HM Government

UK One Health Report
Joint report on human and animal antibiotic use, sales and resistance, 2013

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Background

Antibiotics are critical for treating infections in human and veterinary medicine and increasing resistance in bacteria is considered a major threat in both fields. Minimising the unnecessary and inappropriate use of antibiotics reduces the selective pressure that favours the emergence and spread of resistant bacteria and is an essential component of strategies to safeguard antibiotics critical for treatment of serious human infections. Resistant bacteria from animals and humans can transmit in both directions, through human contact with farm, wildlife or companion animals or their environments, through ingestion of contaminated food (both imported and local produced animal and vegetable or fruit items) and through contact with effluent waste from humans, animals and industry (Figure 1). Thus an integrated – One Health - approach to surveillance and action is needed.
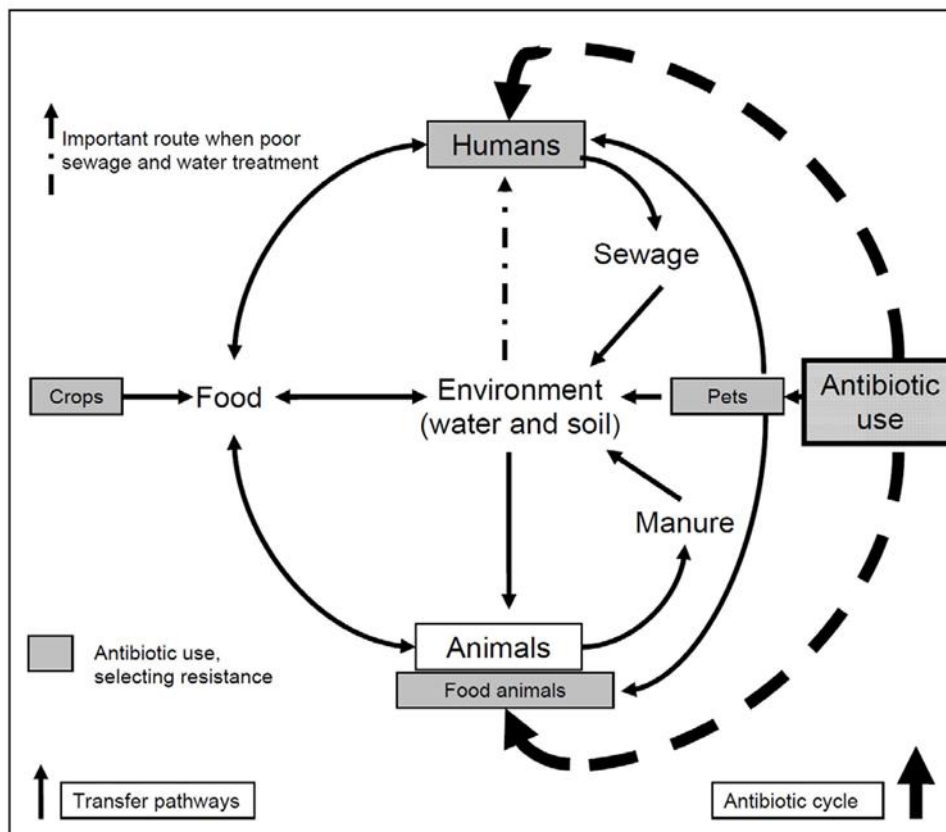
Figure 1. Interactions between humans, animals, food, environment and antibiotics. Interactions occur across local, regional, national and international boundaries with movement of humans, animals, and food within and between countries.

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This report brings together the most recently available UK data on antibiotic resistance in key bacteria that are common to animals and humans and details the amount of antibiotics sold for animal health and welfare and antibiotics prescribed to humans, with the following aims:

- to encourage further joint working between the human and animal sectors
- to identify the emerging and current antibiotic resistance threats in three key bacteria in humans and animals
- to identify differences in surveillance methodology and data gaps that limit our ability to compare trends between the two fields, both within the UK and across Europe
- to evaluate available data from humans and animals side by side and begin to assess the relationship between antibiotic sales, use and resistance across the two sectors
- to develop recommendations to improve the surveillance of antibiotic use and resistance in humans and animals

There are many caveats surrounding interpretation of the data presented in this report and in some cases the methods of data collection vary to such an extent that they cannot be meaningfully compared. This highlights the joint responsibility of the human and animal sectors in tackling antimicrobial resistance (AMR) and the importance of strengthened collaboration between them. The bacteria selected for this report are based on the following: bacteria that are transmitted through the food-borne route (*Salmonella* and *Campylobacter*) and *Escherichia coli*, an important organism that lives in the gut of both humans and animals and can cause opportunistic and invasive disease in all species.

Escherichia coli

In 2013, 35,716 bloodstream infections in people due to *E. coli* were reported, making it the commonest cause of bloodstream infection in the UK. Antibiotic resistance results were available for more than 70% of these infections. Third-generation cephalosporin (cefotaxime and/or ceftazidime) resistance was reported in 10%, ciprofloxacin resistance in 18%, piperacillin-tazobactam resistance in 9% and carbapenem resistance in less than 1%. These are important antibiotics for the treatment of this infection.

In 2013, clinical surveillance yielded 3,320 isolates of *E. coli* from all livestock groups. Resistance to the third-generation cephalosporins cefotaxime and ceftazidime was seen in 11% and 6%, respectively; no antibiotic susceptibility testing (AST) for

ciprofloxacin, piperacillin-tazobactam or carbapenems was performed.[i] Enrofloxacin resistance was 6%; ciprofloxacin is an active metabolite of enrofloxacin, an antibiotic authorised solely for veterinary use. EU harmonised surveillance from pigs reported <1% of cefotaxime and ciprofloxacin resistance; carbapenems and piperacillin-tazobactam were not tested.[ii]

Campylobacter

Campylobacter gastroenteritis was the most common human-acquired bacterial zoonosis (infections in animals that can be transmitted to humans), with 66, 575 cases reported in 2013. The majority of infections are self-limiting and do not require antibiotic treatment. However, in cases of invasive infection, severe disease or when individuals are immunocompromised, antibiotic treatment is required. Antibiotic resistance results were available for approximately 45% of bacterial isolates. Ciprofloxacin resistance was reported in 42% and erythromycin resistance in 2.5%. EU-harmonised surveillance of AMR in healthy pigs at slaughter yielded 141 *Campylobacter coli* isolates with 13% ciprofloxacin resistance and 28% erythromycin resistance. Similar surveillance performed in broiler chickens found 31% ciprofloxacin resistance in 61 *C. jejuni* isolates, 55% resistance in 33 *C. coli* and 3% erythromycin resistance in 33 *C. coli*.

Salmonella

As with *Campylobacter*, *Salmonella* infections are frequently self-limiting and require no treatment; however, antibiotics may be necessary in severe cases. In 2013, 8,459 human cases of non-typhoidal *Salmonella* infections were reported in the UK through routine laboratory surveillance, with more than 70% referred to the reference laboratories for speciation and antibiotic resistance testing. Resistance to cefotaxime and ciprofloxacin was noted in 2% and 16% of tested isolates, respectively.

Salmonella species vary depending on the animal species from which they are isolated. Clinical and statutory surveillance of *Salmonella* in animals showed very different resistance profiles across animal species: antibiotic resistance was uncommon in *Salmonella* species from sheep or cattle but more frequent in *Salmonella* species from pigs or turkeys. EU-harmonised surveillance was performed in healthy broilers, layers, turkeys and pigs in 2013. Cefotaxime resistance was rare: in *Salmonella* isolated from pigs it was 2% and was not detected in other animals. Ciprofloxacin resistance was not detected. In 2,276 isolates from clinical surveillance cefotaxime and ciprofloxacin resistance were rare. Cefotaxime resistance was detected in less than 1% of pig isolates, and not in isolates from other animals, and ciprofloxacin resistance was only detected in poultry; 1% and 7% respectively for chickens and turkeys.

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i. These antibiotics are not used in livestock.
ii. These antibiotics are not used in livestock

Antibiotic prescriptions and sales in humans and animals

In 2013, total antibiotics dispensed to humans through prescriptions was 531.2 tonnes[iii] and total sales for animal use comprised 418.7 tonnes[iv]. Consumption of systemic antibiotics and intestinal antibiotics in humans equated to 135mg per kg of human biomass. Sales of antibiotics for systemic, intramammary and intestinal use in food-producing animals equated to 55.6mg/kg.

The most frequently used antibiotics in humans were penicillins (64%) and tetracyclines (10%). Antibiotics sold for animal use were most frequently tetracyclines (43.5%) and penicillins (21.7%).

Four antibiotic groups are defined by the World Health Organisation (WHO) as critically important for human use: macrolides, quinolones, cephalosporins and glycopeptides. More of these antibiotics are used in humans than animals.

Discussion

This report is an important first step in building the data required to contain antibiotic resistance and to develop coordinated surveillance activities in human and animal health across the UK and Europe. For the three bacteria in this report, significant resistance is identified from human and animal surveillance across a wide range of antibiotics. Inference on the spread of resistance in terms of the methods of transfer of genes and bacteria is outside the scope of this report.

In the collation of data for this report, we have brought together human and animal antibiotic resistance data from the four UK health administrations, and in addition highlighted the initial results from the EU harmonised monitoring of AMR in food-producing animals. We have also collected and compared antibiotic use across humans and animals.

This work has highlighted the following key public health recommendations for national human and animal organisations to take forward. The next report will update on the progress towards these recommendations.

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iii. This includes data from all publicly funded prescriptions in primary care and secondary care. This is incomplete as there is no method to collect private prescriptions. The estimated total is c 590 tonnes.
iv Based on using the human ATC codes to ensure comparability. For all ATC codes, the total sales of antibiotics sold for use in animals is 420 tonnes.

Recommendations

Recommendation 1

Public health organisations should work with clinical laboratory colleagues to ensure that all *Salmonella* species are sent to the relevant reference laboratories for speciation and antimicrobial susceptibility testing. The referral form should include data on foreign travel, including countries visited, in the previous four weeks.

Recommendation 2

Public health organisations should scope the development of a national sentinel surveillance system for *Campylobacter* isolates collected from human infections. In addition, public health organisations should highlight the importance of identifying *Campylobacter* to a species rather than genus level, as different species have different antibiotic profiles.

Recommendation 3

Public health organisations should support the work of professional organisations to transition UK clinical laboratories to a single standardised nationally agreed methodology for routine antibiotic testing in 2016.

Recommendation 4

Public health organisations should work with professional organisations to develop guidance related to recommended antibiotic and bacterial combinations, which should be tested and reported by clinical laboratories for key One Health pathogens. Animal health organisations should review the antibiotics tested from clinical veterinarian samples and through the EU harmonised monitoring in animals to align with key antibiotics required for human treatment.

Recommendation 5

Human public health reference laboratories should follow the EU protocol for harmonised monitoring of antimicrobial resistance in human *Salmonella* and *Campylobacter* isolates.

Recommendation 6

Public health organisations should explore data available on human sales of antibiotics from manufacturers and holders of human antibiotic marketing authorisations.

Recommendation 7

The Veterinary Medicines Directorate (VMD) will conduct carbapenem resistance monitoring (as part of the EU monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria in accordance with the EU legislation, Commission Decision 2013/652/EU), a year earlier than mandated.

Recommendation 8

VMD will participate in the protocol development of the European Surveillance Veterinary Antimicrobial Consumption (ESVAC) project to collect farm level data from the pig sector; and investigate and facilitate options for collecting accurate antibiotic consumption data at an individual farm level.

Recommendation 9

Public and professional One Health activities should be enhanced through engagement with the European Antibiotic Awareness Day (EAAD) campaign and aligning training programmes for human and animal health professionals.

Recommendation 10

The human and animal surveillance bodies should produce a further report in two years, encompassing robust data collected by the Food Standards Agency (FSA) on the burden of AMR in imported food animals.

Introduction

Antibiotic resistance is a natural phenomenon in which bacteria evolve and develop traits which enable them to survive exposure to antibiotics (1). In the past, the problem of resistance to antibiotics was addressed by developing new antibiotics to which clinically important bacteria were not (at least initially) resistant. However, there is currently a relative lack of new antibiotic classes that are likely to become available for use in the near future. As antibiotics are used in both humans and animals, and since bacteria (including those that are resistant to antibiotics) can pass between the two populations, antibiotic resistance is very much a "One Health" issue. It cannot be tackled effectively without a joined up approach to surveillance and action. The One Health approach is a key part of the UK cross-government five-year antimicrobial resistance (AMR) strategy (including optimal use of antibiotics) 2013-2018 (2).

Why is the One Health approach important?

Bacteria become resistant to antibiotics by either mutation or transfer of resistance genes from other bacteria. In both humans and animals the use of antibiotics provides pressure that favours the selection of resistant strains of bacteria. Resistant bacteria can then spread between humans through person to person contact in the community and in hospitals. Environmental reservoirs are an important vector in hospitals. Increasingly, the impacts of travel and health tourism are also recognised as a route of acquisition of resistant bacteria in humans (3). Furthermore, resistant bacteria from animals and humans can transmit in both directions, through human contact with farm, wildlife or companion animals or their environments, through ingestion of contaminated food (both imported and local produced animal and vegetable or fruit items) and through contact with effluent waste from humans, animals and industry (Figure 1).
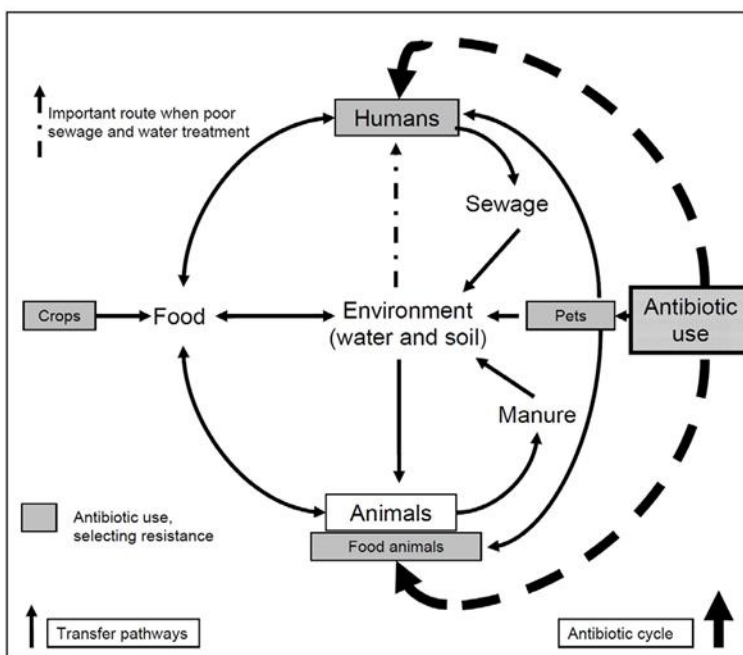
Figure 1. Interactions between humans, animals, food, environment and antibiotics. Interactions occur across local, regional, national and international boundaries with movement of humans, animals, and food within and between countries.

Key One Health bacteria

One of the best understood routes of bacterial transfer between animals and humans is foodborne transmission of bacteria; the commonest are *Campylobacter* and *Salmonella*. If resistance arises in these bacteria then this route is a clear potential avenue for transmission of antibiotic resistance from animals to humans (4). In addition, the commonest bacteria causing infection in humans is *Escherichia coli,* which is also a key commensal bacterium in human and animal gut flora. The scope of this report will therefore focus on resistance in *Campylobacter* spp*., Salmonella* spp. and *E. coli*.

Salmonella spp. and *Campylobacter* spp. are bacteria which occur naturally in animals, without necessarily causing disease, but are recognised causes of zoonotic infections. They are most often associated with foodborne transmission via contaminated meat, and are considered to be the most common cause of bacterial food poisoning in people in the UK. They can also be transmitted to humans via direct contact with animals and less commonly through human-to-human transmission. This report does not include infections due to *S. typhi* or *S. paratyphi*, as more than 99% of UK cases are related to travel abroad. Many cases of *Salmonella* or *Campylobacter* food poisoning are self-limiting and require no treatment; however, antibiotics may be necessary in severe cases. The prospect of reduced treatment options related to antibiotic resistance, therefore poses a well-defined public health concern.

E. coli is a bacterium which lives, predominantly as a commensal organism, in the gastrointestinal tract of animals and humans. Each livestock species normally carries a diverse population of *E. coli* including some dominant and minor types. Many are opportunistic pathogens, able to cause disease in animals under certain circumstances (for example, most can cause bovine mastitis if they get into the bovine udder). Other strains are more specialised and possess certain virulence factors, such as adhesins allowing them to colonise the intestine of calves and cause diarrhoea. Certain strains (for example verotoxigenic *E. coli*), cause gastrointestinal and/or invasive disease in humans following zoonotic transmission from animals.

In the UK, *E. coli* is the most frequent cause of bloodstream infections and urinary tract infections in humans and rates of resistant infections caused by these bacteria are increasing; therefore antibiotic resistance in *E. coli* is a public health priority. While animal strains of *E. coli* constitute a potential reservoir of resistance that can pass to humans by direct or indirect routes, the relative significance of resistance in *E. coli* found in animals to resistance occurring in *E. coli* causing infections in humans is not well elucidated (5). Elucidation of the relationship between resistance in *E. coli* from animals and humans requires integrated surveillance of the resistance profiles of commensal and invasive bacteria from animals and humans. A fuller understanding of the underlying epidemiology of resistance in *E. coli* from animals and humans will aid

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the rational development of interventions aimed at reducing levels of resistance in both veterinary and human medicine.

Importance of monitoring Antibiotic Use

Antibiotics are used in both humans and animal health and welfare both for treatment or prevention of infections. The use of antibiotics is widely accepted as a driver for the selection of resistant bacteria. With limited new antibiotic treatment agents in development, there are less antibiotic options available to treat resistant bacteria causing human and animal infections. Prudent prescribing must occur in both humans and animals to maintain effectiveness of the antibiotics that are considered critically important. It is therefore essential to understand how antibiotics are used and evaluate how prescribing can be optimised in human and veterinary medicine.

This report presents data on antibiotic use in humans from primary and secondary healthcare alongside the quantity of antibiotics sold for use in veterinary medicine. Although not directly comparable, assessment of these antibiotic prescription and sales data enables some understanding of the impact of antibiotic use on the resistance patterns observed. It also highlights the Critically Important Antimicrobials as defined by the World Health Organisation (WHO) (6). The WHO have prioritised four groups of antibiotics (macrolides, quinolones, cephalosporins and glycopeptides) as critically important antibiotics, based on the high numbers of people affected by diseases where a specific antibiotic is the sole or one of only a few options available to treat an infection or where there is high frequency of use of the antibiotic for any indication in human medicine, as usage may favour selection of resistance.

Aims of the report

The first UK "One Health" report on antibiotic usage and resistance in humans and animals was published in 2007, based on selected surveillance data from 2004 (7).

The present report brings together the most recently available data (from 2013) on antibiotic resistance, antibiotic sales (animals) and antibiotic use (humans), with the following aims:

- to encourage further joint working between the human and animal sectors
- to identify the emerging and current antibiotic resistance threats in key bacteria in humans and animals
- to identify differences in surveillance methodology and data gaps that limit our ability to compare trends between the two fields, both within the UK and across Europe
- to evaluate available data from humans and animals side by side and begin to assess the relationship between antibiotic sales, use and resistance across the two sectors
- to develop recommendations to improve the surveillance of antibiotic use and resistance in humans and animals

There are many caveats surrounding interpretation of the data presented in this report and in some cases the methods of data collection vary to the extent that they cannot be meaningfully compared. This highlights the joint responsibility of the human and animal sectors in tackling AMR and the importance of strengthened collaboration between them.

Methods

Antibiotic Resistance

Antimicrobial susceptibility testing (AST) for bacteria

Microbiology laboratories use three main antimicrobial susceptibility testing (AST) methodologies which comprise a mixture of quantitative and qualitative methods, for determining antibiotic resistance. Clinical microbiology laboratories interpret the results of AST using clinical breakpoints (CBP) where clinically susceptible is defined as a level of antimicrobial activity associated with a high likelihood of therapeutic success. Reference microbiology laboratories, in addition to CBP, determine epidemiological cut-offs of resistance (ECOFFs) which separate naïve, susceptible wild-type bacterial populations from isolates that have developed reduced susceptibility to a given antibiotic. ECOFFs are usually lower than CBPs. Both are important as epidemiologists need to be alerted to small changes in bacterial resistance in a timely manner if they are to develop interventions and control measures. The data are presented as CBPs when clinical laboratory surveillance data are used and as ECOFFs where reference laboratory data are available. The CBPs in this report relate to clinical success in treating the bacteria in humans, not animals, regardless of whether the bacteria were isolated from a human or veterinary source.

In this report we have compared the AST results from clinical surveillance data available from humans and animals. In addition, data are presented derived from EU-harmonised surveillance performed on healthy food-producing animals at slaughter.

Human health

The data collated in this report were generated from national databases containing AST results voluntarily submitted from clinical microbiology laboratories, a voluntary passive surveillance system. The variation in AST results available reflects clinical laboratory practice, where each laboratory routinely tests different panels of antibiotics. The samples for which susceptibility test results were collected were from patients receiving clinical care for sepsis (bloodstream infections or bacteraemia) or gastroenteritis (diarrhoea) across the public healthcare systems in the UK. For the purpose of this report, AST results reported as "intermediate" or "resistant" were combined and presented as "non-susceptible". All laboratories participate in national external quality assurance schemes. Where reference microbiology laboratory data were available this is presented and highlighted. Specific country data and differences are highlighted in Annex 1. All *E. coli* and C*ampylobacter* data available were included. Typhoid fever

cases (*S. typhi* and *S. paratyphi*) were excluded as greater than 99% of these cases are imported infections.

Animal health

In the UK, data on antibiotic resistance are collected via two methods: voluntary passive clinical surveillance and EU-harmonised monitoring surveillance of isolates from healthy animals.

In the passive surveillance programme (clinical surveillance) resistance is tested for in bacteria isolated from clinical veterinary samples from livestock. England and Wales have a combined clinical surveillance programme, while Scotland and Northern Ireland conduct separate clinical surveillance programmes. The England and Wales data are also publicly available in the UK-VARSS report, published annually (8). It is important to highlight that there is no statutory legislative requirement to conduct this form of surveillance and data are submitted voluntarily from clinical veterinary laboratories.

The activities, which fall under EU-harmonised monitoring, include structured surveillance programmes for the systematic collection of a representative proportion of isolates of importance to human health from healthy animals at slaughter. The programmes conducted in 2013 were based on the requirements of EU Directive 2003/99/EC (4) 'on the monitoring of zoonoses and zoonotic agents', which obliges Member States to monitor antimicrobial resistance in zoonotic agents. Two surveys were conducted in 2013 in accordance with these requirements: A Pig Abattoir Survey and the Food Standards Agency (FSA) Broiler Abattoir Survey.

Further information on clinical and EU surveillance schemes and antimicrobial susceptibility testing methodology used in animals can be found in Annex 1. Data caveats are presented in Annex 2.

Antibiotic Use

Due to different methods of data collection, it is currently not possible to report comparable data on antibiotic use in humans and animals. Caveats to the data are outlined in Annex 3.

Human Health

Antibiotic use data from primary and secondary care are included in this report, as submitted by the UK to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net). As secondary care data were not available for all countries of the UK before 2013, comparison with veterinary antibiotic sales data was limited to 2013 data. Antibiotics for systemic use and intestinal antibiotics (Anatomical Therapeutic

Chemical (ATC) groups J01, A07AA) were included, expressed as tonnes of active compound. Data were not available from private prescriptions dispensed in the community and private hospitals. Primary care data are available at a patient level in Scotland, Wales and Northern Ireland and aggregated at a General Practice level in England. Hospital data are aggregated dispensed data to wards and patients.

Animal Health

This report covers UK antibiotic sales data for 2013 and includes antibiotics for systemic use, intramammary use and intestinal antibiotics (ATCvet code groups QJ01, QJ51, QA07AA). Total annual sales of all veterinary medicines are supplied by Marketing Authorisation Holders (MAH) to the Veterinary Medicines Directorate (VMD) where they are collated; from this the total weight in tonnes of each antibiotic active substance is calculated. The data represented do not take into account wastage, imports and exports related to antibiotics administered to animals, but they serve as a proxy for usage data.

It is not possible to identify in which species the antibiotics would have been used because many products are authorised for use in more than one animal species. Currently there is no system to collect and collate data on antibiotic use by animal species in the UK. Systems for the collection of data on antibiotic usage in animal species are currently being developed.

Contributing pharmaceutical companies are listed in Annex 4.

Denominators

For the purposes of comparison across human and animal data, the weight of the total UK human population was calculated, using the methodology described in Annex 5 and antibiotic data converted to milligrams per kilogram (mg/kg) estimated biomass (9). For animals, antibiotic sales data are used to estimate to the level of mg/kg for reporting to the EC using the Population Correction Unit (PCU), a method of standardisation between animal populations (9).

Results

Antibiotic Resistance

E. coli

In 2013, 35,716 *E. coli* bloodstream infections in humans were reported in the UK through routine voluntary laboratory surveillance; this accounts for approximately 90% of all clinical cases when compared to the mandatory reporting scheme for *E.coli* bacteraemia . AST varies by laboratory, related to local epidemiology and treatment guidelines; AST results for key antibiotics were available for more than 70% of clinical isolates (Table 1). For the same period, clinical surveillance of bacteria isolated from clinical veterinary samples from livestock reported the susceptibility results for 3,320 *E. coli* isolates from a mix of livestock sampled primarily as part of field disease investigations (Table 1).

Table 1. Human and Animal health: *E. coli* samples and susceptibility testing results (using human clinical breakpoints) to key antibiotics in the UK, 2013

	No. tested (% of total reported)	% non-susceptible	95% CI
Human Health †			
Cefotaxime/Ceftazidime**	23,982 (67)	10	10-11
Ciprofloxacin	28,882 (81)	18	18-19
Gentamicin	30,539 (86)	9	9-10
Meropenem/Imipenem**	26,233 (73)	0.05	0-0.05
Piperacillin/Tazobactam**	28,961 (81)	10	10-11
Animal Health *			
Cefotaxime**	807 (24)	11	9-14
Ceftazidime**	807 (24)	6	5-8
Enrofloxacin$^\beta$	1,906 (57)	6	5-7

† human isolates were identified from blood samples only *Combined result for *E. coli* from cattle, sheep, pigs, turkeys and chickens. Animal isolates were from a mix of clinical samples; there was no veterinary testing of the other listed human antimicrobials ** Not authorised for use in animals

β Enrofloxacin is a more commonly tested fluoroquinolone in animals than ciprofloxacin and is included as an alternative to ciprofloxacin. Surveillance data for enrofloxacin is from England, Wales and Scotland only.

Note: Animal health: This table presents combined clinical surveillance data from England and Wales, Northern Ireland, and Scotland. Different methodologies were used to test for antibiotic susceptibility: BSAC methodology was used in Great Britain and an accredited CLSI method in Northern Ireland.

These isolates represent a range of *E. coli* infections, including coliform mastitis in cattle, colisepticaemia in neonates, as well as those causing diarrhoea in animals. The criterion for testing is that the veterinarian considers the isolate relevant to the disease condition under investigation. The farmer usually funds disease investigation of endemic veterinary diseases privately and the numbers of samples and consequently

E. coli isolates are therefore dependent on the degree to which laboratory investigation is sought. The antibiotic panels tested are selected according to the clinical relevance of the individual case. Resistance is determined based on human CBPs. The proportion of non-susceptible isolates in the animal population is similar to the figures for human isolates.

Further AST results are available in Annex 6 (Table 15) showing susceptibility results from *E. coli* derived from healthy pigs (EU harmonised monitoring). These results capture another key antibiotic for humans, gentamicin, as well as cefotaxime and ciprofloxacin, and shows low levels of non-susceptibility.

Campylobacter spp.

In humans, *Campylobacter* is the most common bacterial organism identified through notifiable infectious intestinal disease surveillance. In 2013, almost 66,575 cases of human *Campylobacter* infection were reported in the UK.. Routine laboratory surveillance data on resistance to at least one drug were available for only 45% of isolates and less than 10% of isolates were speciated. Only 462 isolates (less than 1% of laboratory-confirmed infections) were referred to the reference laboratory in England in 2013; 85% were identified as *C. jejuni* and 11% as *C. coli.* Table 2 shows the results of speciation by the reference laboratory of all *Campylobacter* isolates from blood, urine and faeces from England and Wales in 2013. AST of *Campylobacter* isolates (Table 3) is determined using CBPs by laboratories reporting via clinical laboratory surveillance.

Table 2. Human Health: *Campylobacter* species summary from reference laboratory (England, Wales & Northern Ireland); all isolates (blood, urine, faecal), 2013

Species	No. referred isolates	% of all *Campylobacter* spp.
Campylobacter coli	53	11%
Campylobacter jejuni	392	85%
Campylobacter 'other named'	17	4%
All *Campylobacter* spp.	**462**	**100%**

8 mixed samples excluded

Table 3. Human health: *Campylobacter* spp. clinical blood and faecal samples and susceptibility testing results to key antibiotics (using human clinical breakpoints) in the UK, 2013

	No. tested (% of total reported)	% non-susceptible	95% CI
Human Health †			
Ciprofloxacin	23,425 (35)	42	41-43
Erythromycin	23,137 (35)	2.5	2-3
Tetracycline	2,929 (5)	33	31-35

† human isolates were identified from blood and faecal samples

Campylobacter spp. are not routinely cultured as part of clinical surveillance in the UK, as these species rarely cause disease in livestock. Veterinary EU harmonised monitoring of *Campylobacter* in 2013 recovered predominantly *C. coli* isolates from the intestine of healthy pigs at slaughter, and both *C. coli* and C. *jejuni* from the intestine of broiler chickens also at slaughter. Intestinal isolates were tested as these constitute the usual source of carcass contamination, when this occurs. The proportions of isolates resistant to key antibiotics used to treat human infections differed by Campylobacter species and by animal (Table 4); *C. coli* in general was less susceptible than *C. jejuni*. Broilers are usually considered one of the main sources of *C. jejuni* infections in humans and the absence of resistance to erythromycin is encouraging, though the number of isolates tested was small. This report does not consider the prevalence of the different *Campylobacter* organisms in different animals, which may be of significance when considering the potential risk to human health

Table 4. Animal health: proportion of non-susceptibility (using human clinical breakpoints) in *Campylobacter* spp. in animals by EU harmonised monitoring in the UK, 2013

	Pigs: *C. coli* N=141		Broilers: *C. coli* N=33		Broilers: *C. jejuni* N=61	
	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI
Ciprofloxacin	13	8-20	42	20-60	31	20-44
Erythromycin	28	21-36	3	0-16	0	0-6
Tetracycline	79	72-86	55	36-72	48	35-61

Salmonella

The 'top ten' serotypes of non-typhoidal *Salmonella* isolates recovered from people and referred to the reference laboratories in England and Scotland in 2013 are presented in Table 5. *Salmonella* Enteritidis was the most frequently isolated non-typhoidal *Salmonella* species referred, followed by *S.* Typhimurium (28% and 21% in 2013 respectively). The national reference laboratories receive a subset of isolates for speciation and strain typing.

In 2013, 8,459 non-typhoidal *Salmonella* bloodstream and faecal infections were reported in the UK through routine laboratory surveillance and referrals, with AST results reported for key antibiotics in more than 70% of reports (Table 6). Clinical breakpoints were used to establish non-susceptibility for non-typhoidal *Salmonella,* as these were available on clinical isolates from UK reference laboratories (10).

The *Salmonella* serotypes that contribute to the overall *Salmonella* spp. figure in humans and the different livestock species vary considerably. No *S.* Enteritidis isolates were identified in pigs and only three isolates were identified in chickens through EU-

harmonised surveillance activities in 2013. This impacts on non-susceptibility comparisons due to the differing resistance rates occurring in the different *Salmonella* serotypes.

The isolates obtained through clinical surveillance of gastroenteritis and invasive infections in humans are equivalent to those obtained relating to clinical salmonellosis in animals. Importantly, clinical surveillance in animals also includes the results for isolates recovered from statutory *Salmonella* monitoring of broilers, layers and turkeys under *Salmonella* national control plans, ie where there may be no clinical disease. A total of 2,276 isolates were collected from clinical salmonellosis in animals and through statutory monitoring. Available AST results are presented by human and animal species in Table 6. Resistance patterns across animals vary considerably: antibiotic resistance is uncommon in cattle and sheep and most frequently detected amongst pigs and turkeys. Of note is the low level of non-susceptibility to cefotaxime in isolates from humans and animals, and the relatively higher rate of non-susceptibility to ciprofloxacin in human isolates compared to those from animals.

Table 5. Human health: non-typhoidal *Salmonella* 'top ten' serotypes identified by the reference laboratory; all isolates (blood, urine & faecal), 2013

Serotype	No. referred isolates
Salmonella Enteritidis	2,343
Salmonella Typhimurium	1,561
Salmonella Infantis	263
Salmonella Newport	220
Salmonella Virchow	202
Salmonella Kentucky	156
Salmonella Stanley	154
Salmonella Agona	141
Salmonella Java	141
Salmonella Montevideo	118

Targeted *Salmonella* surveillance was also performed in broilers, layers, turkeys and pigs in 2013 at the UK level in accordance with the recommendations of the European Food safety Authority (EFSA) (4, 11). These results (which include *Salmonella* isolates selected from the national control plan) provide an output in animals, which is comparable across the EU member states (Table 7); the information has been previously published in the EU Summary report on Antimicrobial Resistance.

Table 6. Human and Animal health: Proportion of resistant (using human clinical breakpoints) non-typhoidal *Salmonella* isolates from human clinical surveillance and animal clinical surveillance and isolates recovered from statutory monitoring of animals under *Salmonella* national control plans in the UK, 2013

Antimicrobial	Human n=8459[†]		Cattle n=775[¥]		Chickens n=899[¥]		Pigs n=214[¥]		Sheep n=140		Turkeys n=248	
	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI
Ampicillin	26	25-27	6	5-8	7	6-9	76	70-81	3	1-7	30	25-36
Cefotaxime	2	1-2	0	0-1	0	0-1	<1	0-3	0	0-1	0	0-1
Chloramphenicol	7	6-7	2	1-3	4	3-6	34	28-41	<1	0-5	<1	0-2
Ciprofloxacin*	16	15-17	0	0-1	1	1-2	0	0-1	0	0-1	7	4-11
Gentamicin*	5	4-5	<1	0-1	3	2-5	8	5-12	<1	0-5	<1	0-2
Nalidixic acid	16	16-17	2	1-3	8	6-10	11	7-16	1	0-5	20	15-25
Streptomycin	24	23-25	8	6-11	11	9-14	75	69-80	3	1-7	66	60-72
Sulphonamides	27	26-29	6	5-9	21	19-24	84	78-88	3	1-7	59	53-65
Tetracycline	32	31-34	7	6-9	21	18-23	80	74-86	4	2-9	55	49-62
Trimethoprim	10	9-11	<1	0-2	11	9-13	49	42-56	0	0-1	11	7-15

† Human samples are isolated from faecal specimens except where indicated (by *) where a mix of blood and faecal samples were tested

¥ Mixed clinical samples (originating from clinical surveillance of livestock)

Note: This table presents combined animal health clinical surveillance data from England and Wales, Northern Ireland, and Scotland. Different methodologies were used to test for antibiotic susceptibility: BSAC methodology was used in Great Britain and an accredited CLSI method in Northern Ireland. Chloramphenicol, nalidixic acid, ciprofloxacin and cefotaxime are not authorised in any UK veterinary medicines (although ciprofloxacin is an active metabolite of enrofloxacin, which is authorised for veterinary use).

Table 7. Animal health: Proportion of non-susceptible and resistant isolates (using human clinical breakpoints) of non-typhoidal *Salmonella*, originating from EU harmonised monitoring in the UK, 2013

Antimicrobial	Chickens (Broilers) n=170		Chickens (Layers) n=56		Pigs n=147		Turkeys n=170	
	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI	% non-susceptible	95% CI
Ampicillin	11	7-17	13	5-24	52	44-61	26	20-33
Cefotaxime	0	0-2	0	0-6	2	0-6	0	0-2
Chloramphenicol	15	10-21	0	0-6	28	21-36	16	11-22
Ciprofloxacin	0	0-2	0	0-6	0	0-3	0	0-2
Gentamicin	5	2-9	0	0-6	16	11-23	0	0-2
Nalidixic acid	4	2-8	0	0-6	<1	0-4	14	9-20
Streptomycin	34	21-49	36	23-50	66	58-74	77	70-83
Sulphonamides	NT	NT	NT	NT	NT	NT	NT	NT
Tetracycline	23	17-31	14	6-26	68	60-76	69	61-76
Trimethoprim	18	12-24	2	0-10	29	22-37	13	8-19

NT: Not tested

Antibiotic Use

The total antibiotic use in humans and animals was 949.9 tonnes of active ingredients in the UK in 2013; 56% of total use was in humans. The combined primary and secondary care consumption of systemic antibiotics (ATC groups J01, A07AA)) was 531.2 tonnes in the human sector in the UK in 2013. The breakdown by antibiotic groups is shown in Table 8.

The total quantity of active ingredient antibiotics sold for use in all animal species, ie including livestock, companion animals and horses (ATCvet code groups QJ01, QJ51, QA07AA) was 418.7 tonnes in the UK in 2013, of which 353.6[v] tonnes was authorised for use in food-producing species only.

Table 8. Total systemic antibiotics prescribed in humans from primary and secondary (ATCJ01, A07AA) and sold for all animal use, ie livestock, companion animals and horses (ATCvet QJ01, QJ51, QA07AA, expressed in tonnes active ingredients in the UK, 2013

Antibiotic group	Antibiotics prescribed in humans (tonnes active ingredient)	% of total	Antibiotics sold for animal use (tonnes active ingredient)	% of total
Penicillins	350.1	63.8	90.8	21.7
Tetracyclines	54.6	9.9	182.0	43.5
Macrolides	51.9	9.5	43.0	10.3
Sulfonamides and Trimethoprim	18.3	3.3	60.5	14.5
1st and 2nd generation cephalosporins	17.7	3.2	4.9	1.2
Fluoroquinolones	12.3	2.2	2.6	0.6
Other antibacterials	9.2	1.7	12.6	3.0
Polymyxins	5.1	0.9	0.7	0.2
Monobactams, Carbapenems	3.5	0.6	0.0	0.0
3rd and 4th generation cephalosporins	3.4	0.6	1.2	0.3
Lincosamides	2.4	0.4	13.4	3.2
Glycopeptides	1.6	0.3	0.0	0.0
Aminoglycosides	0.9	0.2	4.3	1.0
Amphenicols	0.1	0.1	2.6	0.6
other quinolones	0.0	0.0	0.0	0.0
TOTAL	**531.24**	**100.0**	**418.7**	**100.0**

There are no authorised veterinary medicines which contain antibiotics from the monobactam/carbapenem, glycopeptide or 'other quinolone' classes.

v Based on using the human ATC codes to ensure comparability. For all ATC codes, total sales of products authorised for food-producing animals only is 355 tonnes.

In an attempt to standardise the data available between the two populations, the estimated biomass for people in the UK has been calculated and a similar measure, the Population Correction Unit (PCU) has been calculated for food-producing species, with 1 PCU being equivalent to 1kg of animal biomass. Only food-producing species are included in the PCU calculation and therefore only antibiotics authorised for use in food-producing species are considered in this mg/PCU analysis. Consumption of systemic antibiotics and intestinal antibiotics in humans equated to 135mg per kg of human biomass. Sales of antibiotics for systemic, intramammary and intestinal use in food-producing animals equated to 55.6mg/PCU.

In 2013, the most common antibiotic groups prescribed in humans were penicillins, tetracyclines and macrolides and the most common antibiotics sold for use in animals were tetracyclines, penicillins and sulfonamides (Figure 2). Consumption and sales of antibiotic groups that are used to treat serious infections in humans are shown in Figure 3.
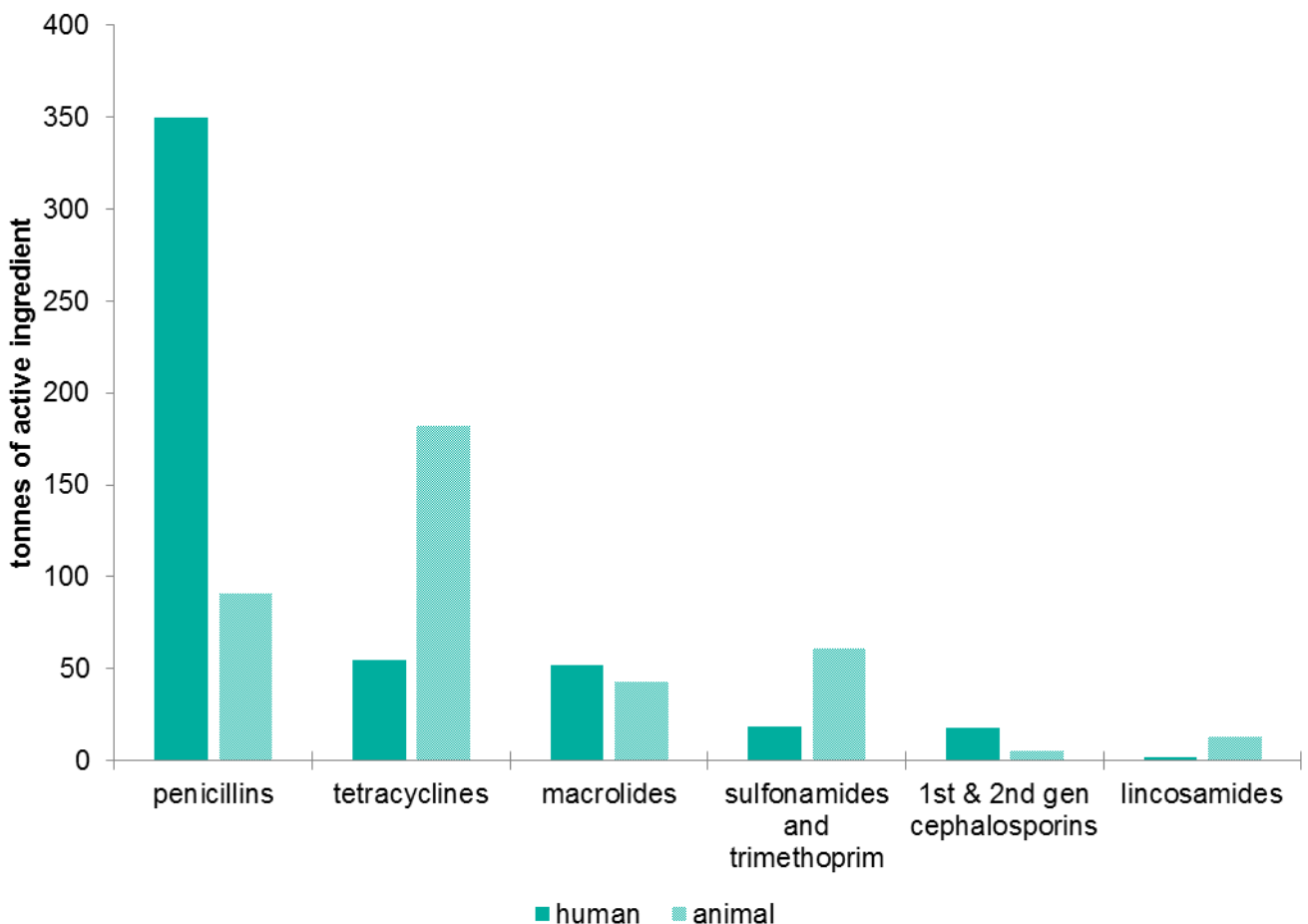
Figure 2. Human and Animal health: Most frequent antibiotic groups prescribed for humans in primary and secondary care/sold for use as veterinary medicines in the UK, 2013 (Animal data are taken from data on veterinary antibiotics for all animals [livestock, companion animals and horses])
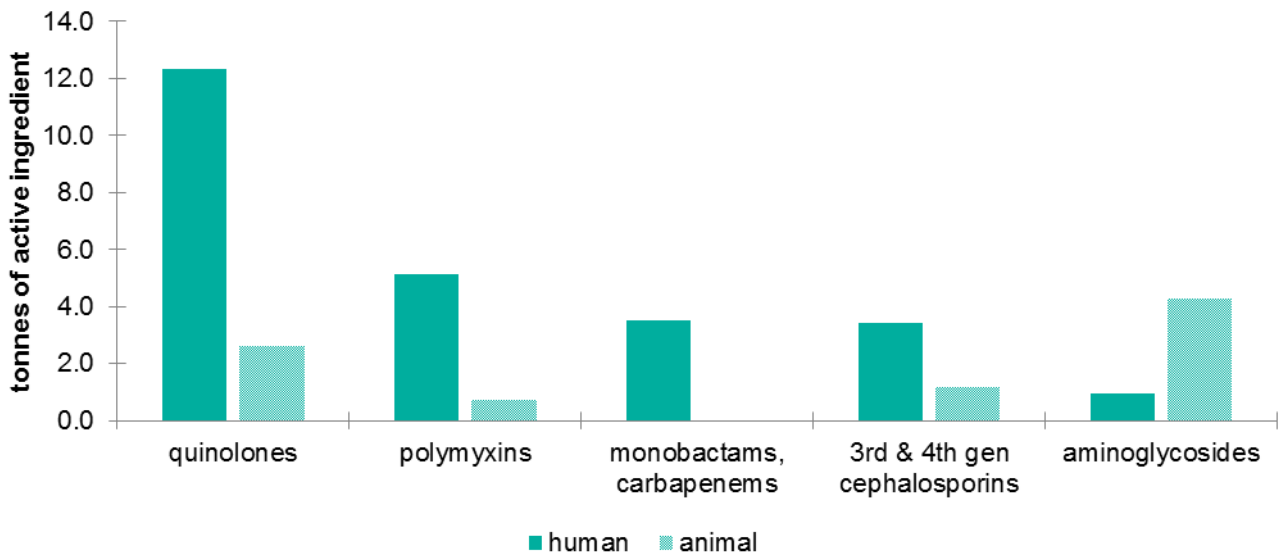
Figure 3. Human and Animal health: Prescriptions and sales of key antibiotics used to treat serious human infections in the UK, 2013 (Animal data are taken from data on veterinary antibiotics for all animals [livestock, companion animals and horses])

WHO, through its expert panel has prioritised key agents based on two specific criteria:
- Sole therapy or one of few alternatives to treat serious human disease
- Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources

Using these criteria, four groups of antibiotics are defined as highest priority critically important antibiotics (Figure 4). See Annex 7 for more information.
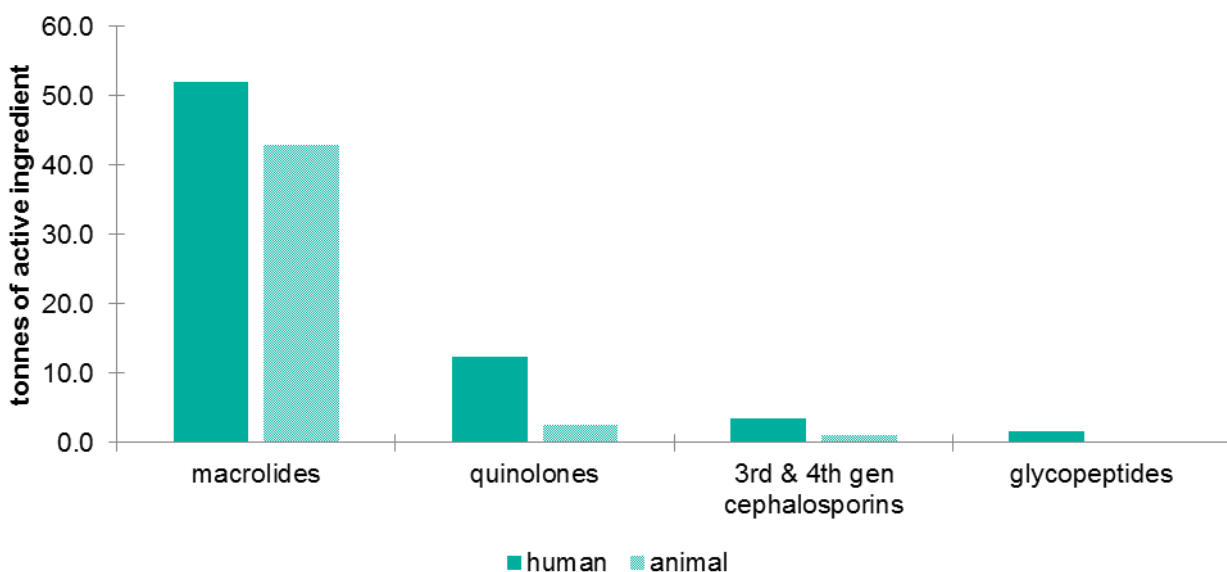
Figure 4. Human and Animal health: Prescription and sales of Critically Important Antibiotics, UK 2013 (Animal data are taken from data on veterinary antibiotics for all animals [livestock, companion animals and horses])

Comparisons with other countries

The EFSA is responsible for examining data on antimicrobial resistance in zoonotic bacteria based on Article 33 in Regulation (EC) 178/2002 and in accordance with Directive 2003/99/EC. The surveillance of AMR within the EU, for human bacteria including *E. coli* from bloodstream infections, is carried out in agreement with Decision No 2119/98/EC of the European Parliament and of the Council of 24 September 1998 and Regulation (EC) no 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control (ECDC).

Antibiotic Resistance

In 2013, 21 EU/EEA countries submitted *Salmonella* data to ECDC, 14 submitted *Campylobacter* data; and 30 submitted *E. coli* blood stream infection data. The majority of countries, including the UK, reported qualitative (susceptible or resistant) data interpreted using CBPs. Qualitative data cannot be re-interpreted to determine ECOFFs. The summary of the UK position of submitted data compared to other countries is highlighted in Table 9.

In 2013, less than 20% of all confirmed human salmonellosis cases and less than 10% of campylobacteriosis cases reported in the EU were tested to one or more antibiotics. Interpretation of these data is difficult and must take into account the wide variation in numbers tested: in some countries AST is performed on all strains and in others only invasive strains are tested against large panels of antibiotics. However, despite this there are some notable points. UK resistance reported is lower than many other European countries, as outlined in Table 9. The UK report *E. coli* bacteraemia data according to the ECDC protocol. This demonstrated that the UK was ranked 22nd for third-generation cephalosporin resistance and ninth for fluoroquinolone resistance among the 30 countries reporting; these positions remain relatively unchanged over the last five years.

Table 9. Comparisons of proportion of resistant isolates to key antibiotics for selected bacteria in humans, UK compared to EU/EEA countries, 2013 (12)

Bacteria	Antibiotic tested	Number of countries that submitted data*	% of resistant isolates from the UK	UK rank, where 1 is the lowest % resistant	Range of % resistance of isolates in EU countries*
E. coli	Third-generation cephalosporins	30	14.7	22	5 (Iceland) – 39.6 (Bulgaria)
	Fluoroquinolones (Ciprofloxacin)	30	16.3	9	10.9 (Norway) – 51.9 (Bulgaria)
Salmonella spp (non-typhoidal)	Cefotaxime	17	0.9	6	0.3 (Slovenia) – 4.2 (Slovakia)
	Ciprofloxacin	22	2.9	13	0.0 (Latvia, Greece) – 53.7 (Malta)
C. jejuni	Ciprofloxacin	15	46.9	4	20.8 (Norway) – 91.5 (Spain)
	Erythromycin	15	2.5	11	0.0 (Austria, Norway) - 18.1 (Malta)
C. coli	Ciprofloxacin	10	47.0	2	36.0 (Slovakia) – 94.3 (Spain)
	Erythromycin	10	7.8	4	0.0 (Austria) – 34.0 (Spain)

*For those countries submitting data on more than 20 isolates

In 2013, 28 member states (MSs) and three non-MSs reported data on AMR in tested *Salmonella*, *Campylobacter* and commensal *E. coli* from livestock to EFSA under Directive 2003/99/EC; 24 of these countries, including the UK reported quantitative MIC or equivalent. The latest report includes data collected in 2013 (12); a summary of the UK position is provided in Table 10. The UK was lowest or joint lowest for seven of the 14 drug-bug combinations, and never highest.

Table 10. Comparisons of proportion of resistant isolates to key antibiotics for selected bacteria in animals, UK compared to EU/EEA countries, 2013 (12)

Bacteria	Animal species	Antibiotic tested	Number of countries that submitted data	% of resistant isolates from the UK	UK rank, where 1 is the lowest % resistant	Range of % resistance of isolates in EU countries
E. coli	Pigs	Cefotaxime	11	0.6	3	0 (Denmark) – 4.7 (Poland)
		Ciprofloxacin	11	1.3	2	0 (Netherlands) – 32.9 (Spain)
Salmonella spp.	Turkeys	Cefotaxime	9	0	1	0 (UK & 6 others) – 3.2 (Poland)
		Ciprofloxacin	9	14.1	1	14.1 (UK) – 96.1 (Spain)
Salmonella Typhimurium	Pigs	Cefotaxime	7	0	1	0 (UK, Croatia, Denmark,Netherlands) – 2.7 (Belgium)
		Ciprofloxacin	7	0	1	0 (UK, Denmark) – 21.4 (Ireland)
Monophasic *Salmonella* Typhimurium	Pigs	Cefotaxime	6	0	1	0 (Belgium, Croatia, Czech Republic, Germany, Denmark, Spain, Finland, Hungary, Ireland, Iceland, Italy, Netherlands, Poland, Switzerland, UK)
		Ciprofloxacin	6	4	2	0 (Denmark) – 13 (Italy)
C. jejuni	Chickens (broiler)	Ciprofloxacin	13	31	4	0 (Iceland, Finland) – 90.3 (Spain)
		Erythromycin	13	0	1	0 (UK & 10 others) – 2.8 (Spain)
C. coli	Chickens (broiler)	Ciprofloxacin	9	42.4	1	42.4 (UK) – 94.1 (Spain)
		Erythromycin	9	3	2	0 (Czech Republic, Germany, Hungary) – 42.6 (Spain)
	Pigs	Ciprofloxacin	7	13.5	2	6.1 (Netherlands) – 93.5 (Spain)
		Erythromycin	7	27	5	2.3 (Finland) – 58.3 (Spain)

Antibiotic Use

In 2013, 27 EU/EEA countries submitted antibiotic consumption data to ECDC (full list and data in Annex 8). However, the data submitted varies substantially between countries depending on data availability: some countries submit reimbursement data and others sales data; two countries submitted total data rather than community and hospital data separately. In 2013, the UK was ranked 16th in community antibiotic consumption, expressed as defined daily doses (DDD) per 1,000 inhabitants per day. The UK had the lowest consumption of both third- and fourth-generation cephalosporin and ciprofloxacin as a percentage of total antibiotic use in primary care across the EU/EEA (Annex 8).

The European Medicines Agency collects veterinary antibiotic sales data annually from EU countries for publication in the European Surveillance of Veterinary Antibiotic Consumption (ESVAC) report. The most recent report covers sales from 26 European countries in 2012 (9). Animal populations vary greatly between countries so in 2009 the ESVAC adopted the PCU as a method of standardisation (for more details see Annex 5).

In 2012, sales of all antibiotics authorised for use in food-producing species in the UK, as reported by ESVAC equated to 66.3 mg/PCU. When compared to other EU countries the UK ranked joint 14th out of 26 (with 1st being the lowest sales and 26th being the highest). Antibiotic sales ranged from 3.8 mg/PCU (Norway) to 396.5 mg/PCU (Cyprus).

Between 2010 and 2012 there was a 2% decrease in the total sales of veterinary antibiotics for use in food-producing animals in the UK from 68mg/PCU to 66mg/PCU. Twenty-five of the European countries that participated in the 2012 ESVAC report were able to submit their variation in sales data (presented as PCU).The UK ranked joint 19th out of 25 countries . Changes in sales over the two year period ranged from a decrease of 49% (Netherlands), to an increase of 10% (Poland).

Regarding sales of third and fourth-generation cephalosporins, fluoroquinolones and macrolides (all of which are recognised as CIAs), the UK ranked 12th out of 21 with CIAs accounting for 9.9% of total sales. This figure ranged from 0.29% of total sales (Iceland) to 23.2% of total sales (Bulgaria).

Discussion

In order to minimise the incidence of infections, control their spread and optimise prescribing of antibiotics, better access to and action of local, national and international antibiotic resistance and use surveillance data are required and underpins the delivery of the UK AMR strategy. Since the UK AMR strategy was launched in 2013, each UK country has focussed activities on improving data collection and outputs in this area. (13,14, 15)

Antibiotic Resistance

This report is an important first step in building the intelligence required to understand current AMR and AMU and to develop coordinated surveillance activities in human and animal health across the UK and Europe. For the three bacteria in this report, significant resistance is identified from human and animal surveillance across a wide range of antibiotics. Further inference on the methods of transfer of genes and bacteria is outside the limits of the reports with the data available.

In the collation of data for this report, we have brought together human and animal clinical AMR laboratory data across the four UK health administrations, and in addition highlighted the initial results from the EU-harmonised monitoring of AMR in food-producing animals. This has highlighted a number of data limitations for the antibiotic resistance patterns:

Firstly, AST from bacteria isolated from humans is performed using a number of different methodologies. Three main methods are used in the UK. Two methods (BSAC and EUCAST) have harmonised their CBPs for determining resistance; and from 2016 BSAC will adopt and support the EUCAST disc diffusion method to improve harmonisation across Europe. The adoption of the EUCAST methodology and breakpoints will further improve the ability to compare data across UK countries and Europe.

Secondly, there is no standardised panel recommended for AST across humans and animals. There are a number of key drug-bug combinations in humans that are not tested in animals as these drugs are not used in the animal population, namely piperacillin-tazobactam, carbapenems and ciprofloxacin (though enrofloxacin which is metabolised to ciprofloxacin is tested). The EU-harmonised protocol for *E. coli* AST includes ciprofloxacin but not piperacillin-tazobactam or carbapenems.

Thirdly, there are a number of potential biases in the samples that are sent to and tested at the Human national reference laboratories. Less than 1% of *Campylobacter* samples are sent to the reference laboratory and less than half of *Campylobacter*

clinical isolates have AST performed at clinical laboratories. In addition, as highlighted in the report there were insufficient data in *Campylobacter* at a species level in humans to include species specific AST results in the report. This is important as AST results in animals demonstrate different resistance patterns by bacterial species and by animal (eg broilers versus pigs).

Finally, while there were large numbers of *Salmonella* isolates from both human and animal specimens, differences in testing exist. While the ECDC recommends performing quantitative AST on *Salmonella* to allow the inference of both ECOFFs and CBPs; this was not available for human clinical isolates. However, EU harmonised surveillance in animals collects detailed resistance data on an extensive range of antibiotics and reassuringly in the food-producing animals tested at slaughter no ciprofloxacin resistance was detected and cefotaxime resistance was only detected at very low levels (2%) and only in pigs.

Antibiotic Use

This report also combines antibiotic use data from humans and animals. Of the total antibiotic use that was measurable in the UK, humans used 56% of total antibiotic tonnes used.

However, this is also measured in different ways. In humans, it is measured through prescriptions dispensed to patients in the community or hospitals. Private prescriptions written in the community or private hospitals are not included. Therefore these data likely underestimate total consumption in humans by approximately 10%. In animals, antibiotic use is measured through sales of veterinary antibiotics by pharmaceutical companies to wholesalers/distributers. Improved standardisation, both within the UK and across Europe, is essential. The differences in humans and animals antibiotic use data is similar to the differences between countries in EU/EEA for human data presented through ESAC-Net, where countries submit data to ECDC based on sales or reimbursement data. ESVAC currently collects sales data in veterinary medicine. Despite these differences, in 2013 the UK was mid-range for antibiotic consumption in humans and animals. While use in humans stabilised in 2013 compared to 2012, it has increased substantially over the last 10 years. This has not been the case for the animal sector where the average sales for animal use was, 413.5 tonnes and oscillated between 346 and 447 tonnes.

The differences in data collection between humans and animals are similar to the differences between the human data submitted from EU/EEA countries to ECDC ESAC-Net. Improved standardisation, both within the UK and across Europe, is essential.

Collaborative working to improve public and practitioner education

European Antibiotics Awareness Day (EAAD), a Europe-wide initiative that takes place annually on 18 November, is part of the UK 5 year Antimicrobial Resistance Strategy. The EAAD 2013 Evaluation Report highlighted that EAAD continues to be an excellent platform for raising professional and public awareness about antibiotic overuse and resistance.

In, 2014 PHE co-ordinated EAAD activities in England in collaboration with the Department of Health, the Veterinary Medicines Directorate (VMD), the devolved administrations (Scotland, Wales, Northern Ireland), professional bodies/organisations, and local authorities. These groups and the Antibiotic Guardian campaign work together towards a joint human and animal "One Health" initiative. The Antibiotic Guardian implemented a pledge-based behaviour change strategy to help improve behaviours regarding antibiotic prescribing and use in both healthcare professionals and members of the public. By 30 November 2014, 11,833 people made a pledge across the One Health initiative (Figure 5). The goal for 2015 is to raise awareness and the number of pledges to 100,000.
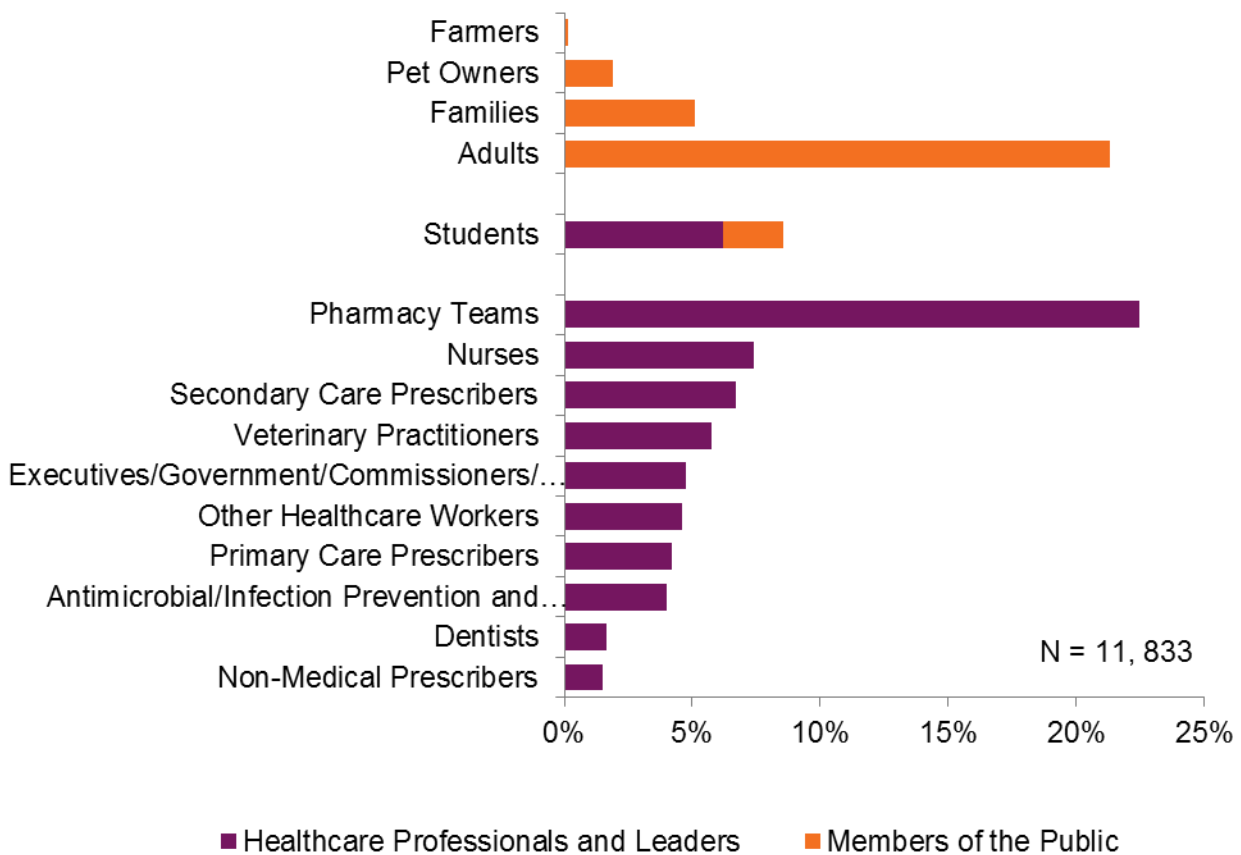
Figure 5. Antibiotic Guardian campaign distribution of pledges by target groups in the UK, 2014

Recommendations

Recommendation 1

Public health organisations should work with clinical laboratory colleagues to ensure that all *Salmonella* species are sent to the relevant reference laboratories for speciation and testing. The referral form should include data on travel abroad, including countries, in the previous four weeks.

This will allow accurate epidemiological data to be collected on species, AST, the ability to review differences in isolates that were more likely acquired in the UK versus abroad, improved comparisons across Europe and focussed treatment based on likely country of origin in the future.

Recommendation 2

Public health organisations should scope the development of a national sentinel surveillance system for *Campylobacter* isolates collected from human infections. In addition, public health organisations should highlight the importance of identifying Campylobacter to a species rather than genus level,

This would allow national data on species, AST and travel history to be collected on a robust sampling frame to determine antibiotic resistance and impact of travel on *Campylobacter* resistance in human campylobacteriosis. It would also ensure that treatment, where necessary, is based on robust epidemiological data.

Recommendation 3

Public health organisations should support the work of the BSAC to transition clinical laboratories to EUCAST methodology and breakpoints in 2016.

This will allow more robust, reliable and comparable data to be collected using the national passive surveillance systems.

Recommendation 4

Public health organisations should work with BSAC and the UK Standards for Microbiology Investigations to develop guidance related to recommended antibiotic and bacterial combinations, which should be tested and reported by human clinical laboratories for key One Health pathogens. Clinical laboratories should continue to report all notifiable diseases and AST results to the national surveillance organisation.

Animal health organisations should review the antibiotics tested against isolates from clinical veterinarian samples and through the EU harmonised monitoring in animals.

This would reduce the variability in testing and reporting that currently is evident across clinical laboratories and would improve the robustness of the current passive surveillance systems. It would also allow the early ascertainment of emerging threats, the development of risk assessments and interventions to minimise the spread of antibiotic resistance.

Recommendation 5

Human public health reference laboratories should follow the EU protocol for harmonised monitoring of antimicrobial resistance in human *Salmonella* and *Campylobacter* isolates. This includes speciation, typing, AST using quantitative methodology on recommended antibiotic panels, specific testing for antibiotic resistant enzymes and whole genome sequencing. Where current resources are inadequate scoping of requirements should occur.

This will improve the comparison of trends in the occurrence of antibiotic resistance of human *Salmonella* and *Campylobacter* infections, including comparison with food/animal isolates and provide information of the genetic determinants of resistance that are important for public health recognition of cross-border threats in Europe.

Recommendation 6

Public health organisations should explore data available on human sales of antibiotics, from manufacturers and holders of human marketing authorisations.

This will allow a determination of data gaps in current surveillance in humans and improve the comparability of data across humans and animals.

Recommendation 7

VMD should conduct carbapenem resistance monitoring (as part of the EU harmonised monitoring of key bacteria from the 01 January 2014 in accordance with the legislation, Commission Decision 2013/652/EU on the 'monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria'), a year earlier than mandated. This legislation details the requirements to monitor antimicrobial resistance in *Salmonella* spp., *Campylobacter* spp., and *E. coli* in various livestock populations at slaughter, as well as meat products at retail. In 2016, 2018 and 2020 isolates of *E. coli, Campylobacter* and *Salmonella* from broilers and turkeys will be examined for resistance, while in 2015, 2017 and 2019 isolates of *E. coli* and *Salmonella* from pigs

will be examined. The *E. coli* from pigs will be screened for carbapenem resistance a year ahead of schedule.

Recommendation 8

The VMD should participate in the protocol development of the ESVAC project to collect farm level data from the pig sector. This programme will be extended in 2015, further rolled out to look at antibiotic consumption in the poultry and cattle sectors over the next three years. The VMD will investigate and facilitate options for collecting accurate antibiotic consumption data at an individual farm level.

This will improve the antibiotic use data available in animals and allow improved farm level and species level ecological analysis and its relationship to antibiotic resistance to be defined.

Recommendation 9

The One Health approach should be enhanced in public and professional activities through engagement with EAAD campaign and aligning and integrating this approach to training programmes for human and animal health professionals.

This is a crucial component to develop cross-sectoral understanding and improved working in the future.

Recommendation 10

The human and animal surveillance bodies should produce a further report in two years. Future work must include detailed data from the Food Standards Agency to improve knowledge on antibiotic resistance detected in UK and imported food sold in supermarkets and other outlets.

This will ensure that progress with these recommendations is reported and surveillance developments in support of the UK AMR strategy occur.

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Glossary of acronyms and key words

AFBI	Agri-food and Biosciences Institute (Formally known as the Department of Agriculture and Rural Development).
AMC	Antimicrobial Consumption
Aminoglycosides	A closely related group of bactericidal antibiotics derived from bacteria of the order Actinomycetales. Polycationic compounds that contain an aminocyclitol with cyclic amino-sugars attached by glycoside linkages. Sulphate salts are generally used. They have broadly similar toxicological features.
AMR	Antimicrobial Resistance.
AMRAP	Antimicrobial Resistance Action Plan, Northern Ireland.
AMRHAI	Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (PHE)
APHA	Animal and Plant Health Agency
ATC	Anatomic Therapeutic Chemical
Antibiotic	A drug that destroys or inhibits the growth of bacteria. The action of the drug may be selective against certain bacteria.
Antimicrobial	A compound, which at low concentrations, exerts an action against microorganisms and exhibits selective toxicity towards them. The term includes any substance of natural, synthetic or semi-synthetic origin that is used to kill, or inhibit the growth of, microorganisms (bacteria, fungi, protozoa and viruses).
Antimicrobial resistance	Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.
Antimicrobial stewardship	Antimicrobial stewardship is a key component of a multifaceted approach to preventing emergence of antimicrobial resistance. Good antimicrobial stewardship involves selecting an appropriate drug and optimising its dose and duration to cure an infection while minimising toxicity and conditions for selection of resistant bacterial strains.
AST	Antimicrobial Susceptibility Testing: using laboratory methods to determine whether a bacterium is susceptible to a drug in vitro

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Antimicrobials	An antimicrobial is a drug that selectively destroys or inhibits the growth of micro-organisms.
ARHAI	Antimicrobial Resistance and Healthcare Associated Infections
ASP	Antimicrobial Stewardship Programme
Bacteraemia	The presence of bacteria in the bloodstream
BAPCOC	Belgian Antibiotic Policy Coordination Committee
Bioavailability	The amount of a drug that reaches the tissue(s) of the body where it is required to act.
β-Lactams	Naturally occurring or semi-synthetic antibiotics characterised by the presence of a β-lactam ring. This class of antibiotics include penicillins, cephalosporins, carbapenems and monobactams. β-Lactams work by inhibiting synthesis of the bacterial cell wall.
BSAC	British Society for Antimicrobial Chemotherapy
Carbapenemases	Enzymes that hydrolyze (destroy) carbapenems and other β-lactam antibiotics, especially in members of Enterobacteriaceae family are increasing worldwide and an emerging threat.
Carbapenems	Carbapenems are broad-spectrum β-lactam antibiotics, in many cases the last effective antibiotic against multiple resistant gram-negative bacterial infections.
CBP	Clinical Breakpoints
CCG	Clinical Commissioning Group
CIAs	Critically Important Antibiotics
CMO	Chief Medical Officer
Colisepticaemia	A systemic infection with the bacterium *Escherichia coli* where *E. coli* can usually be isolated from blood and internal organs.
CPE	Carbapenemase-producing Enterobacteriaceae
CRO	Carbapenem Resistant Organism
CSL	Central Science Laboratory
DANMAP	Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans

DARC	DEFRA Antimicrobial Resistance Committee
DARD	Department of Agriculture and Rural Development
DEFRA	Department for Environment, Food & Rural Affairs
DH	Department of Health
DSCs	Disease Surveillance Centres of the Scottish Agricultural College.
EAAD	European Antibiotic Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre of Disease Prevention and Control
ECOFF	Epidemiological cut-offs
EFSA	European Food Safety Authority
Empiric Therapy	Prescription of an antibacterial before the causative agent of an infection is known
Enterobacteriaceae	A family of gram-negative bacilli that contains many species of bacteria that normally inhabit the intestines. Enterobacteriaceae, that are commonly part of the normal intestinal tract flora, are referred to as coliforms.
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	Extended-Spectrum β-Lactamase
ESPAUR	English Surveillance Programme for Antimicrobial Utilisation and Resistance
ESVAC	European Surveillance of Veterinary Antibiotic Consumption
EU	European Union
Extended-Spectrum β-Lactamases (ESBL)	Extended-Spectrum β-Lactamases (ESBL) are enzymes produced by bacteria making them resistant to penicillins and cephalosporins. Resistance to third- generation cephalosporins in *E. coli* (and other Enterobacteriaceae) is a broad indicator of the occurrence of ESBLs.
Fluoroquinolone	A sub-group of the quinolone compounds, having the addition of a fluorine atom and the 7-piperazinyl group. Broad-spectrum antibacterials with properties more suited to the treatment of systemic infections.
FSA	Food Standards Agency.

HPS	Health Protection Scotland (formerly SCIEH).
HSCIC	Health and Social Care Information Centre
Incidence	The number of new events/episodes of a disease that occur in a population in a given time period.
Indication	An infection that indicates the requirement for antibacterial therapy.
Infection	Invasion and multiplication of harmful microorganisms in body tissues.
Macrolides	A large group of antibiotics mainly derived from *Streptomyces* spp. Weak bases that are only slightly soluble in water. They have low toxicity and similar antimicrobial activity with cross-resistance between individual members of the group. Thought to act by interfering with bacterial protein synthesis.
MDR	Multi Drug Resistant.
MIC	Minimum Inhibitory Concentration.
Microorganism	An organism that is too small to be seen by the naked eye. Microorganisms include bacteria, fungi, protozoa and viruses.
NEQAS	National External Quality Assurance Scheme
NHS	National Health Service.
NHS England	National Health Service England
NISRA	Northern Ireland Statistics and Research Agency.
Normal flora	The microorganisms that normally live in or, on the body, and contribute to normal health. When antimicrobial agents are used to treat infections, there are changes to the normal flora.
PACT	Prescribing Analysis and Cost.
PHE	Public Health England (formerly HPA)
PPA	Prescription Prescribing Authority.
Prophylaxis	Any means taken to prevent infectious disease. For example, giving antibiotics to patients before surgery to prevent surgical site infections; or in animals to prevent an infection one or a group of animal(s) when another animal in a herd has been diagnosed with an infection.
SAC	Scottish Agricultural College.

ScotMARAP	Scottish Management of Antimicrobial Resistance Action Plan
SEERAD	Scottish Executive Environment and Rural Affairs Department.
SGSS	Second Generation Surveillance System
SSRL	Scottish *Salmonella* Reference Laboratory.
STRAMA	Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance
Sulphonamides	A group of bacteriostatic compounds that interfere with folic acid synthesis of susceptible organisms. They all have similar antimicrobial activity but different pharmacokinetic properties. See also trimethoprims.
Surveillance	The systematic collection of data from the population at risk, the identification of infections using consistent definitions, the analysis of these data and the dissemination of the results to those who collected the data, those responsible for care of the patients and those responsible for prevention and control measures.
Tetracycline	A group of antibiotics derived from *Streptomyces* spp. They are usually bacteriostatic at concentrations achieved in the body, and act by interfering with protein synthesis in susceptible organisms. All have a broad spectrum of activity.
Third-generation cephalosporins	Third-generation cephalosporins have a broad-spectrum of activity and further increased activity against gram-negative organisms.
Trimethoprims	Compounds with a similar action to sulphonamides, acting by interfering with folic acid synthesis, but at a different stage in the metabolic pathway. Display a similar spectrum of activity to, and are often used in combination with, sulphonamides. Due to synergistic effects between these classes of drugs, lower doses can achieve the same effect.
UK	United Kingdom.
UK CPA	United Kingdom Clinical Pathology Accreditation
VMD	Veterinary Medicines Directorate, Defra.
WHO	World Health Organisation

ANNEX 1

Antimicrobial Resistance data - Methods

Human data

Bacteria are defined as clinically resistant when the degree of resistance observed in vitro is associated with a high likelihood of therapeutic failure. However, this is for a given drug concentration and may potentially be overcome with alterations of dose, considering pharmacokinetics and pharmacodynamics in the individual patient. The breakpoints used to determine antimicrobial susceptibility at the clinical laboratories are CBP.

England

Clinical laboratories perform AST using a variety of methods: EUCAST [The European Committee on Antimicrobial Susceptibility Testing], BSAC [The British Society for Antimicrobial Chemotherapy] and CLSI [Clinical Laboratory and Standards Institute]); with a mix of automated (eg VITEK, Phoenix) and manual laboratory methods (eg disc and E-test).

E. coli are sent to reference laboratories when unusual resistance profiles are detected at clinical laboratories. Unless a clinical laboratory can identify the *Salmonella* to species level, these are sent to the reference laboratory; approximately 80% of reported isolates are sent to the reference laboratory. The Reference laboratory uses CBPs and ECOFFs. *Campylobacter* are sent where there is a public health response to a potential outbreak or where the clinical laboratory wishes to further speciate and AST; less than 1% of clinical isolates are sent to the reference laboratory.

Data on the susceptibility of each pathogen to key antibiotics were obtained for England from the PHE national database for notifiable diseases and AST results (Second Generation Surveillance System, SGSS). Additional *Campylobacter* and *Salmonella* information was obtained from the PHE Gastrointestinal Bacteria Reference Unit (GBRU) based on samples referred to the unit.

Scotland

VITEK 2 systems were used to determine the susceptibility for the majority of blood (and urine) isolates from Scotland. Other methods (such as agar dilution and Etest®) may have been used for testing of some types of isolates/agents. Selective reporting may also have occurred, where laboratories have chosen only to test and/or report susceptibility results against certain agents for clinical reasons. EUCAST susceptibility

testing methodology (and breakpoints) were gradually introduced in the diagnostic and reference laboratories in Scotland during 2012-2013. ECOFFS are not used in Scotland in neither clinical nor reference laboratories.

Microorganism and AST data were obtained from all diagnostic laboratories in Scotland and participating reference laboratories via ECOSS (Electronic Communication of Surveillance in Scotland), an electronic data link from microbiology laboratories to Health Protection Scotland.

Northern Ireland

Northern Ireland microorganism and AST data were retrieved from CoSurv, the electronic system by which all clinical diagnostic laboratories in Northern Ireland report data voluntarily to the Public Health Agency from their own laboratory information systems.

Wales

Microorganism and AST data were extracted from the Welsh DataStore systems. DataStore collects all data stored on the hospital laboratory information systems and maps information into a pseudo-anonymised standardized format.

Veterinary data

Clinical surveillance

Clinical surveillance relies on the submission of diagnostic samples by private veterinary surgeons and farmers to the Animal and Plant Health Agency (APHA) Veterinary Investigation Centres, Scotland's Rural College (SRUC) and the Agri-Food Biosciences Institute (AFBI) in England and Wales, Scotland, and Northern Ireland, respectively. Where clinically relevant, culture and antibiotic susceptibility testing, are performed. Depending on the circumstances of the individual case the bacteria tested may be pathogens or commensals. The results are recorded and assessed for patterns of resistance on a continuous basis.

In addition to the diagnostic submissions, under the Zoonoses Order (1989) all laboratories in the UK are required to report any isolation of *Salmonella* from a food producing species to the APHA; in Northern Ireland these isolates are reported to DARD who feed back to APHA (16). The isolate may then be requested by APHA for serotyping and antibiotic susceptibility testing. Isolates of *Salmonella* are also collected as part of the National Control Programme (NCP) for *Salmonella* in poultry in accordance with Regulation (EC) No 2160/2003 on the 'control of *Salmonella* and other specified food-borne zoonotic agents' (17). Under this NCP, samples are taken

regularly from commercial breeding chickens, laying chickens, broilers and turkey flocks, according to the criteria stated in the Control of *Salmonella* in Broiler, Poultry and Turkey Orders. These data are included in the clinical surveillance results presented in this report,

The government *Salmonella* databases are dynamic and are constantly updated as isolates from private laboratories and follow up investigations are reported, Consequently, the number of isolates reported may vary slightly between government reports collated at different points in time.

EU harmonised monitoring

Pigs

- **Pig Abattoir Survey**: This study was part of a large-scale monitoring programme conducted to estimate the prevalence of a range of different organisms including *E. coli, Campylobacter* spp. and *Salmonella* spp*.,* and to investigate antibiotic resistance in *Campylobacter coli*, in UK pigs at slaughter. To achieve this, caecal samples from 637 pigs were collected at several UK abattoirs which together accounted for approximately 80% of UK throughput of all finishing pigs. Of the bacterial isolates recovered from the caecal samples, 141 *C. coli* and 157 *E. coli* isolates were taken forward for susceptibility testing, in accordance with recommendations of the European Food Safety Authority (EFSA) to avoid clustering so that individual farms were represented only once. This was done to ensure comparability with similar data collected in other EU Member States.
- **Food Standards Agency (FSA) Broiler Abattoir Survey**: This structured survey was conducted in 2013 to monitor the prevalence of *C. coli* and *Campylobacter jejuni* in UK broiler chickens at slaughter. Sampling was conducted in accordance with the EU technical specifications laid out in Commission Decision 2007/516/EC (18). To achieve this, caecal samples were collected from UK broilers at slaughter and antibiotic sensitivity testing was carried out on 61 *C. jejuni* and 33 *C. coli* bacterial isolates recovered.
- Commensal *E. coli* (N=157) were recovered from culture of 157 caecal samples on non-selective MacConkey agar plates. A single, randomly-selected *E. coli* colony was thereby collected from each caecal sample in accordance with EFSA's recommendations (EFSA, 2007).
- 215 caecal samples were cultured for *Campylobacter* spp. using standard methods, and 71% yielded *C. coli*. [13% yielded other *Campylobacter* spp. but these were not subjected to susceptibility testing]. 141 isolates were eligible for susceptibility testing according to EFSA's recommendations (one isolate, per farm, per year).
- 626 caecal samples were cultured for *Salmonella,* according to standard methods. Of these, 147 yielded *Salmonella* eligible for susceptibility testing according to EFSA's recommendations (one isolate, per serovar, per farm, per year).

- In addition, 637 porcine caecal samples were cultured on media selective for ESBL-producing *E. coli*, and 23.4% of pigs proved positive for such ESBL *E. coli*. These isolates were not subjected to susceptibility testing, but were confirmed genetically to possess extended-spectrum beta-lactamase genes. Similarly, the type of ESBL gene carried was determined.

Chickens (broilers)

- Antibiotic susceptibility testing of *Campylobacter* spp. was performed using a standardised broth micro-dilution method to determine their MIC against a range of antibiotics, in accordance with the recommendations of EFSA (EFSA, 2007).
- Antibiotic susceptibility testing was performed on the 94 *Campylobacter* spp. isolates recovered in the study. Of these 94 isolates, 33 were *C. coli* and 61 were *C. jejuni*. Epidemiological cut-off values (ECVs) were used to assess susceptibility as described in the EU technical specifications within Commission Decision 2007/516/EC.

Table 11. Breakpoints used for the MIC testing for EU harmonised monitoring

Antibiotic	Salmonella		Campylobacter jejuni		Campylobacter coli		E. coli	
	ECOFF (mg/l)	CBP (mg/L)	ECOFF (mg/l)	CBP (mg/L)	ECOFF (mg/l)	CBP (mg/L)	ECOFF (mg/l)	CBP (mg/L)
Ciprofloxacin	≥ 0.06	≥ 2	≥ 1	≥ 1	≥ 1	≥ 1	≥ 0.06	≥ 2
Gentamicin	≥ 2	≥ 2	≥ 1	-	≥ 1	-	≥ 2	≥ 8
Trimethoprim	≥ 2	≥ 16					≥ 2	≥ 4
Streptomycin	≥ 32	≥ 16	≥ 2	-	≥ 2	-	≥ 32	≥ 16
Ampicillin	≥ 4	≥ 16					≥ 4	≥ 16
Cefotaxime	≥ 0.5	≥ 4					≥ 0.5	≥ 4
Sulphonamide	≥ 256	≥ 4					≥ 256	-
Chloramphenicol	≥ 16	≥ 16					≥ 16	≥ 16
Nalidixicacid	≥ 16	≥ 32	≥ 16	-	≥ 16	-	≥ 16	≥ 32
Tetracycline	≥ 8	≥ 16	≥ 2	≥ 4	≥ 2	≥ 4	≥ 8	≥ 16

England, Scotland, & Wales

Susceptibility tests described were performed (unless otherwise stated) using a disc diffusion technique on Isosensitest Agar (Oxoid) with appropriate media supplementation where necessary for fastidious organisms. The method used in Great Britain is identical to that recommended by the British Society for Antimicrobial Chemotherapy (BSAC). Isolates have been classed as either sensitive or resistant based on human clinical breakpoints. Where published breakpoints are available from

BSAC then these have been used for the interpretation of the veterinary antibiotic susceptibility results.

Northern Ireland

An accredited CLSI method is used for testing and interpreting zones of inhibition. However, in Northern Ireland, *Salmonella spp.* isolates are also tested for Furazolidone, Framycetin, Apramycin and Spectinomycin using in-house breakpoints.

Table 12. Antibiotic disc concentrations use, England, Wales and Scotland

Antibiotic	Disc Charge (micrograms)	*Salmonella*	*E. coli*
Ciprofloxacin	1	R≤ 16 mm R≥1mg/l	NA
Gentamicin	10	R≤ 19 mm R≥4mg/l	NA
Trimethoprim	25	R≤ 15mm R≥4mg/l	R≤ 15mm R≥4mg/l
Streptomycin	10	R≤ 13mm R>8mg/l	R≤ 12mm R>~8mg/l
Ampicillin	10	R≤14 mm R>8mg/l	R≤14 mm R>8mg/l
Cefotaxime	30	R≤ 29mm	R≤ 29mm
Sulphonamide	300	≤ 13 mm	NA
Chloramphenicol	30	NA	R≤ 20mm R>8mg/l
Nalidixic acid	NA	R≤ 13 mm	NA
Tetracylcine	10	R≤ 13 mm R>8mg/l	R≤ 13 mm R>8mg/l
Enrofloxacin	5	NA	R≤13mm

Table 13. Clinical and Laboratory Standards Institute (CLSI) method, Northern Ireland

Antibiotic	Disc	Expected Zone diameter (mm)		
		Resistant	Intermediate	Susceptible
Ampicillin	AMP10	≤13	14-16	≥ 17
Chloramphenicol	C30	≤ 12	13-17	≥ 18
Gentamycin	CN10	≤ 12	13-14	≥ 15
Kanamycin	K30	≤ 13	14-17	≥ 18
Streptomycin	S10	≤ 11	12-14	≥ 15
Sulphonamides	S3.300	≤ 12	13-16	≥ 17
Tetracycline	TE30	≤ 11	12-14	≥ 15
Trimethoprim	W5	≤ 10	11-15	≥ 16
Furazolidone*	FR100	≤ 13	14-16	≥ 17
Naladixic acid	NA30	≤ 13	14-18	≥ 19
Ciprofloxacin	CIP5	≤ 15	16-20	≥ 21
Cefotaxime	CTX30	≤ 22	23-25	≥ 26
Ceftazidime	CAZ30	≤ 17	18-20	≥ 21
Amoxicillin / Clavulanic acid	AMC30	≤ 13	14-17	≥ 18

ANNEX 2

Antimicrobial Resistance – Caveats/limitations of data

Human

The four UK health administrations have methods for data collection of antibiotic resistance, though there are differences in how these are managed. For the majority of bacteria resistance is collected through passive surveillance systems, collecting microbiology results from clinical laboratories. Additional information is collected through reference laboratory surveillance. Over 70% of *E. coli* bacteraemia and *Salmonella* infections have AST results available. However, less than 50% of *Campylobacter* isolates have susceptibility testing and where this is performed it is predominantly limited to erythromycin and ciprofloxacin. Less than 1% of *Campylobacter* isolates are sent to the Reference laboratory, where they are tested against a wide array of antibiotics. Table 14 highlights the number of antibiotics tested in *Salmonella* across human and animal species.

Different antibiotic susceptibility testing methodologies are used in England and Wales, Scotland, and Northern Ireland. England, Wales and Scotland utilise the BSAC methodology to determine resistance/susceptibility to an antimicrobial based on human clinical breakpoints, whilst in Northern Ireland, an accredited CLSI method utilising different antimicrobial concentrations is used for testing. **The amalgamated results of such UK wide monitoring should be interpreted with caution.** There was a phased transition by the Scottish diagnostic laboratories from CLSI to EUCAST breakpoints in 2012 – 2013. In Wales, all microbiology laboratories are currently moving to EUCAST AST methodology and previously used BSAC methodology.

Scotland

- Limited data are provided on *Campylobacter* bacteraemias
- Selective reporting may have occurred, where laboratories have chosen only to test and/or report susceptibility results against certain agents for clinical reasons
- EUCAST susceptibility testing methodology was gradually introduced in the diagnostic and reference laboratories during 2012-2013, which for some antimicrobials may have resulted in small proportions of isolates changing from being reported as 'susceptible' under CLSI methodology to now being reported as 'resistant' under the new EUCAST methodology. In particular the reporting of susceptibility to co-amoxiclav may have been affected by this change.

Northern Ireland

- Four of the five Trusts in Northern Ireland use EUCAST as clinical breakpoints, adopting the standard in December 2011 to begin in January 2012, and have followed EUCAST's yearly updates since then. Prior to this, they used the 2008 CLSI standard (M100-S18). The Western Trust laboratory still uses CLSI.

Table 14. Number of *Salmonella* tested against antimicrobials, by species in the UK, 2013

Antimicrobial	Human (N =8459*)	Cattle¥ (N=775)	Chickens ¥ (N=899)	Pigs ¥ (N=314)	Sheep (N=140)	Turkeys (N=248)
	No.tested	No. tested	No. tested	No. tested	No. tested	No. tested
Ampicillin	6,707	775	899	314	117	249
Cefotaxime	6,646	0	0	212	0	0
Chloramphenicol	6,683	673	899	212	117	249
Ciprofloxacin	6,968	0	899	0	0	249
Gentamicin	6,693	673	899	212	117	249
Nalidixic acid	6,708	775	899	212	140	249
Streptomycin	6,683	673	899	212	117	249
Sulphonamides	6,645	673	899	212	117	249
Tetracycline	6,683	775	899	314	140	249
Trimethoprim	6,759	673	899	212	0	249

Veterinary

- Isolates that are obtained through scanning surveillance cannot be considered to accurately reflect the bacterial populations present within the general animal populations present in the UK. It is pertinent to highlight that the levels of resistance demonstrated by the isolates presented here may be higher than those seen in the wider bacterial populations present within animals in the UK as samples are more likely to be submitted where cases have been unresponsive to initial antibiotic therapy; and thus the isolates tested may have already been exposed to selective pressure(s).
- This method of obtaining isolates is considered to be a "passive" form of surveillance. The samples obtained are not randomly selected and are therefore susceptible to bias. For example, geographical proximity of a farm or veterinary practice to a diagnostic laboratory may have an impact on the submission rate of samples. Clinical (scanning) surveillance may therefore over-represent certain geographical areas and the animal populations within those areas.
- Furthermore, veterinary surgeons have the option to submit samples to private laboratories rather than to APHA laboratories. At this stage, it is not possible to determine the proportion of the total number of samples submitted for susceptibility testing in the UK that are processed by APHA laboratories, and

therefore it is not known how representative these samples are of total diagnostic submissions.

- These data detail the number of bacterial isolates that underwent sensitivity testing, not the number of animals from which samples were submitted. In fact, several bacteria may have been cultured from an individual animal).

- The diagnostic tests performed on a sample are dependent on the individual case; ie isolates of the same bacterial species are not always tested against the same panel of antibiotics. Therefore, if resistance is not detected in one isolate, it may not mean that resistance is not present, just that it was not tested for. This is especially true of commensal organisms

- In GB, where published breakpoints are available from BSAC then these have been used for the interpretation of the veterinary antibiotic susceptibility results. It is important to note that this assumes that the level of antibiotic achieved at the site of infection in the animal is similar to that achieved in a human treated with the same antibiotic; of course this assumption may not always be correct, not least because different concentrations may be achieved at the site of infection in animals as a consequence of different dosing regimens or the result of differing pharmacokinetics in different animal species.

- For some veterinary antibiotic and organism combinations, there are no published breakpoints available using either the BSAC method or other methods. Published breakpoints are therefore not available for all animal species and for all of the bacterial organism/antibiotic combinations which may require testing. In these cases, in Great Britain, a uniform cut-off point of 13mm zone size diameter has been used to discriminate between sensitive and resistant strains; an intermediate category of susceptibility has not been recorded. This breakpoint is the historical APHA veterinary breakpoint and although it has been used for a considerable number of years, published validation data are not available for a number of organism/antibiotic combinations.

- However, it is pertinent to note that where the majority of isolates of a particular organism are highly resistant or fully susceptible to an antibiotic, breakpoint issues can affect a surprisingly low number of isolates (or no isolates).

- *Escherichia coli* isolates are not collected from routine samples from healthy livestock in Northern Ireland. Only clinical cases submitted for post-mortem investigation when colibacillosis, or similar diseases, will proceed to isolate pathogenic *E. coli*. AMR testing on *E. coli* isolates is mainly performed if samples are coming from <2-week old calves and animals with bovine mastitis.

- With regards to *E. coli*, each country in the UK sets their own criteria for testing AMR in *E. coli* from clinically sick animals and these criteria are not uniform. The data for isolates of E. coli are not categorised by age groups in this report. This is pertinent to highlight as the prevalence of resistant isolates in younger animals is known to be greater than adults – and as such this combined result is open to bias.

ANNEX 3

Antimicrobial Consumption – Sources and caveats/limitations of data

Human consumption data

Table 15. Sources of primary and secondary care antibiotic prescribing data by country

	Primary care	Secondary care
England	*Data source*: NHS Business Services Authority (national Prescription Cost Analysis) *Includes:* all antibiotic prescriptions dispensed in the community from GP, out-of-hours, dentists, non-medical prescribers and prescriptions written in hospitals dispensed in the community.	*Data source*: IMS Health *Includes*: 99% of secondary care providers dispensed prescription for hospital inpatients, outpatients and ambulatory care
Northern Ireland	*Data source*: Health and Social Care Board Medicines Management Information team, using information contained on prescription forms received and paid through the Business Service Organisation's FPS Pharmaceutical Payment System *Includes*: Prescriptions written by GPs, dentists and non-medical prescribers for antibiotics and dispensed from community pharmacies or by dispensing doctors.	*Data Source:* Trust pharmacy services operating the JAC Medicines Management Suite system. *Includes:* JAC records supply of all medications to wards/units within a hospital; information on antimicrobial usage has been obtained by analysis of this stock movement.
Scotland	*Data source*: Prescribing Information System (PIS) database, maintained by Information Service Division (ISD), of NHS National Services Scotland (NSS). The information is supplied to ISD by Practitioner and Counter Fraud Services strategic business unit of NSS who is responsible for the processing and pricing of all prescriptions dispensed in Scotland *Includes:* Prescriptions written by GPs, dentists and non-medical prescribers and from prescriptions written in hospitals dispensed in the community.	*Data source*: Hospital Medicines Utilisation Database (HMUD). This database held by ISD collects information from hospital pharmacy systems across Scotland and presents standardised information on use of medicines using a web-based system. *Includes:* Data on antibiotic use in secondary care
Wales	*Data source:* Prescribing Services Unit (PSU), NHS Wales Shared Service Partnership. The data are collected from prescriptions that are submitted to PSU by dispensing contractors at the end of each month from prescriptions that have been dispensed *Excludes:* private prescriptions.	*Data source:* Welsh national medicines database, Medusa *Includes:* stock data for all acute hospitals in Wales *Excludes:* Singleton hospital; non-acute, or community hospitals.

Veterinary antimicrobial sales data

- Sales data do not permit accurate analysis of antibiotic consumption by animal species or production category. Some formulations of antibiotics are authorised with indications for use in more than one species, eg pigs and poultry. It is not possible to ascertain from sales data in which species the product was used.

- A volume of antibiotic may represent many doses in small animals or few doses in large animals. Therefore it is not possible to predict the number of doses (consumption) that the sales volume represents. Even within a species group there may be variations in animal size.

- Changes in volumes of sales data should be considered in parallel with changes in the UK animal population over the corresponding time period. The populations of animal species are an important denominator and may vary quite markedly from year to year depending on market conditions for livestock derived food; the greater the number of animals, the greater the potential need for antibiotic treatment. Similarly variations in the size of the animals being treated should be taken into consideration as larger animals will require a larger total volume of antibiotics over a treatment period.

- To try and address the variation in animal populations and demographics, over time and between countries, the ESVAC project has developed a Population Correction Unit (PCU), a calculation that estimates the weight of the animal (or group of animals) receiving an antibiotic at the most likely time of administration. This unit is now used across EU member states and is currently the best approximation of consumption. We have used this form of analysis in this report.

- Sales data in general over estimate use, as not all antibiotics sold will be used. There is natural wastage resulting from pack sizes that do not meet dose need, and from drug expiry.

- The sales data represented in this report do not take into account imports or exports of products. For the purpose of this report it is assumed that all products sold in the UK remain in the UK and nothing is imported.

- Medication sold for use in humans may be used in animals under certain circumstances, according to the prescribing cascade; figures on such use are not included in the data presented.

ANNEX 4

Veterinary Antimicrobial Sales data – Contributing Pharmaceutical Companies and Other Marketing Authorisation Holders 2011-2013

Alfasan Nederland BV, Animalcare Limited, aniMedica GmbH, Bayer Plc, Bimeda Chemicals Ltd, Boehringer Ingelheim Ltd, Ceva Animal Health Ltd, Chanelle Animal Health Ltd, Continental Farmaceutica SL., CP Pharma Handelsgesellschaft mbH, Cross Vetpharm Group Ltd, Cyton Biosciences Ltd, Dechra Ltd, Divasa – Farmavic S.A., Dopharma Research B.V., ECO Animal Health, Ecuphar N.V., Eli Lilly & Company Ltd, Emdoka bvba, Eurovet Animal Health B.V., Fort Dodge Animal Health Ltd, Forte Healthcare Ltd, Forum Products Limited, Franklin Pharmaceuticals Ltd, Globamed, Global Vet Health S.L, Harkers Ltd, Huvepharma N.V., I.C.F. Sri Industria Chimica Fine, Industrial Veterinaria S.A., Intervet UK Ltd, Janssen-Cilag Ltd, Kela N.V., Krka Dd, Laboratorios Calier S.A., Laboratorios Hipra S.A., Laboratorios Karizoo S.A., Laboratorios SYVA S.A.U, Laboratorios Velvian, S.L. 132, Lavet Pharmaceuticals Ltd, Le Vet B.V., Merial Animal Health Ltd, Miklich Laboratorios S.L, Minster Veterinary Practice, Nimrod Veterinary Products Ltd, Norbrook Laboratories Ltd, Novartis Animal Health UK Ltd, Oropharma N.V., Pharmaq Ltd, Phibro Animal Health SA, Quvera Ltd, Qalian Ltd, Sogeval S.A., SP Veterinaria, S.A., Triveritas Ltd, Tulivin Laboratories Ltd, Universal Farma S.L, Univet Ltd, Vétoquinol UK Ltd, Vetpharma Animal Health S.L, Virbac S.A, VMD NV, Zoetis

ANNEX 5

Human biomass/Population Correction Unit

Human biomass

Data on the UK human population were taken from Population Estimates Summary for the UK, mid-2013, Office for National Statistics. The body weights used to estimate human biomass are based on EFSA recommendations (9):

- a body weight of 70 kg should be used as default for the European adult population (aged above 18 years)
- a body weight of 12 kg should be used as default for European toddlers (aged 1-3 years)
- a body weight of 5 kg should be used as default for European infants (aged 0-12 months)

Calculation of the Population Correction Unit

The sales of antibiotics may be affected by the number and size of animals in a country.

The Population Correction unit (PCU) is a theoretical unit which estimates the total weight of animals in a population at the most likely time of treatment and allows standardisation of sales between different populations. The sales of antibiotics are divided by the total estimated weight of animals in a population to give the mg/PCU, which is an estimate of mg/kg of animal biomass

$$\text{PCU} = \begin{array}{c}\text{Total number of}\\ \text{each species of}\\ \text{food producing}\\ \text{animals in the UK*}\end{array} \quad \text{X} \quad \begin{array}{c}\text{Theoretical weight}\\ \text{when antibiotic}\\ \text{treatment is most likely}\\ \text{to take place**}\end{array}$$

This includes cattle, pigs, sheep, goats, poultry (broilers) and fish.
*** The average weight of each category of animal at treatment used in the PCU calculation can be found in the 2005- 2009 ESVAC report (19)*

The calculation of mg/PCU for this report:

$$\text{mg/PCU} = \frac{\text{Total amount of antibiotics sold for use in food producing animals (tonnes X10}^9)}{\text{PCU}}$$

Data sources for the calculation of the PCU:

- The population of food producing animals, to animal species level is obtained from the Agriculture in the UK Report, compiled by Defra (20). The live weight of animals slaughtered for food is sourced directly from Defra.
- The live weight of fish slaughtered in the UK annually, is supplied by CEFAS (Centre for Environment, Fisheries and Aquaculture Science)
- Import and export figures are sought from TRACES (TRAde Control and Expert System) which are provided by European Surveillance of Veterinary Antimicrobial Consumption (ESVAC).
- The theoretical weight when antibiotic treatment is most likely to take place is supplied by ESVAC; further details can be found in the ESVAC report (19)

Variation of PCU calculation in different published reports

- In the calculation of mg/PCU in this report the weight of antibiotics sold for use in food producing species only considers antibiotics indicated for systemic, intramammary and intestinal use, to be directly comparable to human data. The calculation of mg/PCU included in the UK VARSS report and ESVAC does not exclude any antibiotics on the basis of their route of administration.
- The ESVAC approach is to calculate the weight of the antibiotic active substance plus its salt. The salt is excluded from the calculation in this report and the UK-VARSS report.
- The ESVAC approach to calculating mg/PCU assumes that all veterinary antibiotics apart from tablets are sold for use in livestock. In this report and the UK-VARSS report the calculation covers products authorised only for use in food producing species.
- The ESVAC approach is to include horses as a food producing species in the calculation, horses are not included in the calculation in this report or the UK VARSS report.

Variation between Biomass calculations and PCU calculations

- For the estimation of biomass of the populations of live food-producing animals, standard weights at an age when animals are most likely to receive treatment are used, whereas the calculated human EU population – and age class – weighted biomass is based on an EU average weight. Thus, the calculations of the two denominators are not based on the same principle. Data on consumption of antimicrobials by age class are reported to ESAC-Net by only a few countries. In many countries, the consumption of antimicrobials is probably higher in children, adolescents and the elderly than in adults in general, but this could not be taken into consideration because of the lack of data.

ANNEX 6

Animal health - Additional Antibiotic Resistance data

Table 14. Animal health: Proportion of resistant *E. coli* in animals, reported by clinical surveillance (using human clinical breakpoints) in the UK, 2013

	No. Resistant/No. Reports (% non-susceptible)
All veterinary*	
Ampicillin	1,894/2,861 (66)
Chloramphenicol	421/806 (52)
Colistin	not tested
Gentamicin	not tested
Amikacin	298/1,114 (27)
Streptomycin	579/1,310 (44)
Trimethoprim/Sulphonamide	1,348/3,312 (41)
Tetracycline	1,843/2,861 (64)
Nalidixic acid	not tested
Ciprofloxacin	not tested
Cefotaxime	91/807 (11)
Cefoxitin	not tested
Ceftazidime	51/807 (6)
Tobramycin	not tested
Temocillin	not tested
Ertapenem	not tested
Meropenem or Imipenem	not tested

*Combined result for *E. coli* from cattle, sheep, pigs, turkeys and chickens. Animal isolates were a mix of clinical samples
Note Table 15 is an extension of table 1, showing the additional antimicrobials tested in animals

Table 15. Animal health: Proportion of non-susceptible isolates of *E.coli* from pigs, collected through EU harmonised monitoring in the UK, 2013

	No. Resistant/No. Reports (% non-susceptible)
Pigs	**157**
Ampicillin	47/157 (30)
Chloramphenicol	35/157 (22)
Colistin	No clinical breakpoints
Erythromycin	Not tested
Gentamicin	4/157 (3)
Amikacin	Not tested
Streptomycin	93/157 (59)
Sulphonamides	No clinical breakpoints
Tetracycline	105/157 (67)
Trimethoprim	65/157 (41)
Nalidixic acid	2/157 (1)
Ciprofloxacin	1/157 (1)
Cefotaxime	1/157 (1)
Cefoxitin	Not tested
Ceftazidime	Not tested
Tobramycin	Not tested
Temocillin	Not tested
Ertapenem	Not tested
Meropenem or Imipenem	Not tested

ANNEX 7

WHO – Critically Important Antimicrobials for Human Medicine

The list of critically important antibiotics is based on two criteria (6)

1.   An antimicrobial agent, which is the sole or one of limited available therapy to treat serious human disease
2.   Antimicrobial agent is used to treat diseases caused by either: (1) organisms that may be transmitted to humans from non-human sources or, (2) human diseases caused by organisms that may acquire resistance genes from non-human sources.

Antimicrobials that meet both criteria are critically important for human medicine. There are four antibiotics that are currently regarded as CIAs: macrolides, 3rd and 4th generation cephalosporins, quinolones and glycopeptides.

The EMA Committee for Medicinal Products for Veterinary use (CVMP)) were consulted on the risk to public health from the development, emergence and spread of resistance consequent to use of antimicrobials in veterinary medicine. CVMP recommend that the antimicrobials on the WHO list of CIAs should be grouped into three categories:

- Category 1 as antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited,
- Category 2 as antimicrobials used in veterinary medicine where the risk for public health is estimated higher and
- Category 3 as antimicrobials not approved for use in veterinary medicine.

Only fluoroquinolone and third and fourth-generation cephalosporins are considered at Category 2

ANNEX 8

Table 16. Consumption of antibiotics for systemic use (ATC group J01) in the community (primary care sector) in Europe, 2013

Country	Total Antibiotics (expressed as DDD per 1000 inhabitants per day)	Rank	Consumption of third- and fourth-generation cephalosporins expressed as percentage of the total antibiotics	Consumption of fluoroquinolones expressed as percentage of the total antibiotics
Austria	16.26	9	3.90%	9.00%
Belgium	29.64	24	<0.1%	8.90%
Bulgaria	19.91	14	2.90%	12.70%
Croatia	21.1	15	2.10%	7.00%
Cyprus*	-	-		
Czech Republic	19	13	0.30%	4.60%
Denmark	16.4	10	<0.1%	3.10%
Estonia	11.72	2	<0.1%	7.60%
Finland	18.35	11	<0.1%	4.60%
France	30.14	26	5.20%	6.00%
Germany	15.79	7	2.70%	9.00%
Greece	32.02	27	0.30%	6.40%
Hungary	13.84	5	2.50%	14.30%
Iceland*	21.85	17	0.40%	5.20%
Ireland	23.81	20	0.40%	3.70%
Italy	28.63	23	7.10%	12.10%
Latvia	13.5	4	0.30%	7.50%
Liechtenstein	-	-		
Lithuania	18.54	12	<0.1%	4.90%
Luxembourg	-	-		
Malta	23.81	21	1.70%	12.30%
Netherlands	10.83	1	<0.1%	7.00%
Norway	16.22	8	<0.1%	3.30%
Poland	23.31	18	<0.1%	5.00%
Portugal	-	-		
Romania*	29.77	25	3.10%	11.00%
Slovakia	23.63	19	3.20%	9.20%
Slovenia	14.53	6	0.50%	7.60%
Spain	24.2	22	2.00%	11.40%
Sweden	12.99	3	0.20%	5.50%
United Kingdom	21.46	16	<0.1%	1.90%

*Country provided only total care data