARC	Defra Antimicrobial Resistance Coordination group www.vmd.defra.gov.uk/vet/antibiotic_darc.aspx	The Defra Antimicrobial Resistance Coordination (DARC) Group was set up in 1999 to take forward, within Defra, recommendations made by the House of Lords Select Committee on antimicrobial resistance.
DEFRA	Department for the Environment, Food and Rural Affairs www.defra.gov.uk	Defra is the UK government department responsible for policy and regulations on environmental, food and rural issues.
EFSA	European Food Safety Authority www.efsa.europa.eu	EFSA leads in the European Union (EU) on the risk assessment regarding food and feed safety, providing scientific advice to other bodies including EMEA (below).
EMEA	European Medicines Agency www.ema.europa.eu	Located in London, EMEA is responsible for the scientific evaluation and licensing of medicines - both human and veterinary - produced by pharmaceutical companies for use in the European Union.
NFU	National Farmers' Union www.nfuonline.com	Represents a membership of 55K farmers in the UK.
HPA	Health Protection Agency www.hpa.org.uk	Formerly the lead government agency on infectious diseases, chemicals and poisons, radiation and emergency response for PHE (below), HPA became part of PHE on 1 April 2013.
PHE	Public Health England www.gov.uk/government/organisations/public-health-england	PHE is an executive agency of the government's Dept of Health and its mission is to improve the nation's health and address inequalities. Public Health England was established on 1 April 2013 to bring together public health specialists from more than 70 organisations into a single public health service.
PHLS	Public Health Laboratory Service www.hpa.org.uk	Now part of Health Protection Agency/Public Health England
RUMA	Responsible Use of Medicines in Agriculture www.ruma.org.uk	RUMA aims to promote a co-ordinated and integrated approach to best practice in the use of medicines. Its membership comprises farming and pharmaceutical companies.
VLA	Animal Health and Veterinary Laboratories Agency www.defra.gov.uk/ahvla-en	Animal Health and Veterinary Laboratories Agency (AHVLA) is an executive agency working on behalf of the Department for the Environment, Food & Rural Affairs (Defra), Scottish Government and Welsh Government. The agency was formed on 1 April 2011, following the merger of Animal Health and the Veterinary Laboratories Agency.
VMD	Veterinary Medicines Directorate www.vmd.defra.gov.uk	The body that provides advice to Government Ministers on all aspects of the authorisation and use of veterinary medicines, including farm antibioitics; oversees the regulation, assessment and surveillance of veterinary medicines; and manages the research and development programme of the Department for the Environment, Food and Rural Affairs (Defra). It also co-ordinates Defra's work on antimicrobial resistance via the Defra Antimicrobial Resistance Coordination (DARC) Group.
WHO	World Health Organisation www.who.int	WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters.


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"From a doctor's point of view, I do not believe it is wise to use antibiotics routinely in healthy farm animals. Each unnecessary use of antibiotics increases the pressure on bacteria to develop resistance. The current scientific consensus is that we are running out of antibiotics, and resistance is rising. We risk facing a post-antibiotic era, where bacterial infections in humans may in future no longer be treatable. We are already careful with antibiotic use in humans. The principles of antibiotic use in animals are exactly the same. The potential costs of this to long-term human health are almost unimaginable."

Dr Sara Ritchie GP

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