CASE STUDY OF A HEALTH CRISIS

How human health is under threat from over-use of antibiotics in intensive livestock farming

A report for the Alliance to Save Our Antibiotics

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THE ALLIANCE TO SAVE OUR ANTIBIOTICS

A world without effective antibiotics is a terrifying but real prospect. Indeed, as more antibiotic-resistant strains of bacteria emerge it is not a question of if, but when. A concerted effort could persuade policy-makers to act decisively to hold off this threat. The aim of the Alliance is to enable doctors, vets, farmers, retailers, health and consumer groups to work together to 'Save Our Antibiotics'.

Save Our Antibiotics

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FOREWORD

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It is a surprisingly often-held prejudice that germs are generally bad, and therefore should be eradicated by whatever means possible wherever we find them. However, microbes have been around for billions of years longer than humans and will surely out-survive our species. Without microbes, we would all die. It is therefore essential that humans learn how to live in better synergy with microbes, rather than seeing our fundamentally dependent relationship as adversarial.

Antibiotics have saved numerous lives and have rightly been termed 'wonder drugs'. However, as the social determinants of health have improved in developed countries and as antibiotics have become widely available, more and more antibiotics have been consumed for less and less benefit in many settings. This wastes resources, medicalises self-limiting conditions, unnecessarily increases the risk of unwanted effects, and drives antibiotic resistance.

The reasons for high levels of inappropriate use in human medicine are to be found in a range of health service factors, past experiences, and complex beliefs and attitudes. The challenge is to reserve antibiotics for those who will achieve meaningful clinical benefit and to keep them away from those who are unlikely to benefit.

Some infections have become almost impossible to treat because of antibiotic resistance. The problem is global, with national borders quite porous to microbes and the resistance they transmit. A view of the world as one integrated unit is an essential step in formulating effective solutions to increasing resistance. The alternative is to live in expectation that new antibiotics will be developed 'just in time'. However, the pipeline of new antibiotics does not look promising, especially for agents effective against gram-negative organisms. Antibiotic stewardship is therefore a crucial element in our fight to preserve the precious reservoir of antibiotic susceptibility that humanity has left to it.

A significant contribution comes from over-reliance on routine use of antibiotics in farming. This report outlines how antibiotics have been inappropriately used in intensive farming ['factory farming'] and reveals that many of the challenges facing veterinary medicine are analogous to those in human medicine. For example, there are insufficient well-validated, point-of-care, rapid diagnostic tests to guide decisions about whether and what antibiotic class to prescribe; there is pressure on veterinarians to be proactive rather than conservative, and relationships between farmers and veterinarians can also be a crucial influence on prescribing decisions. As in human medicine, in the absence of clear scientific evidence, decisions favouring prescribing 'just in case' are more likely.

Many research challenges remain around antibiotic use in farming. For example, where are the well-conducted, randomised, controlled trials that should be underpinning many of the antibiotic prescribing decisions faced by veterinarians in their everyday practice? Where are the studies of the complex array of influences on veterinarians' prescribing decisions, and what interventions are effective in promoting evidence-based prescribing for animals?

"Relationships between farmers and veterinarians can be a crucial influence on prescribing decisions."

It is not tenable to regard animal medicine as having marginal relevance to human health. Systems are interlinked; this report describes viewpoints and evidence focusing on one very important complex and intersecting system which, thus far, has been under-emphasised in the broad programme of preserving antibiotic susceptibility. The challenge now is to focus on antibiotic stewardship programmes that take a holistic view, incorporating all domains of antibiotic use.

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In 2006 he won the John Fry Medal, awarded by the Royal College of General Practitioners 'to a younger member of the College who has promoted the discipline of general practice through research and publishing as a practising GP'.

EXECUTIVE SUMMARY

In microbial terms, human medicine is facing a looming threat. Antibiotics are failing to keep pace with the speed at which bacteria are adapting to resist them: the situation is so acute that the Director-General of the World Health Organization (WHO), Dr Margaret Chan, warned on World Health Day 2011 of *"a post-antibiotic era, in which many common infections will no longer have a cure and once again, kill unabated."* (7th April 2011)[1]

In this 'post-antibiotic era', humankind would have no effective antibiotics left with which to treat typhoid, tuberculosis, pneumonia, tetanus, diphtheria, syphilis, gonorrhea or meningitis among others. Such diseases would first become resistant to particular antibiotics and eventually untreatable with all available antibiotics.

Time is running out

Every time a person or animal receives a dose of antibiotics, this is an opportunity for resistant bacteria to develop. The greatest risks arise when humans or animals receive low doses, as this offers ideal conditions for bacteria to hone resistance.

Committees charged to investigate over the past two (and more) decades have raised alarm bells, recommending urgent action to curb low-level use of antibiotics in farming[2, 114]. The world's public-health experts, from the EU, the U.S. and the WHO, are agreed that resistant bacteria are created in food animals by antibiotic use and that these resistant bacteria are being transmitted to people. More recently, high-level public health authorities including the European Medicines Agency and the European Food Safety Authority have stated publicly that it is essential to curb antibiotic use in farming, and the time to act is now, before it is too late. Yet despite this, the veterinary drugs industry and factory-farming lobby continue to dispute the science and oppose major reforms.

This report now pulls together and sets out convincing evidence that over-use of antibiotics in farm animals has already resulted in the following:

- farm animals are breeding grounds for antibiotic-resistant strains of *Salmonella*, *Campylobacter* and *E. coli*;
- farm animals harbour antibiotic-resistant strains of MRSA that could become virulent;

and has contributed to:

- diminishing effectiveness in human medicine of critically important antibiotics such as cephalosporins.

When antibiotics are used in industrial-style farming ('factory farming') at low-level doses across many animals, rather than to treat specific sick animals, this is patently to compensate for the 'sickness-inducing environment'[3] they are kept in. **We assert that such misuse of antibiotics is unnecessary, unethical and irresponsible.**

Numerous studies quoted in this report show that antibiotic-resistant bacteria can be transmitted:

- to people working with animals or raw meat;
- through the food chain itself, from farm to table, if meat or eggs are incorrectly cooked;
- generally through the environment i.e. via the air, water or soil.

Alliance to Save Our Antibiotics

To combat entrenched practice and take on corporately backed lobbying in the industrial farming sector, three established organisations have joined forces to help focus the emerging concerns from consumers, from the health sector, medical sector, veterinary sector and farming sector, and point the way to sustainable change.

- Compassion in World Farming
- The Soil Association
- Sustain

A mask for poor animal welfare

Factory farming accounts for at least 80% of the animals farmed each year in the EU – at least five billion animals (mainly pigs and poultry).[4] This report shows that the underlying reason for food-animal-related antibiotic resistance is the dependence on antibiotics of this type of intensive farming. Animals not in need of treatment are nevertheless dosed with antibiotics to compensate for the suppression of their immune systems – brought on by overcrowding, early weaning, high stress and other aspects of the unnatural production systems in which they are reared.

RESIDUES – A SEPARATE ISSUE

Antibiotic resistance is not to be confused with antibiotic residues in food. Questions remain about official 'safe limits' set for such residues. But the monitoring of residues in animal products may be a smokescreen for a greater danger to human health – antibiotic resistance – examined in this report. For antibiotic residues see Appendix 2.

The Alliance is not calling for a total withdrawal of all antibiotic treatment of animals. On the contrary, we believe it is vital to maintain the effectiveness of antibiotics for treating actual sick animals, and protecting animals during a disease outbreak, so reducing suffering and maintaining good welfare.

PHOTO: © COMPASSION IN WORLD FARMING

The Alliance suggests that antibiotics are being used to prop up a 'sickness-inducing environment', i.e. to prevent animals from becoming sick due to the conditions in which they are forced to live.

TOWARDS A POST-ANTIBIOTIC ERA: THE COUNTDOWN HAS STARTED

The official monitoring agency for antibiotic use on farms in the Netherlands, published in 2007 its own estimate that the average Dutch pig ending up as bacon, ham and pork was on antibiotics for nearly 20% of its life (p10).

A study in the Netherlands found 22 out of 26 meat chicken farms visited had more than 80% of their flock testing positive for antibiotic-resistant *E. coli* (p11).

Dutch pig farmers are 760 times more likely than the general population to test positive for NT-MRSA, a strain of MRSA carried by pigs (p13).

A study of *Campylobacter* bacteria in live chickens in Belgium found over 60% resistant to ciprofloxacin, an antibiotic widely used in human medicine (p18).

Recent research has found that flies and cockroaches on intensive pig farms frequently carry antibiotic-resistant bacteria (p15).

Key recommendations (summary)

1. **An EU-wide reduction strategy**
   The European Commission and Member States must urgently develop a more robust strategy to reduce antibiotic use in agriculture to a minimum. This should be linked to a legally-binding timetable for the phased ending of all routine prophylactic, non-therapeutic use of antibiotics. It should include the following:

- a target to reduce overall antibiotic use on EU farms by 50% by 2015;
- specific controls on the use in livestock of 'critically important' human antibiotics;
- the closing of the loophole whereby antibiotics are still being used as growth promoters in the EU.

2. **Monitoring and reporting**
   What is most urgently needed is a harmonisation across all EU countries of the existing systems of monitoring and reporting, as well as more detailed collection of data on the extent of antibiotic usage, to ensure that the EU is making rapid progress towards reducing antibiotic use on farms.

3. **Vets – support and enforcement**
   Vets would shoulder most responsibility for implementing a reduction strategy. Training should be given in how farmers can protect animals from disease outbreaks without antibiotics i.e. the practice of good husbandry (see *Practical strategies for preventing disease*, p20). Lessons could be learned from the Netherlands, where vets can be fined for inappropriate prescribing of antibiotics in animal feed.

4. **Farmers – support and incentivisation**
   EU agricultural policy should inherently promote a move away from industrial livestock production (factory farming) to forms of animal husbandry that positively improve animal health and welfare, such as extensive grassland rearing and integrated crop-livestock farming (for example, organic systems). There should be financial incentives to shift to higher welfare farming.

5. **Pricing structures**
   Retailers should support the transition by pricing food to reflect the higher welfare and better quality of the product, and pass these premiums directly to farmers.

For *Key recommendations* in full, see page 22.

CHAPTER 1

Antibiotic use in farm animals – history and emerging concerns

"May I ask whether we have all gone mad... to give penicillin to pigs to fatten them? Why not give them good food, as God meant them to have?" Colonel Gomme-Duncan MP, 1953 [5]

Antibiotics are medicines derived from natural substances produced as defence systems by micro-organisms to inhibit or kill competing bacteria (see Glossary for fuller definitions). This capability makes them unique for controlling potentially deadly infectious diseases caused by a large variety of pathogenic bacteria. Health experts universally acknowledge they are a precious resource.

Conserving this precious resource is not easy. The first mass-produced antibiotic, penicillin, derived from the *Penicillium* fungus, is the classic example. Treatment of bacterial infections in people with the then-new wonder drugs penicillin and streptomycin began in the mid-1940s. But resistance to penicillin began to emerge in hospitals within a couple of years of its first public use and between 1947 and 1954 controls were introduced in the UK to restrict the use of antibiotics to therapeutic use on prescription by a doctor, veterinarian or dentist.

First use in farm animals

In farm animals, penicillin was first used experimentally in 1942 – before it was widely available to doctors. Trials in the U.S. and UK had shown that pigs and poultry fed low doses of penicillin or tetracycline grew faster. The practice of using antibiotics for 'growth promotion' was born. Subsequent studies showed that hens laid more eggs, sows produced more surviving piglets and cows gave more milk when given low doses of antibiotics.

By the mid-1950s, a number of antibiotics, including penicillin, were permitted as 'growth promoters' in the UK – although the pharmaceutical companies preferred the more benign-sounding description of 'digestion enhancers'. Growth-promoting antibiotics could be bought and used in animal feed without a veterinary prescription[6] – a practice encouraged by politicians keen to provide their electorates with cheap food.

In 1953, the UK Parliament passed the Therapeutic Substances (Prevention of Misuse) Act – legislation far less effective than its name suggested. While it extended the controls already in existence on the therapeutic use of penicillin, streptomycin and chlortetracycline, it opened the door to unrestricted use of penicillin and chlortetracycline in the feed of pigs and poultry for growth promotion – without veterinary prescription. The Bill had an easy passage through Parliament, with only one MP, Colonel Gomme-Duncan, raising strong concerns.

The then UK Minister for Health Iain Macleod, confidently brushed aside any voices of disquiet: *"I am assured by the Medical Research Council …that there will be no adverse effect whatever upon human beings"*,[7] an assurance which nearly 60 years on, has proved to be dangerously hollow. During the 1960s, a series of major

AVOPARCIN – ROUTE OF RESISTANCE

From 1993 onwards, scientists in the EU started to find increasing numbers of otherwise healthy people carrying the superbug Vancomycin Resistant *Enterococci* (VRE),[14] which affects patients with kidney problems. There was also concern because vancomycin is the most important antibiotic for treating people infected with the superbug MRSA.

Meanwhile in the U.S., the VRE bacteria were found only in hospitals where vancomycin was used regularly, and not in the wider community. How could resistance have developed in bacteria outside the healthcare setting, and why was it only found in the EU?

The answer lay in a closely-related antibiotic, avoparcin, that had been used widely in the EU as a growth promoter in poultry. As avoparcin had never been authorised for use in U.S. agriculture, scientists concluded that the community VRE in Europe had been caused by avoparcin use in intensive poultry production,[15] probably through gene transfer in the gut of people who had ingested resistant animal *Enterococci*.[16]

The European Food Safety Authority acknowledges that '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'.[17]

Avoparcin was banned by the EU in 1997.

outbreaks of *Salmonella* led to thousands of people being hospitalised and resulted in the deaths of at least four children. The world's first recorded strain of multi-drug-resistant *Salmonella* was attributed to irresponsible use of antibiotics on farms and a joint committee was set up under Professor Michael Swann to investigate.[8]

It is clear from its recommendations put to Government in 1969 that the Swann Committee wanted to ban all non-essential use of medically important antibiotics in agriculture.[9] However, in the end, the Government succumbed to industry pressure and accepted that those antibiotics which had little or no application as therapeutic agents in man or animals could be used (without prescription) for growth promotion purposes. Antibiotics that *were* for therapeutic use were required by law to be prescribed by a vet.

The Committee had also advised that advertising antibiotics to farmers should be prohibited, recognising that if the drug companies could persuade farmers that a product was vital for their livestock's performance, they would put pressure on their vets to prescribe it – a key recommendation also blocked by industry lobbying. Four decades on, the UK is now the only country in the EU to permit direct advertising of antibiotics to farmers.

Categories of antibiotic use on farms

Therapeutic use – for treatment of disease
This is where infected animals receive a course of antibiotics. Treatment usually occurs at high doses for a relatively short period of time. However, on many intensive farms if a few animals are found to be sick, the whole flock or herd will be given antibiotics to prevent the disease spreading (metaphylaxis). There is not always a clear distinction between what is properly termed 'therapeutic' i.e. the treatment of individual sick animals, and 'preventive' i.e. mass treatment of uninfected animals ahead of a possible wider disease outbreak.

Prophylactic use – for prevention of disease
This involves giving low, sub-therapeutic doses of antibiotics to animals via their feed or drinking water (i.e. en masse), when they are not showing signs of disease but when there is thought to be a risk of infection. Treatment will frequently last for several weeks. Dairy cows routinely have antibiotic 'infusions' in their udders to prevent outbreaks of mastitis, a practice known as 'Dry Cow Therapy'. Non-routine, acceptable prophylactic use of antibiotics would include treating an individual animal vulnerable to developing an infection, for example, a cow that has had a difficult birth.

'Growth promotion' – to increase growth-rate and productivity
Use of Antibiotic Growth Promoters (ABGPs) is technically no longer permitted in the EU, but the dosages at which antibiotics are fed for prophylactic use are often sufficiently low to have a growth-promoting effect. Use of ABGPs is legal and widespread in the U.S. and globally. Very low sub-therapeutic doses of antibiotics are given to animals (particularly intensively-reared pigs and poultry) in their feed. Treatment is continuous and can last for a large part of the animal's life. The antibiotics suppress some bacteria in the gut, reducing the energy expended on digestion and leading to an increased yield in terms of growth rates and productivity from the animal. However, research shows that 'benefits' from the use of growth promoters are more noticeable in sick animals or those 'housed in cramped, unhygienic conditions'.[10]

The EU ban

Although concerns had been expressed about growth promoters from the 1960s onward,[11] it was 40 years before EU policy-makers considered there was sufficient scientific evidence confirming the link between low doses of antibiotics in animal feed and the increase in antibiotic resistance in bacteria to related drugs used in human medicine. Individual countries had already banned antibiotic growth promoters: Sweden banned all use as far back as 1986; in Denmark, avoparcin was banned as a growth promoter from 1995; a ban on virginiamycin followed in 1998[12] and a voluntary ban on all growth promoters was agreed later that year.[13]

Eventually, between 1997 and 2006 the EU banned the use for growth promotion of nine antibiotics: avoparcin; virginiamycin; tylosin phosphate; bacitracin zinc; spiramycin; avilamycin; flavophospholipol; monensin and salinomycin – as well as two non-antibiotic pharmaceuticals, carbadox and olaquindox.

Members of the public might believe (understandably) that the ban all but eliminated routine antibiotic use in animal production. Yet the fact is that most EU consumers are still eating food from animals routinely dosed with antibiotics. This is because prophylactic and metaphylactic use are widespread.

Current regulations in the EU

Ultimately, it is the EU that authorises antibiotics, and indeed all veterinary medicines, for their particular use in specific animals as outlined on page 9. Vets are responsible for adhering to these authorised uses. Some leeway is given for 'off-label' use of antibiotics on animals other than those specified for that particular drug, allowing a veterinary surgeon to prescribe unauthorised antibiotics to avoid 'unacceptable suffering'.[18] A derogation under EU legislation allows some farmers to manufacture their own medicated feed on-farm using authorised pre-mixes.[19] Over 600 farms in the UK have been authorised under this derogation, whereas only 19 farms hold such authorisations in France.[20]

CHAPTER 2

Animals on antibiotics – a symptom of a sick farming system

"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[21]

Every time an animal receives a dose of antibiotics it gives any bacteria present an opportunity to develop resistance to that drug. This can occur either through the multiplication of bacteria that have a particular resistant mutation or through 'horizontal' transfer of resistance genes between bacteria. Resistance to antibiotics has been described as 'the best-known example of rapid adaptation of bacteria to a new ecosystem'.[22]

Reliance on frequent, prolonged, low-dose use of antibiotics creates ideal conditions for antibiotic-resistant strains of bacteria to develop. By the turn of the 21st century, approximately half of all antibiotics produced in the world were destined for use in food animals. [23] According to one estimate, in the U.S. that rises to over 80%, with 70% of that being used not for treating actual sick animals, but preventively and as growth promoters.[24] These non-therapeutic uses have enabled the exponential increase in factory farming globally by controlling the spread of infections that are inevitable when large numbers of animals are kept closely confined.

Pigs and poultry

Piglets in intensive systems are usually weaned at four weeks of age, so the sow can be made to conceive again quickly, producing more than two litters each year. Under more natural conditions, sows would wean their young at 3-4 months of age when their immune systems are fully functional. Pigs weaned at just one month old i.e. at the new EU minimum of four weeks of age, are much more prone to develop post-weaning diarrhoea, which makes them more vulnerable to serious infections such as swine dysentery. Consequently, many intensive pig farmers start adding antibiotics to pig-feed once piglets are weaned, and continue to give them medicated feed of one sort or another throughout their six-month lives.

Pigs and poultry are the animals most likely to be reared in factory-farm conditions, crowded together in very large numbers and kept indoors for most, if not all, of their lives. Not surprisingly, they are also the two species given the most frequent and greatest quantity of antibiotics:

- Around 90% of all UK farm antibiotic sales are for pigs and poultry.[25]
- In 2008, pigs accounted for around 60% of the tonnage of antibiotics (active ingredient) sold in the UK and 80% of doses in Denmark.[26, 27]

As they account for the greatest share of antibiotic use in the UK, pigs are a key species to consider in some detail. All of the 13 antibiotics that can be administered in the form of mass-medication to animals' feed and water for a period of days, weeks or longer for any one prescription (and prescriptions can be repeated) are related to drugs already used or under trial for use in human medicine (see table opposite).[28]

Dairy cow infections

Dairy cattle across Europe are routinely treated with antibiotics, particularly to prevent mastitis (a common and painful udder infection). With the exception of organic herds, many dairy cows will routinely receive up to on average two antibiotic treatments each year, one to prevent and one to treat mastitis. The preventive practice – known as Dry Cow Therapy (DCT) – generally involves infusing antibiotic liquid via pipette into all four quarters of the udder (right) while the cow is 'dried off' from producing milk a couple of months before giving birth. The birth of the calf then starts off the annual milk production cycle again.

DCT is widespread: in the Netherlands in 2008, for example, records show that more than 90% of the country's dairy cows had DCT as a routine preventive against mastitis.[29] With the exception of organic dairy farms, 'blanket dry cow therapy', where all cows have antibiotics infused into all four quarters of their udders at the time of being 'dried off' ahead of calving again, is standard practice on most conventional dairy farms in the UK. This has been the case since the 1960s when *The Five Point*

Antibiotics authorised for use in the feed and/or water of pigs in the UK for the prevention and/or control of infection.[30]

ANTIBIOTIC NAME	ANTIBIOTIC CLASS	AUTHORISED FOR CONTROL AND/ OR PREVENTION OF:	PERIOD OF USE PER PRESCRIPTION
amoxycillin	beta-lactam tetracycline phenicol	*Streptococcus suis* in weaned piglets (e.g. meningitis)	14 days
apramycin	aminoglycoside	bacterial enteritis in young pigs (e.g. *E-Coli* infection)	Up to 28 days
chlortetracycline (3 products)	tetracycline	respiratory and systemic infections, including meningitis (*S. suis*), rhinitis, pneumonia	5-7 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'
phenoxymethyl-penicillin	beta-lactam	*S. suis* (meningitis and septicaemia); pathogens causing pneumonia	Up to 6 weeks
spectinomycin	aminoglycoside	bacterial enteritis caused by *E-coli*	3-5 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	15-21 days
trimethoprim + sulfadiazine	trimethoprim / sulphonamide	infections in fattening pigs	5 days
tylavosin (acetylis-ovaleryltylosin)	macrolide	pneumonia, dysentery	7-10 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'

Plan For Control of Mastitis in Dairy Herds was developed at the National Institute for Research in Dairying in conjunction with the Central Veterinary Laboratory, which emphasises the use of prophylactic antibiotics at drying off.[34]

As well as an emphasis on prophylactic use of antibiotics for every cow at drying-off, the *Five Point Plan* also relies on an aggressive culling policy for disease-susceptible animals. While the accepted view has been that local use of antibiotics in the udder poses less risk for the development of resistant bacteria,[30] recent research from the U.S. has linked increased resistance in cows' faecal bacteria to the routine prophylactic use of antibiotics in Dry Cow Therapy.[31] In addition, it has been recognised by the European Committee on Veterinary Medicinal Products that the practice

PHOTO: © AGRIPICTURE IMAGES / ALAMY

Dry Cow Therapy (DCT) is standard practice and is symptomatic of the approach that uses antibiotics before any infection is present.

of feeding milk containing antibiotic residues to calves may select for antibiotic resistant bacteria in calves.[32,33]

Reliance on DCT reflects the short, high-pressure, stressed lives that modern intensive dairy cows endure, and that preventive medication is facilitating. There is no doubt that shifting from such routine reliance on antibiotics will be a huge challenge for many farmers, as well as presenting a major welfare issue, though several studies confirm that organic dairy farmers are able to manage mastitis without routine reliance on DCT using antibiotics[34] (which is not permitted under EU organic standards). (See: *Practical strategies for preventing disease through breeding and good husbandry*, page 20.)

In general, though, the trend is in the other direction towards increased intensity of production. On many European farms, dairy cows only live for between 3-4 lactations (a lifespan of around 5-6 years for a cow entering the herd as a 2-year-old heifer), before they are culled due to infertility or illnesses indicating the animal's physiological exhaustion. Under less intensive systems, a dairy cow can live longer.[35] The Farm Animal Welfare Council has given its opinion that, 'if well looked after', UK dairy cows should have a lifespan 'of at least 8 years'.[36]

Antibiotic use per animal

The Netherlands has gone further than most in calculating how many doses of antibiotics each farm animal gets over its lifetime (the UK has no such detailed breakdowns, but usage is likely to be similar). MARAN, the Dutch monitoring agency for antibiotic use, estimated in its 2008 report [37] the average use of antibiotics over the lifetime of different farm animals:

- The average meat pig living for 191 days was exposed to 30 antibiotic doses from birth to 74 days old, and 5 doses during the fattening period, i.e. exposure for 35-37 days. **The average pig ending up as bacon, ham and pork was on antibiotics for nearly 20% of its life.**
- An average broiler (meat) chicken living 42 days was exposed to antibiotic doses for 5 days i.e. 12% of its life.
- 90% of dairy cows had DCT treatments every year. Dairy calves had antibiotics seven days out of their 56-day weaning period.

In comparison, the average UK citizen has 0.75 prescriptions for antibiotics per year.[38]

CHAPTER 3

The food-poisoning bugs – *Salmonella, Campylobacter, E-Coli*

"Resistant Salmonella and Campylobacter 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 is prominent."

European Food Safety Authority Panel on Biological Hazards (2008) [39]

There is convincing evidence of the risks to human health from over-reliance on antibiotics in intensive livestock. The prevalence of antibiotic-resistant and multi-resistant food poisoning bacteria is increasing.[40] Over the last decade, public health scientists have argued that antibiotic resistance leads to food-borne infections in humans that:

- are more severe and last longer;
- are more likely to lead to infections of the bloodstream and to hospitalisation;
- are more likely to lead to death.[41]

When food poisoning bugs like *Campylobacter*, *Salmonella* or *E. coli* become resistant, if doctors need to treat an affected patient with antibiotics, finding the effective antibiotic causes a delay which could prove fatal.

Across the EU in 2009 there may have been up to

REPORTED FOOD-BORNE INFECTIONS IN THE EU [42]

Campylobacter: 198,252 reported human cases in 2009

Salmonella: 108,614 reported human cases in 2009

Campylobacter: found in 31% of fresh broiler chicken meat [i] samples

Salmonella: found in 5.4% of fresh broiler chicken meat [ii] and 0.7% of fresh pigmeat samples [iii]

Actual number of infections may be 8-10 times the number of reported cases [44,45] allowing an estimate of 2.5-3 million illnesses due to food-borne *Campylobacter* and *Salmonella* in the EU in 2007-8.

[i] Range between Member States 0% to 95.8%
[ii] Range between Member States 0% to 36.1% at retail level
[iii] Range between Member States 0% to 3.5% at retail level

TESTS FOR THE PRESENCE OF MULTI-RESISTANT FOOD-BORNE BACTERIA

France (1992-2002): for *Campylobacter coli* isolated from skin and faeces of chickens, resistance to ampicillin increased from 2.0% to 36.8%, resistance to nalidixic acid (a quinolone) from 2.0% to 45.1%, to enrofloxacin (a fluoroquinolone) from 2.1% to 38.6%, to tetracycline from 56.0% to 83.2% and to erythromycin from 36.0% to 61.7%. For *C. coli*, resistance on free-range farms was less than on standard commercial farms, presumably reflecting differences in antibiotic use.[46]

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.[47]

Italy (1999-2001): *Salmonella* strains isolated from humans, food and farm animals showed high rates of resistance to antibiotics tests, except for cefotaxime (third 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 antibiotic-resistant *Salmonella* which can be transmitted to people.[48]

UK (2007-2008): in official tests on bacteria found in fresh retail chicken, 87% of the *Campylobacter* isolates and 41% of the *Salmonella* isolates were resistant to at least one antibiotic (indicating an increase in resistant *Campylobacter* since 2001).[49]

three million cases of food-poisoning caused by the top two food bacteria, *Campylobacter* and *Salmonella*. Official health advice tends to be that such infections can be avoided by people taking precautions such as washing their hands before preparing food, ensuring meat products and eggs are thoroughly cooked, keeping meat and vegetable chopping boards separate. All sensible suggestions, but the fact remains that already millions of people are succumbing to food-borne infections (see box, page 10), and these are caused by bacteria that are rapidly becoming resistant to antibiotics (see box above).

ESBLs: new origins of resistance

Extended Spectrum Beta-lactamases (ESBLs) and AmpC beta-lactamases are types of enzymes produced by certain strains of bacteria, which make them resistant to virtually all the beta-lactam antibiotics, including the penicillins and third and sometimes fourth generation modern cephalosporins. Beta-lactams are some of the most important antibiotics in human medicine, amounting to nearly two-thirds of all antibiotics used to treat humans globally. The ESBL genes can also be transferred horizontally between bacteria, passing on the ability to produce resistant enzymes.

In the UK, ESBL-type *E. coli* causes an estimated 50,000 cases of urinary tract infection (UTI) per year and of these, 2,500 lead to blood infection.[50] Because ESBLs usually confer resistance to a range of drugs, 'the choice of agents to treat these infections is diminishing.'[51]

Although the majority of infections with ESBL-producing bacteria occur within healthcare settings, food animals are also a known source of these bacteria. According to scientists at the Faculté de Médecine Pierre et Marie Curie in Paris, poultry have been a 'primary food source' for infection with ESBL-enzyme carrying cephalosporin-resistant *Salmonella*.[52] In 2009, the European Medicines Agency (EMA) also concluded that drug treatment of farmed animals is one likely source of resistance to third generation cephalosporins and that 'the concentrations [of ceftiofur in the intestines of treated animals] are high enough to select for resistance'.

Despite such warnings, by 2006, the majority of EU countries had authorised the cephalosporins ceftiofur and/or cefquinome for systemic treatment and cefquinome for intra-mammary use – i.e. infusion into the udder as Dry Cow Therapy. Cefquinome (fourth generation) is authorised in the UK for DCT and for the treatment of clinical mastitis. It is also licensed for the treatment of respiratory and other infections in pigs and piglets. Ceftiofur is not licensed for use in poultry,

PHOTO: © PHOTOTAKE INC. / ALAMY

Certain E.coli bacteria can produce ESBLs, enzymes that make them resistant to a whole class of antibiotics.

but is believed to be widely used off-label (legal under certain conditions, but not meant to be routine).

ESBLs in intensive farm settings

A survey from the UK Veterinary Laboratories Agency published in February 2010 found that ESBL-producing *E. coli* appeared to be widespread in poultry settings, with positive tests on individual birds returned in:

- 52.2% of chicken slaughterhouses;
- 57.1% of broiler production companies (chicken farms);
- 5.2% of turkey rearing farms;
- 6.9% of turkey breeding farms.[53]

The first cases of ESBL-producing *Salmonella* from UK farm animals have been reported in pigs[54] and were associated with the use of ceftiofur to control and treat illness in piglets.[55] Studies by Danish scientists have shown that injecting pigs with ceftiofur increases resistant *E-coli* in the pigs.[56] *E-coli* developed resistance in half of pig farms studied where ceftiofur was used and in only 10% of the farms where it was not used.[57]

From animals to people

The widespread prevalence of ESBL-producing bacteria on farms across Europe is not in doubt, nor is the capacity of these bacteria to be transferred to people, putting them at risk of life-threatening infections. In the Netherlands, on every one of 26 broiler chicken farms visited by researchers some birds gave positive tests for ESBL-producing *E. coli* and on 22 of the farms the prevalence was more than 80%. Genetic analysis of the plasmids (see Glossary) carrying the resistance genes indicated that, 'in the Netherlands, poultry has contributed to the distribution of ESBL-carrying plasmids towards humans'.[58]

Further strong indications that ESBL genes, plasmids and *E. coli* are transmitted from farm livestock to people through the food chain came from Dutch microbiologists in 2011. Of clinical samples of *E. coli* taken from people, 35% in total carried ESBL genes. Genetic comparison with *E. coli* found in retail poultry meat and in live chickens showed that nearly 1 in 5 (19%) of the *E. coli* samples taken from people carried ESBL genes on plasmids that were 'genetically indistinguishable from those obtained from poultry meat'. Nearly all (94%) of the retail poultry meat samples contained ESBL-producing bacteria, and 39% of those were of genetic types also found in human samples.[59] The 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.'

E. coli outbreak: seeking the source

May 2011 saw a major *E. coli* outbreak in Germany, where nearly 4,000 people were infected and around 50 died.[60] The strain involved, O104:H4, was highly virulent and produced a toxin known as the shiga toxin. As well as being resistant to most of the beta-lactam antibiotics, the strain was also resistant to tetracycline, streptomycin, some quinolones, trimethoprim/sulphamethoxadole and some aminoglycosides.[61] To find such a high level of resistance in shiga-toxin producing *E. coli* was surprising, as shiga-toxin producing *E. coli* infections are not usually treated with antibiotics, so resistance would not have developed through that route. Contaminated beansprouts from an organic farm in North Germany were eventually said by officials to be 'most likely the source'.

But that did not explain where the *E. coli* had actually originated, as the farm had no animals and did not use any manure. The high level of resistance suggested that this new pathogenic strain evolved in an environment where there was high antibiotic use (in other words, unlikely to be from organically farmed animals).

As an article in *Nature News* surmised, 'agricultural use of antibiotics is a possible suspect', warning that the 'increased movement of shiga-toxin-producing phage means that even more unusual and dangerous strains could be on the horizon'.[62]

PHOTO: © COMPASSION IN WORLD FARMING

Tests suggest that ESBL-producing E. coli may already be present in the majority of intensively farmed broiler chicken settings in the UK and the Netherlands.

CHAPTER 4

Livestock-related MRSA – reaching the human community

"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".

European Commission, 2009 [63]

The most infamous multi-resistant 'superbug' is Methicillin Resistant *Staphylococcus Aureus*, commonly known by its acronym, MRSA, with an estimated 96,000 cases in England in 2004. *Staphylococcus aureus (S. aureus)* bacteria are frequently present on the skin, or in the nose and mouth of people, without causing illness. Problems arise if the bacteria get into wounds following surgery, during other hospital treatment or simply via damaged skin. Complications can range from minor infections and abscesses to life-threatening diseases such as pneumonia, meningitis, endocarditis (a heart infection) and blood poisoning.

Until a few years ago, MRSA was found almost exclusively in hospitals. Hospitals have responded vigorously to the threat, requiring people entering and leaving hospital to use sterilising fluid on their hands. However, more recently it has also become a problem outside hospitals, and increasingly causes illness in people who have had no contact with hospitals. Known as 'community-acquired' MRSA, such outbreaks have been identified in the U.S., UK, Canada, Australia, New Zealand, Finland, Ireland, France, Germany, Switzerland, the Netherlands and Japan.[64]

The European Medicines Agency has described MRSA infection as presenting 'a major public health problem worldwide'. Vancomycin, one of the powerful antibiotics most often used to treat MRSA, can only be given intravenously, which means that MRSA infections acquired outside of hospitals necessitate hospital admittance.

'Pig' MRSA

A Soil Association report recounts how by 2004-2005 pigs had developed a previously unknown strain known as MRSA ST398 (or NT-MRSA) which was then spreading to people.[65] The first recorded cases of human colonisation by 'pig' MRSA were in a Dutch baby girl and her parents, who were pig farmers, and it is now estimated that 50% of Dutch pig farmers are carrying the new strain – 760 times the average in the population at large.[66]

By 2007, livestock-related MRSA was starting to spread to the wider population and caused over 20% of cases of MRSA in the Netherlands[67] – although the strain is still overwhelmingly associated with farmers, vets and their families. Ironically, before 2006 the Netherlands had one of the lowest recorded rates in the world of MRSA among its human population and in its hospitals.

So far, this new strain of animal-acquired MRSA has relatively low virulence (its ability to cause invasive disease), compared to the many other strains of MRSA infecting humans. That could change if it acquires greater virulence through horizontal gene transfer. This is something Dutch scientists believe is only 'a matter of time', so increasing 'its ability to cause disease in humans'.[68]

Although MRSA ST398 was first found in intensively reared pigs in the Netherlands, it has now been found in chickens, dairy cows and veal calves across Europe, as well as on the bodies of those working on those farms or in slaughterhouses. Not surprisingly it can be transferred from the live animal to their meat. In 2009, the Dutch Food and Consumer Safety Authority (VWA) reported that MRSA was found in 11.9% of around 2,200 raw meat samples for retail sale; including 35.3% of turkey meat,

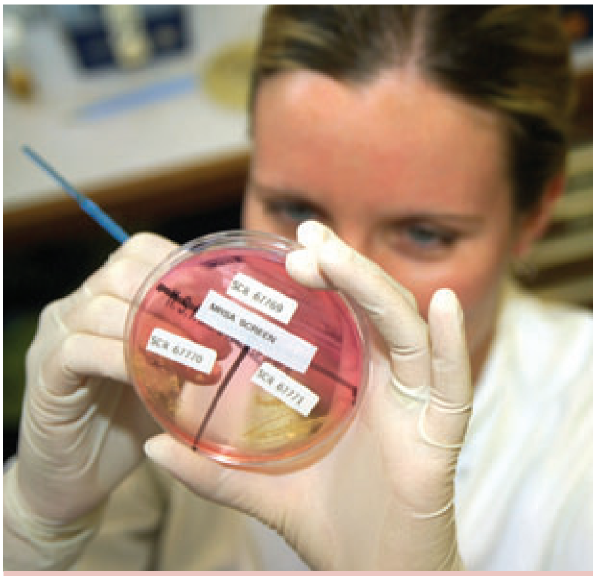


PHOTO: © ZAK WATERS / ALAMY

Huge efforts to contain MRSA appear to be insufficient; the appearance of virulent strains in the community is a 'matter of time'.

10.6% of beef, 15.2% of veal, 16.0% of chicken meat and 10.7% of pig meat. Most were the 'pig' type MRSA ST398.[69]

It is not surprising that this new strain of a superbug emerged first in intensively reared pigs, as of all farmed animals pigs receive the most frequent doses of antibiotics during their lives. The Netherlands is one of the major intensive pig producers in Europe, rearing nearly 24 million pigs in 2009, and exporting 11.2 million live pigs to other EU countries, particularly to Germany.[70] Hence the European Food Safety Authority (EFSA) predicted that, 'It seems likely that MRSA ST398 is widespread in the food animal population, most likely in all Member States with intensive animal production.'[71]

A 'preliminary' EU-wide study of pig breeding farms by EFSA in 2008 found MRSA ST398 present in Germany, Belgium and Spain (all of which import pigs from the Netherlands), but none on farms in Ireland, Sweden and UK, nor Norway and Switzerland. (The tests were carried out on dust samples collected on each farm, not on the pigs themselves, which may have underestimated the real level of infection).[72]

Of 175 MRSA samples from pigs tested in 2005-2006, all were found to be resistant to tetracyclines, the antibiotic class most widely used in the pig industry in the Netherlands, the UK and elsewhere.[73] Dutch scientists and government officials have had no hesitation in pointing the finger at the intensive pig industry and its reliance on antibiotics for the rise and rapid spread of farm-animal MRSA. Dik Mevius, Professor of Microbial Resistance at the Animal Sciences Group of Wageningen University commented, 'Tetracycline, more or less all over the world, is one of the most used antibiotics in animal production. It's quite likely that this usage of tetracyclines is one of the reasons that these MRSA are so commonly present.'[74]

MRSA in UK cows

In June 2011, the authoritative medical journal The Lancet Infectious Diseases published findings of the first-ever documented cases of MRSA in British farm animals. Scientists found 15 cases of a completely new type of MRSA in bulk milk from dairy farms in England.[75]

The study also showed that the new MRSA is already infecting people in England and Scotland. In collaboration with the Health Protection Agency and the Scottish MRSA Reference Laboratory, 26 suspect MRSA cases were identified in England, and 16 possible cases were found in Scotland. Testing showed 15 of the English cases and 12 of the Scottish cases had been caused by the new MRSA (though not from drinking milk as pasteurisation kills the bacteria).

CHAPTER 5

The threat to human health – risk levels assessed

"Antibiotics are life-saving drugs, but many bacteria are now resistant to them. In some diseases, because of resistance, the last line of defence has been reached."

Sir Liam Donaldson, UK Chief Medical Officer, Annual Report, 2008[76]

Antibiotic-resistant bacteria bring serious risks for individual patients through:

- failure of initial antibiotic treatment, so making infections more difficult to treat;
- limiting the range of effective antibiotics;
- leading to more severe illnesses, hospitalisations and higher death rates;
- forcing use of more expensive drugs, that could have more severe side-effects.[77,78,79,80]

In turn, healthcare systems throughout the world will need to:

- commit more time and money to treating patients with infections;
- cope with a higher number of hospitalisations;
- purchase and store a greater range of more expensive drugs;
- acquire expertise to recognise and treat side effects.

This will bring higher overall costs to national healthcare systems worldwide; where increased costs cannot be met, patients will suffer the consequences.

Young children are particularly vulnerable to bacterial infections. Around one third of common *Salmonella* infections and 20% of *Campylobacter* infections occur 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. An American hospital paediatrician concerned at the risks created by antibiotics in agriculture for children's health commented in

2003, 'Children, particularly very young children, are at high risk of developing infections with drug-resistant organisms linked directly to the agricultural use of antimicrobials.' [81]

For people who contract ESBL-type resistant infections the consequences are serious, because the treatment options are at best limited when key antibiotics like the cephalosporins are not effective. The third generation cephalosporins (such as ceftriaxone) are drugs of choice for treating children with severe, invasive *Salmonella* infections and for treating *E. coli* blood infections. ESBL-type resistance is often linked with resistance to other antibiotics, including the fluoroquinolones, which are first-line drugs for 'empiric' treatment (when immediate treatment is needed, without waiting for diagnostic test results) of adults – often the elderly – with severe *Salmonella* infections.

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'.[82] 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.[83]

Antibiotic-resistant infections also particularly affect people with compromised immune systems. A multi-resistant form of *Salmonella Typhimurium*, known as DT104 was reported in 2005 to account for the majority of *S. Typhimurium* infections among HIV-infected people in America. DT104 infections were also found to be more likely to invade the bloodstream than other strains of *Salmonella*.[84]

Transmission from animals

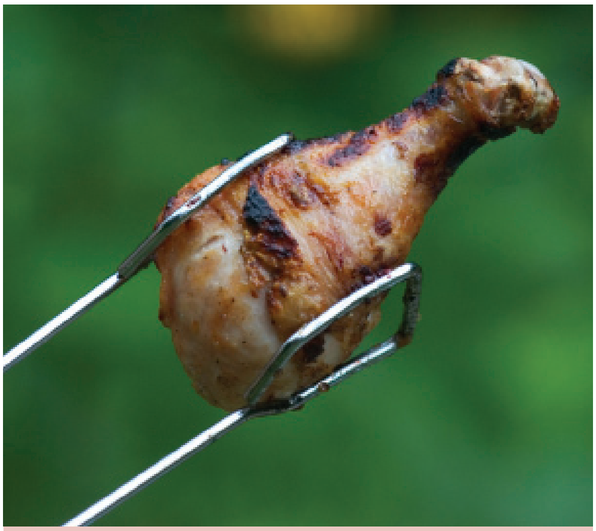
Resistant bacteria colonise food animals, sometimes without causing disease in the animals themselves, but if they are present they can be passed on to people who work with animals or meat, via food or generally out into the wider environment through the animals' manure or even in airborne particles. The bacteria can then spread further from person to person.

Direct contact with infected animals

Handling pigs and poultry and working in a farm environment puts people at risk of picking up resistant bacteria from the animals' bodies or from their faeces. Studies in the Netherlands in 2001-2002 showed the same genetic patterns of resistance in *E. coli* samples taken from turkeys and broiler chickens and from the farmers and slaughterhouse workers who were handling them.[85,86]

Eating contaminated food

Contamination of meat generally results from faecal material getting onto the carcass during the slaughter and evisceration process (when the animals' guts are removed). Contaminated meat can contaminate other foods in domestic or restaurant/catering kitchens. The European Food Safety Authority (EFSA) has estimated that live chickens colonised with *Campylobacter* are 30 times more likely to result in contaminated meat than unaffected birds.[87]



COVER PHOTO: ISTOCKPHOTO

Contaminated meat that has been inadequately cooked leads to contaminated food.

Via the environment

Resistant bacteria can be transferred in water, through the soil and by air. Animals excrete a significant amount of the antibiotics they are administered, making their manure a potential source of antibiotics and antibiotic-resistant bacteria which can enter soil and groundwater. In the U.S., tetracycline-resistance genes have been found in groundwater 250m downstream from the slurry lagoon of a pig farm and to have spread among the local soil microbes.[88]

In the Netherlands, 14% of people living near turkey farms where avoparcin was used were found to carry enterococcal bacteria resistant to the closely related human antibiotic, vancomycin.[89] 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 and in the air of cars driving behind a lorry transporting poultry.[90]

Recent research has also found that flies and cockroaches on intensive pig farms frequently carry antibiotic-resistant bacteria. The researchers concluded: 'House flies and German [common] cockroaches in the confined swine production environment likely serve as vectors and/or reservoirs of antibiotic-resistant and potentially virulent *Enterococci* and consequently may play an important role in animal and public health.'[91] Similarly, a study of antibiotic usage on a U.S. farm found that 'resistant bacteria move from animal to animal, in this case from bull to calf, to pigs to chickens, presumably through the air'. Farm workers were colonised for several weeks by *E. coli* bacteria picked up from a bull. The researchers concluded: 'There is no containment of ... antibiotic-resistant bacteria in the farm environment.'[92,93]

CHAPTER 6

Sharing the medicine cabinet – the overlap in animal and human antibiotic use

"The widespread use of antimicrobials ... in livestock production has intensified the risk for the emergence and spread of resistant micro-organisms. This raises particular concern since the same classes of antimicrobials are used both in humans and animals." World Health Organization, 2007[94]

There are more than 15 different antibiotic classes. Antibiotics belonging to the same class share similar chemical structures, modes of action and range of effectiveness. So bacteria that have developed resistance to a particular antibiotic are more likely to develop resistance to a closely-related antibiotic.

The table below sets out overlaps in the classes of antibiotics used in both human medicine and for treating livestock. It shows that considerable quantities of the same active ingredient are used in farm animal antibiotics as for related human antibiotics:

- 4 times the weight of tetracycline antibiotics used in animals compared to humans;
- 5 times the weight of sulphonamides;
- Over 20 times the weight of aminoglycocides.

These summary figures suggest some very high levels of use of the same class of antibiotics in animal treatment as relied upon in human medicine. However, as noted in a Joint Opinion of the European Medicines Agency and other expert bodies of 2009, comparisons of human and animal usage by weight of active ingredient should be interpreted 'with caution due to large differences between the doses applied among the various animals and humans and thus does not reflect the number of treatments received by either animals or humans'.[95] Nevertheless, it demonstrates that the same classes or 'families' of antibiotics as those relied upon in human healthcare *are* used in farm animals, in several cases in considerable quantity.

Comparisons based on weight alone cannot give a complete picture, because a single dose of a

Classes of antibiotics and their reported use in human medicine or sale for use in animals, by tonne of active ingredient, UK, 2007[96]

Class of antimicrobial (NB: specific examples of antibiotics in each class are illustrative only and do not imply use in both humans and animals in UK)	Prescribed for human use 2007 in community, all UK countries (tonnes)	Prescribed for human use 2007 in hospitals, England and Wales only (tonnes)	Tonnes of 'therapeutic veterinary antimicrobial products' sold in UK 2007 (tonnes)[i]
tetracyclines	43.9	1.1	174
sulphonamides / trimethoprim	10.9	3.9	73
ß-lactams (e.g. penicillins, cephalosporins)	249.5	56.0	72
of which: cephalosporins	31.9	11.6	6
aminoglycosides (e.g. streptomycins)	< 0.1	0.5	20
macrolides (e.g. erythromycin, tylosin)	47.3	6.2	33
quinolones / fluoroquinolones (e.g. ciprofloxacin, enrofloxacin)	11	4.7	2
other (includes vancomycin for human use)	15.1	1.0	14

[i] Pets account for 4% of total sales.

modern antibiotic can weigh a lot less than a single dose of some of the older antibiotics, creating the false impression of reduced usage. For example, the same weight of the active ingredient of fluoroquinolone is capable of treating 70 times as many animals as the same weight of active ingredient for tetracycline.[97]

This is of particular concern, because as bacteria on factory farms have developed resistance to the older antibiotics, the intensive livestock industry has switched to newer, 'lighter' and more powerful antibiotics, such as the fluoroquinolones and the modern cephalosporins. The concern is borne out by the recent effort by the European Medicines Agency (EMA) to ascertain use of farm antibiotics across the EU.[98] While the survey of data from eight Member States found a modest overall decrease of 8.2% in sales across the five-year study period, the EMA emphasised this should not be taken to 'imply that the number of animals treated has decreased'. There was a decrease in sales of some antibiotics, but an increase in the sales of the third and fourth generation cephalosporins, which have more doses per equivalent weight.

Cephalosporins are one of the classes of antibiotics that the World Health Organization classifies as 'critically important' drugs for human medicine.[99]

Cephalosporins: 'critically important'

So while farm animal usage by weight of the third and fourth generation cephalosporins and fluoroquinolones in the table on page 16 may be lower than other classes, consideration by weight alone does not mean they are being used sparingly or responsibly. The demonstrated uptake of these 'critically important drugs in human medicine' for use in livestock is of great concern to the Alliance.

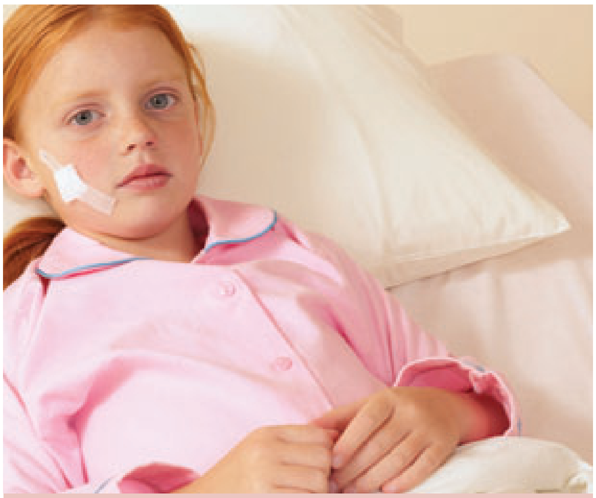


PHOTO: © FANCY / ALAMY

The third and fourth generation cephalosporins are used to treat children with severe Salmonella and E. coli infections. Therefore use of these antibiotics should be restricted in animal medicine.

The EU's Committee for Medicinal Products for Veterinary Use (CVMP) recommended in 2009 that: 'Authorisation of products for prophylactic use of systemically administered cephalosporins should always be limited to specific circumstances and carefully considered.' It added that: 'Use of systemically administered cephalosporins for groups or flocks of animals such as use of oral cephalosporins in feed or drinking water should be strongly discouraged.'[100] These recommendations are seemingly falling on deaf ears: by 2008 around 20 EU Member States had authorised products containing third or fourth generation cephalosporins for injection into food animals and for intra-mammary infusion (Dry Cow Therapy).

The modern cephalosporins (third and fourth generation) are essential for human medicine because they were developed to withstand the beta-lactamase enzymes which deactivate the older beta-lactam antibiotics. They are too important for human health to be wasted on propping up industrial farming systems.

Fluoroquinolones – damage done

One of the main fluoroquinolones (also classed by WHO as 'critically important') commonly used in human medicine is ciprofloxacin (brand name 'Cipro'). Ciprofloxacin is relied on by doctors as a 'first-line' treatment for severe *Salmonella* and *Campylobacter* infections in adults (it is also effective against plague and anthrax, potential biological weapons).

Unfortunately, the fluoroquinolone-based drug enrofloxacin (brand name Baytril), which is related to ciprofloxacin, is also used widely in the global poultry industry. Over-use of enrofloxacin in poultry has been implicated in the increasing problem of *Salmonella* infections in people becoming resistant to 'Cipro'.

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 (see box on page 18). Countries where enrofloxacin was approved for use in poultry production between the later 1980s and the mid-1990s include Austria, Canada (withdrawn in 1997), Denmark, France, Italy, Japan, the Netherlands, Spain, Turkey, the UK and the U.S.

An EU survey of resistance in food-borne 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. Resistance varied between 5% and 38% for *Salmonella* and from 20% to 64% for *Campylobacter*.[101] In contrast, in Australia, which has never authorised quinolones for use in poultry, fluoroquinolone resistance of *Campylobacter* isolated from people who had locally-acquired infections (i.e. not acquired from foreign travel) has remained relatively low.[110]

On the basis of the evidence that the use of enrofloxacin in poultry was contributing to resistance to ciprofloxacin in bacteria infecting humans, the U.S. 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 drugs industry. In March 2004, the Administrative Law Judge in the FDA's case found that the manufacturer had 'not shown Baytril use in poultry to be safe'.[112]

Unlike the U.S. the EU permits enrofloxacin in poultry production. Baytril is authorised in the UK for treatment of respiratory and digestive system infections in pigs, cattle and poultry, including calves and piglets, and can be administered to whole flocks of poultry via their drinking water.[113]

ENROFLOXACIN: THE CASE AGAINST...

The Netherlands (1982-1989): Use of enrofloxacin in the drinking water of poultry was followed by emergence of fluoroquinolone-resistant *Campylobacter* strains in both poultry and humans. In the four years before its introduction in poultry, fluoroquinolone-resistant *Campylobacter* were absent in the Netherlands, suggesting that 'the resistance observed is mainly due to the use of enrofloxacin in the poultry industry'.[102]

Belgium (1998): 'Alarmingly high rates of resistance to ciprofloxacin' were found, including 62.1% of *Campylobacter coli* samples and 44.2% of *Campylobacter 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'.[103]

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'.[104]

U.S. (1996-1998) A rapid rise in resistance to quinolones in *Campylobacter jejuni* infections in people coincided with the licensing of fluoroquinolones for use in poultry. Public health scientists concluded that 'the use of fluoroquinolones in poultry has had a primary role in increasing resistance to quinolones among *C. jejuni* isolates from humans'.[105]

Brazil (2001): 18.2% of *Campylobacter jejuni* isolated from children with diarrhoea were resistant to the fluoroquinolones ciprofloxacin and norfloxacin. The study's conclusion was this 'suggests an animal origin of this resistance' related to veterinary use of enrofloxacin.[106]

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 were resistant to 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*.[107]

China (1999-2000): Of *Salmonella* strains isolated from retail chicken produced in China in 1999-2000, 32% were resistant to nalidixic acid (an antibiotic of similar quinolone type to ciprofloxacin), whereas no isolates from meat imported from the U.S. were resistant. 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 U.S.[108]

Turkey (1992-2000): The first fluoroquinolone resistant *Campylobacter* strains from broiler chickens were 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'.[109]

CHAPTER 7

Avoiding non-essential use – a blueprint for better farming

"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." Resolution of Environment Committee of the European Parliament, Oct 2011[114]

Antibiotics are used as 'pharmaceutical props' for inhumane systems that would not be viable without their routine use. Yet often disease outbreaks could be minimised or prevented by good husbandry, hygiene and an improved living environment. Where that is the case the Alliance argues that prophylactic use of antibiotics is unnecessary. Hence it is calling for an end to all non-essential use of antibiotics (see *Key recommendations*, page 22).

Reducing non-essential use

Some observers argue that the non-essential use of antibiotics on farms in the UK – or even the EU as a whole – is declining. In fact all that is certain is that currently, because of inconsistent or non-existent monitoring, no one can say exactly what is happening. For example, the UK's Veterinary Medicines Directorate (VMD) confirmed in 2010[115] that 'there is no central record kept of the use of antimicrobials in animals in the UK'.

To reduce non-essential use it will be necessary to monitor usage closely. Indications are that overall usage is still very high in some EU countries, and there are indications that use of several important antibiotics have been increasing. Reflecting this uncertainty in October 2011, the Environment Committee of the European Parliament adopted a resolution stating: 'Despite the ban of the use of antibiotics as growth promoters, there seems to be ***no significant decrease*** [our italics] in the consumption of antibiotics in the veterinary sector, which continue to be used systematically for 'prophylactic' purposes due to unsustainable agricultural practices.' [116]

To date the records and studies of the amounts of antibiotics intended for use in farm animals have presented a confusing picture that justifies the Alliance's recommendation for a universally recognised system of monitoring and reporting across the EU (See *Key recommendations*, page 22). In the UK, from 1998 to 2005, reported sales of 'therapeutic' antibiotics for food animals (excluding 'growth promoters') remained at a level of around 370 to 400 tonnes of active ingredient per year. However antibiotic usage per animal in the UK may have increased in real terms during that time due to the reducing numbers of animals over that period. Reported antibiotic sales for UK food animals *did* in fact decrease from 2006, when the EU ban on antibiotic growth promoters came into force, but was at 327 tonnes in 2008 [117] when there were 12% fewer cattle and around 40% fewer pigs than in 1998. Overall tonnage of antibiotics sold for food animals was slightly higher in 2009 than for 2008.[118]

Relying on such figures, the VMD has stated that there has been ***no change*** [our italics] in the tonnage of antibiotics sold per tonne of animals (rather than number of animals) slaughtered for food over the last 4 years ending 2009.[119] Yet the VMD itself admits that its figures 'should only be regarded as indicative of overall trends in sales'.

A study for the European Commission of the use of medicated feed across the EU concluded that evaluation by weight alone is no proof of reduced reliance on antibiotics. While data supplied for the study indicated that total consumption of antibiotics in the UK, for example, measured in tonnes of active substance, declined by 12% between 2002 and 2007, in terms of *potency,* antibiotic consumption declined by only 1%.[120]

Due to the increasing level of medical concern about antibiotic resistance, 10 EU countries have recently introduced programmes to monitor usage of antibiotics in animals, while a further 12 have started or are starting to collect consumption data. Known by their various acronyms, these include: DANMAP in Denmark, SVARM in Sweden, AFSSA in France, NORM-VET in Norway, FINRES-VET in Finland, MARAN in the Netherlands, the German Antibiotic Resistance Strategy (DART) and in the UK as overseen by the VMD.

A study on antibiotic sales data for nine of the countries over the period 2005 to 2009 was published just as this report for the Alliance to Save Our Antibiotics was being finalised.[121] That study by the European Medicines Agency (EMA) estimated antibiotic usage per kg of animals in each country for eight EU countries that had kept records: Czech Republic, Denmark, Finland, France, Netherlands, Norway, Sweden, UK, and also for Switzerland. Antibiotic usage per kg of animals was found to have decreased on average by 8.2% from 2005 to 2009 for these eight EU countries. ***This is far from the very substantial reduction that is really needed,*** and even that modest decrease may be misleading, because, as stated in the previous chapter, the decrease reported by EMA was mainly in sales of older tetracylines, which require a higher 'heavier' dose, while the sales of several other antibiotics that provide 'more punch per pound' and require lower doses actually increased.[123] The fluoroquinolones and the third and fourth generation cephalosporins were among the more potent, lower-dose antibiotics whose use increased between 2005 and 2009.

The EMA study also noted the 'substantial difference in the prescribing patterns [of antibiotics]…between the countries'.[123] It has become clear that what is needed is monitoring not only of the amounts of antibiotics used, but also of the way they are prescribed and used (see *Key recommendations*, page 22).

Presenting the findings at a seminar in September 2011,[124] the official who was leading the study put up a graph that appeared to indicate a correlation between sales of antibiotics and incidence of antibiotic resistance. This graph was not included in the published report.

An earlier study also by scientists from the EMA compared antibiotic use in 10 different European countries[125] and found that antibiotic use in Finland, Sweden and Norway was approximately four times (in Norway's case, five times) lower than for the UK, and approximately eight times lower than in the Netherlands. The study measured antibiotic use per weight of slaughtered pigs, poultry and cattle plus estimated weight of live dairy cattle. (Although the Netherlands, as a major exporter of live animals, would have received an overestimate of the true amount used per animal.)

Denmark's use was higher, but still only half the UK level. In 1992, an average of 100mg of antibiotics was used to produce each kilo of Danish pigmeat, but by 2008 it had been halved to 49 milligrams per kilo. Denmark's use of antibiotics per kilo of pork produced is about a fifth that used in intensive pig farms in the U.S. Yet Denmark has sustained its position as the world's largest exporter of pork produce.[126]

The fact that antibiotic use varies so widely between farms across Europe, besides reflecting the more concerted efforts Sweden and other Nordic countries have been making to reduce antibiotic use on farms since the 1980s, indicates ***there is scope for reduction through regulation, oversight and changes in farming practice***.[126]

Certainly, Europe is ahead of the U.S. where it has been estimated that 80% of all antibiotics produced are used in animals, with 70% of that total used for non-therapeutic treatment – much of it for growth promotion.[127] The situation

Practical strategies for preventing disease through breeding and good husbandry

Switching to extensive production systems

Less intensive systems, such as organic farms, have been shown to achieve higher levels of animal health together with lower levels of antibiotic use than intensive production systems. Recent studies in the UK[134,135], Norway[136] and Sweden[137] found 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 farms that rely on routine prophylactic antibiotics. In Norway, organic cows have been shown to have lower somatic cell counts (high counts indicate infection) in milk than conventional herds[138] and in Sweden organic dairy cows were found to have better udder health during production and as little as half the level of mastitis when checked at slaughter, compared to non-organic herds.[139]

Breeding animals for 'positive health', rather than as production units.

Breeding animals for robustness and positive health is increasingly recognised as an essential part of sustainable animal farming.[140,141] In contrast, intensive farming often uses animals bred primarily for high levels of production which put them under metabolic or physiological stress and increased risk of weakened immune systems – e.g. dairy cattle breeds selected primarily for milk production.[142,143]

Avoidance of 'mixing' unfamiliar animals

Introducing unfamiliar animals to a group or 'mixing' is a well-known source of stress and increases the risk of transmitting infections. According to the British Pig Executive in 2009, mixing is a 'danger time' for some infections and may require pigs to be medicated 'strategically' with antibiotics in feed or water.[144]

Later weaning

If too early or poorly managed, weaning can cause stress and lead to disease. Intensively reared piglets can legally be weaned and removed from their mother at 28 days old in the EU, as opposed to the minimum 40 days required under Soil Association organic farming standards (with a recommendation not to wean piglets until 56 days), or 3-4 months in natural conditions).[145] The stress of early weaning commonly causes diarrhoea and increased susceptibility to infection – and so leads to routine reliance on the antibiotics used to compensate. Later weaning helps to ensure that animals are more independent of their mother nutritionally, immunologically and psychologically, reducing stress and risk of scouring (acute diarrhoea, most frequently from *E.coli* infection).[146]

PHOTO: © COMPASSION IN WORLD FARMING

Later weaning allows proper, natural development of immunity.

Lower stocking densities

Intensively farmed meat chickens are confined for life in crowded and barren sheds, where by EU law they can be stocked at the equivalent of 42kg of birds per m^2 (reduced in the UK slightly to 39 kg/m^2) or around 20 birds per m^2. Typically 20-80,000 birds are kept in one shed, entirely covering the floor as they grow larger.

PHOTO: © COMPASSION IN WORLD FARMING

Free-range birds are less densely stocked; straw bales are provided for perching, fresh air is allowed to circulate.

Avoidance of 'thinning'

In densely stocked flocks, a proportion of birds may be removed for slaughter early ('thinned'), in order to meet the legal stocking density. This causes stress and increases risk of infection. According to the EFSA Panel on Biological Hazards, avoiding thinning reduces the risk of *Campylobacter* infection to consumers by 25%.[147]

Reducing journey times

Longer journeys increase stress and result in increased susceptibility to disease and increased shedding of pathogenic agents, including bacteria.[148] EFSA's Scientific Panel on Animal Health and Welfare advised, 'Transport should therefore be avoided wherever possible and journeys should be as short as possible.'[149] The Alliance backs the call from Compassion in World Farming for an EU-wide limit of eight hours for all journeys.

Ensuring adequate colostrum levels

The 'first milk', produced in all nursing mammals, contains key antibodies protecting against disease, and should be given to all newborn piglets and calves.

Maintaining air quality

Respiratory disease can be reduced by maintaining good air quality and ventilation in animal housing.

Veterinary health plan

A regularly reviewed veterinary health plan should be drawn up between the farmer and the veterinary surgeon. The best plans focus on establishing good management and husbandry practices to minimise reliance on medicines – including correct choice of breed of animal for the specific farm environment; providing high-quality feed; access to pasture and regular exercise for the animals; appropriate housing and stocking densities – as well as the routine veterinary visits, disease checks and recording of all outbreaks and treatments.

These practical ways for farmers to manage and prevent disease outbreaks comprise a blueprint for better farming, i.e. farming aimed at maintaining 'positive health' in animals, rather than resorting to drugs to circumvent likely disease due to poor welfare conditions. Farmers alone cannot effect such a change: a move to better farming systems will need the intervention of policy makers and the support of both retailers and consumers.

has prompted the U.S. human well-being and environmental charity, The Pew Trust, to run a major public campaign to raise awareness of the issue and to end all non-essential use of antibiotics in agriculture.[128]

While follow-up research to the EU ban shows some success in reducing some types of antibiotic resistance substantially,[129] it will take time to assess the full impact as, according to EFSA's review of resistance in food-borne zoonoses (diseases that can be transmitted from animals to humans) of 2010, 'the resistance genes still remain present in the bacterial population for a number of years'.[130]

The loophole of therapeutic use

The ban on growth promoter use of antibiotics in Europe has not in any case halted all other non-essential uses in animal production. On the contrary, there have been increases in some uses of therapeutic antibiotics, in ways that the Alliance would argue are not therapeutic. In the Netherlands, total 'therapeutic' antibiotic use doubled between 1999 and 2007 (mg of antibiotic per kg of live animal). The number of daily doses per animal year increased by 72% for broilers and by 27% for fattening pigs in 2007 compared to 2004. According to the 2007 report on antibiotic usage in The Netherlands: 'A part of the increase in therapeutic antibiotic use in the years 1998 to 2006 may be accounted for by a substitution of growth promoters.'[131]

A number of antibiotics while banned as growth promoters are still licensed to be used as therapeutic or preventive medicines. One of those banned, Tylosin, is authorised for adding to pig feed to prevent and control enteritis 'until the end of the period of risk'.[132] Similarly, Lincomycin, used as a 'growth promoter' in the U.S., is currently licensed as a therapeutic antibiotic in the UK.

The routine use of antibiotics in agriculture is associated closely with industrial livestock systems – indicated by the fact that around 90% of all farm antibiotic sales in the UK are for pigs and poultry,[133] the farm animals that are most frequently intensively reared. It is possible that animals can only be raised under such conditions through routine prophylactic use of antibiotics at low doses to suppress infections.

Such systems inevitably compromise the animals' health and weaken their natural immune systems, and without antibiotics this would result in disease development and spread. Our position is that such systems are both unethical and unsustainable.

KEY RECOMMENDATIONS

The Alliance to Save Our Antibiotics recommends the following actions

An EU-wide robust reduction strategy

The European Commission and Member States must urgently develop a more robust strategy to reduce antibiotic use in agriculture to a minimum. This should be linked to a legally-binding timetable for the phased ending of all routine prophylactic, non-therapeutic use of antibiotics. In effect, this would restrict treatment to individual sick animals under veterinary supervision, and to groups of animals where a disease has broken out within that group.

This strategy should include:

- a target to reduce overall antibiotic use on EU farms by 50% by 2015;
- the immediate closing of the loophole whereby via a veterinary prescription antibiotics can still be used in the EU as 'growth promoters' and as cheap insurance against the possibility of a disease outbreak;
- specific controls on all use in livestock of two antibiotic classes identified and prioritised as 'critically important' for human medicine by the WHO – the quinolones, and third and fourth generation cephalosporins. These should only be used in life-threatening situations where tests or local knowledge indicate that no other antibiotics would be effective. In addition, the use of fluoroquinolones in poultry should be prohibited, as in the U.S. The use of third and fourth generation cephalosporins in poultry should be prevented by removing the right of vets to use these drugs 'off-label' [i] ;
- The macrolide antibiotics are also classed by the WHO as 'critically important'. Their main current use in pig and poultry production is prophylactic and thus should be phased out. In dairy farming they are often relied on for the treatment of disease due to their superior penetration (the macrolide tylosin is the most frequently injected antibiotic on dairy farms). All therapeutic use in cattle, pigs, poultry and other species should be limited to situations where no equally effective antibiotics are available.

[i] No third or fourth generation cephalosporins are licensed for use in poultry in the EU, however vets can still use them 'off-label' at their own discretion.

- active promotion of, and support for rearing systems and husbandry that positively improve animal health and welfare.

[The Netherlands has already put forward proposals to reduce usage from 2009 levels by 20% by 2011 and by 50% by 2013.[150] France has also set a 25% reduction target for farm animal use of antibiotics over five years.]

Monitoring and reporting

What is most urgently needed is a harmonisation across all EU countries of the existing systems of monitoring and reporting, as well as more detailed collection of data on the extent of antibiotic usage, to ensure that we are making rapid progress towards reducing antibiotic use on farms. In tandem, the European Commission should conduct and publish an annual review of the state of antibiotic use in agriculture and the associated patterns of resistance.

Greater political and financial support should be given to the existing national and EU programmes of monitoring and testing farm animals for resistant bacterial strains in order to enable the EU to collate and publish the relevant data.

This should include monitoring of:

- antibiotic usage and prescribing patterns in farm animals – including the reasons for use;
- prescribing patterns most likely to encourage antibiotic resistant strains or gene transfer;
- levels of resistance to antibiotics in a wide range of indicator bacteria;
- progress and compliance with overall antibiotic reduction.

All processes need to be transparent and the information freely and publicly available. Testing should include bacterial samples from live animals on farms, farm environments, farmers, veterinary surgeons and workers in contact with the animals, as well as carcasses in slaughterhouses, and meat, milk and eggs on sale.

Research to reduce antibiotic resistance

The European Commission should develop programmes of research to reduce antibiotic use through farming systems and management which improve animal health and welfare by reducing stress and the risk of disease.

Outreach to vets and farmers

More training and advice needs to be given to veterinarians and farmers on strategies to minimise the use of antibiotics and the development of antibiotic-resistance.

Save Our Antibiotics – the need to act

The Alliance further calls for action at all levels of society to reduce our reliance on antibiotics, including awareness-raising directed at:

- Doctors
- Veterinary Surgeons
- Farmers
- Retailers
- Consumers
- The public

Doctors

Many problems with antibiotic-resistant infections are caused exclusively by the over-use of antibiotics in human medicine. Key causes are:

- over-prescribing by doctors – to satisfy patients' demand for the 'pill for all ills';
- patients failing to complete courses of treatment – enabling some bacteria to survive and develop resistance.

The UK Government and British Medical Association (BMA) should continue to run public information campaigns (e.g. European Antibiotic Awareness Day, November 18) on these points.

Veterinary Surgeons

In the UK, the British Veterinary Association (BVA) in 2009 took the welcome step of issuing eight-point plan for the responsible administration and use of antibiotics which, if adhered to by all UK vets, would be a positive contribution to reducing routine and unnecessary reliance on antibiotics. The Alliance also welcomes the joint letter issued by the BVA and BMA in July 2011 urging 'all vets and doctors to ensure that they are using antimicrobials responsibly' and which acknowledged 'it is equally important that non-medical and non-veterinary use is seriously restricted'.[151]

Yet, as this report shows, overall use of antibiotics in livestock has not been reduced sufficiently. More needs to be done. If voluntary guidance does not reduce non-essential prescribing of antibiotics, then enforceable controls should be introduced, as in the Netherlands where vets can be fined for inappropriate prescribing of antibiotics in animal feed.

Vets, like doctors with their patients, can find themselves under pressure to prescribe antibiotics. In the UK, pharmaceutical companies can advertise directly to farmers – a key source of such pressure. The Alliance, like the BVA, is calling for the UK government to ban all advertising of antibiotics directly to farmers (as is the case in other EU countries).

The veterinary profession's main emphasis (and the bulk of a vet's income) should be derived from pre-empting disease outbreak by advice on good husbandry practice and early diagnosis, and from treatment of individual animals.

Farmers

Pressure on farmgate prices has driven intensification across many sectors – for farm animals this has resulted in their metabolism, health and welfare being compromised to maximise production of milk, meat, and eggs – with a resulting dependence on antibiotics to mask the consequent stresses on the animal and contain disease outbreaks.

A significant percentage of antibiotic use falls to a relatively small number of farms. In the Netherlands in 2007 it was found that just 25% of all farms accounted for nearly 50% of the total use of antibiotics.[152] In the UK, 640 farms are authorised to manufacture medicated feed on farm.[153] These figures suggest that changes in practice on a relatively small number of farms could make a significant difference.

Denmark has introduced a 'yellow card' system for farmers, under which control of antibiotic use is focussed at the farm level. Expected thresholds of antibiotic use are set for different types of farm and if that threshold is exceeded then farmers are required to take corrective action; fines can also be imposed.

An obvious and available strategy for farmers wishing to reduce their reliance on antibiotics is to switch to less-intensive animal rearing systems. Research published by Defra in 2006 compared antibiotic use on 13 organic pig and poultry farms with that on 12 non-organic farms. The research found that compared to the non-organic farms, the level of antibiotic use on organic farms 'was very low, with many of the farms never using antimicrobials'.[154]

A recent U.S. study comparing the prevalence of antibiotic-resistant bacteria in poultry houses that had recently switched to organic methods with the remaining non-organic poultry houses, indicated a much lower incidence of resistant bacteria in the newly organic poultry houses. 42% of *Enterococcus faecalis* bacteria remained multi-drug-resistant in the non-organic poultry houses, compared to 10% isolated from the newly-converted organic houses. For *Enterococcus faecium*, the contrast was even greater, with 84% of the bacteria multi-drug-resistant in the non-organic poultry houses against 17% for those recently converted.[155]

Retailers

Europe's consumers and citizens have made it overwhelmingly clear that they do not want food from animals fed with antibiotics. In the 2010 Special Eurobarometer survey on food-related risks, 30% of respondents were 'very worried' about the possibility of residues of antibiotics in food (See Appendix 2), a similar level of concern as for food containing pollutants such as mercury, dioxins and pesticides.[156]

Sociological studies funded by the EU in seven countries (France, UK, Hungary, Italy, Norway, Sweden and the Netherlands) show people associate antibiotic use in food animals with lower standards of food safety, food quality and animal welfare – and specifically with 'factory-farming', where 'increased production is favoured at any cost' to human health or animal welfare.[157]

The major food retailers should:

- address their customers' concern by offering foodstuffs produced from livestock reared without routine reliance on antibiotics;
- require their suppliers to demonstrate minimum use of antibiotics and zero reliance on routine use.

To achieve this retailers could increase the range of animal produce on sale from farming systems able to demonstrate lower-reliance on antibiotics.

The key step retailers can take to help reduce misuse of antibiotics is to pay farmers prices that enable them to supply milk, meat, eggs and other animal products from farming systems that require minimal use of antibiotics.

The retailers should also use their considerable influence to lobby the government and EU to support such systems.

Consumers and the public

Many people believe (understandably) that the ban on antibiotic growth promoters in the EU has all but eliminated antibiotic use in animal production. Yet most of Europe's consumers are still eating food from animals routinely dosed with antibiotics.

Consumer groups, public health bodies, campaign organisations and family doctors must help people to make the link between the food they choose to buy and eat and the long-term effectiveness of the antibiotics they rely on to protect themselves and their families from harmful infections.

They should also lobby the responsible EU and UK government agencies to provide transparent and accessible information on the true situation of antibiotic use in human food production and its impacts on human health. Food animals are exposed to antibiotics on more occasions and for a greater proportion of their lives than would ever happen to an average healthy human being. Yet government agencies such as the UK's Food Standards Agency and Health Protection Agency are failing to give people the full picture of antibiotic use in intensive-farming.

To conserve the 'precious resource' of antibiotics, consumers should ask for food produced with minimal use of antibiotics. Consumers are not just consumers of food, but also of antibiotics as prescribed by doctors. As such, consumers must address their own personal reliance on antibiotics, using them only for significant health problems and always completing the full course of treatment.

The future of farming

Finally, as the key cause of antibiotic resistance in agriculture is factory-farming, there is a need for fundamental reform so that lower-intensity, higher-welfare animal farming becomes the norm throughout Europe.

Agricultural policy and farming subsidies should promote a move away from industrial livestock production (factory farming) to rearing systems and husbandry that improves animal health and welfare (i.e. more sustainable and humane forms of animal husbandry, such as extensive grassland rearing and integrated crop-livestock farming). Such systems are available and are commercially viable. In the EU this should include:

- active promotion of such systems;
- more training and advice for vets and farmers;
- Common Agricultural Policy reform that uses subsidies in future to encourage systems that don't use antibiotics prophylactically, while discouraging those that do.

The EU has done more than most other regions of the world to monitor farm animal welfare and outlaw some of the worst intensive farming practices (battery cages, sow stalls, veal crates).

EU reforms have had an important impact in encouraging similar changes in practices worldwide, through either voluntary action by industry or through law.

The EU should now take the lead again with effective action to end the misuse of antibiotics in farming, and ensure the conditions are provided for the animals to maintain good health based on their own immune systems rather than through routine reliance on antibiotics.

This would be in the interests of Europe's farmers, establishing their reputation globally for high-quality standards while meeting the demand of their customers, who seek higher standards of animal welfare, more transparency and better quality in their food production.

GLOSSARY AND APPENDICES

Antibiotics Medicines used to control infectious diseases in humans and animals.

Derived originally from substances produced by one micro-organism which have the ability to kill or inhibit the growth or multiplication (reproduction) of other micro-organisms. These have then been identified and cultured naturally or synthetically to create the 'wonder drugs' that human medicine has come to rely upon to fight once commonplace infections and enable increasingly complex and invasive surgery.

The vast majority of antibiotics are used to kill or inhibit the growth of bacteria.

Antibiotics are subdivided into two categories, broad spectrum and narrow spectrum, based on the number and types of bacteria they affect. Broad spectrum antibiotics are effective against many types of bacteria, while 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.

Antibacterials Substances that kill or inhibit the growth of bacteria on human and environmental surfaces, i.e. hygiene aids like antibacterial cleansers and hand sanitizers.

Antimicrobials Drugs, chemicals, or other substances 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. Antibiotics are a type of antimicrobial, but not all antimicrobials are antibiotics. For example, anti-viral drugs and anti-fungal drugs are also antimicrobials, but not antibiotics. Antimicrobial agents include antibacterials, antibiotics, antivirals, antifungals, and antiparasitic drugs.

Antivirals Substances that kill or inhibit the growth of viruses.

Bacteria Microscopic, single-celled organisms that are present everywhere, including on our skin and in our gut (where they aid our digestion). Beneficial bacteria have been exploited for thousands of years by humans in brewing, cheese-making and as aids to healthy digestion in 'pro-biotic' yoghurt. However, many forms of bacteria are harmful to humans and can cause life-threatening infections and death.

Colostrum The 'first milk' produced by all nursing mammals, including humans, providing key antibodies that build the new-born's immune system.

Dry Cow Therapy 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. This 'dry' period typically lasts for around 60 days before the cow again gives birth (to produce milk, a cow has to have given birth). The new-born calf usually stays with its mother for a couple of days – long enough to have received the rich immunity boosting special milk, colostrum. Thereafter, the calf is reared away from its mother, who re-enters the herd for milking for around 305 days. Three months after giving birth, she will be artificially inseminated or 'served' by a bull so as to become pregnant again and sustain the milk production cycle. The dry period is seen as a particularly vulnerable period when the cow's udder can be prone to various infections – mastitis being the most common. Hence, the practice of 'Dry Cow Therapy', when in addition to adjusting the animal's diet, antibiotics are inserted ('infused') up the teats into the udder to prevent infections.

First-line treatment The recommended initial treatment of any ailment, illness or disease on the basis of observed evidence that it works.

Genes A segment of 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/Gram-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 A major cause of increasing antibiotic resistance, whereby genes and the information they contain are transferred between bacteria that are not directly related, i.e. the genetic information is not passed on by the usual process of descent from a parent.

Metaphylactic Where, although only a few animals are found to be sick, the whole flock, herd or group of animals is treated to prevent disease spread.

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'). The term microbe tends to be used to refer to the harmful, disease causing micro-organisms - including both bacteria and viruses.

Pathogenic Capable of causing disease.

Plasmid A small loop of genetic material, not part of the chromosomes, that can be easily transferred between bacteria. Plasmids contain a few genes, which usually code for proteins, especially enzymes, some of which confer resistance to 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.

Residues When drugs are administered to food animals, residues of the drugs can remain in food products such as meat, eggs and milk. Regulation is intended to ensure that any traces of drugs ingested by people are below a safe limit. A 'withdrawal period' of days, weeks or months before an animal that has been treated can go for slaughter and so enter the human food-chain is required for antibiotic drugs (See Appendix 2).

Resistance The ability of bacteria or other micro-organisms to survive and reproduce in the presence of antibiotic drugs that were previously effective against them.

Shiga toxin Toxin produced by the Shigella dysenteriae bacteria and named after the scientist Kiyoshi Shiga, who first described it.

'Superbugs' 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.

Therapeutic The treating of individual sick animals or people.

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. Viruses infiltrate the host body and use it to reproduce; whereas bacteria can survive and reproduce independently. 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.

APPENDICES

APPENDIX 1:
Frequently occurring diseases of different farm animals likely to be treated with antibiotics.[158]

SPECIES	CONDITION	FLOCK/HERD USE OF ANTIBIOTICS?	INDIVIDUAL USE OF ANTIBIOTICS?
dairy cows	mastitis (infection of the udder)	yes, for prevention	yes
	uterine infections		yes
calves	enteritis	yes	
	pneumonia	yes	yes
	diphtheria	yes	yes
	umbilical infections		yes
	septicaemia		yes
	foot-rot		yes
breeding sows	joint infections		yes
	foot-rot		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 infection	yes	
	septicaemia	yes	
	yolk sac infection (newly hatched chicks)	yes	

APPENDIX 2:
Antibiotic residues

When antibiotics are administered to food animals, residues can remain in food products such as meat, eggs and milk. Regulation is intended to ensure that the traces of drugs that are ingested by people are kept below a safe limit. A 'withdrawal period' of days, weeks or months is set after administration of an antibiotic drug, during which the animal cannot go into the food-chain. Codex Alimentarius, the international food standards agency of the Food and Agriculture Organisation and the World Health Organization, publishes the 'Maximum Residue Limits' (MRLs) of certain veterinary drugs that are considered to be safe in food. Questions remain, however, about the scientific robustness and objectivity of decisions about 'safe limits' to drug residues in food.

At EU and national levels, MRLs are set for drugs that have been approved for use in food animals. Monitoring is carried out under European Directive 96/23/EC by testing samples of meat, imports and other foods for residues that are over the accepted limit. In Britain, sampling is carried out by the Veterinary Residues Committee and through a National Surveillance Scheme. Nearly 38,000 samples were tested in 2008,[159] corresponding to 4 samples per 100,000 of the 893 million animals slaughtered annually for food in the UK.[160]

The Veterinary Residues Committee has reassured consumers that 'British farmers use medicines responsibly' and that 'most samples tested contain no detectable residues of antibiotics'.[161] In 2008 the total number of samples tested that contained antibiotic residues above the accepted limit was low (only 77 samples contained any veterinary medical product). But within these, at least one sample was found containing the following antibiotics at over the action level or MRL:[162]

- Eggs: sulphonamide, enrofloxacin (12 times over the 'action level')
- Milk: first generation cephalosporin (2.5 times the MRL)
- Chicken and turkey meat: chlortetracycline (samples at 2.8 and 2.2 times the MRL)
- Calf kidney: amoxicillin, sulphonamide (sample at 2.7 times the MRL), florfenicol
- Pig kidney: chlortetracycline (samples at 2.8, 3.5 and 4.5 times the MRL), oxytetracycline

Residues at concentrations below the action level or MRL are not recorded in the public surveillance reports, so greater numbers of animal-derived foods may be contaminated with traces of the antibiotics or other veterinary drugs that the animals received during their lives.

This report does not specifically address the issue of antibiotic residues in food.

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CASE STUDY OF A HEALTH CRISIS

How human health is under threat from over-use of antibiotics in intensive livestock farming

A report for the Alliance to Save Our Antibiotics

Save Our Antibiotics

About this report
Over-use of antibiotics is recognised as the main reason for the increase in antibiotic resistance. In particular, low-level use of antibiotics (such as incompleted courses of treatment) allows the new strains with their potentially deadly resistance to develop. Human antibiotic over-use may well be the chief culprit, but in intensive animal farming there are some appalling lapses of common sense, namely the routine low-level use of antibiotics (metaphylaxis and prophylaxis), the use worldwide of antibiotics as growth promoters (technically banned in the EU) and the continued widespread use of certain antibiotics that should be banned for use in farm animals outside exceptional circumstances. This report identifies the most objectionable current practices, makes key recommendations for immediate restrictions and proposes a viable alternative model of good animal health.

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