NHS National Services Scotland

Scottish One Health Antimicrobial Use and Antimicrobial Resistance in 2018 Annual Report

Health Protection Scotland

An Official Statistics publication for Scotland

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Contents

Introduction

Antimicrobial resistance (AMR) poses an urgent threat to human health as antimicrobials are essential to modern medicine. Increasing levels of resistance to existing antimicrobials, and in particular antibiotics used to treat bacterial infections, means that some infections are becoming more difficult or even impossible to treat. The inappropriate use of antimicrobials in humans and animals and exposure through environmental contamination and food is driving a rise in AMR globally yet there are few new antibiotics under development.

The scale and threat posed by AMR is well described[1;2] and the publication in January 2019 of the United Kingdom (UK) Government's new five year National Action Plan (NAP),[3] alongside a longer term 20 year vision,[4] affirms that AMR remains a crucially important public, clinical and political issue.

The UK NAP and vision were developed collaboratively with input from Scotland and the other devolved administrations. The core ambition is to have a world in which AMR is contained, controlled and mitigated. It recognises that AMR cannot be eradicated and that it will take time to achieve this ambition.

The 20-year vision describes the contribution of the UK to the global effort to contain and control AMR by lowering the burden of infection, optimising use of antimicrobials and the development of new diagnostics, therapies, vaccines and interventions. The UK NAP for 2019 to 2024 focuses on three keys areas:

1. Reducing need for and unintentional exposure to antimicrobials
2. Optimising use of antimicrobials
3. Investing in innovation, supply and access to tackle AMR

Central to achieving this vision is the "One Health" approach encompassing humans, animals, environment and food. An effective response requires a coordinated and concerted effort that spans these fields and the UK NAP is strongly focused on applying a One Health approach to tackling AMR. The Scottish programme has incorporated a One Health ethos for a number of years and the new UK NAP affirms the importance of this wider approach to tackling AMR.

Structures to support delivery of the five-year strategy are currently being developed both at Scottish and UK level. Within Scotland there will be a Scottish One Health National AMR Action Plan (SOHNAAP) Group. The purpose of this group will be to translate the UK NAP into the Scottish context, to support a national approach to the UK NAP, coordinate stakeholders and deliverables and to foster a collaborative approach to the delivery of the One Health actions required.

Robust intelligence and evidence for action are essential to supporting the vision to contain and control AMR. The Scottish One Health Antimicrobial Use and Antimicrobial Resistance

(SONAAR) programme at Health Protection Scotland (HPS) develops epidemiological evidence to inform the development of local and national interventions and initiatives in human and animal health.

This is the tenth year that an annual report on antimicrobial use (AMU) and AMR has been published. In the last ten years the content of the report has continually evolved to reflect the requirements of stakeholders ensuring that the report remains clinically relevant and can be utilised to inform national policies and clinical practice. Originally the report solely focused on the human elements of AMU and AMR, however, for the third year the report includes animal AMR data and for the first time includes animal AMU data and environmental AMR data. HPS will continue to expand these areas in future years, reflecting support for the 'One Health' approach to containing AMR. In addition to adopting a 'One Health' approach, HPS have worked with stakeholders to improve both the ascertainment and quality of data contained within the report and now receive data from all settings (human, animal and environmental). Work will continue to improve data capture in the coming year.

Tackling AMR will be challenging and require concerted and sustained efforts across the One Health spectrum. The burden of drug resistant infections is already substantial compared to that of other infectious diseases,[1] therefore, the urgency of this problem cannot be overstated and the time for robust action is now.

Main Points

Antimicrobial use in humans

- Reducing the Scottish population's unnecessary exposure to antibiotics is critical to containing and controlling antimicrobial resistance
- Total antibiotic use in humans has decreased by 6.2% since 2014
- More than half of all antibiotic use in Scotland was Access antibiotics promoted by the World Health Organisation (recommended first line narrow spectrum agents)
- Antibiotic use in primary care has decreased by 10.2% since 2014; the lowest figure since data became available in 1993
- 27.3% of the Scottish population received at least one course of antibiotics prescribed in primary care
- One in ten antibiotics in primary care were prescribed by nurses; twice as many as five years ago
- Antibiotic use in acute hospitals has increased by 16.0% since 2014 (unadjusted for changes in patient population)
- The Scottish antimicrobial stewardship programme will continue to work with clinicians to improve patient outcomes and minimise antibiotic resistance through minimising inappropriate antibiotic use in humans

Antimicrobial use in animals

- For the first time, antimicrobial use data from a sample of small animal veterinary practices were available
- Nearly one in five consultations resulted in an antibiotic being prescribed; nine in ten of these were not from the group of antibiotics considered to be high priority critically important in humans
- Scotland's Healthy Animals website provides guidance for vets and animal keepers on disease avoidance and antimicrobial stewardship

Antimicrobial resistance in humans

- There were an estimated 1,424 drug resistant bacteraemia during 2018; the majority caused by drug resistant Gram-negative bacteria
- The incidence of Gram-negative bacteraemia, including *Escherichia coli* bacteraemia, and associated resistance to key antibiotics has remained stable over the last five years
- The incidence of *Escherichia coli* and *Klebsiella pneumoniae* urinary tract infections and associated resistance to the majority of key antibiotics has remained stable over the last five years
- The incidence of carbapenemase producing organisms (CPO) has increased significantly since 2014 though there was no change between 2017 and 2018
- Resistance to vancomycin has significantly increased in *Enterococcus faecium* blood isolates with 43.2% of isolates non-susceptible

- A focus on preventing all infections, but in particular Gram-negative infections, is required to reduce the emergence and transmission of AMR and it is important to remain vigilant to AMR across all species
- The National Infection Prevention and Control Manual provides infection prevention and control guidance to support clinicians involved in healthcare delivery
- 7.0% of cases of gonorrhoea were resistant to some extent to azithromycin, an antibiotic used to treat this infection. 2.1% of cases showed a high level of resistance to azithromycin

Antimicrobial resistance in animals

- Monitoring AMR in animals is a vital component of understanding and mitigating risk of AMR across the entire ecosystem
- Non-susceptibility for veterinary clinical isolates has been relatively stable since 2014
- Intelligence relating to AMR in animals will continue to be developed to inform the evidence base

What is the current burden of drug resistant infections in Scotland?

Reducing the burden of drug resistant infections is critical to controlling AMR by reducing the need for antimicrobials and reducing the risk of further spread of drug resistant micro-organisms. In Europe in 2015, there was an estimated 671,689 infections with antibiotic resistant bacteria, accounting for 33,110 attributable deaths and 874,541 disability adjusted life years.[1]

Robust epidemiological intelligence is required to measure the burden of infection and to monitor and evaluate interventions designed to reduce the burden. The UK five year NAP describes specific targets for reducing drug resistant infection burden including a target to reduce a specified set of drug-resistant infections by 10% by 2024 and reduce healthcare associated Gram-negative bacteraemia by 50% by 2023/24.[3] In order to understand the current burden in the Scottish population, a preliminary analysis to describe the number of bloodstream infections (BSI) caused by antibiotic resistant bacteria of key public health concern was undertaken.

In 2018, there were an estimated 1,424 BSI caused by antibiotic resistant bacteria of public health concern (Table 1, and see Appendix). There were 1,216 and 208 Gram-negative and Gram-positive antibiotic resistant bacteraemia, respectively. Drug resistant bacteraemia caused by Gram-negative bacteria accounted for 85.4% of all drug resistant bacteraemia. Importantly, nearly a quarter of *Escherichia coli* bacteraemia (ECB) in Scotland were resistant to one or more key antibiotics, accounting for over 1,000 cases. Whilst *E. coli* accounted for the majority of drug resistant infections, vancomycin resistant *Enterococcus faecium* were the second most common organism. The overall burden of infection was low; however, the proportion of resistance to vancomycin was 43.1%.

These preliminary analyses will be further developed in collaboration with UK colleagues to measure and monitor the wider burden and impact of drug resistant infections (including other infection types) using methods developed by Cassini et al.[1]

Table 1: Estimated number of antibiotic resistant bacteraemia in Scotland, 2018, by organism

Micro-organisms (n=total number of bacteraemia)	Estimated number of resistant bacteraemia	% resistant to at least one key antibiotic
Gram-negative bacteraemia (n= 6,107)	**1,216**	19.9
E. coli (n=4,738)	1,090	23.0
K. pneumoniae (n=782)	108	13.8
K. oxytoca (n=218)	6	2.9
Acinetobacter spp. (n=76)	0	0.0
P. aeruginosa (n=293)	12	4.1
Gram-positive bacteraemia (n=2,889)	**208**	7.2
E. faecium (n=318)	137	43.1
E. faecalis (n=446)	1	0.2
S. aureus (n=1,585)	70	4.4
S. pneumoniae (n=540)	0	0.0
Total bacteraemia (n=8,996)	**1,424**	15.8

[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Burden of AMR Key Points

- Reducing the burden of drug resistant infections is critical to controlling and containing AMR
- 1,424 drug resistant bacteraemia during 2018, the majority caused by drug resistant Gram-negative bacteria
- Nearly a quarter of *E. coli* bacteraemia resistant to one or more key antibiotics, accounting for over 1,000 cases in 2018
- Continued focus on reducing Gram-negative infections is essential
- Robust intelligence and metrics are required to plan, prioritise and evaluate interventions to reduce the burden

Results and Commentary

Antimicrobial Use

Antibiotic use in humans

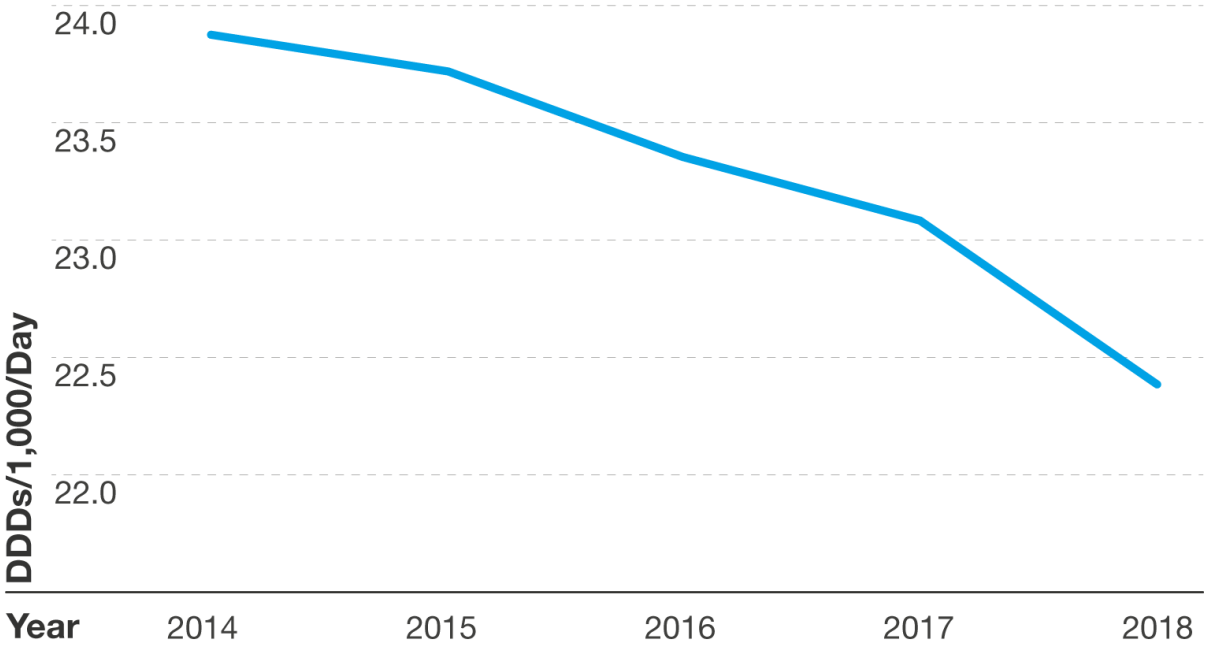
Antibiotics are crucial medicines required in modern healthcare both to treat and to prevent infections. This report includes data from five years up to 2018, 90 years since Sir Alexander Fleming discovered penicillin. In the decades that followed, his discovery saved millions of lives across the world. Fleming understood the need to be careful with how antibiotics are used and how the use of antibiotics would lead to development of drug resistant infections. His predictions were correct and evidence has proven that antibiotic use and AMR are inextricably linked.

The optimisation of the use of the currently available antibiotics is a key objective in the UK NAP.[3] In Scotland, the Scottish Antimicrobial Prescribing Group (SAPG) coordinates an antimicrobial stewardship programme (ASP) working with clinicians across the National Health Service (NHS) in Scotland to improve patient outcomes and minimise antibiotic resistance through minimising inappropriate antibiotic use in humans.

At the core of the ASP coordinated by SAPG is work to reduce the population's unnecessary exposure to antibiotics in two main areas. Firstly, antibiotics should not be used for self-limiting infections such as sore throats and coughs in otherwise fit and healthy people, and secondly when antibiotics are needed, the right antibiotic, at the right dose for the right duration, should be used.

In 2018, the total use of antibiotics in humans across all settings was 22.4 defined daily doses (DDD) per 1,000 population per day (DDD/1,000/day); 6.2% lower ($p<0.001$) than in 2014 (Figure 1, and see Appendix). This shows that progress has been made over the past five years. However, further behaviour change is required by clinicians and the public to build on and accelerate this progress if the UK NAP[3] ambition to reduce antibiotic use in humans by 15% by 2024 is to be achieved. Such progress is required to minimise the development and impact of drug resistant infections in Scotland.

Figure 1: Total number of daily defined doses per 1,000 population per day for all antibiotics prescribed in Scotland, 2014 to 2018, by year

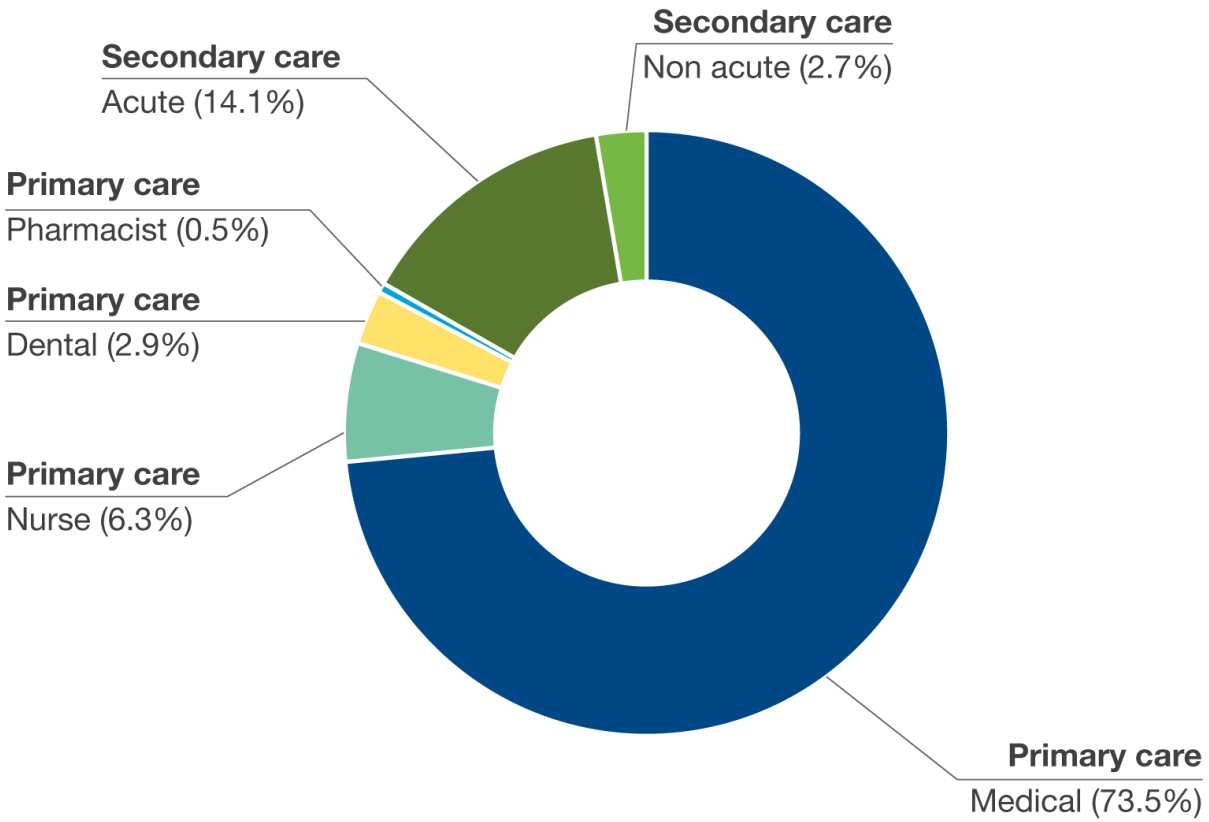


[Data source: Information Services Division (ISD)]

The ‘defined daily dose’ (DDD) is the technical measurement of medicines use used in surveillance of antibiotic use. DDD values for antibiotics are assigned by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology. In 2018, updated DDD values for some commonly used antibiotics were assigned and implemented by the WHO. These new DDDs have been applied to all antibiotic use data throughout this report. This means the data presented in this report cannot be directly compared to previously published SONAAR reports.

Antibiotics are used across all settings in the NHS where care is provided. In 2018, 83.2% of antibiotic use (DDDs) occurred in primary care (community setting) with the remainder in secondary care (hospital setting). Antibiotic use in acute hospitals accounted for 14.1% of antibiotic use in humans (DDDs) with non-acute hospitals accounting for 2.7% (Figure 2, and see Appendix). ASPs are required in all settings to optimise antibiotic use.

Figure 2: Percentage of all antibiotics prescribed (daily defined doses, DDDs) in Scotland by prescriber type, for 2018



[Data source: Information Services Division (ISD)]

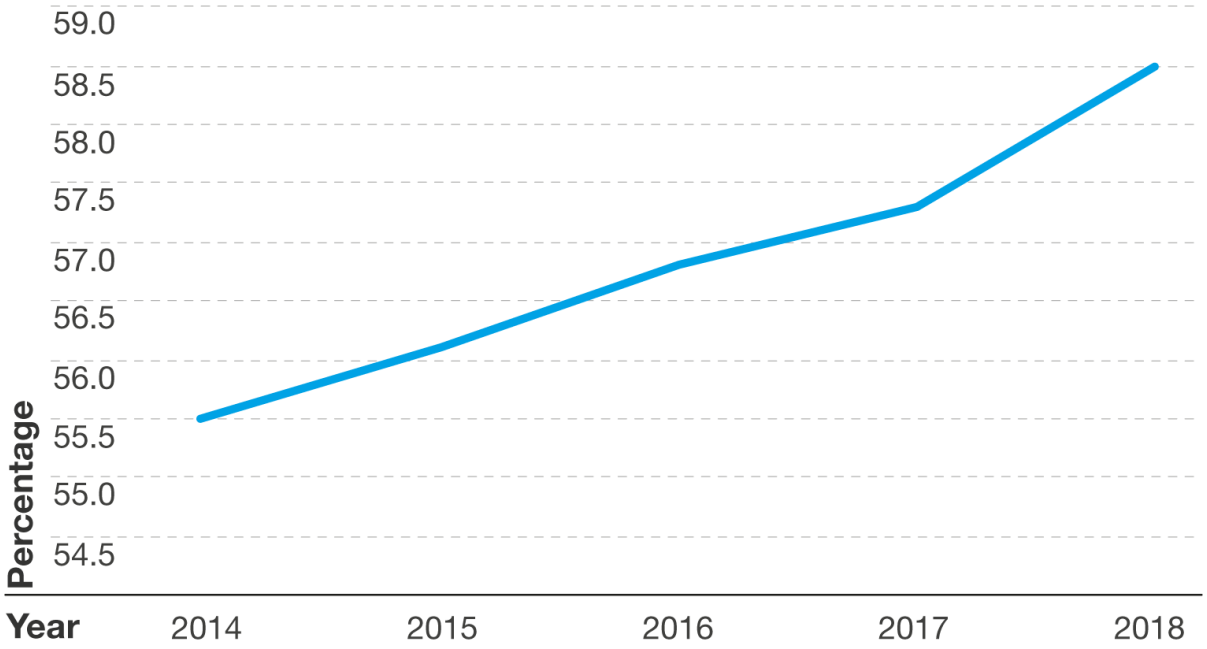
Increasingly antibiotic prescribing is being undertaken by a range of healthcare professionals in Scotland. In 2018, of the total use of antibiotics (total DDDs) where the prescriber type can be determined (in primary care only), medical prescribers accounted for 73.5% of antibiotic use followed by nurses (6.3%), dentists (2.9%) and pharmacists (0.5%) (Figure 2).

Most infections in humans are treated empirically where the bacteria causing the infection and its susceptibility to antibiotics are not known with certainty at the point of prescribing. To support clinicians, guidance on appropriate antibiotic choice for commonly encountered infections are in place across all settings. Guidance aims to promote use of narrow spectrum antibiotics for the most appropriate (shortest effective) duration and reduce use of unnecessarily broad-spectrum antibiotics. Both unnecessarily prolonged and broad spectrum therapy are critical and modifiable prescribing factors which are higher risk for promotion of antibiotic resistance development.

The Essential Medicines List developed by the WHO promotes use of the Access group antibiotics, classified as those that should be used as first line treatment for most common infections. Since 2014, Access antibiotics have accounted for an increasing proportion of total antibiotic use in Scotland which suggests clinicians are following prescribing

guidelines. In 2018, Access antibiotics accounted for 58.5% of combined antibiotic use in humans (DDDs in all primary care and secondary care) (Figure 3, and see Appendix).

Figure 3: Percentage of all antibiotics prescribed (daily defined doses, DDDs) in Scotland that belonged to the 'access' group, 2014 to 2018, by year



[Data source: Information Services Division (ISD)]

Total Antibiotic Use in Humans Key Points

- Antibiotic use in humans decreased by 6.2% since 2014
- The majority of antibiotic use occurs in primary care
- Antibiotics prescribed by a range of clinicians
- Increasing use of WHO Access group antibiotics
- Reducing antibiotic use and using the right antibiotic for the right length of treatment is vital
- Continued development of antimicrobial stewardship programme in Scotland will support clinicians to achieve further improvements

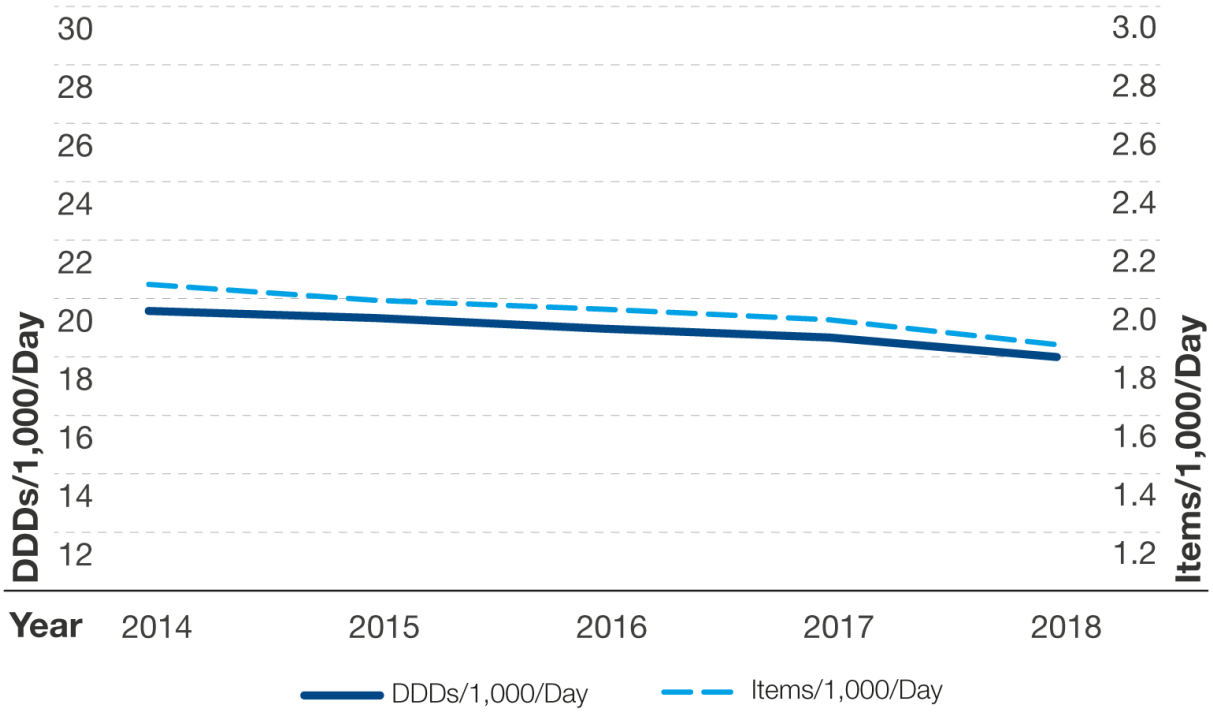
> "The global threat from antibiotic resistant infections is well documented. Increasing reports of untreatable antibiotic resistant infections from around the world as a result of unregulated over use of antibiotics is of grave concern. Implementing WHO advice about using Access group antibiotics is a helpful intervention to tackle resistance. I am encouraged by data from Scotland showing high use of Access antibiotics across both community and hospital settings."
>
> **Dr Andrew Seaton**
> Consultant in Infectious Disease, Chair of Scottish Antimicrobial Prescribing Group

Antibiotic use in primary care

Acute infection is a common reason for patients to present to healthcare professionals in primary care and antibiotics are one of the most commonly prescribed class of medicines. Antibiotic use in primary care (community setting) accounted for 83.2% of total antibiotic use (DDDs) in 2018. Evidence suggests that the majority of drug resistant infections are acquired in the community,[5] therefore optimising antibiotic use in this setting is crucial to tackle AMR.

In 2018, the use of antibiotics in primary care (excluding dental prescribing) was 1.84 items per 1,000 population per day; 10.2% lower ($p<0.001$) than in 2014 (Figure 4, and see Appendix). This is the sixth consecutive annual decrease and means that antibiotic prescribing in primary care is at its lowest point since data became available in 1993. When expressed using DDD, antibiotic use was 18.0 DDD per 1000 population per day; 8.3% lower ($p<0.001$) than in 2014. The proportion of the Scottish population that received at least one course of antibiotics (in primary care, excluding dental) was 27.3% in 2018 compared to 30.6% in 2014, the lowest proportion since data became available in 2010.

Figure 4: Antibiotic prescribing in primary care (excluding dental prescribing) in Scotland, 2014 to 2018, by daily defined doses per 1,000 population per day (DDDs/1,000/Day) and items per 1,000 population per day (Items/1,000/Day), by year



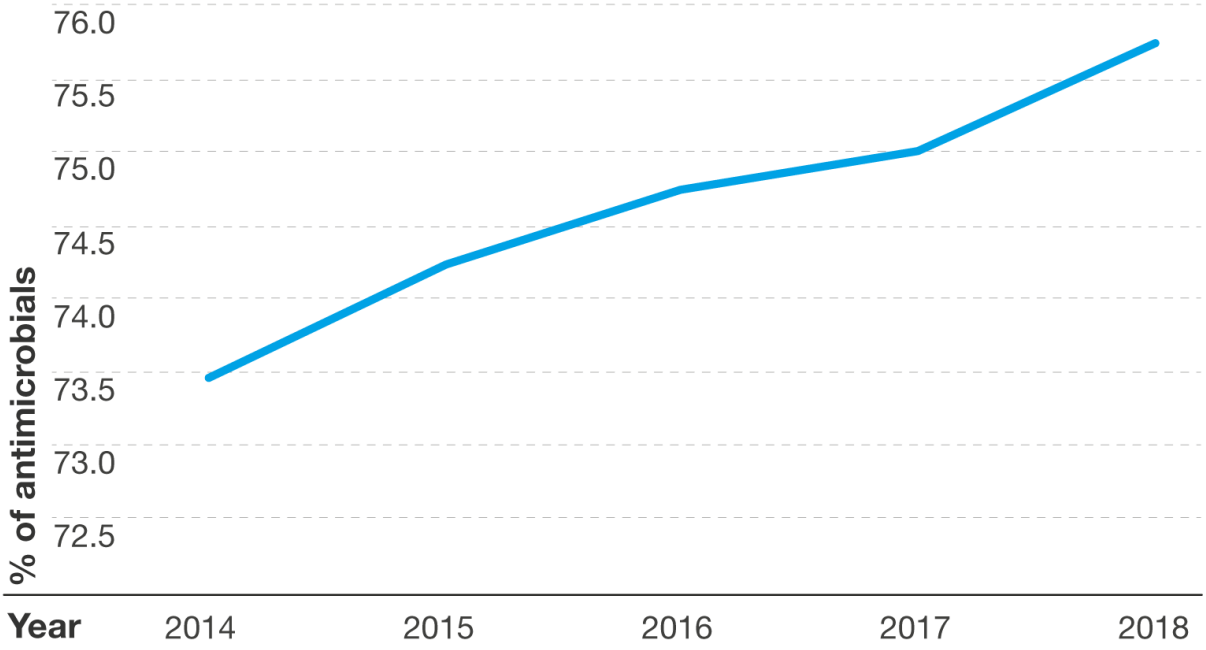
[Data source: Information Services Division (ISD)]

The UK NAP has an ambition to reduce antibiotic use in humans by 15% by 2024.[3] To achieve this challenging target new stewardship approaches will be required and since the majority of antibiotic use is in primary care, new interventions need to be developed. In

reviewing the progress to date and future strategies, the ASP coordinated by SAPG can be considered as different 'ages of antimicrobial stewardship'. The first two ages focused on 'what to prescribe' and 'whether to prescribe' and these two ages suggest that once an area is targeted for improvement by SAPG, NHS board Antimicrobial Management Teams (AMTs) working with primary care teams can implement interventions locally to affect behaviour change and address unwarranted variation in practice.

The 'what to prescribe' age of the ASP focused on reducing the use of certain broad-spectrum antibiotics due to their association with AMR and *Clostridioides difficile* infection. Guideline driven empirical antibiotic treatment for common infections in primary care remains an important element of optimising antibiotic use to reduce the inappropriate use of broad-spectrum antibiotics. In 2018, 75.8% of antibiotic items dispensed in primary care (excluding dental prescribing) were from the WHO Access group, i.e. recommended first line narrow spectrum agents, suggesting that clinicians are following local prescribing guidelines (Figure 5). For more detail on use of particular antibiotics and antibiotic classes, see Appendix.

Figure 5: Percentage of all antibiotics prescribed (items) in primary care (excluding dental prescribing) in Scotland that belonged to the 'access' group, 2014 to 2018, by year

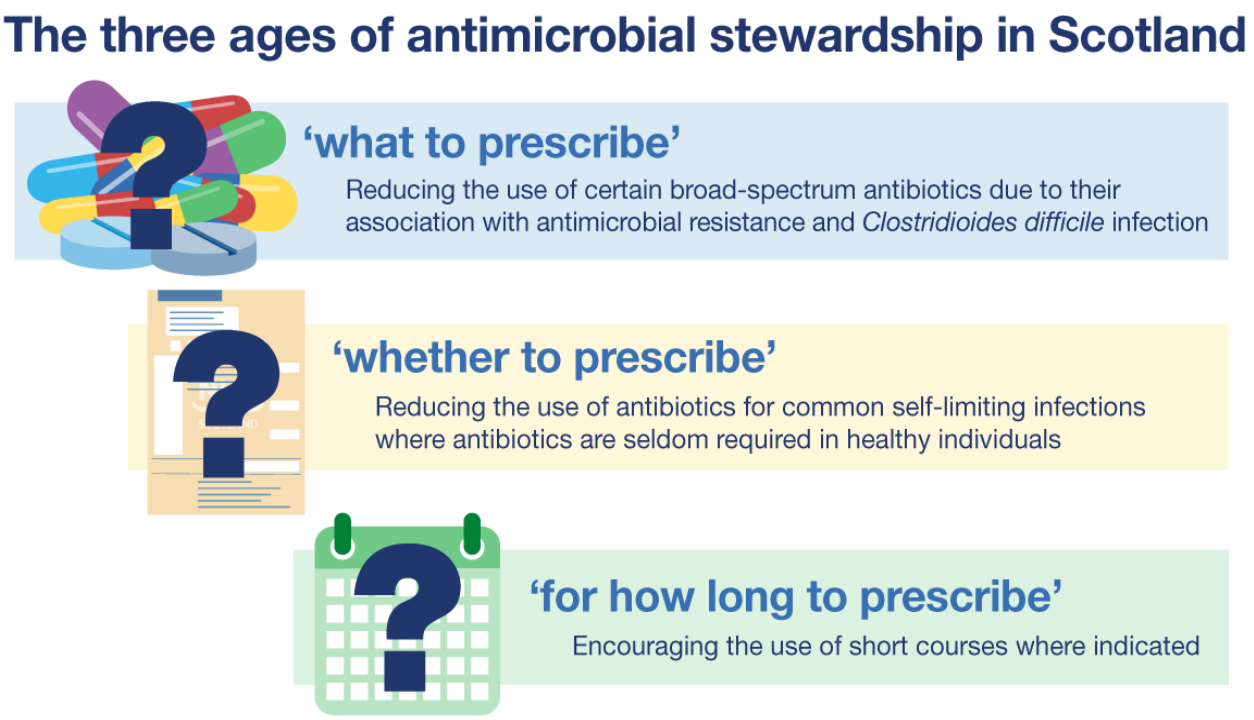


[Data source: Information Services Division (ISD)]

At the core of the 'whether to prescribe' age of the ASP in Scotland over the last five years has been a series of interventions that aim to reduce antibiotic use in healthy people who present with self-limiting common infections such as coughs, colds, sore throats and earache. Reductions in antibiotic use in primary care suggest that clinicians are changing their prescribing behaviours and engaging with their patients and the public to bring about

appropriate antibiotic use. However, there is potential for further reductions in antibiotic use as demonstrated by the Netherlands and Scandinavian countries, preserving antibiotic effectiveness for the future.[6]

To support the ambitions of the UK NAP, SAPG needs to consolidate improvements and accelerate the optimisation of antibiotic use through new interventions. A third age of antimicrobial stewardship is required and this should focus on 'for how long to prescribe'.



Duration of treatment in primary care

The existing guidance template for management of common infections in primary care produced for many years by Public Health England (PHE) and followed by NHS boards in Scotland has recently merged with guidance from the National Institute for Health and Care Excellence (NICE). This supports using shorter courses of antibiotics in community infections and represents an opportunity for new improvement work.[7]

For management of respiratory infections, guidance published to date recommends that where antibiotics are required (recognising antibiotics are not always needed) five days treatment in the community is sufficient.

Table 2 shows the proportion of prescriptions for the antibiotics recommended for treatment of respiratory tract infections in the NICE guidance that were prescribed for five, seven and 10 days and other lengths of treatment during 2018.

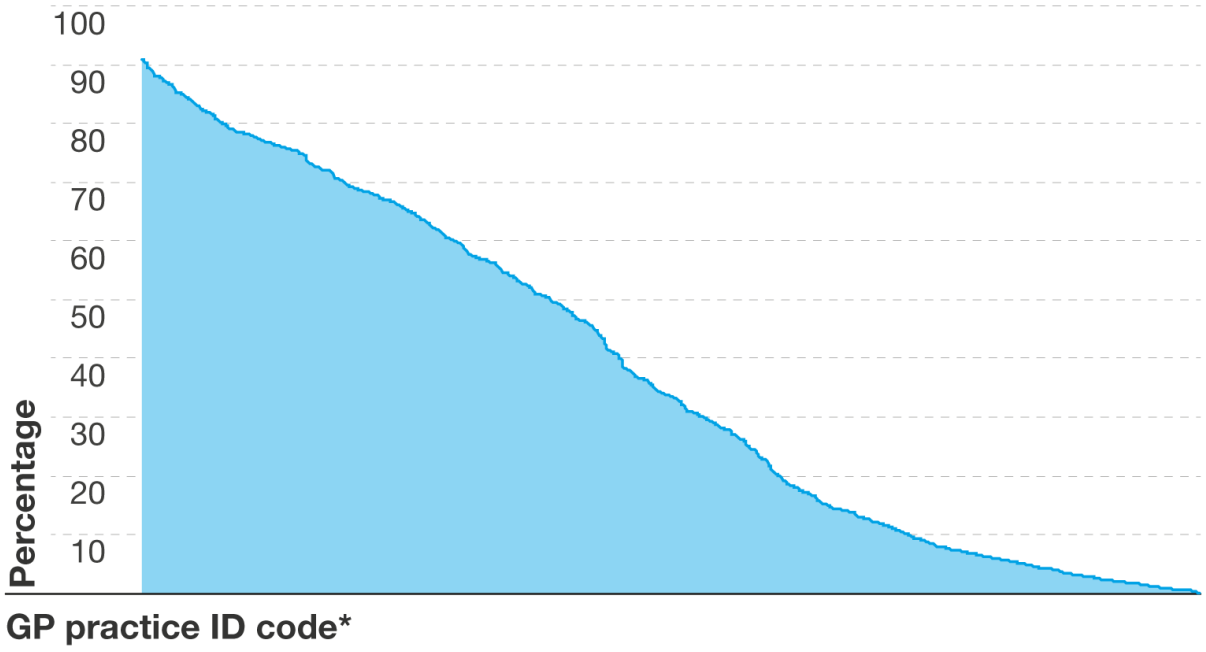
Table 2: Proportion of antibiotics (items) in general practice prescribed for respiratory tract infections in 2018, by treatment duration

Antibiotic	5 days	7 days	10 days	Other
Amoxicillin 500mg	38%	55%	1%	6%
Clarithromycin 250mg	10%	60%	2%	29%
Clarithromycin 500mg	21%	73%	2%	5%
Co-amoxiclav 500/125	11%	76%	2%	11%
Co-amoxiclav 250/125	7%	66%	2%	25%
Doxycycline 100mg	10%	58%	0%	31%
Erythromycin 250mg	4%	27%	1%	68%
Pen V 250mg	4%	38%	38%	20%

[Data source: Information Services Division (ISD)]

These data suggest the most common length of treatment used in NHSScotland during 2018 was seven days. There was variation between NHS boards and general practitioner (GP) practices (Figure 6) on the proportion of prescriptions for amoxicillin 500mg capsules which are for five day courses.

Figure 6: Proportion of amoxicillin 500mg capsule prescriptions with 5 day course durations in 2018, by GP Practice



[Data source: Information Services Division (ISD)]
*Note: There are 935 individual GP practice ID codes.

The impact of reducing seven day courses to five day courses on total antibiotic DDDs is described in Table 3.

Table 3: Potential reductions in antibiotic use (DDD) with increased use of five day antibiotic courses of amoxicillin 500mg, co-amoxiclav 250/125, co-amoxiclav 500/125, clarithromycin 250mg, clarithromycin 500mg, doxycycline 100mg, erythromycin 250mg and pen V 250mg

Proportion of 7 day treatments becoming 5 day treatments	Reduction in total antibiotic DDD
25%	1.3%
50%	2.6%
75%	3.9%
100%	5.2%

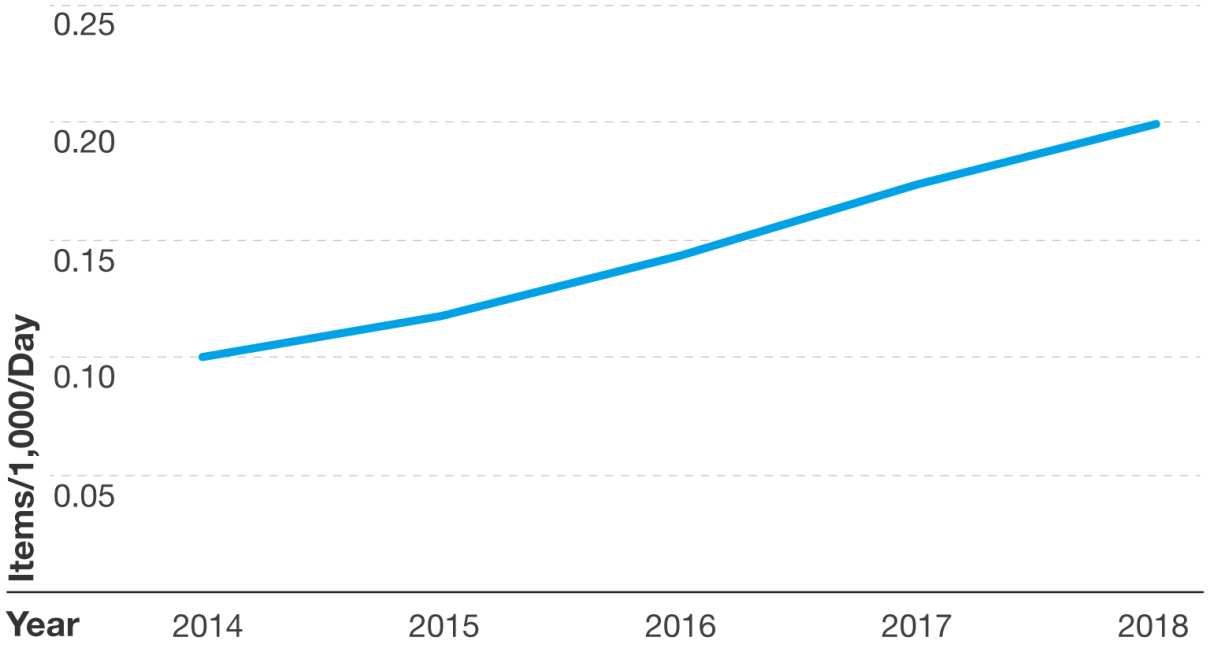
[Data source: Information Services Division (ISD)]

SAPG has agreed to lead work to encourage the use of five day courses of antibiotics where indicated. Switching to five day courses would support reduction in total antibiotic use to achieve the ambitions of the UK NAP but more importantly will reduce the pressure for the development of resistance as well as reducing other potential antibiotic related adverse events.

Prescribers in primary care

Prior to the introduction of legislation to permit non-medical prescribing, antibiotics in the community were prescribed by medical and dental prescribers. In parallel with transformation across primary care, prescribing roles continue to evolve and in 2018 antibiotic prescribing has become a multi-disciplinary effort with non-medical prescribers taking on prescribing rather than it being only a role of doctors and dentists. Prescriptions issued by GPs account for the majority of antibiotics dispensed (items) in primary care. In 2018, nurses accounted for 1 in 10 (10.0%) of all antibiotic items dispensed in primary care in Scotland. Since 2014, the number of items prescribed by nurses has doubled ($p<0.001$) (Figure 7, and see Appendix) and WHO Access antibiotics (items) accounted for 86.3% of nurse prescribing suggesting good compliance with local guideline recommendations.

Figure 7: Antibiotic prescribing by nurses in primary care in Scotland (items per 1,000 population per day; Items/1,000/Day), 2014 to 2018, by year

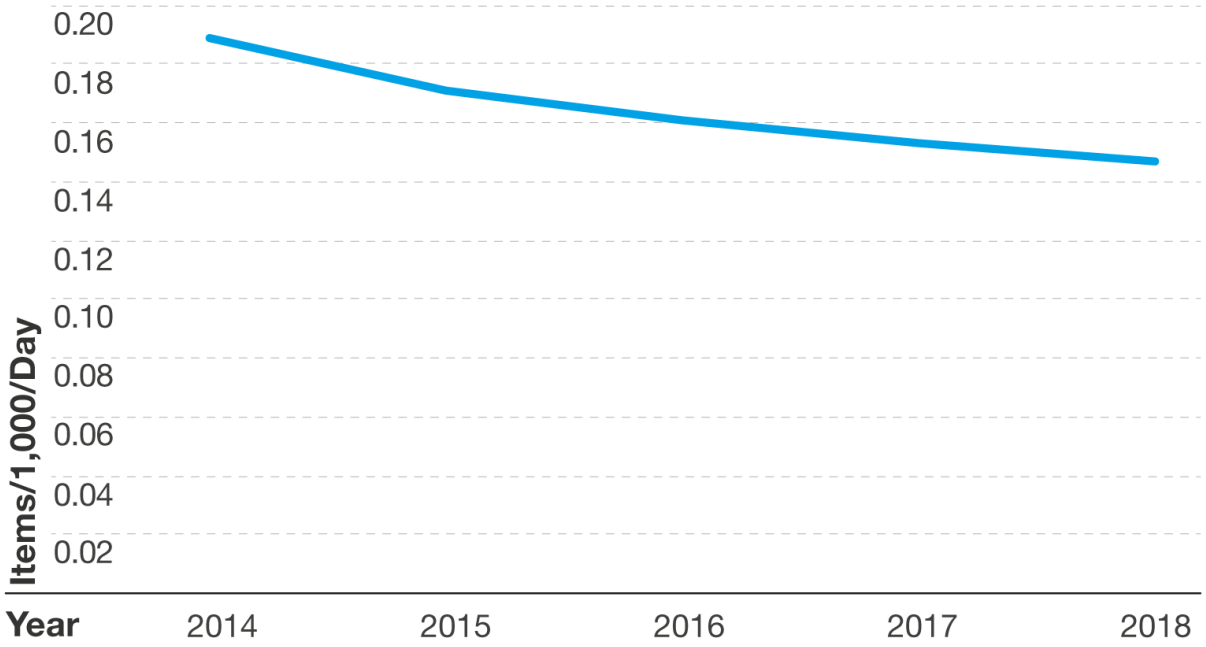


[Data source: Information Services Division (ISD)]

Nurses in all sectors of care support patients to achieve the best outcomes and minimise harm from antibiotic use through safe medicines management. It is likely that nurse prescribing will continue to grow therefore it is essential that all nurses and particularly nurse prescribers are included in interventions to optimise antibiotic use.

The use of antibiotics by dentists continues to decrease, accounting for 7.4% of total antibiotic use (items) in primary care in 2018, similar to the proportion reported in 2017. There have been annual reductions in antibiotic use (items) by dentists and in 2018 this was 22.4% lower than in 2014 and at the lowest rate on record (Figure 8, and see Appendix).

Figure 8: Antibiotic prescribing by dentists in primary care in Scotland (items per 1,000 population per day; Items/1,000/Day), 2014 to 2018, by year



[Data source: Information Services Division (ISD)]

Dentists can prescribe a limited range of antibiotics on NHS prescription in Scotland with two antibiotics, amoxicillin (68.0%) and metronidazole (28.4%) accounting for the majority of dental antibiotic use (items). The SAPG dental antimicrobial stewardship subgroup was established in 2018 to coordinate work by stakeholders and support optimisation of dental antibiotic use. This subgroup has commenced work to explore opportunities and evidence to support a re-introduction of phenoxymethylpenicillin as the first line antibiotic in dental infections in preference to amoxicillin and to review the place of metronidazole in dental infections.

The role of community pharmacists in the management of infection continued to evolve in 2018 with implementation of the Pharmacy First service. This enables people with symptoms of certain infections to be reviewed by a community pharmacist to support self-care, provide timely antibiotic treatment or referral to other NHS services. In 2018, there were 57,514 antibiotic prescriptions written and dispensed by pharmacists in Scotland, representing 1.5% of total antibiotic use in primary care (items) compared to 0.5% in 2017. As transformation of primary care continues to meet the changing demands on health and social care services in Scotland, the antimicrobial stewardship role for pharmacists and in particular community pharmacists will increase.

Antibiotic Use in Primary Care Key Points

- The majority of antibiotic use occurs in primary care
- Antibiotic use in primary care has decreased by 10.2% since 2014, the lowest rate on record
- All clinicians in primary care must optimise use to safeguard antibiotics
- Over three quarters of antibiotics used were WHO Access group antibiotics
- A focus on optimising antibiotic use through encouraging shorter courses of antibiotics is important

> "It is encouraging to see year on year reductions in antibiotic use in primary care since 2013. This demonstrates effective engagement of primary care teams with interventions to improve how infection symptoms are managed and engagement of patients in decisions about prescribing antibiotics. However, there is still variation in use of antibiotics for self-limiting infections and longer courses than necessary of antibiotics for common infections. Continued focus on a team approach to managing infection is required to make further progress and protect our antibiotics for future generations."
>
> **Dr Gail Haddock**
> General Practitioner, NHS Highland, Vice-chair of Scottish Antimicrobial Prescribing Group

Antibiotic use in acute hospitals

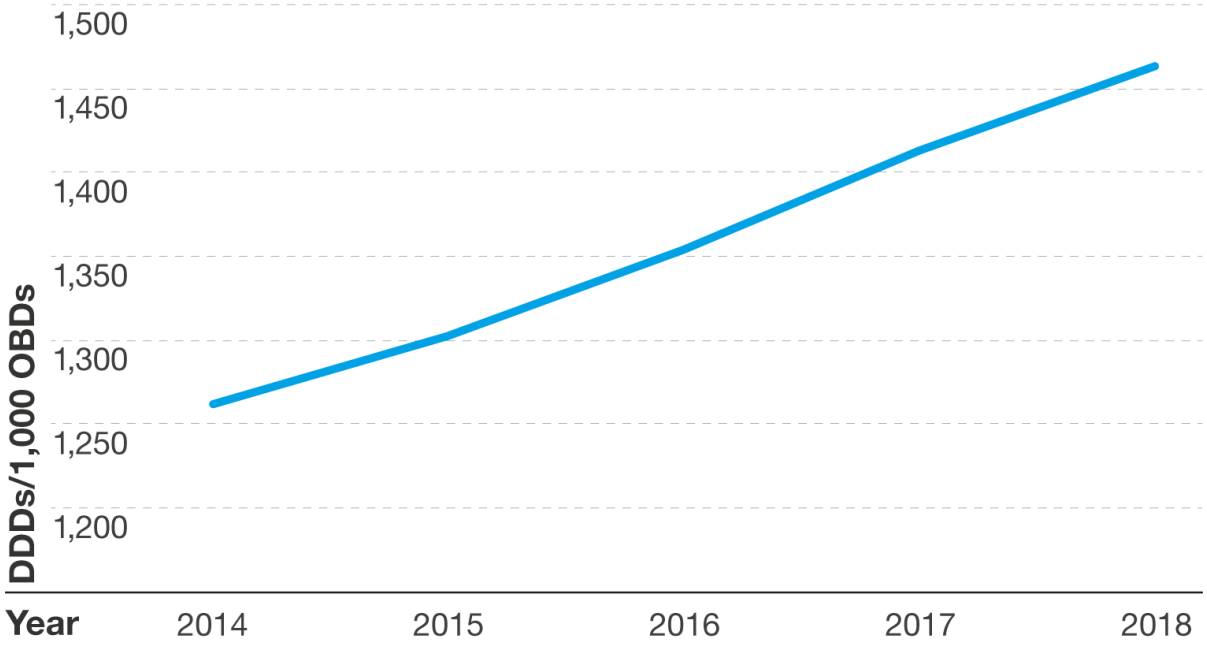
Infections can result in admission to hospital and infections can also be acquired in hospitals. Infections can occur in anyone but can be more serious in people with other co-morbidity and if the infection is caused by multi-drug resistant (MDR) bacteria. Much of the routine healthcare undertaken in hospitals is possible because antibiotics can be used to prevent or treat infections. Antibiotic use in hospitals is common with one in three people in Scottish hospitals receiving antibiotics on any day.[8] A greater range of antibiotics, including broad and very broad spectrum agents are required to manage more complex, severe and resistant infections therefore stewardship is important to optimise antibiotic use in hospital patients.

Hospital based ASP aim to ensure people receive the most appropriate antibiotic (i.e. the correct antibiotic, at the right dose by the correct route) for the right duration. This ensures effective treatment to optimise outcomes for people treated and will cause the least harm through development of resistance and other adverse effects.

In 2018, 14.1% of total antibiotic use (DDDs) in humans occurred in acute hospitals. The use of antibiotics in Scotland's acute hospitals in 2018 was 1,463.5 DDD per 1,000 occupied bed days (OBD); 16.0% higher ($p<0.001$) than in 2014 (Figure 9 and see Appendix). This trend in increasing antibiotic use is contrary to the downward trend seen in

primary care. It is not possible to determine any impact that changes in the acute hospital population has had on the rate of antibiotic use over time. Further intelligence is required to support assessment of the impact of ASP on antibiotic use by developing models that can adjust rates of antibiotic use for factors such as patient mix over time.

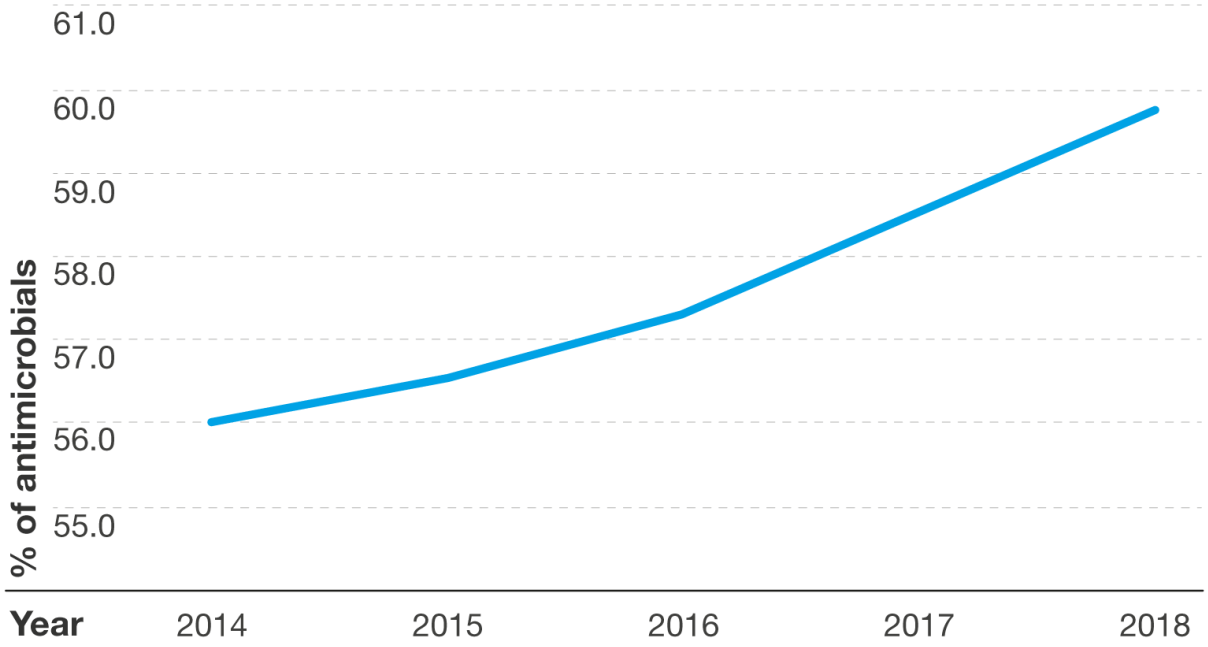
Figure 9: Antibiotic prescribing in acute hospitals in Scotland (daily defined doses per 1,000 occupied bed days; DDDs/1,000 OBDs), 2014 to 2018, by year



[Data source: Information Services Division (ISD)]

At the centre of most hospital based ASP are strategies such as guidelines for empirical management of infection and use of antibiotic formularies to minimise the use of broad-spectrum antibiotics and increase the use of narrower spectrum antibiotics where possible. In 2018, 59.7% of antibiotic use (DDDs) in acute hospitals was Access group antibiotics compared to 56.0% in 2014 (Figure 10). For more detail on use of particular antibiotics and antibiotic classes, see Appendix.

Figure 10: Percentage of all antibiotics prescribed (daily defines doses, DDDs) in acute hospitals in Scotland that belonged to the 'access' group, 2014 to 2018, by year



[Data source: Information Services Division (ISD)]

Getting the initial choice of antibiotic right, although important, represents only one aspect of antimicrobial stewardship in hospital. Equally important is making sure patients receive the correct antibiotic by the appropriate route of administration once further investigations are available and response to treatment has been observed. Ensuring patients do not receive unnecessary intravenous (IV) antibiotics (when oral therapy would suffice) and do not receive antibiotics for any longer than clinically necessary are key areas for antimicrobial stewardship in hospitals.

In 2018, SAPG commenced work to support clinicians to reliably implement timely clinical review of patients receiving antibiotics. This ensures that treatment is personalised based on clinical signs and symptoms and microbiology results and that the intended duration of treatment is documented in the notes and on the medicine chart. Work by SAPG is also underway to encourage the use of shorter antibiotic courses where published evidence of effectiveness supports this. Optimising duration of treatment in line with evidenced based practice will minimise unnecessary exposure of patients to antibiotics and will support the ambition to reduce antibiotic use to prevent the development of resistance.

National work to improve the initial recognition and management of deteriorating patients with suspected sepsis, may have contributed to the increase in antibiotic use in acute hospitals. In 2018, IV antibiotics accounted for 30.0% of total antibiotic use (DDDs) in acute hospitals compared to 28.2% in 2014. Many people receive IV antibiotics when they are admitted to acute hospitals with signs and symptoms that may be suggestive of infection. A key focus for the SAPG work to support reliable clinical review is for patients started on IV

antibiotics to have a documented management plan within 72 hours. This will reduce unnecessary continuation of antibiotics, ensure personalised treatment and appropriate IV to oral switch with associated benefits for patients of reduced risk of device related infections and potential for earlier discharge from hospital. To measure progress with achieving reliable and timely review of IV antibiotic therapy, a national indicator has been developed with a target that use of IV antibiotics in hospitals will be no higher in 2022 than it was in 2018. This is intended to contribute to reduction in total antibiotic use in humans, a key ambition of the UK NAP.

Antibiotic Use in Acute Hospitals Key Points

- Using antibiotics to prevent and treat infection is vital in modern healthcare
- Infections can be more serious in people with other co-morbidity or if caused by a multi-drug resistant bacteria
- Antibiotic use is hospitals continues to increase
- 59.7% of antibiotics used in acute hospitals were WHO Access group antibiotics
- Focus on limiting duration of treatment in line with guidelines is an important part of antimicrobial stewardship

> “Early initiation of antibiotics has saved lives in people with suspected sepsis but an unintended consequence has been an increase in antibiotic use with resultant risk of antimicrobial resistance in our hospitals. We need all clinical teams to take responsibility for minimising antibiotic-related harm today and protecting antibiotics for the future by regular review of patient’s antibiotic plan and stopping antibiotics when they are no longer needed. We have developed resources to support clinical teams with reliable and timely review of patients receiving IV antibiotics. This will support improved communication and have benefits for patients and clinical teams as well as helping us to protect antibiotics for future generations.”
>
> **Dr Stephanie Dundas**
> Consultant in Infectious Diseases, Lead clinician for Scottish Antimicrobial Prescribing Group Hospital Antibiotic Review Programme

Antibiotic use in animals

In the same way that optimisation of antibiotic use in humans is required to tackle the risk of AMR, the optimisation of antibiotic use in animals is also important. Historically, data on antimicrobial use in animals has comprised of sales data compiled at the UK level and published in the annual Veterinary Antimicrobial Resistance and Sales Surveillance (VARSS).[9] The publication of animal AMU data in the Responsible Use of Medicines in Agriculture Alliance (RUMA)[10] Targets Task Force Report of 2018 and VARSS Report of

2018 demonstrate serious commitment to antimicrobial stewardship in livestock species as part of a One Health response to AMR in the UK.

For the first time, this report includes Scottish small animal antibiotic use data. These data were made available from Scottish veterinary practices contributing to the Small Animal Veterinary Surveillance Network (SAVSNET) and provide an opportunity to further describe antibiotic prescribing in the animal compartment of the One Health ecosystem.

In order to optimise disease avoidance and prescribing in veterinary practice; improve education, training and public engagement; and provide better access to and use of surveillance data in animal sectors, Scotland's Healthy Animals website (https://www.scotlandshealthyanimals.scot/) was developed. The website was developed with stakeholders in the animal health sector and brings together expert advice on keeping animals healthy. Trusted guidance is signposted for all animal keepers and their vets, for countryside users, for wildlife and rescue centres, and hosts Scotland's Poultry Hub for poultry keepers, in particular smallholders.

The Small Animal Veterinary Surveillance Network

SAVSNET is an initiative from the University of Liverpool, funded by the Biotechnology and Biological Sciences Research Council**.** The key aims of the network are to:

- monitor disease trends over time and highlight appropriate interventions
- identify populations at risk and monitor treatments and outcomes
- provide data resources for academics and others
- improve general public awareness of small animal diseases and prevention
- provide a route to clinical benchmarking for vets in small animal practice

The SAVSNET data were collected via electronic health records within the practice management systems of first opinion veterinary practices (these record species, breed, date or year of birth, sex, nature of condition being treated and antibiotic treatments supplied, and postcode) and from the veterinary diagnostic laboratories. These data are submitted voluntarily by participating veterinary practices and therefore cannot be interpreted as being representative of all of Scotland. Nevertheless, they provide additional important intelligence relating to another aspect of antibiotic use in the One Health ecosystem.

This important data stream will be further developed and the data presented in this report provide an important first impression of AMU in companion animals in Scotland and will enable practitioners to evaluate their own data compared to this preliminary national data.

Antimicrobial Use (AMU) Summary

A summary of the available data is provided in Table 4. Between 2015 and 2018, 16 small veterinary practices in Scotland contributed data from a total from 202,791 individual consultations and 64,265 individual animals. Nearly one in five consultations resulted in the prescription of at least one antibiotic (18.1%, 95% CI 17.9 to 18.3). The percentage of consultations that resulted in the prescription of an antibiotic has shown a downward trend between 2015 and 2018 (p<0.001). High priority critically important antibiotics (HP-CIA) are identified according to the categorisation by the Antimicrobial Advice ad hoc Expert Group (AMEG) of the European Medicines Agency (EMA) and include fluoroquinolones, 3rd and 4th generation cephalosporins and colistin.[11;12] One in ten antibiotics prescribed were HP-CIA (10.7%, 95% CI 10.4 to 11.0) and this also decreased between 2015 and 2018 (p<0.001).

Table 4: Summary characteristics for companion animals in Scottish veterinary practices, extract from SAVSNET database, 2015 to 2018 inclusive

	2015	2016	2017	2018	Total
Number of contributing practices	9	11	11	15	16
Number of individual animals	15,140	26,646	26,138	30,145	64,265
Number of antibiotics prescribed	7,336	13,963	12,360	11,633	45,292
Number of consultations	28,539	61,542	57,886	54,824	202,791
Number of consultations resulting in prescription of at least one antibiotic	5,882	11,241	10,006	9,585	36,714
Percentage of consultations resulting in prescription of at least one antibiotic	20.6% (95% CI=20.1 to 21.1)	18.3% (95% CI=18.0 to 18.6)	17.3% (95% CI=17.0 to 17.6)	17.5% (95% CI=17.2 to 17.8)	18.1%(95% CI=17.9 to 18.3)
Percentage of total antibiotic prescribed that were high priority*	11.9% (95% CI=11.2 to 12.7)	11.1% (95% CI=10.6 to 11.6)	10.4% (95% CI=9.9 to 10.9)	9.7% (95% CI=9.2 to 10.3)	10.7% (95% CI=10.4 to 11.0)

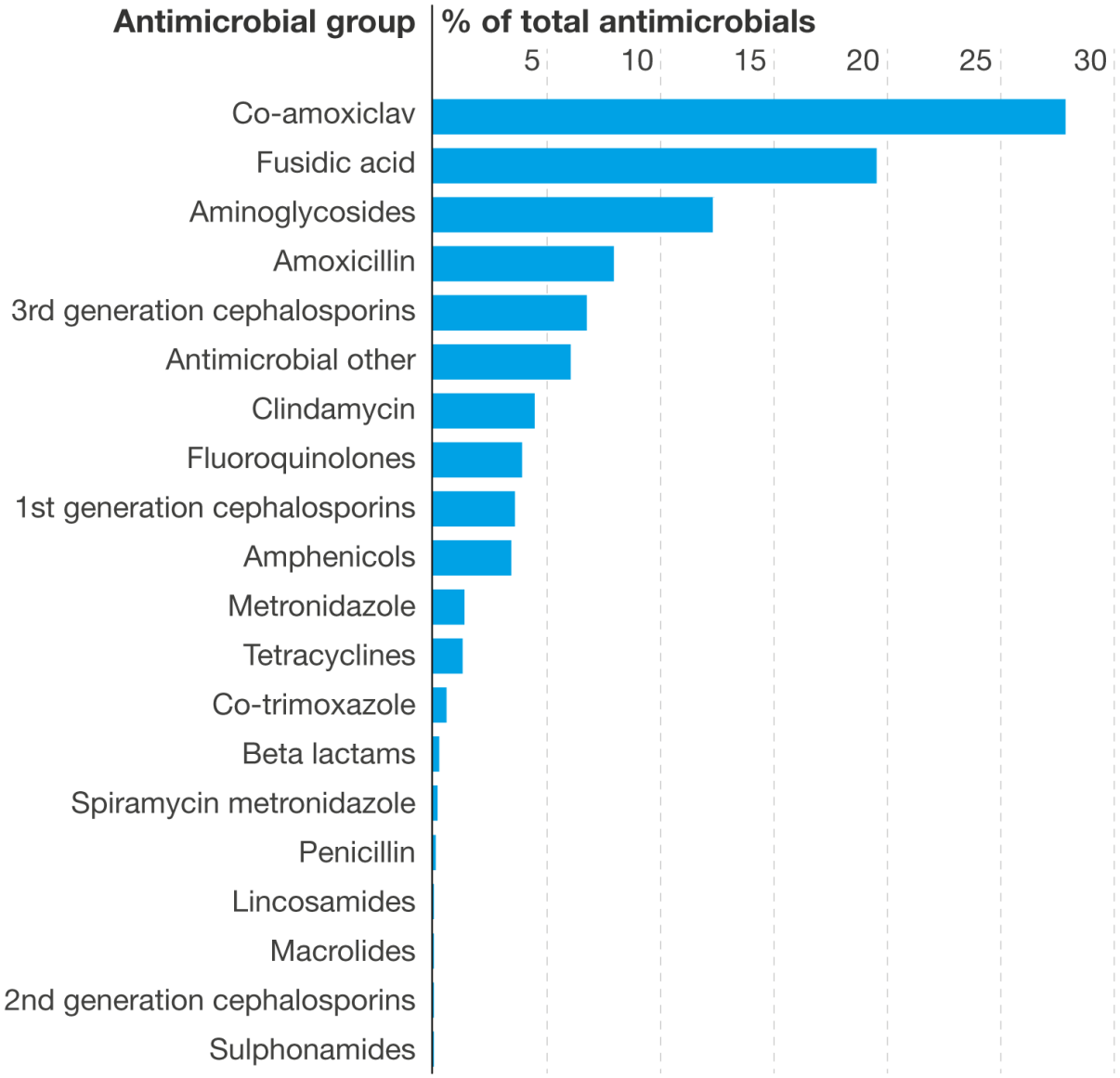
Note: *High priority antibiotics included; cefovecin, ciprofloxacin, enrofloxacin, marbofloxacin, ofloxacin, orbifloxacin, pradofloxacin.

[Data source: The Small Animal Veterinary Surveillance Network (SAVSNET)]

Antibiotic groups

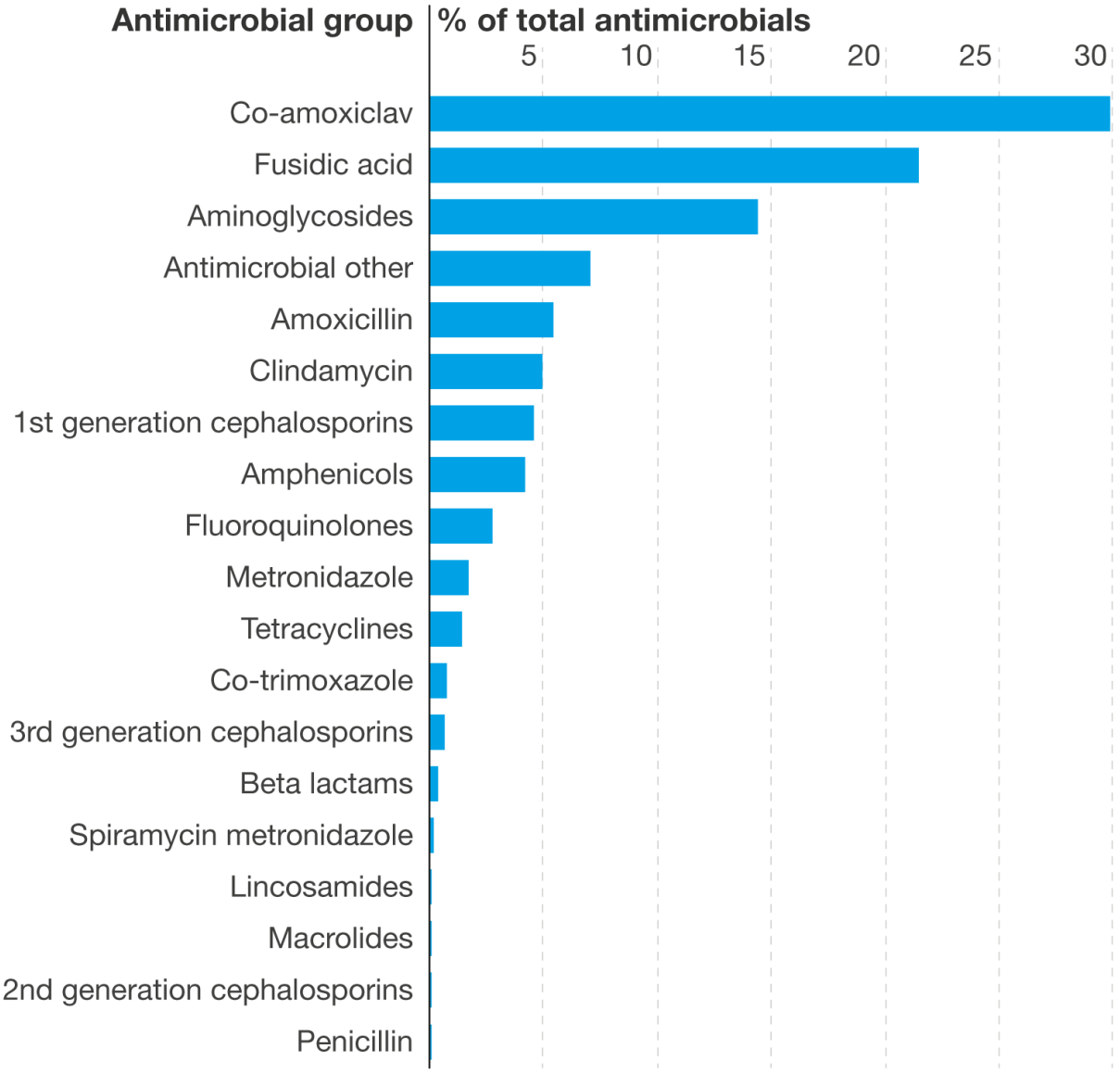
The most frequently prescribed antibiotic group was co-amoxiclav (27.9%), followed by fusidic acid (19.6%) and aminoglycosides (12.3%) (Figure 11). The most frequently prescribed antibiotic group for dogs was also co-amoxiclav (29.9%) (Figure 12), the most frequently prescribed antibiotic group for cats was 3rd generation cephalosporins (30.1%) (Figure 13) and the most frequently prescribed antibiotic group for 'other' companion animal species was fluoroquinolones (63.4%) (Figure 14).

Figure 11: Distribution of total antibiotics prescribed to all animals, SAVNET, 2015 to 2018, by antimicrobial group



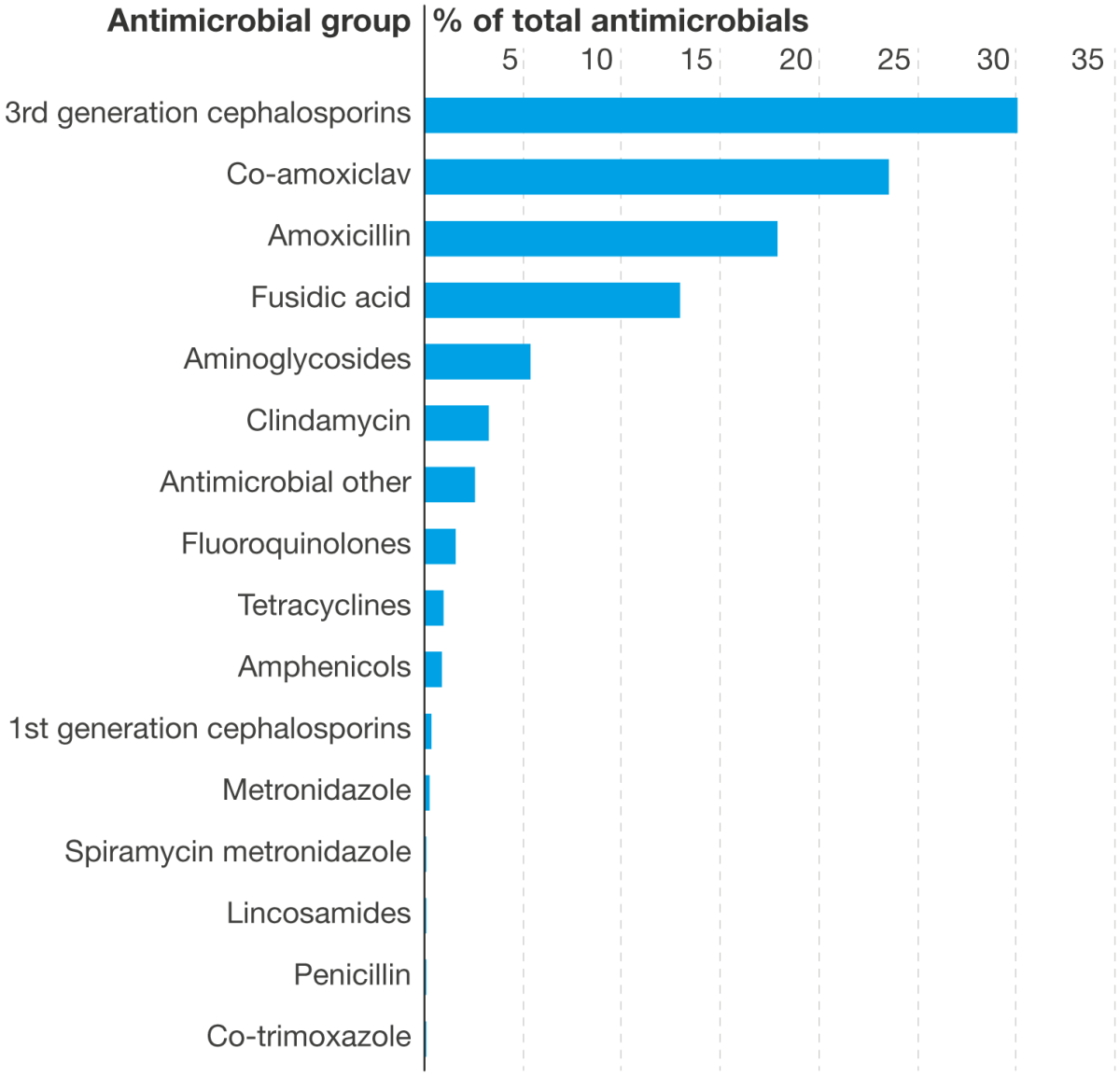
[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

Figure 12: Distribution of total antibiotics prescribed to dogs, SAVSNET, 2015 to 2018, by antibiotic group



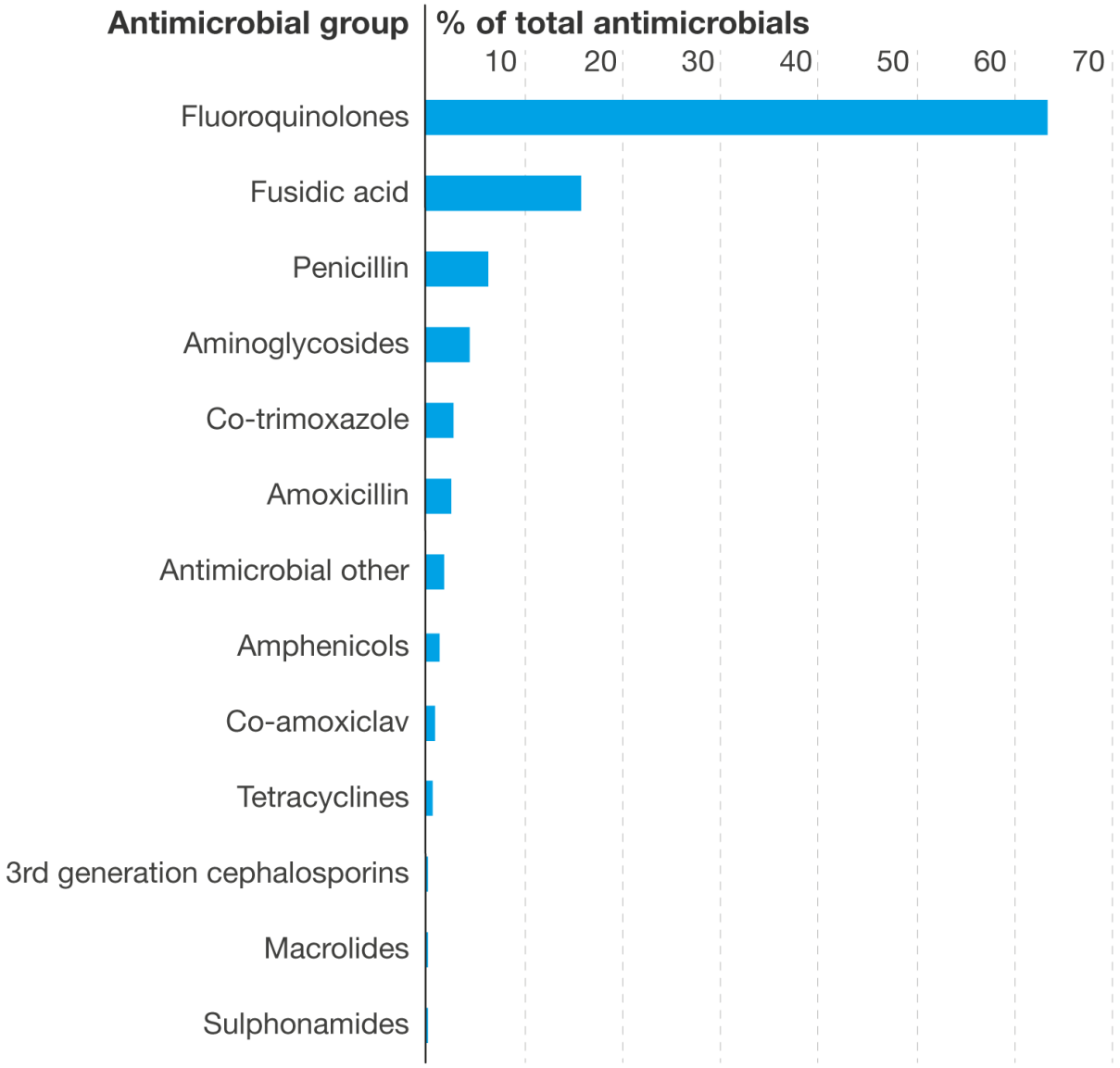
[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

Figure 13: Distribution of total antibiotics prescribed to cats, SAVSNET, 2015 to 2018, by antibiotic group



[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

Figure 14: Distribution of total antibiotics prescribed to 'other' companion animals, SAVSNET, 2015 to 2018, by antibiotic group



[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

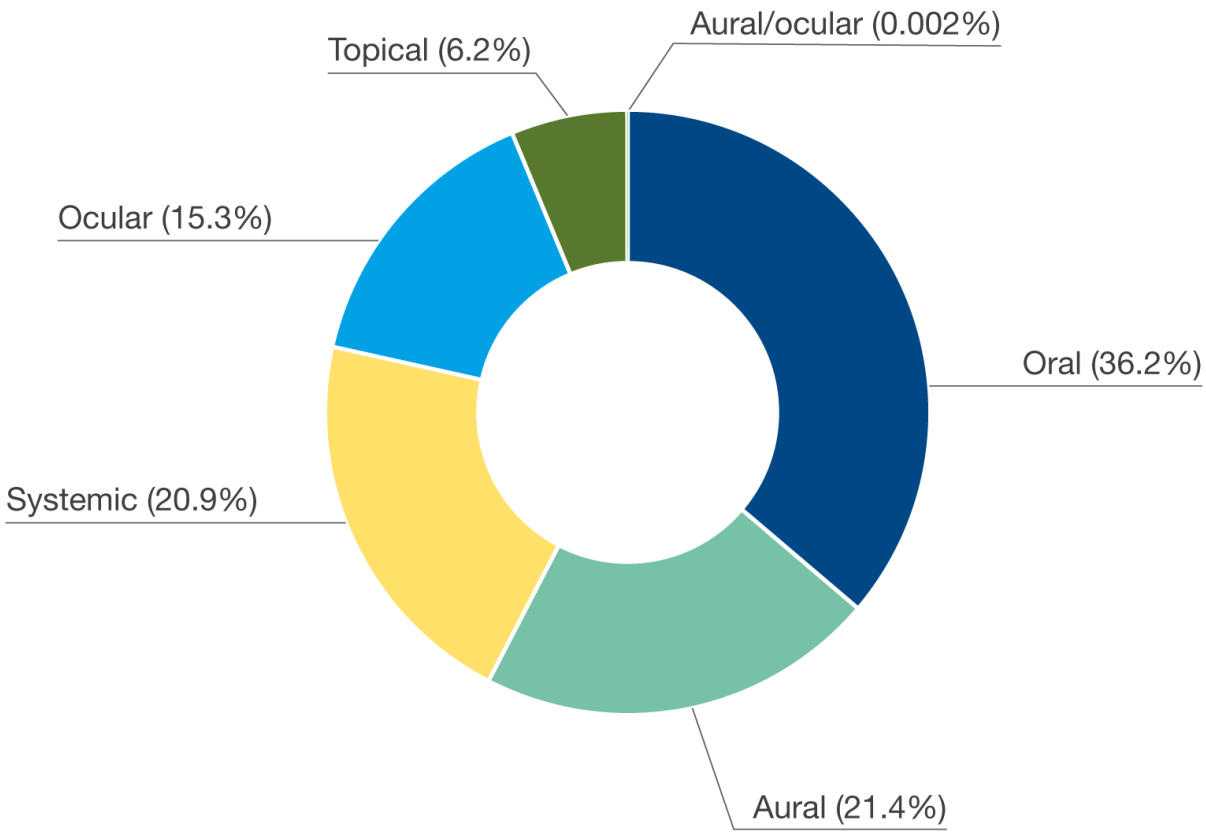
Note: This group comprised birds, rabbits, reptiles and small mammals.

Route of Administration

The route of administration of antibiotics overall and by companion animal group is shown in Figure 15, Figure 16, Figure 17 and Figure 18.

It is important to be aware of the contextual realities of veterinary practice in companion animals when interpreting this information: e.g. some species are notoriously difficult to medicate by some routes of administration; for some species there is a very limited range of therapeutic options due to either or both toxicity and licensing of products for use in a particular species.

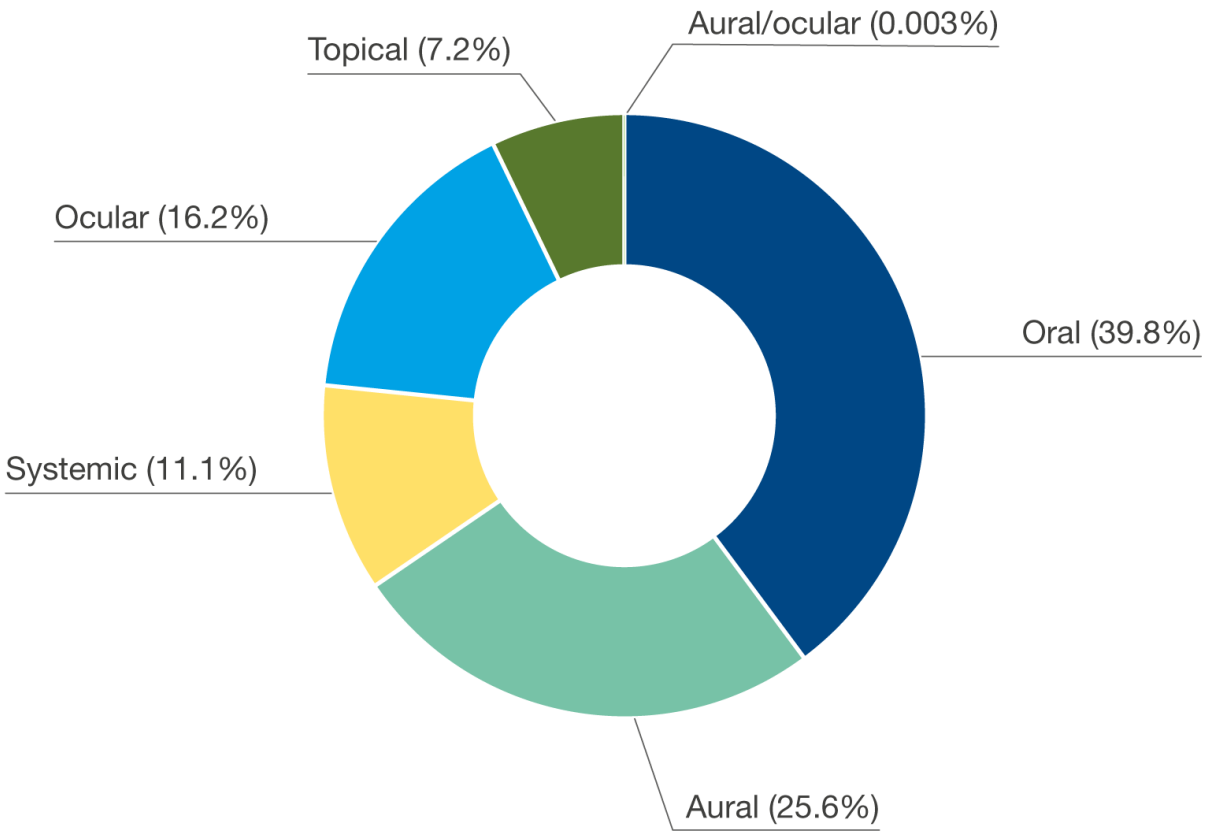
Figure 15: Route of administration of antibiotics for all companion animal species



Note: Excluding records with missing route data.

[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

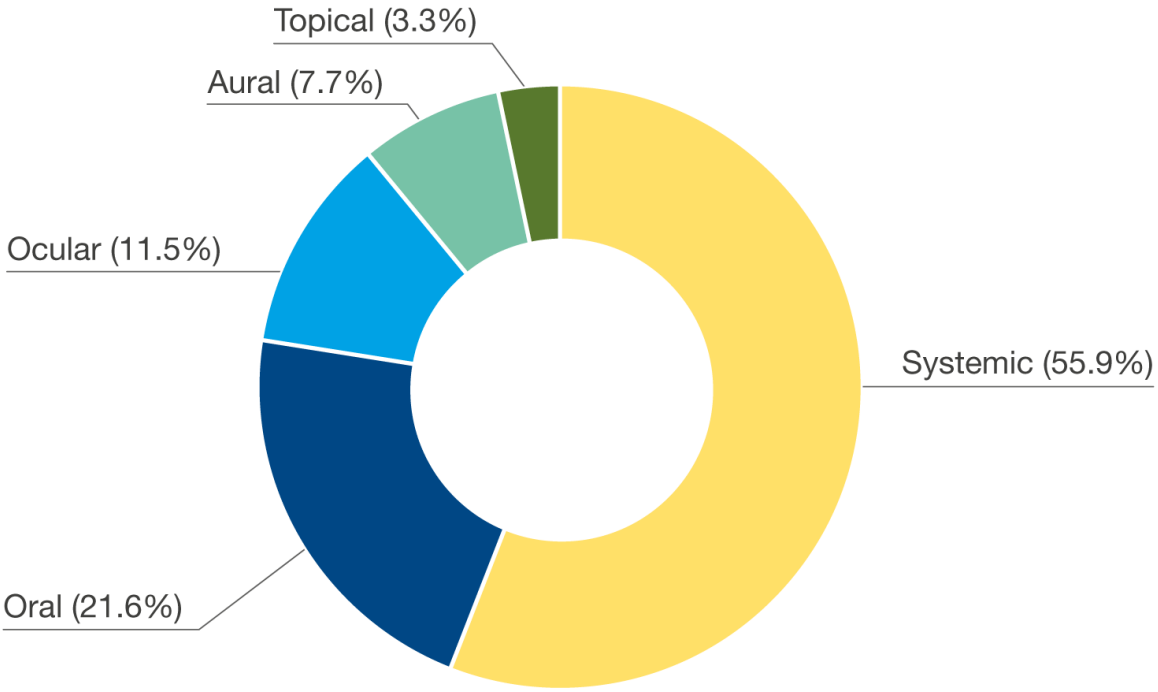
Figure 16: Route of administration of antibiotics for dogs



Note: Excluding records with missing route data.

[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

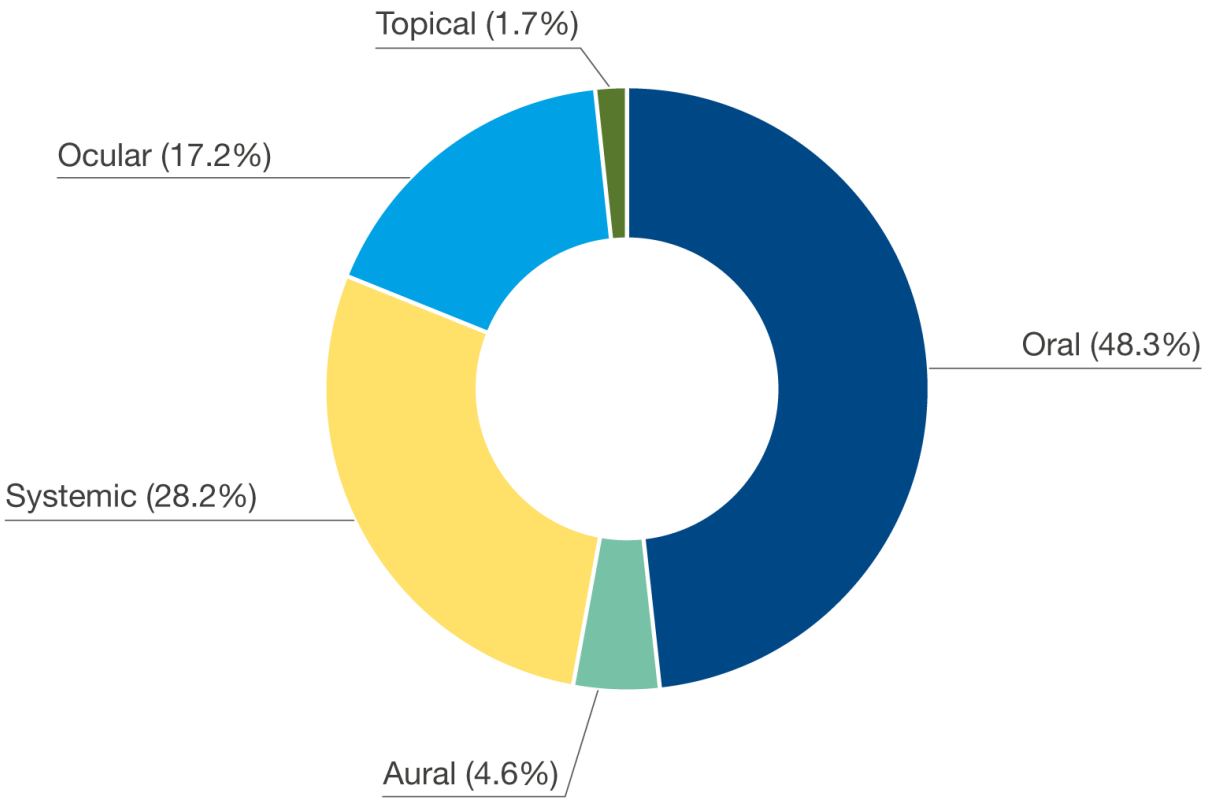
Figure 17: Route of administration of antibiotics for cats



Note: Excluding records with missing route data.

[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

Figure 18: Route of administration of antibiotics for 'other' companion animals



Note: Excluding records with missing route data.

[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

Animal Antimicrobial Use Key Points

- Antimicrobials are very important medicines in animal species
- Antimicrobial use in companion animals reported for the first time in Scotland
- Preliminary data contribute to developing evidence base pertaining to AMU in animals and the impact on AMR
- Engagement and support from animal stakeholder groups essential in the development of this intelligence
- Further close working with SAVSNET to encourage practices to participate in the network is important
- Scotland's Healthy Animals website provides guidance for vets and animal keepers on disease avoidance and antimicrobial stewardship

"The SAVSNET collaboration is very exciting as, for the first time, we can review large data sets (i.e. tens of thousands of animals and thousands of bacterial isolates). I'd encourage more practices and laboratories to sign up. This will allow practices to benchmark themselves against national data, which will greatly help local antimicrobial stewardship policies."

Dr Tim Nuttall
Senior Lecturer in Small Animal Veterinary Dermatology, The University of Edinburgh

Antimicrobial Resistance

Antimicrobial resistance in humans

AMR is a global public health threat and urgent action is required to ensure the preservation of the effectiveness of antibiotics, ensuring that we can continue to prevent and treat infections. Procedures taken for granted such as surgical antibiotic prophylaxis and cancer chemotherapy may become increasingly risky.[2] Additionally the healthcare costs associated with treatment of drug resistant infections are much higher than those caused by non-resistant micro-organisms. This is due to prolonged hospital stays, additional diagnostic tests and the need to use more expensive therapies.[13]

Data, as presented in this report, are essential to provide evidence to prevent, control and contain AMR, drive appropriate prescribing, inform national policy and preserve the effectiveness of antibiotics for future generations.

This section of the report focuses on AMR of key public health importance in Scotland. Additional data published in the appendix can be used to make comparisons to other European countries.

Infections caused by Gram-negative bacteria

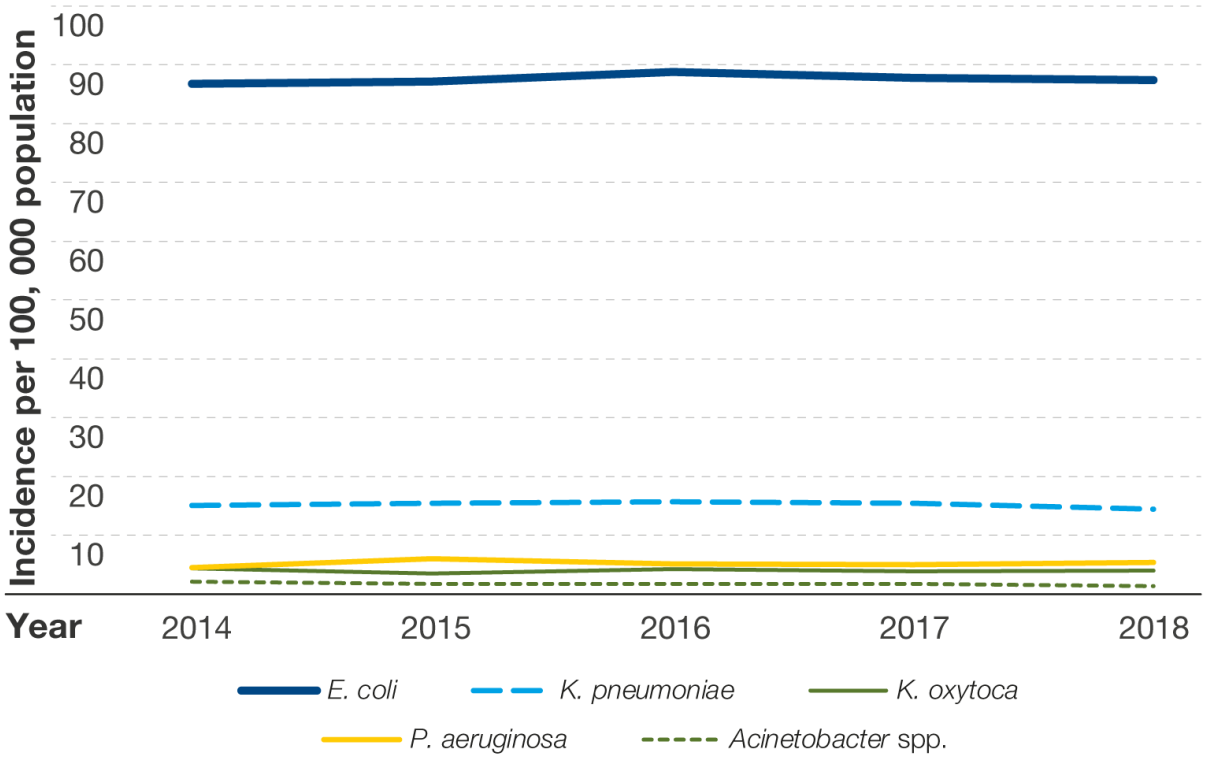
Gram-negative bacteria are an important cause of serious infections in both healthcare and community settings. Globally, the prevalence of these infections is increasing and Gram-negative BSI are associated with excess morbidity, mortality and length of hospital stay. [14;15]

The reduction of healthcare associated Gram-negative infections is one of the priority areas identified in the UK NAP to tackle AMR.[3] The UK NAP includes a target to reduce Gram-negative bacteraemia by 25% by 2021/22 and 50% by 2023/24. A number of important Gram-negative bacteria are considered to be endogenous opportunistic pathogens, and for many, including *E. coli*, there is currently insufficient evidence to indicate that improvements in infection prevention practice alone will result in significant reductions in healthcare associate infections (HCAI) caused by these micro-organisms.[16] Furthermore, there are no accepted decolonisation strategies for individuals found to be colonised with Gram-negative bacteria.[17]

Antibiotic exposure is recognised as being associated with major changes to the composition of the gut microbiome, resulting in decreased bacterial diversity and an increase in the frequency of opportunistic Gram-negatives.[18] Therefore, as described already within this report; effective antibiotic stewardship, including limiting the use unnecessary antibiotics, is key to reducing the potential burden of resulting invasive Gram-negative infections.[16;19]

The incidence of key Gram-negative bacteraemia is described in Figure 19. The incidence of bacteraemia caused by these bacteria has remained stable over the last five years. *E. coli* was the most common cause of Gram-negative bacteraemia in 2018 in Scotland, followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella oxytoca* and *Acinetobacter* spp.

Figure 19: Incidence of Gram-negative bacteraemia per 100,000 population in Scotland, 2014 to 2018, by five most frequently reported organism and year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Escherichia coli bacteraemia

Incidence of clinical cases of *E. coli* bacteraemia

E. coli bacteraemia (ECB) typically develops as a complication of a primary infection or following use of medical devices, including urinary catheters. Mortality due to ECB can be high (ranges from 10-35% for 30-day all-cause mortality in published studies), especially when associated with MDR isolates.[19]

The incidence of ECB has remained stable in Scotland over the last five years. In 2018, there were 4,738 cases of ECB which equates to an incidence of 87.3 per 100,000 population (Figure 19), compared to an incidence of 67.7 per 100,000 population for the most recent available data (2017), from England, Wales and Northern Ireland.[20]

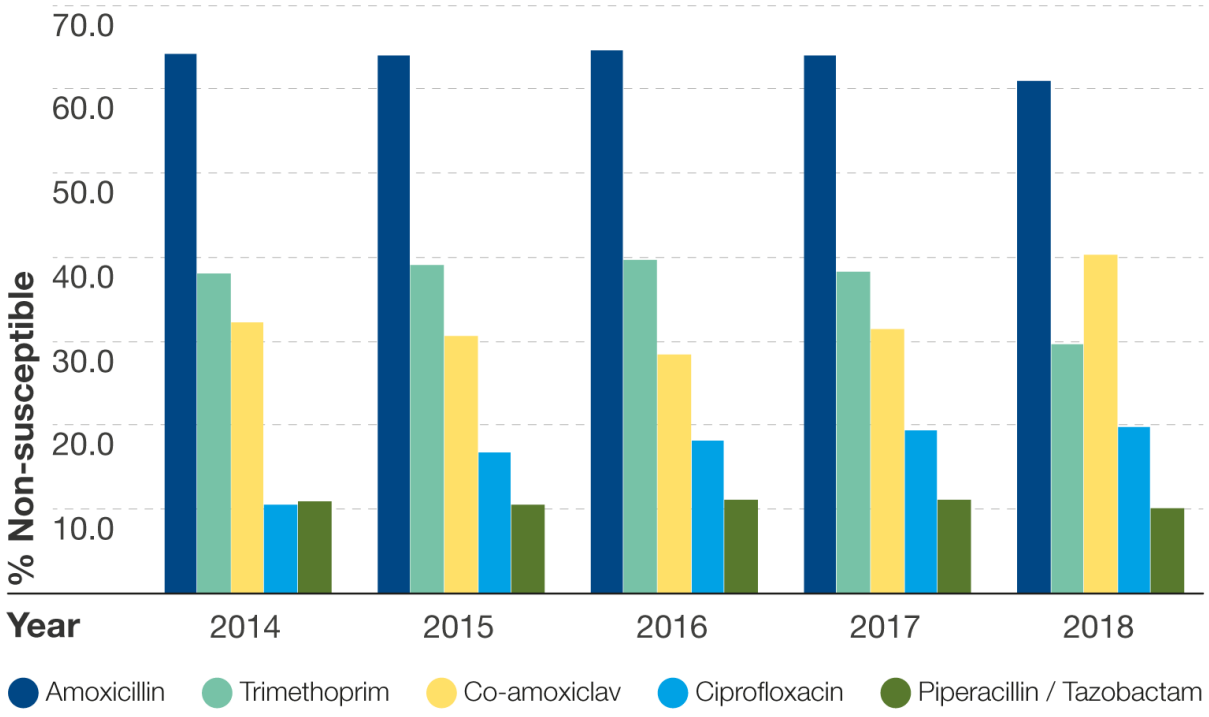
Non-susceptibility in *E. coli* blood isolates

In part, due to high associated incidence, *E. coli* infections pose a significant antibiotic resistance burden. Isolates resistant to third generation cephalosporins, carbapenems and/or colistin are considered to be of particular public health concern. Notably, since 2007, the number of deaths in the European Union (EU) attributable to infections caused by third generation cephalosporin or carbapenem resistant *E. coli* isolates has increased by more than four times.[1]

In 2018, 60.9% of *E. coli* blood isolates were non-susceptible (resistant or intermediate) to amoxicillin, 40.3% to co-amoxiclav, 29.7% to trimethoprim, 19.8% to ciprofloxacin and 10.2% to piperacillin/tazobactam (

Figure 20). The majority of isolates were susceptible to the remainder of antibiotics (see Appendix). No colistin resistant isolates have been reported in Scotland in the last five years. Colistin testing is currently only performed on a small number of MDR isolates and broth microdilution (BMD) testing is the only currently recommended method for colistin antimicrobial susceptibility testing (AST). Susceptibility trends among ECB isolates were broadly comparable to the most recent equivalent PHE data.[20]

Figure 20: Non-susceptibility of *Escherichia coli* bacteraemia (ECB) isolates in Scotland, 2014 to 2018, for five antimicrobials most frequently associated with non-susceptibility, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Non-susceptibility in *E. coli* blood isolates (to 18 reported antibiotics) has been stable or decreased over the last 5 years, for the majority of agents (see Appendix). The exceptions to this were overall increases in non-susceptibility to cefuroxime (7.6%, $p<0.001$), ciprofloxacin (15.6%, $p<0.001$) and co-amoxiclav (8.4%, $p<0.001$) between 2014 and 2018, and while there was no increase for either cefuroxime or ciprofloxacin between 2017 and 2018, non-susceptibility to co-amoxiclav increased from 31.5% in 2017 to 40.3% in 2018 ($p<0.001$). Unlike as described from collective European level data,[1] a recent study from England demonstrated that ciprofloxacin (but not cephalosporin or carbapenem) non-susceptibility was associated with increased mortality in patients with ECB.[19]

Non-susceptibility to temocillin, over the assessed time period, has increased. This is primarily due to an increase in isolates reported as being intermediate via VITEK® testing. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) do not specify break-points for temocillin, and it is understood that Scottish laboratories use British Society for Antimicrobial Chemotherapy (BSAC) interpretation of results, where no intermediate category exists. The reporting of intermediate isolates will be further investigated by HPS and for temocillin, it is recommended that resistance, rather than non-susceptibility data is observed. Over the last five years, temocillin resistance in *E. coli* blood isolates has increased (26.6%, $p<0.001$), although between 2017 and 2018, no increase was observed.

Furthermore, there was also an increase from 31.5% to 40.3% ($p<0.001$) associated with non-susceptibility to co-amoxiclav between 2017 and 2018. This is considered to be due to a change in susceptibility testing method, with the 2018 data considered to be most accurate, and is not likely to represent a true increase in non-susceptibility to this agent. This is further demonstrated by no change in non-susceptibility to amoxicillin during this time period.

Enhanced surveillance of *E. coli* bacteraemia

A national enhanced surveillance programme for ECB has been mandatory in Scotland since April 2016. The surveillance system collects enhanced information on patient characteristics; origin and source of the ECB; and risk factors for ECB including a history of healthcare.[21] The availability of these data provides an opportunity to further characterise the epidemiology of ECB caused by drug resistant *E. coli*. Better intelligence relating to the risk of AMR in Scottish cases of ECB will inform interventions to reduce the risk of cross-transmission and better directed treatment of drug resistant ECB.

A preliminary analysis to describe AMR in ECB isolates was undertaken using the enhanced surveillance data pertaining to the origin of ECB (hospital acquired, healthcare associated or community infection) from 2017 and 2018. Table 5 describes the percentage of ECB that were non-susceptible to key antibiotics for community infection and for ECB associated with any healthcare (including hospital acquired). The hospital acquired ECB isolates and healthcare associated (not hospital acquired) isolates were grouped together as there was no significant difference in the non-susceptibility profiles between these groups. For more information on the non-susceptibility in ECB isolates by all origins, including the presentation of hospital acquired and healthcare associated (not hospital acquired) infection separately, see Appendix. The percentage of ECB that were non-susceptible to key antibiotics was higher for all antibiotics, with the exception of meropenem, in the healthcare associated ECB isolates compared with community ECB. There were no ECB reported to be non-susceptible to meropenem.

The availability of the enhanced surveillance data has, for the first time, provided preliminary epidemic intelligence relating to drug resistant ECB in Scotland and highlights that those associated with healthcare are more likely to be non-susceptible to key antibiotics than community infections. Future work will enable further characterisation of non-susceptibility

profiles in ECB including examining the source of the ECB e.g. urinary, hepatobiliary. This intelligence will be used to inform the development of interventions to reduce Gram-negative bacteraemia and other drug resistant infections, key targets described in the UK NAP.[3]

Table 5: Percentage of ECB isolates non-susceptible to selected antibiotics by origin of infection (community or healthcare (including hospital acquired)), January 2017 to December 2018

Antimicrobial name	Percentage of tested isolates from a community source that were non-susceptible	Percentage of tested isolates from a healthcare (including hospital acquired) source that were non-susceptible	Comparison between all healthcare/hospital associated and community
Amoxicillin	58.3 (95%CI: 56.9 to 59.7)	68.7 (95%CI: 67.3 to 70.1)	<0.001
Aztreonam	5.9 (95%CI: 5.3 to 6.6)	10.9 (95%CI: 10.0 to 11.9)	<0.001
Cefotaxime	6.1 (95%CI: 5.4 to 6.9)	10.9 (95%CI: 9.9 to 11.9)	<0.001
Ceftazidime	6.2 (95%CI: 5.5 to 7.1)	10.7 (95%CI: 9.6 to 11.8)	<0.001
Cefuroxime	14.5 (95%CI: 13.5 to 15.5)	20.9 (95%CI: 19.7 to 22.1)	<0.001
Ciprofloxacin	15.5 (95%CI: 14.5 to 16.5)	26.2 (95%CI: 24.9 to 27.5)	<0.001
Co-amoxiclav	31.2 (95%CI: 29.9 to 32.5)	42.2 (95%CI: 40.7 to 43.6)	<0.001
Gentamicin	7.4 (95%CI: 6.7 to 8.2)	14.2 (95%CI: 13.2 to 15.3)	<0.001
Meropenem	0.0 (95%CI: 0.0 to 0.1)	0.00 (95%CI: 0.0 to 0.1)	0.5
Piperacillin / Tazobactam	8.6 (95%CI: 7.9 to 9.5)	13.7 (95%CI: 12.7 to 14.7)	<0.001
Trimethoprim	32.4 (95%CI: 31.0 to 33.7)	44.6 (95%CI: 43.1 to 46.1)	<0.001

[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Bacteraemia caused by other Gram-negative micro-organisms

Collectively, the top four non- *E. coli* causes of Gram-negative bacteraemia in Scotland account for a lower incidence than that due to *E. coli* alone. Nonetheless, these are important pathogens, representing a significant burden of infection.

Incidence of clinical cases of *Klebsiella pneumoniae* and *Klebsiella oxytoca* bacteraemia

Klebsiella spp. and in particular *K. pneumoniae,* are an important cause of Gram-negative bacteraemia. Invasive *K. pneumoniae* infections are typically more likely to affect patients with co-morbidities and result in higher 90-day mortality than *E. coli* infections. [22]

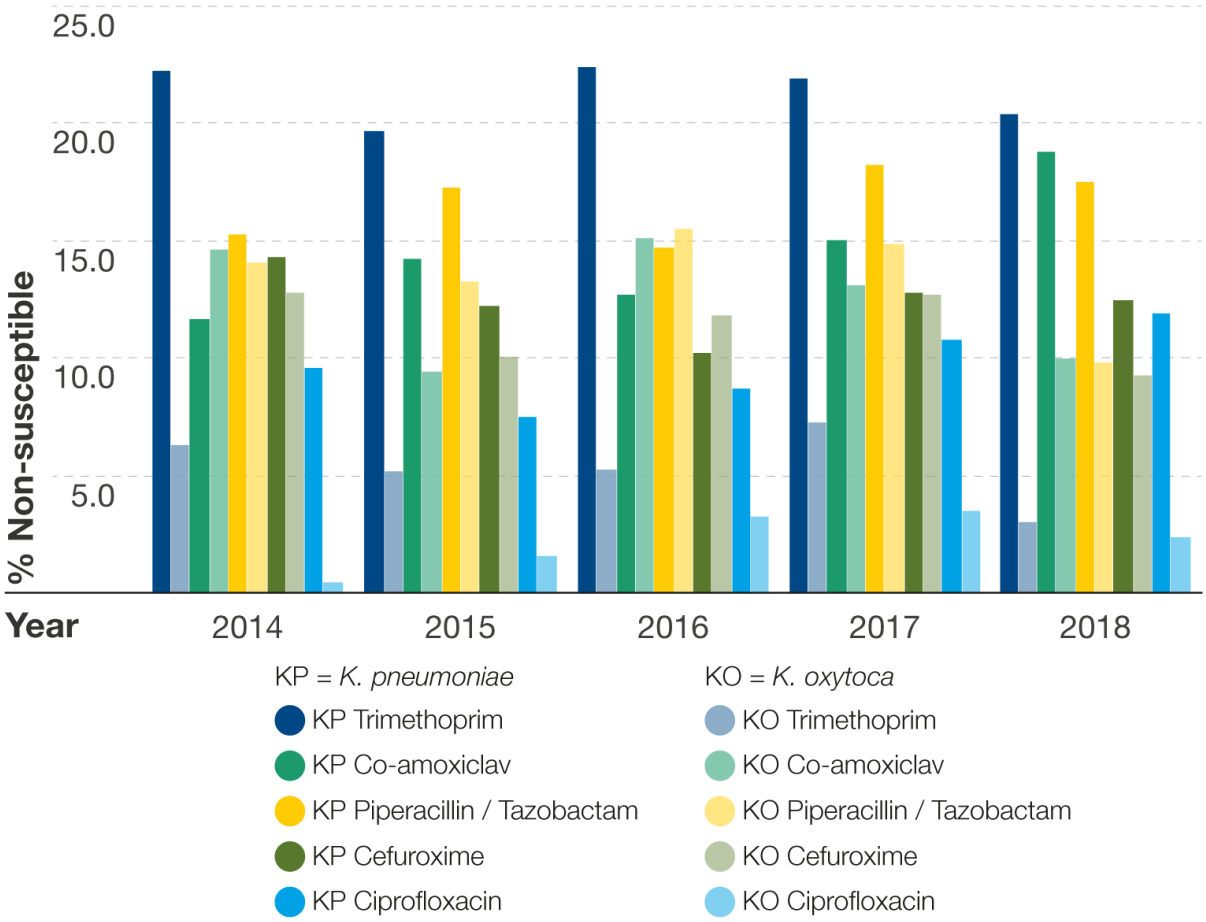
The incidence of both *K. pneumoniae* and *K. oxytoca* bacteraemia over the last five years in Scotland has remained stable (Figure 19). In 2018, 782 cases of *K. pneumoniae* and 218 cases of *K. oxytoca* bacteraemia were reported, equating to an incidence of 14.4 and 4.0 per 100,000 population, respectively, compared to an incidence of 12.3 and 2.8 per 100,000 population, respectively, for the most recent available data (2017), from England, Wales and Northern Ireland. [23]

Non-susceptibility in *Klebsiella pneumoniae* and *Klebsiella oxytoca* blood isolates

Similar to *E. coli, K. pneumoniae* resistant to third generation cephalosporins, carbapenems and/or colistin is considered to constitute a significant public health AMR threat. In particular the number of infections and attributable deaths associated with carbapenem resistant *K. pneumoniae* increased significantly (by more than six times) in the EU/EEA, during the period 2007-2015.[1] Furthermore, it is recognised that the propensity of *K. pneumoniae* to spread in hospital environments correlates with increased resistance. [24]

Susceptibility among *K. pneumoniae* and *K. oxytoca* blood isolates has generally remained stable over the last five years, other than observed increases in co-amoxiclav (12.8%, $p < 0.001$) in *K. pneumoniae* isolates specifically, the reason for which is explained in the ECB section above. In 2018, 20.4% of *K. pneumoniae*/3.0% *K. oxytoca* isolates were non-susceptible to trimethoprim, 18.8%/10.0% to co-amoxiclav, 17.5%/9.8% to piperacillin/tazobactam, 12.5%/9.3% to cefuroxime and 11.9%/2.4% to ciprofloxacin (Figure 21). The majority of isolates were susceptible to the remainder of antibiotics (see Appendix). Susceptibility trends among *K. pneumoniae* and *K. oxytoca* bacteraemia isolates were broadly comparable to the most recent equivalent PHE data. [23] No colistin resistant isolates have been reported in Scotland in the last five years.

Figure 21: Non-susceptibility of *Klebsiella* bacteraemia isolates in Scotland, 2014 to 2018, for five antimicrobials most frequently associated with non-susceptibility, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Incidence of clinical cases of *Pseudomonas aeruginosa* bacteraemia

Due to the propensity of *P. aeruginosa* isolates to develop resistance and for invasive infections to arise particularly in immunocompromised patients or those with chronic conditions; patients with BSI caused by this micro-organism tend to be more aggressively managed than those with BSI due to most other Gram-negative bacteria. Despite this, it has recently been demonstrated that extended duration of treatment does not improve clinical outcomes for patients with *P. aeruginosa* BSI, [25] although use of combination therapy may improve patient survival. [26]

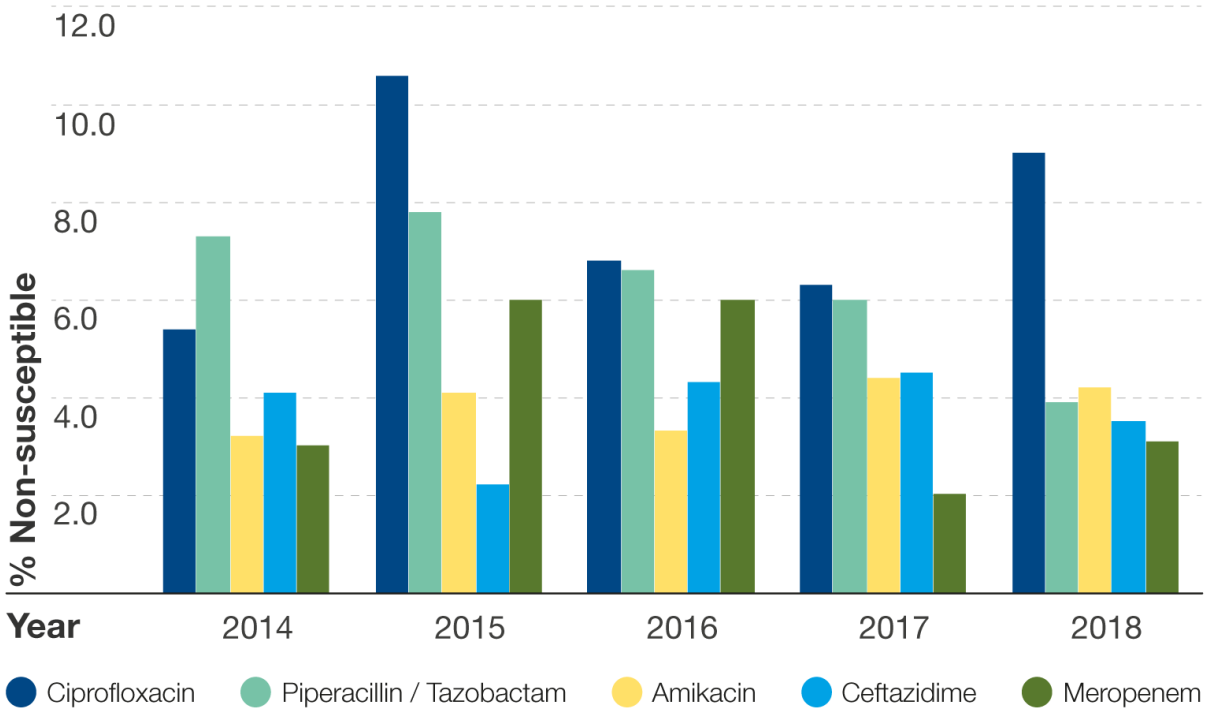
The incidence of *P. aeruginosa* bacteraemia over the last five years in Scotland has remained stable (Figure 19). In 2018, there were 293 cases of *P. aeruginosa* bacteraemia in Scotland which equates to an incidence of 5.4 per 100,000 population, compared to an incidence of 8.1 per 100,000 population for the most recent available data (2017), from England, Wales and Northern Ireland.[27]

Non-susceptibility in *P. aeruginosa* blood isolates

P. aeruginosa is intrinsically resistant to a broad range of antibiotics and any additional acquired resistance limits treatment options. [28] In addition to carbapenem and colistin resistance which is particularly concerning, isolates which are MDR (resistant to 3 or more agents, see Appendix) also require close monitoring due to the further impact of this for potential treatment choices. Attributable deaths in the EU/EEA associated with infections caused by carbapenem and MDR isolates increased in the period 2007-2015.[1]

Non-susceptibility in *P. aeruginosa* blood isolates has generally remained stable over the last five years for all reported agents. In 2018, 9.0% of isolates were non-susceptible to ciprofloxacin, 4.2% to amikacin, 3.9% to piperacillin/tazobactam, 3.5% to ceftazidime and 3.1% to meropenem (Figure 22). Susceptibility trends among *P. aeruginosa* blood isolates were broadly comparable to the most recent (2017) equivalent PHE data.[27] No colistin resistant isolates have been reported in Scotland in the last five years.

Figure 22:Non-susceptibility of *Pseudomonas aeruginosa* bacteraemia isolates in Scotland, 2014 to 2018, for five antimicrobials most frequently associated with non-susceptibility, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Incidence of clinical cases of *Acinetobacter* spp. bacteraemia

BSI due to *Acinetobacter* spp. are more common in critically ill patients and those with long-term healthcare contact. Consequently, risk factors for development of BSI due to these

species include presence of indwelling central venous catheters, receipt of total parenteral nutrition and prior receipt of chemotherapy. [29]

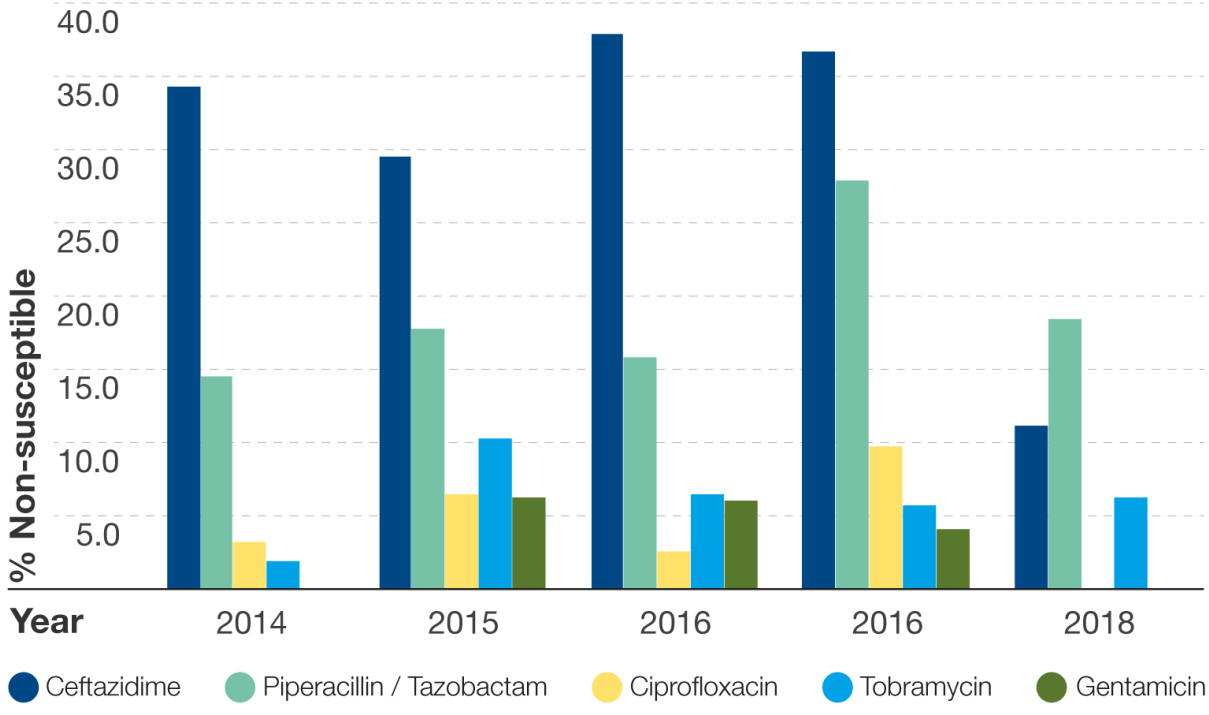
The incidence of *Acinetobacter* spp. bacteraemia over the last five years in Scotland has remained stable (Figure 19). In 2018, there were 76 cases of *Acinetobacter* spp. bacteraemia in Scotland which equates to an incidence of 1.4 per 100,000 population, compared to an incidence of 1.6 per 100,000 population for the same year, for England, Wales and Northern Ireland. [30]

Non-susceptibility in *Acinetobacter* spp. blood isolates

Acinetobacter spp. are recognised as being intrinsically resistant to various antibiotics and for their ability to acquire genes encoding resistance determinants. [28;31] Similar to *P. aeruginosa*, infections associated with carbapenem and/or colistin resistant isolates, as well as MDR isolates are of particular concern due to very limited treatment options.

Susceptibility in *Acinetobacter* spp. isolates has generally remained stable over the last five years, although the small annual number of isolates reported does not allow determination of statistical significance. In 2018, 18.4% of isolates were non-susceptible to piperacillin/tazobactam, 11.1% to ceftazidime and 6.3% to tobramycin. No isolates were reported as being non-susceptible to ciprofloxacin or gentamicin, but in previous years, a small number of isolates (<10%) have typically been reported as being non-susceptible to these agents (Figure 23).

Figure 23: Non-susceptibility of *Acinetobacter* species bacteraemia isolates in Scotland, 2014 to 2018, for five antimicrobials most frequently associated with non-susceptibility, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Susceptibility trends among *Acinetobacter* spp. blood isolates were broadly comparable to equivalent PHE data, taking into account reasonable variation associated with small numbers reported in Scotland. [30] In 2018, no blood isolates were reported as being resistant to meropenem, although since 2018, there has been an increase in reported meropenem resistance in isolates from all specimen sites. Despite this, the prevalence of resistance in Scottish isolates remains low and is also lower than the European average.[32] As recommended by the European Centre for Disease Prevention and Control (ECDC) Rapid Risk Assessment on carbapenem resistant *A. baumannii* in healthcare settings published in 2016; an increased focus is needed to ensure cases are being detected and to control outbreaks, in order to prevent these micro-organisms from becoming endemic in all European regions. [33] Further information relating to carbapenemase producing organisms (CPO) can be found in the CPO section of this report. No colistin resistant isolates have been reported in Scotland in the last 5 years.

AMR in Gram-negative Bacteria Key Points

- Gram-negative bacteria are a common cause of serious infections in both healthcare and community settings
- AMR in Gram-negative bacteria significantly contributes to the overall burden of AMR
- *E. coli* most common cause of Gram-negative bacteraemia and contributes significantly to burden of AMR
- Incidence of Gram-negative bacteraemia and associated AMR has remained stable though remains a significant concern
- AMR in ECB is higher in healthcare associated infections than those with community source
- Focus on preventing Gram-negative infections required to reduce the emergence and transmission of AMR

Urinary Tract Infections caused by Gram-negative bacteria

Due to the high prevalence of urinary tract infections (UTI) in both community and healthcare settings, these constitute a significant public health priority. Frequent recurrence rates and increasing antibiotic resistance among urinary bacteria threaten to increase the burden of these infections. In turn, the development of resistance in urinary isolates can act as an early warning of resistance in bacteria causing more serious infections.[34] Increasing resistance necessitates judicious use of antibiotics. Knowledge of the common causative pathogens, including local susceptibility patterns, are essential in determining appropriate empiric therapy. [35]

An important aspect of reducing the incidence of Gram-negative bacteraemia is the prevention and management of primary infections, including UTI. The Scottish UTI Network (SUTIN) was established in 2015 by HPS with the aim of achieving a cohesive approach for

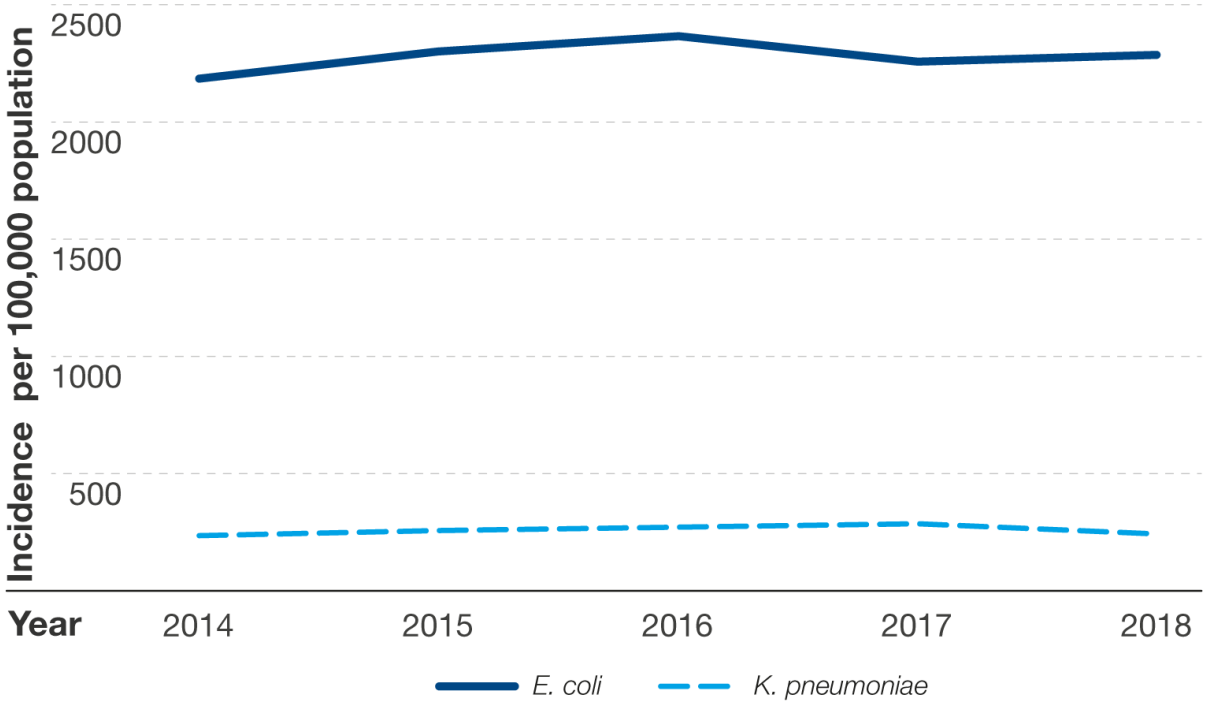
all UTI reduction work. As an example of recent work, in 2018 the SUTIN developed a national hydration campaign to raise awareness of the benefits of good hydration.[36]

Escherichia coli and *Klebsiella pneumoniae* urinary tract infections

The majority of Gram-negative BSI are considered to arise due to primary UTIs,[36] therefore, to achieve significant reductions in morbidity and mortality caused by ECB in particular, interventions aimed at preventing UTI are necessary. A recent study from England indicated that ECB bacteraemia with a urogenital focus was associated with reduced mortality in comparison to other sources of infection.[19]

In 2018, there were 123,955 cases of *E. coli* from urine samples reported to the Electronic Communication of Surveillance in Scotland (ECOSS) system, equating to an incidence of 2,285 per 100,000 population (Figure 24). The incidence has increased by 0.7% over a five year period (p<0.001). In the same year, 11,013 cases of *K. pneumoniae* were reported; an incidence of 203 per 100,000 population (Figure 24), which although also increased over the assessed time period (by 1.3%, p<0.001), decreased by 15.6% (p<0.001) between 2017 and 2018.

Figure 24: Incidence of *Escherichia coli* and *Klebsiella pneumoniae* urinary isolates per 100,000 population in Scotland, 2014 to 2018, by organism and year



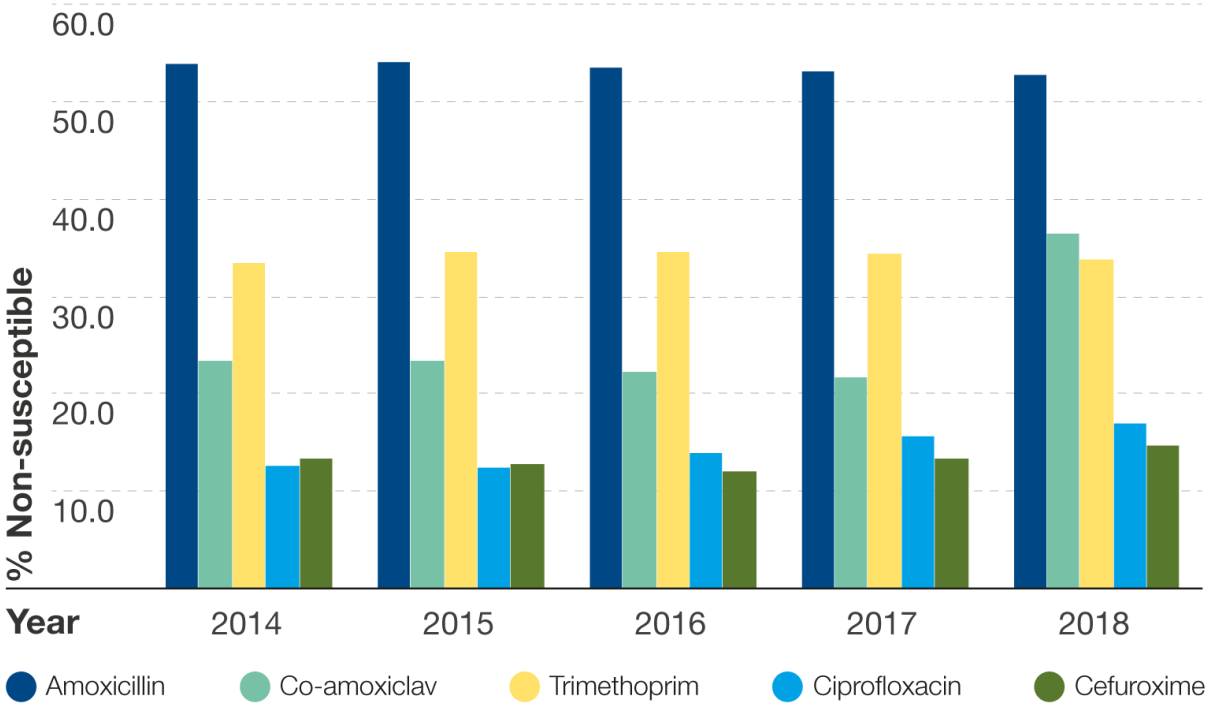
[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Non-susceptibility in *Escherichia coli* urinary isolates

UTI caused by antibiotic resistant Gram-negative bacteria are a concern due to limited therapeutic options, particularly oral antibiotics available in the community setting. Gram-negative bacteria, specifically Enterobacterales, are common causes of both community and hospital acquired UTI. In particular, these micro-organisms can acquire genes that encode for multiple antibiotic resistance mechanisms, including extended-spectrum beta-lactamases (ESBL) and carbapenemases.[35]

For the first time, non-susceptibility to 19 antibiotics has been assessed within this report (see Appendix). In 2018, 52.8% of urinary isolates were non-susceptible to amoxicillin, 36.5% to co-amoxiclav, 33.8% to trimethoprim, 16.9% to ciprofloxacin and 14.7% to cefuroxime (Figure 25).

Figure 25: Non-susceptibility of *Escherichia coli* urinary isolates in Scotland, 2014 to 2018, for five antimicrobials most frequently associated with non-susceptibility, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Non-susceptibility in *E. coli* urinary isolates to the majority of antibiotics has remained stable or decreased over the last five years (see Appendix). Exceptions to this include non-susceptibility to ceftazidime, cefuroxime, ciprofloxacin, gentamicin and pivmecillinam, where there was an overall increase of 3.1%, 3.2%, 10.4%, 6.3% and 4.9%, respectively ($p<0.001$) since 2014. There was also an increase observed for co-amoxiclav non-susceptibility (21.7% to 36.5%, $p<0.001$) between 2017 and 2018, however as mentioned previously, this is considered to be due to a change in susceptibility testing method, and is not considered to represent a true increase in non-susceptibility to this agent.

Fosfomycin non-susceptibility data is included for the first time for both BSI and urinary *E. coli* and *Klebsiella* spp. isolates. A recent paper from France [37] demonstrated that plasmid-associated fosfomycin resistance has emerged in *E. coli* isolates and although presence of this resistance mechanism has not been assessed in Scottish isolates, fosfomycin non-susceptibility in *E. coli* urinary isolates has remained stable over the last five years. A further study [38] assessing fosfomycin resistance in urinary *E. coli* isolates from the UK found that the small number of isolates which were fosfomycin resistant, were not associated with plasmid mediated resistance. The authors concluded that fosfomycin remains a viable option for the treatment *of E. coli* in uncomplicated UTIs in the UK. Although currently less than 1% of blood isolates are tested for fosfomycin non-susceptibility in Scotland, more than 85% of urinary isolates are tested, in comparison to reports from England indicating that approximately 30% of urinary isolates were tested in 2017. [39] Laboratory testing and reporting of this and other agents enables robust monitoring of resistance in Scottish isolates and use of fosfomycin when required.

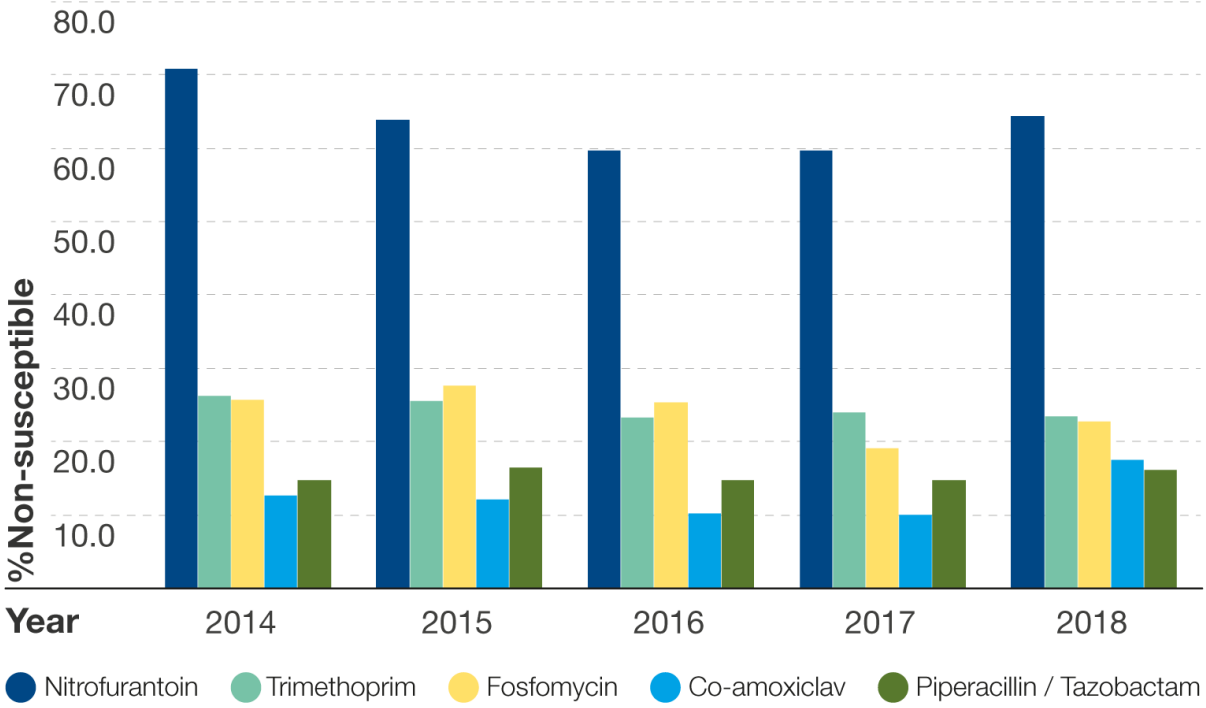
Non-susceptibility in *K. pneumoniae* urinary isolates

In 2018, 64.4% of urinary isolates were non-susceptible to nitrofurantoin, 23.5% to trimethoprim, 22.7% to fosfomycin, 17.5% to co-amoxiclav and 16.1% to piperacillin/tazobactam (Figure 26).

Non-susceptibility in *K. pneumoniae* urinary isolates to the majority of antibiotics has remained stable or decreased over the last five years (see Appendix). The exceptions to this were non-susceptibility to ciprofloxacin, where there was an overall increase of 9.0% ($p<0.001$) since 2014, and non-susceptibility to co-amoxiclav, where there was an overall increase of 7.6% ($p<0.001$) since 2014.

In addition, as described in the BSI and *E. coli* UTI sections above, increases, particularly between 2017 and 2018, were observed for non-susceptibility to co-amoxiclav (10.0% to 17.5%, $p<0.001$).

Figure 26: Non-susceptibility of *Klebsiella pneumoniae* urinary isolates in Scotland, 2014 to 2018, for five antimicrobials most frequently associated with non-susceptibility, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

It should be noted that bias in over-reporting of non-susceptible urinary isolates is considered to exist as urine samples tend to be obtained more frequently from patients with failed empirical treatment. Albeit, non-susceptibility in *E. coli* BSI isolates, in particular, was greater than non-susceptibility in *E. coli* urinary isolates, for the majority of antibiotics. This is considered to primarily be due to the fact that blood isolates are typically obtained more frequently from hospitalised patients, who are more likely to have received prior antibiotic therapy. Due to high reported resistance to amoxicillin (including intrinsic resistance in *Klebsiella* spp.), most Scottish guidelines recommend either trimethoprim or nitrofurantoin as first line empiric agents for the treatment of uncomplicated UTI.[40]

Non-susceptibility in urinary isolates from male patients and children

UTI in men are generally considered to be complicated due to the presence of accompanying urological factors and prostate involvement, which may lead to complications including chronic bacterial prostatitis or urinary stones. The development of antibiotic resistance further complicates the clinical management of UTI in males.[41] Antibiotic prophylaxis is on rare occasions recommended for the prevention of UTI in men.[42]

In most children, UTI are simple acute infections which resolve with appropriate antibiotic therapy. In a small minority, UTI are associated with significant underlying abnormalities

including congenital renal tract malformations and if recurrent infections occur, may lead to renal scarring.[43]

Scoping work has commenced assessing resistance in these subsets of the population and will be reported in 2020.

AMR in Urinary Tract Infections Key Points

- UTI are amongst the most common infections diagnosed in community, healthcare and hospital settings
- AMR in urinary isolates considerably adds to the burden of AMR
- *E. coli* is the most common bacteria isolated from urine specimens followed by *K. pneumoniae*
- AMR in *E. coli* and *K. pneumoniae* urinary isolates has remained stable or decreased over the last five years for the majority of antibiotics

Carbapenemase producing organisms

Gram-negative bacteria producing carbapenemase enzymes that inactivate carbapenem antibiotics pose a significant public health threat, leaving few therapeutic options.[44] Infections caused by CPO are associated with high rates of morbidity and mortality and can have severe clinical consequences.[45] Carbapenems are an important class of very broad-spectrum antibiotics which are normally reserved for serious infections caused by antibiotic resistant Gram-negative bacteria (including Enterobacterales).

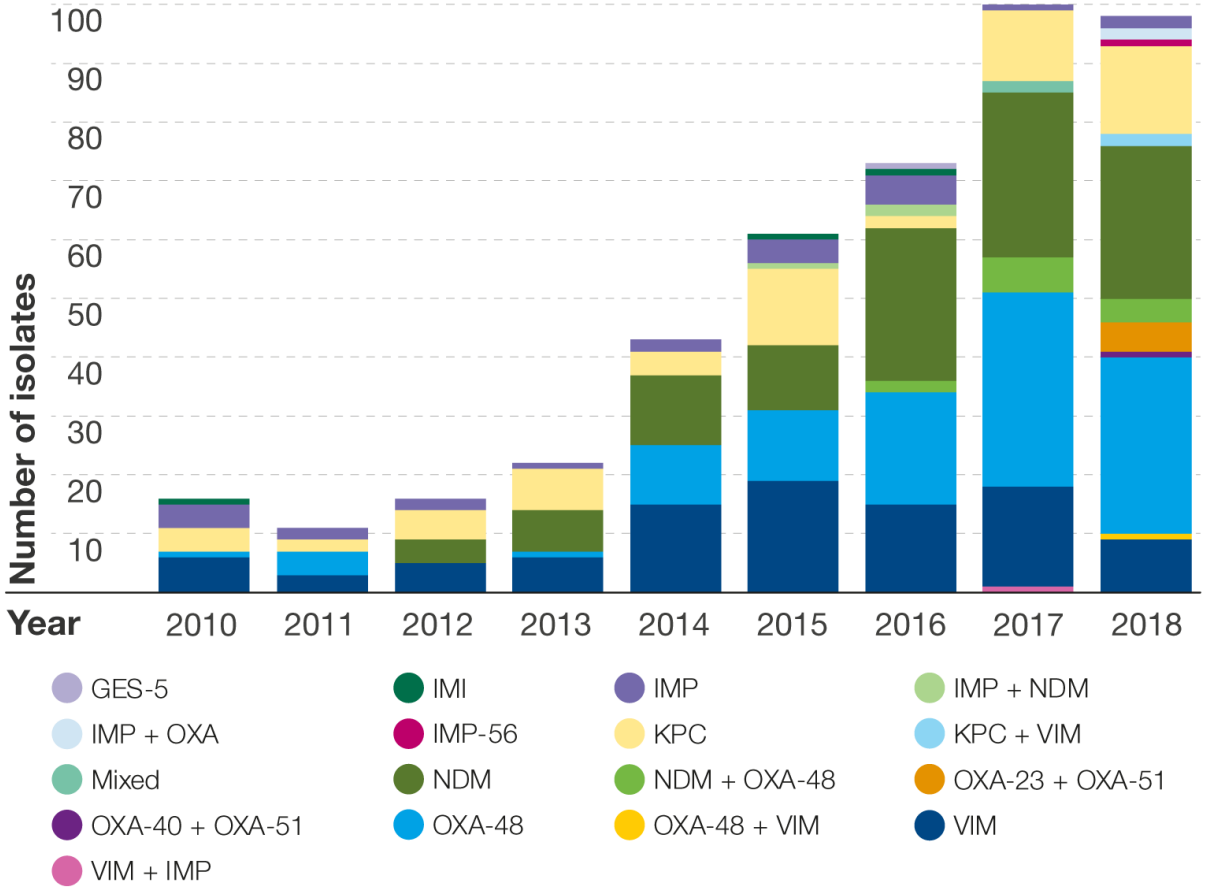
The Scottish AMR Satellite Laboratory currently test CPO isolates to identify the bacterial micro-organism/group and all carbapenemase enzymes or enzyme combinations. The CPO described in this report were isolated from both screening and clinical specimens including from urine, respiratory and blood samples.

In 2018, 98 isolates were reported compared to 100 isolates in 2017. The majority of CPO identified were carbapenemase producing Enterobacterales (CPE), (n=88, 89.8%), and the remaining were non-fermenters such as *Acinetobacter* spp. and *P. aeruginosa* (n=10, 10.2%). The most frequently identified enzyme gene was oxacillinase (OXA-48) (n=35, 35.7%) followed by New Delhi Metallo-beta-lactamase (NDM) (n=30, 30.6%). Figure 27 shows the number of CPO isolates by enzyme type and see the Appendix for the supporting data by micro-organism.

The incidence of CPO per 100,000 population is described in Figure 28. The incidence has increased significantly since 2014 though was no significant difference between 2017 and 2018 (p=0.9). Half of the isolates were from female cases and the median age was 60 years (range 0 to 102, inter-quartile range (IQR) 51 to 77). Female cases were significantly older than male cases (67 years versus 55 years, p=0.008). The UK's five-year NAP for AMR states that carbapenem-resistant Gram-negative infections should be added to the list of

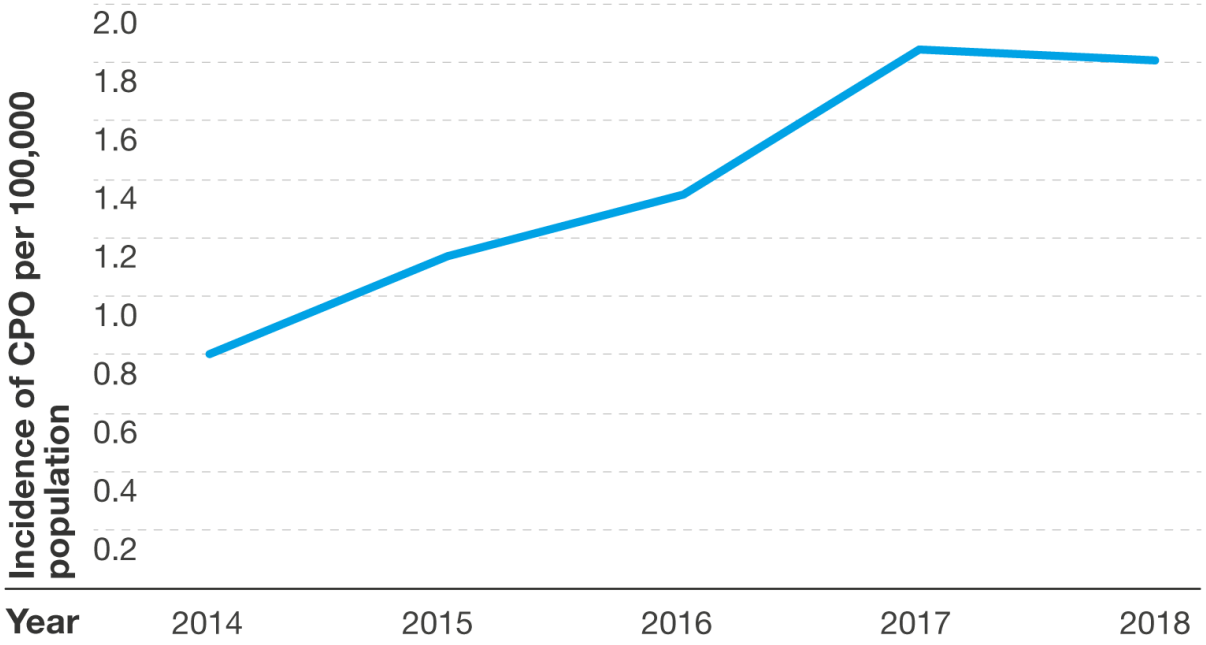
notifiable diseases in existing laboratory reporting systems,[3] supporting the development of CPO epidemic intelligence. Further characterisation of cases of CPO in Scotland is essential and future plans include further interrogating linked datasets. This improved epidemic intelligence will inform interventions to reduce transmission of CPO including the further development of the national CPE admission screening policy.[46]

Figure 27: Number of carbapenemase producing organisms (CPO) isolates (first isolation from all body sites) reported in Scotland by AMRHAI (PHE) and the Scottish AMR Satellite Laboratory, 2010 to 2018, by enzyme type and year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Figure 28: Incidence of carbapenemase producing organisms (CPO) per 100,000 population in Scotland, 2014 to 2018, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS) and National Records of Scotland (NRS)]

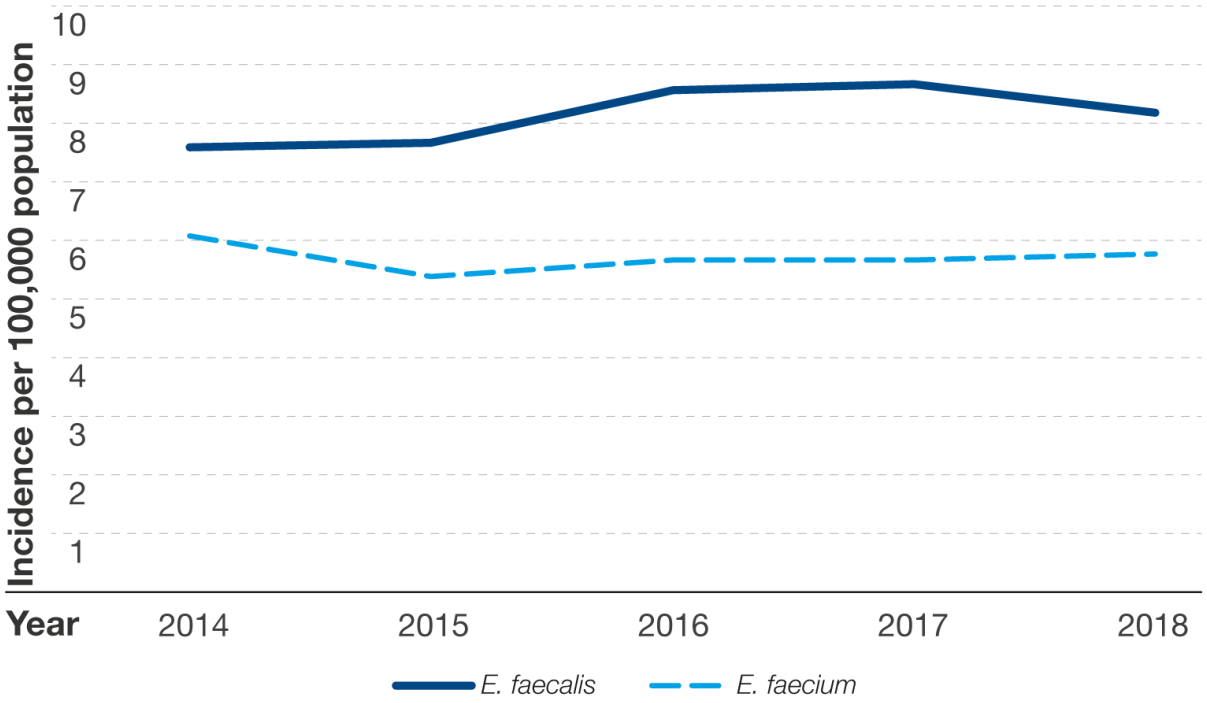
Antimicrobial resistance in *Enterococcus* species

Enterococci are natural gastrointestinal tract colonisers of both humans and animals, typically exhibiting low level virulence. Both microbial and host factors are known to influence the development of resistance to various antibiotics and the micro-organisms ability to disseminate resistance determinants, as well as to colonise various environments, including hospitals. In addition, the increasing number of patients who are hospitalised and receive multiple antimicrobial agents favours the ability of resistant micro-organisms such as vancomycin resistant enterococci (VRE) to cause infection.[47]

Incidence of clinical cases of *Enterococcus faecalis* and *Enterococcus faecium* bacteraemia

In 2018, 446 cases of *E. faecalis* and 318 cases of *E. faecium* bacteraemia were reported. The incidence of *E. faecalis* bacteraemia (8.2 per 100,000 population) *and E. faecium* bacteraemia (5.8 per 100,000 population) has remained stable since 2014 (Figure 29). The collective incidence of *E. faecium* and *E. faecalis* bacteraemia in 2018 in Scotland was similar to that reported from England, Wales and Northern Ireland for *Enterococcus* species (13.3 per 100,000 population).[48]

Figure 29: Incidence of *Enterococcus faecalis* and *Enterococcus faecium* bacteraemia per 100,000 population in Scotland, 2014 to 2018, by organism and year

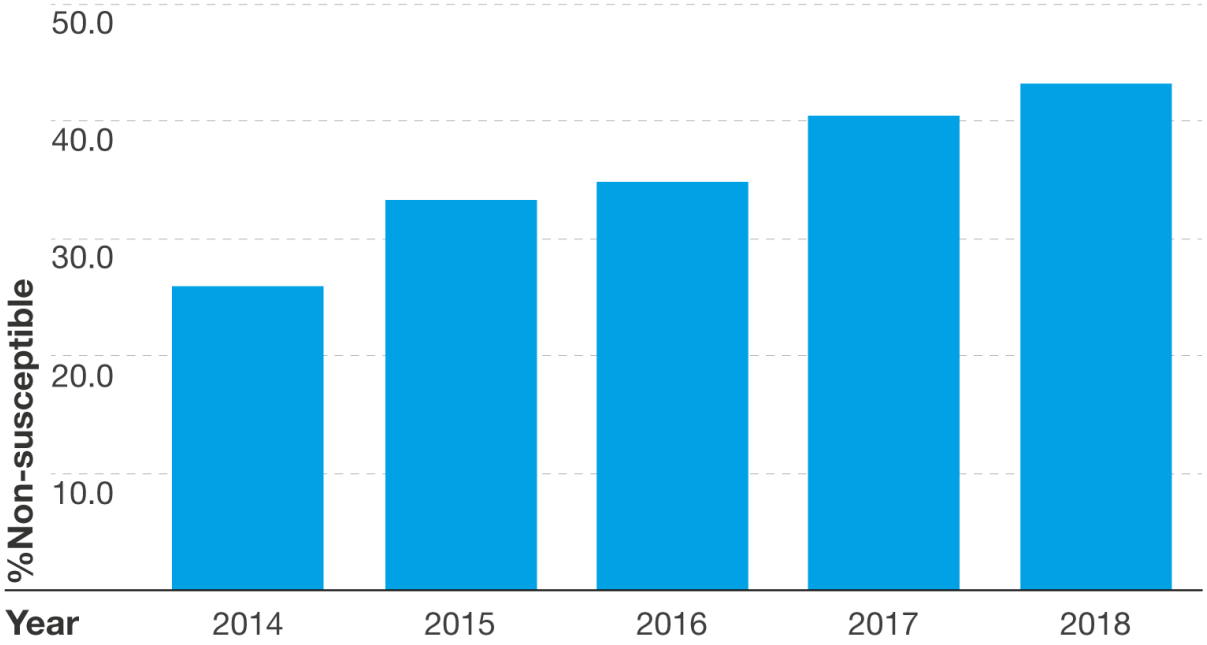


[Data source: Electronic Communication of Surveillance in Scotland (ECOSS) and National Records of Scotland (NRS)]

Vancomycin non-susceptibility in *Enterococcus* spp. blood isolates

Despite the incidence of enterococcal bacteraemia remaining relatively low and stable in Scotland, based on the latest European data from 2017;[49] only Cyprus had higher reported vancomycin non-susceptibility (43.9%) in invasive *E. faecium* isolates, in comparison to that reported in Scotland (40.4%) for *E. faecium* blood isolates, for the same year.[50] In 2018, this has increased to 43.2% ($p<0.001$) in Scotland (Figure 30). Non-susceptibility has continued to increase in Scotland annually, while other neighbouring countries including England and Ireland have observed decreases in non-susceptibility in recent years.[48] In contrast, only one *E. faecalis* blood isolate was reported as being non-susceptible to vancomycin in 2018.

Figure 30: Non-susceptibility of *Enterococcus faecium* bacteraemia isolates to vancomycin in Scotland, 2014 to 2018, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Linezolid and tigecycline have been increasingly used over the past decade as last-line agents to treat VRE infections; however, resistance has been reported and although still rare, is typically reported following clinical use of these antibiotics. [51] Non-susceptibility to these agents remains low in Scotland. In 2018, no *E. faecalis* or *E. faecium* blood isolates were reported as being non-susceptible to linezolid. Similarly, no *E. faecalis* isolates were reported as being non-susceptible to tigecycline though two *E. faecium* isolates (0.7%) were non-susceptible to the agent (see Appendix).

Risk factors for the development of vancomycin resistance in enterococci

There is no national policy for VRE screening in Scotland although some NHS Boards have local policies for screening in certain high risk patients. VRE screening in other countries is also variable and is typically restricted to patients considered to be high risk for colonisation/infection.[52]

Although various studies have indicated that development of vancomycin resistance in animals may be related to emergence of resistance in humans, it is generally agreed that animal-associated VRE most likely reflects past use of the glycopeptide growth promoter avoparcin, whereas human-associated VRE is a result of antibiotic consumption in hospitals, as the most likely contributing factor.[47;51]

In 2019, the SONAAR Team at HPS conducted a literature review to identify risk factors for the development of vancomycin resistance in enterococci to attempt to elucidate reasons for

high vancomycin resistance in Scottish isolates. A number of risk factors, particularly vancomycin use and prior hospitalisation/extended duration of hospital stay were identified. As expected, VRE colonisation was also found to be a risk factor for the development of VRE infection. Vancomycin consumption in Scotland is considered to be lower than the European average, which indicates that prescribing alone cannot account for the high prevalence observed.

A record linkage study (unpublished data) has also been conducted by HPS to identify risk factors and outcomes for VRE infection in hospitalised patients in Scotland. Between 2010 and 2016, there was a considerable difference between prevalence of vancomycin resistant *E. faecium* between NHS Boards (ranging from 13-52%). Approximately 75% of isolates were considered to have been healthcare associated and Intensive Care Unit (ICU) stay in the 30 days prior to infection was identified as a risk factor.[53] Work is ongoing, in collaboration with key stakeholders, to further investigate this high level of vancomycin resistance.

AMR in *Enterococcus* species Key Points

- *Enterococcus* spp. have the propensity to survive for long periods in harsh environments
- Concern that the transfer of the *vanA* gene from *Enterococcus* spp. into *Staphylococcus* spp. would severely limit treatment options for serious infections
- Incidence of *E. faecalis* bacteraemia and *E. faecium* bacteraemia has remained stable since 2014
- 43.2% of *E. faecium* are resistant to vancomycin
- Vancomycin resistance has continued to increase in Scotland
- Further work required to identify the appropriate public health actions

“Antibiotic use in the UK has been steadily reducing in the last 3 years, and it is reassuring that antibiotic resistance rates, as shown in this report, have remained stable over this period.

However, the battle against antibiotic resistant organisms is a generational fight that will require the combined efforts of the clinicians, scientists, veterinarians, farmers and the public to ensure that the antibiotics we currently have, to treat patients, remain active and effective.

To that end, surveillance, as used in generating this report, is essential in ensuring we have early warning systems that rapidly identify where resistance might develop. Identifying resistance hotspots will allow prescribers to continue to give patients the most effective antimicrobials to treat their infections.”

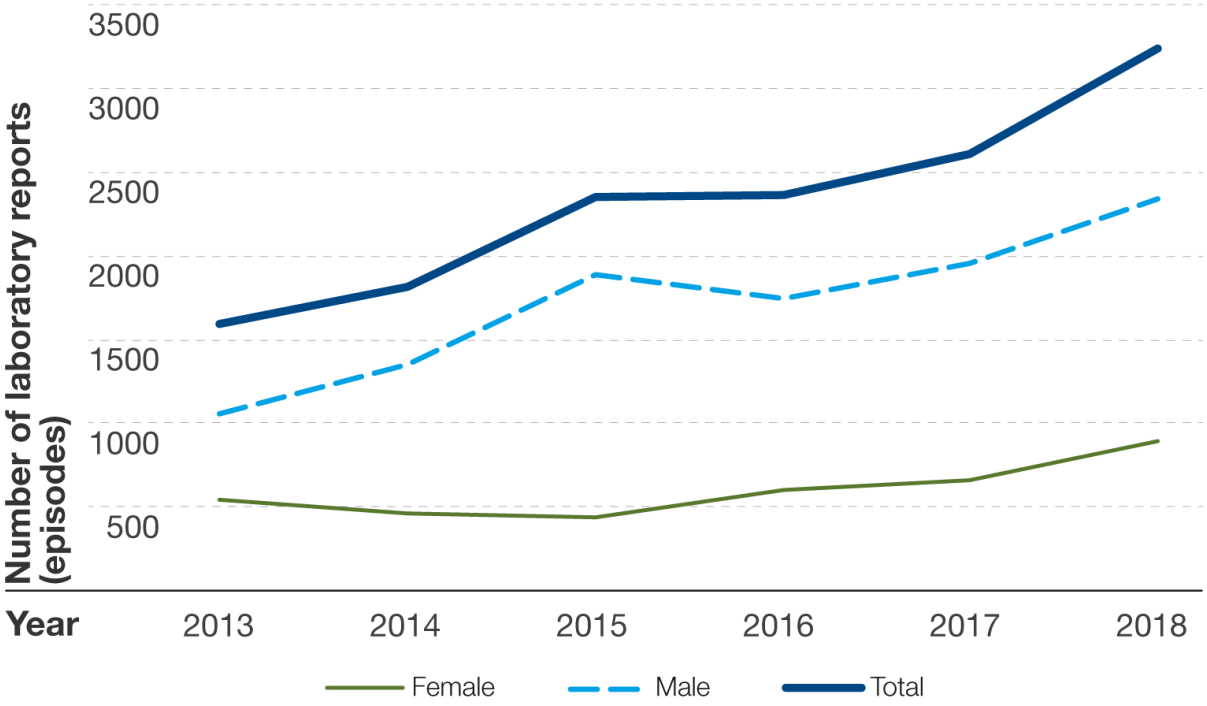
Professor Alistair Leanord

Director of Scottish Microbiology Reference Laboratories, Glasgow

Antimicrobial resistance in *Neisseria gonorrhoeae*

In Scotland, in 2018, 3,233 episodes of *N. gonorrhoeae*, an incidence of 91 per 100,000 population aged 15 to 64 years, were reported. Of these, 72.3% (2,339) were male, 27.6% (893) were female and, for one episode (0.03%) the gender was unspecified (Figure 31).

Figure 31: Number of laboratory reports (episodes) of *Neisseria gonorrhoeae* in Scotland, 2013 to 2018, by sex and year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

The Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) performs gonococcal antibiotic surveillance in Scotland (GASS) and the annual report is published on the HPS website.[54] The reference laboratory tests *N. gonorrhoeae* isolates for sensitivity to seven antibiotics. Of 1,652 episodes of gonococcal infections tested for susceptibility in 2018, 49% (802) were resistant to one or more antibiotics which is the same proportion as that observed in 2017 (49%), greater than in 2016 (42%) and similar to 2015 (50%).[55]

A change to the recommended treatment regimen was agreed in 2018 and the new British Association for Sexual Health and Human Immunodeficiency Virus (HIV) (BASHH) guideline was published in January 2019; however, antibiotic prescribing practice for gonorrhoea infections likely changed during 2018 to reflect the new approach, while the guideline was in its consultation phase. First line treatment changed from a dual antibiotic regimen consisting of ceftriaxone and azithromycin to a single higher dose of ceftriaxone.[56] One isolate with decreased susceptibility to ceftriaxone was recorded in 2018. Of note, however, is the

continuing detection of increased resistance to azithromycin in 7.0% (n=115/1,652) of isolates. Of the 115 azithromycin resistant isolates, 35 demonstrated high level azithromycin resistance (HL-AziR) (this represents 2.1% of all isolates tested); however, as these isolates were sensitive to ceftriaxone, affected individuals could be treated successfully. Further details are available in the GASS report.[54]

AMR in *N. gonorrhoeae* Key Points

- Threat of antibiotic-resistant gonorrhoea is a major public health concern
- Global reporting of extensively drug resistant (XDR) gonorrhoea highlights the importance of continuing antibiotic resistance surveillance
- *N. gonorrhoeae* isolates highly resistant to azithromycin is low in Scotland but has increased from 0.3% in 2015 to 2.1% in 2018.
- It is essential that monitoring continues and all cultures are sent to the SBSTIRL for resistance testing to help guide the choice of effective treatment.

> "With the emergence of extensively-drug resistant gonorrhoea, it is more important than ever that surveillance of antibiotic resistance in sexually transmitted infections continues. Paired with effective follow up of sexual partners, this will ensure patients continue to receive optimal treatment and care."
>
> **Dr Kate Templeton**
> Director of Scottish Bacterial Sexually Transmitted Infections Reference Laboratory, Edinburgh

Antimicrobial resistance in *Mycoplasma genitalium*

Mycoplasma genitalium is emerging as a sexually transmitted infection (STI) of interest. Infection with *M. genitalium* causes symptoms similar to other sexually transmitted infections, notably chlamydia and gonorrhoea, with pain on urination in men and inflammation of the cervix in women. Individuals sometimes have no symptoms. Untreated infection can lead to reproductive morbidities including pelvic inflammatory disease (PID) in women.

A *M. genitalium* polymerase chain reaction (PCR) testing service for the whole of Scotland was established in January 2018, offered by Molecular Microbiology, NHS Lothian. The test is available to those who meet certain criteria which include symptomatic individuals who test negative for *N. gonorrhoeae* and *Chlamydia trachomatis* and/or who remain symptomatic despite antibiotic treatment. Testing for macrolide and fluoroquinolone resistance by Sanger sequencing is also performed by SBSTIRL.

In 2018, 64.5% (n=40/62) of samples tested by SBSTIRL had a mutation associated with macrolide resistance. Of the 51 samples that were tested and successfully sequenced, 11.8% (n=6/51) were positive for fluoroquinolone resistance-associated mutations. Five of the six samples had detectable macrolide and fluoroquinoline resistance. The proportion of Scottish isolates with mutations associated with macrolide and fluoroquinolone resistance in 2018 is consistent, if not slightly higher, than estimates from other developed countries which range from 20% to 50% for macrolides and 5% to 33% for fluoroquinolones.[57] However, data on antibiotic resistance in *M. genitalium* are lacking.[58]

BASHH has published treatment guidelines (accredited by the National Institute for Health and Care Excellence (NICE)) to help reduce the likelihood of *M. genitalium* becoming highly resistant to a number of first and second line antibiotics[58] Effective treatment of *M. genitalium* is of important public health interest due to the high levels of macrolide resistance. There are overlaps with treatment of chlamydial and gonococcal infection and, thus, challenges to good antibiotic stewardship arise when individuals are receiving doses of antibiotics for other STI. Both follow up of all current sexual partners and a test of cure are recommended to ensure that all individuals who are receiving treatment are monitored for their response to treatment.

AMR in *Mycoplasma genitalium* Key Points

- *Mycoplasma genitalium* is recognised as an important treatable STI
- AMR is well established with high levels of macrolide resistance.
- 65% of Scottish isolates tested had a macrolide resistance-associated mutation and 12% had a fluoroquinolone resistance-associated mutation
- It is important that resistance monitoring takes place, alongside relevant testing and diagnosis, to advise on appropriate treatment regimes

Candidaemia

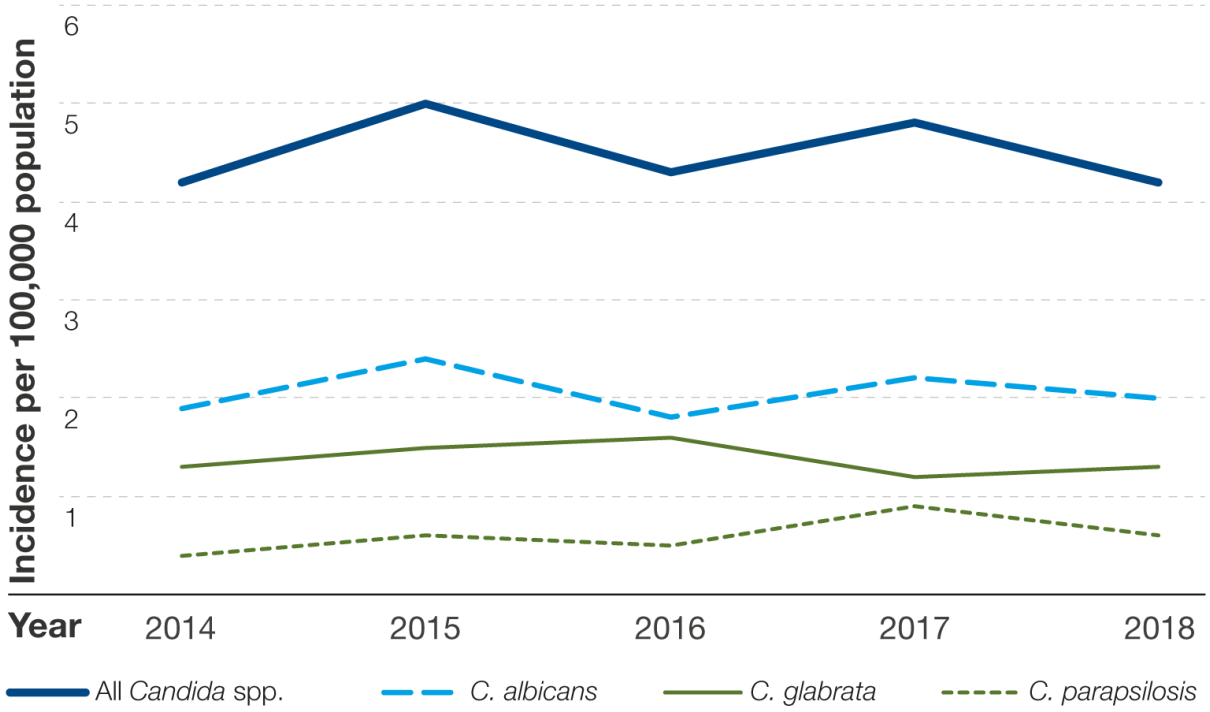
The incidence of candidaemia is increasing globally.[59] Immunocompromised critically ill patients in particular constitute a population with a high risk of developing candidaemia, which is typically associated with high mortality, even despite administration of appropriate antifungals.[60]

In addition to proving a therapeutic challenge, invasive infections also pose a diagnostic challenge, as although blood culture has a relatively low sensitivity for the diagnosis of invasive candidiasis, it is currently the main technique relied on.[59] In addition, culture is currently required to enable antifungal susceptibility testing to be carried out. In Scotland and elsewhere, biomarker assays are being used more routinely to aid in the diagnosis of these infections.

Incidence of clinical cases of candidaemia

In 2018, there were 227 cases of candidaemia, equating to an annual incidence was 4.2 per 100,000 population, which is similar to rates since 2014 (Figure 32). In addition, this is broadly comparable to data from England, Wales and Northern Ireland which collectively have an incidence of 3.3 per 100,000 population.[61]

Figure 32: Incidence of candidaemia per 100,000 population in Scotland, 2014 to 2018, overall, by most frequently reported organism and year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Non-susceptibility in *Candida* spp. blood isolates

Antifungal use is associated with the development of antifungal resistance, with MDR being of particular concern. In terms of common *Candida* spp; *Candida albicans* is typically sensitive to most antifungal agents, whilst *Candida glabrata* often exhibits decreased susceptibility to certain antifungals, in particular triazoles (e.g. fluconazole and voriconazole).[62-64]

Non-susceptibility in candidaemia isolates to commonly used antifungals has been broadly stable since 2014 (see Appendix), although small annual numbers of reported isolates does not allow determination of statistical significance. Of note, in 2018 fluconazole non-susceptibility in *C. glabrata* isolates was 59.3% in Scotland versus 45% in England.[61] Two methods for the interpretation of susceptibility results are used variably in laboratories in both Scotland and the rest of the UK; Clinical and Laboratory Standards Institute (CLSI) and EUCAST; breakpoints of which vary for fluconazole. As it is not possible to differentiate between use of these methods, fluconazole non-susceptibility results for *C. albicans* and *C. glabrata* should be interpreted with caution. Fluconazole resistance remains low (<5%) in *C. albicans* isolates in both Scotland and England.

Generally, antifungal resistance in *Candida* spp. is relatively uncommon. Specifically, no candidaemia isolates were reported as being non-susceptible to amphotericin B and only one *C. albicans* isolate was reported as being non-susceptible to caspofungin in 2018. Work to standardise susceptibility testing and reporting is currently underway in Scotland and the rest of the UK.

Candida auris

The identification and emergence of *Candida auris* as a highly resistant species, associated with multiple outbreaks globally, is a further public health issue.[65] Isolates of *C. auris* identified in the UK have been relatively susceptible, although all have been fluconazole resistant and it is considered that the apparent high transmissibility associated with the species is partly responsible for outbreaks in healthcare settings.[61;66]

In 2017, PHE produced guidance for the laboratory investigation, management and infection prevention and control for cases of *C. auris*, which was endorsed for use in Scotland in 2018.[67] Whilst no cases of *C. auris* have been reported in Scotland to date, it is important to continue to monitor the situation.

Use of antifungals

In acute hospitals, triazoles and echinocandins are the main antifungals used in the prevention and treatment of invasive fungal disease. In 2018, triazoles accounted for 76.3% of antifungal use in acute hospitals, with echinocandins accounting for 5.9%. The use of triazoles in acute hospitals in 2018 was 14.3% lower ($p<0.001$) compared to 2014, whereas use of echinocandins increased by 17.0% ($p<0.001$) over the same period. For more detail

on the use of antifungals, see Appendix. It is to be hoped recent recommendations on the management of candidaemia will impact on the increased use of echinocandins.

AMR in Candidaemia Key Points

- Candidaemia causes significant morbidity and mortality
- Antifungal resistance in *Candida* species is relatively uncommon
- Work to standardise susceptibility testing and reporting is currently underway in Scotland and the rest of the UK
- 227 cases of candidaemia in 2018 and the incidence has remained stable
- AMR in candidaemia isolates to commonly used antifungals has been broadly stable
- No cases of *C. auris* have been reported in Scotland to date
- Development of the antimicrobial stewardship programme to optimise the use of antifungals in Scotland will continue

> "I am delighted to see that for the second year data on both antifungal use and resistance have been reported in SONAAR. *Candida* spp. is a significant cause of invasive disease and it's encouraging to see that antifungal resistance has remained stable however it remains important to continue to monitor emerging resistance among fungal infections."
>
> **Professor Brian Jones**
> Consultant Medical Microbiologist NHS Greater Glasgow and Clyde,
> Chair of SAPG Antifungal Stewardship Subgroup

Exceptional resistance identified through the HPS AMR Alerts Early Warning System (AMR-EWS) in 2018

National monitoring of exceptional phenotypes enables a timely scientific and public health response to potential emerging AMR issues. Detection of emerging AMR is critical to contain the development and spread of resistance at a national, regional and local level and allows HPS to gather intelligence relating to national trends and to communicate any identified issues with other public health bodies, as necessary.

An AMR alert micro-organism early warning system (AMR-EWS); Surveillance of Antimicrobial Resistance in Scotland (SARIS) was established in 1998, as collaboration between HPS, then known as the Scottish Centre for Infection and Environmental Health (SCIEH) and the Scottish Microbiology Association (SMA). Scottish diagnostic laboratories were asked to voluntarily report pre-agreed alert micro-organisms (significant resistant bacteria considered to be of a potential epidemic and/or public health risk) to HPS. This system was replaced with a revised electronic based EWS in 2005. Subsequently, in June

2017, HPS, in conjunction with the Scottish Microbiology and Virology Network Antimicrobial Susceptibility Testing (SMVN AST) subgroup and the relevant Scottish Reference Laboratories, produced a revised list of resistant bacteria (exceptional phenotypes) based on EUCAST guidance from 2016.

In 2018, the SONAAR team at HPS introduced an electronic process to run a twice weekly interrogation of ECOSS to identify exceptional resistance phenotypes and contact the submitting laboratory requesting confirmation of reported resistance. All alerts are assessed by HPS and if of potential public health concern are drawn to the attention of the wider public health community for appropriate action.

The exceptional phenotypes monitored in the HPS AMR-EWS are also detailed in Appendix 13 of the National Infection Prevention & Control Manual (NIPCM) as a mandatory alert micro-organism/condition list.[68] Local monitoring ensures that microbiology clinicians, infection prevention and control teams (IPCTs), health protection teams (HPTs) and AMT, as appropriate, are aware of each identified case as per local protocols. Resulting local actions which may occur include:

- Screening for colonisation;
- Assessing risk factors for emergence of resistance;
- Ensuring appropriate contact precautions are put in place;
- Ensuring that patients are isolated, if necessary.

A short life working group comprising of representatives from the HPS SONAAR team and the SMVN-AST subgroup was convened in 2019 to review the AMR-EWS and Table 6 of Appendix 13 (will occur annually thereafter). Proposed changes will be implemented by the end of 2019.

2018 AMR-EWS alert results

The below summary is based on de-duplicated (one isolate per patient per micro-organism/resistance per year) AMR-EWS alert results for a time period spanning 1st January 2018- 31st December 2018.

The following caveats should be noted when interpreting the results:

1. The identification of an alert is dependent on laboratories actively performing AST and submitting results to ECOSS. This may result in underreporting, or no reporting, of a particular micro-organism/antibiotic resistance combination if there is limited or no testing performed.
2. In addition, it is possible that in a small number of instances, not all data related to exceptional resistance is currently captured by ECOSS. A programme of work to enhance the data captured was implemented in 2019 by the Scottish Health Protection Network
3. (SHPN) Public Health Microbiology Team and it is anticipated that this will improve the quality of the data captured by the system.

4. As the below summary outlines all exceptional micro-organism/antibiotic combinations, in some instances, isolates which are reported as being resistant to multiple agents in the same class of antibiotics, may be counted separately i.e. meropenem and imipenem resistant *A*. *baumannii*.

Approximately 20% of isolates identified via the AMR-EWS were communicated as having had occurred due to testing/reporting errors. Informing laboratories of these increases vigilance for errors and improves the information available at a local level. The remainder of isolates were confirmed as having the exceptional resistance phenotype (Table 6).

Table 6: Laboratory confirmed isolates by total number, January 2018 to December 2018.

Micro-organism/Antibiotic	Number of isolates
Haemophilus influenzae - Ciprofloxacin	131
Neisseria gonorrhoeae - Azithromycin	119
Klebsiella pneumoniae - Meropenem	25
Haemophilus influenzae - Levofloxacin	16
Escherichia coli - Meropenem	15
Haemophilus influenzae - Nalidixic acid	10
Acinetobacter baumannii - Meropenem	9
Haemophilus influenzae - Ceftriaxone	8
Streptococcus anginosus - Ceftriaxone	8
Acinetobacter baumannii - Imipenem	7
Enterococcus faecium - Daptomycin	6
Staphylococcus aureus - Linezolid	6
Enterococcus faecalis - Linezolid	5
Klebsiella pneumoniae - Imipenem	5
Enterococcus faecium - Linezolid	2
Enterococcus faecium - Tigecycline	2
Haemophilus influenzae - Cefixime	2
Klebsiella oxytoca - Imipenem	2
Klebsiella oxytoca - Meropenem	2
Moraxella catarrhalis - Levofloxacin	2
Streptococcus anginosus- Cefotaxime	2
Streptococcus pneumoniae- Rifampicin	2
Bacteroides fragilis- Metronidazole	1
Bacteroides ovatus- Metronidazole	1
Bacteroides uniformis- Metronidazole	1
Corynebacterium urealyticum- Vancomycin	1
Enterobacter cloacae- Meropenem	1
Escherichia coli- Imipenem	1

Haemophilus influenzae- Cefotaxime	1
Enterococcus faecalis- Daptomycin	1
Group A Streptococcus- Vancomycin	1
Group B Streptococcus- Teicoplanin	1
Haemophilus influenzae- Cefotaxime	1
Moraxella catarrhalis- Ofloxacin	1
Neisseria gonorrhoeae- Cefixime	1
Staphylococcus capitis- Linezolid	1
Staphylococcus epidermidis- Tigecycline	1
Staphylococcus haemolyticus- Vancomycin	1
Streptococcus anginosus- Penicillin	1
Total	**403**

[Data source: Electronic Communication of Surveillance in Scotland (ECOSS) System]

The annual number of isolates with reported exceptional resistance varies by micro-organism/antibiotic. Some micro-organisms, although still considered to be rare (prevalence typically ≤ 1%), are identified on a weekly basis i.e. ciprofloxacin resistant *Haemophilus influenzae*, azithromycin resistant *N. gonorrhoeae* and carbapenem resistant Gram-negatives. Public health actions, by microbiology laboratories and others including local IPCT and HPT, are well established for these micro-organisms in particular.

Following the aforementioned review of Appendix 13 (Table 6) of the NIPCM and the AMR-EWS, a number of changes have been recommended. These include removal of the most common AMR alert currently reported; *H. influenzae* resistant to fluroquinolones. Following a review of the epidemiological picture in Scotland, it was decided, that unlike that observed in many other European countries, fluroquinolone resistance in this micro-organism, although still unusual, is no longer considered to be exceptional in Scotland. The SONNAR team will continue to monitor trends in resistance in *H. influenzae* out with the AMR-EWS. Furthermore, additions have been suggested including, for the first time, significant resistant fungi.

Exceptional Phenotype Monitoring Key Points

- Monitoring of exceptional resistance phenotypes is critical for identifying emerging AMR threats
- National monitoring is essential for collating and developing epidemic intelligence at national level
- Most common exceptional phenotypes identified were *Haemophilus influenzae* – ciprofloxacin, *Neisseria gonorrhoeae* – azithromycin and *Klebsiella pneumoniae* – meropenem
- Monitoring emerging exceptional phenotypes enables the development of appropriate public health action

"An early warning system is essential to reduce the burden of antimicrobial resistance as it provides timely feedback on emerging AMR issues. This increases our ability to promptly manage interventions, ensuring appropriate patient management, thus reducing morbidity and mortality.

The SMVN has collaborated with Health Protection Scotland to review the EWS exceptional phenotype list to ensure it remains clinically relevant to the Scottish population."

Dr Mairi MacLeod

Consultant Medical Microbiologist NHS Greater Glasgow and Clyde, Chair of Scottish Microbiology and Virology Network (SMVN) Antimicrobial Susceptibility Testing (AST) Subgroup

Antimicrobial resistance in humans and animal: *Salmonella* in Scotland

Salmonella is a Gram-negative bacterium, ubiquitous in nature and a common cause of gastrointestinal illness in humans. It is the second most commonly reported cause of bacterial infectious intestinal disease in Scotland after *Campylobacter* spp..[69] *Salmonella* is usually a self-limiting infection and treatment with antibiotics is not routinely recommended. However, in some individuals, antimicrobial therapy may be required, particularly for severe or extra-intestinal infections.

Salmonella is a zoonosis - a wide range of domestic and wild animals can act as a reservoir, including cattle, sheep, pigs, poultry, reptiles and household pets. Infected animals are often asymptomatic. In recent years, fresh produce such as fruits and vegetables have been recognised as vehicles of transmission[70-72] where contamination can occur at multiple steps along the food chain. Feeder mice and reptiles have also been recognised as a source of *Salmonella* with related outbreaks.[73]

Salmonella is notifiable in humans and a reportable animal pathogen in the UK. All medical diagnostic laboratories are required to forward suspect isolates from humans to the Scottish

Salmonella, *Shigella*, *Clostridiodes difficile* Reference Laboratory (SSSCDRL) and all veterinary diagnostic laboratories isolating *Salmonella* spp. from livestock species are required to send suspect isolates for confirmation and typing to the SSSCDRL. Human and animal *Salmonella* isolates are tested for susceptibility to 15 antibiotic agents of veterinary and human health significance. The availability of data from isolates from different source populations (humans and animals) processed in exactly the same way by the same laboratory offers an opportunity to monitor the trends in resistance whilst developing the inference to evaluate the epidemiological linkages at play.

Human and animal non-typhoidal *Salmonella*

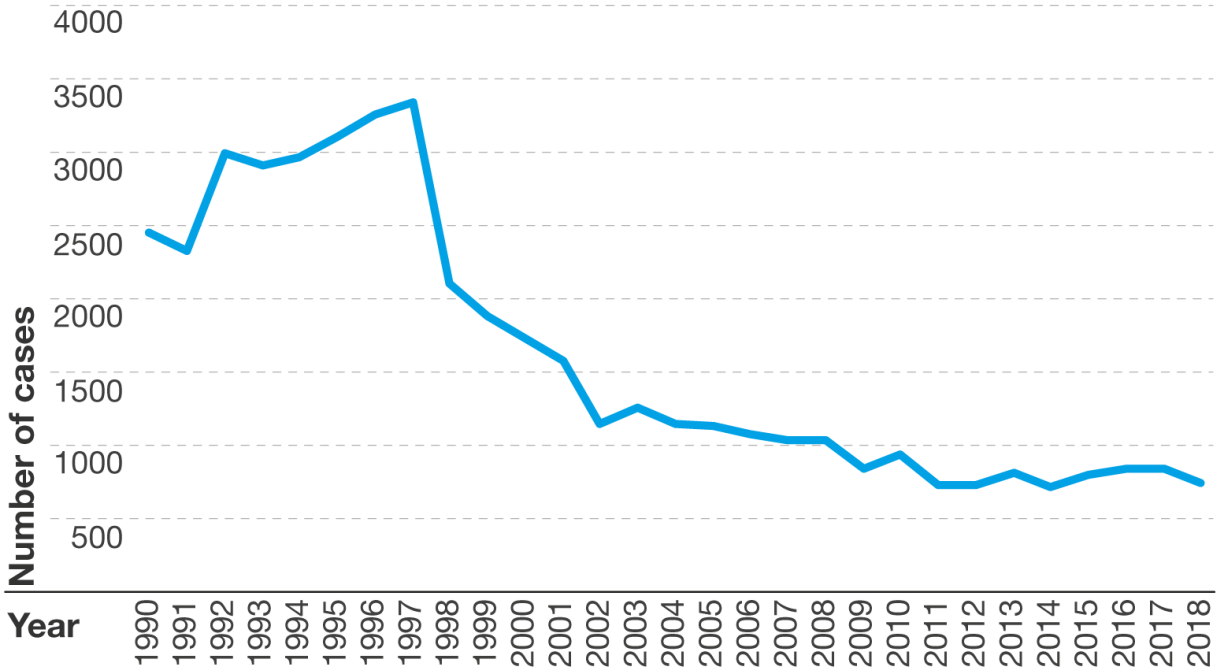
Human

In the late 1990s mass poultry vaccination programmes were introduced to combat *Salmonella* infections originating from consumption of poultry products, resulting in a significant decline in the number of human cases reported, particularly *Salmonella* Enteritidis phage type (PT) 4.[74]

In 2018, there were 751 reported cases of Salmonella, a decrease of around 10% on the 840 reports in 2017 (p=0.03) (Figure 33). *Salmonella* Enteritidis and *Salmonella* Typhimurium were the most commonly reported serotypes accounting for 55.1% of cases. This figure is comparable with previous years; between 2013 and 2017, around 53.5% of cases were represented by these two serotypes.

In 2018, 26.9% of cases were thought to have acquired their infection abroad. This figure, however, is an underestimate as HPS does not receive travel histories for all cases.

Figure 33: Number of laboratory-confirmed human *Salmonella* cases in Scotland, 1990 to 2018, by year

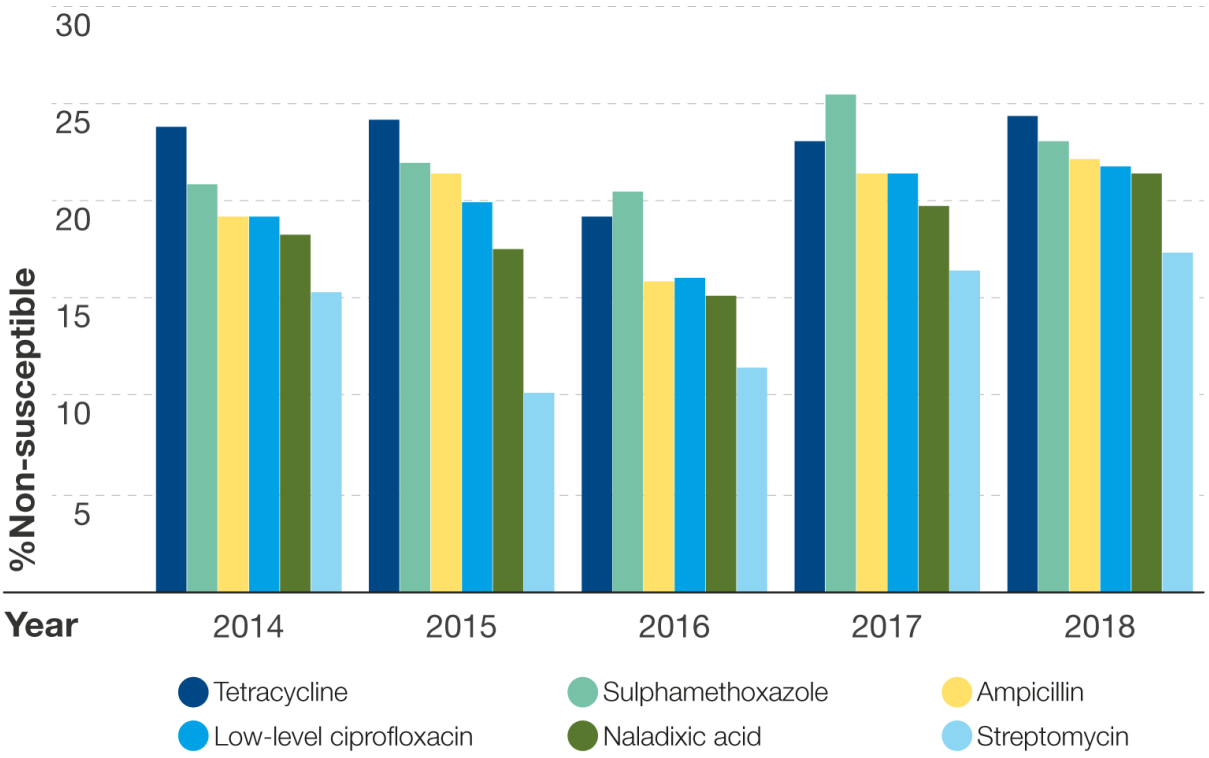


[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Susceptibility of human non-typhoidal *Salmonella*

In 2018, 59.0% of human *Salmonella* isolates were fully susceptible to all antibiotics tested (see Appendix). Non-susceptibility to all antibiotics has remained stable over the last 5 years (2014 to 2018) with no change in non-susceptibility for tetracycline (p=0.8), sulphamethoxazole (p=0.09), ampicillin (p=0.21) low level (<0.125mg/L) ciprofloxacin (p=0.14) and naladixic acid (p=0.05) (Figure 34). However, non-susceptibility in streptomycin significantly increased between 2014 and 2018 (p=0.005).

Figure 34: Non-susceptibility of human *Salmonella* isolates in Scotland, 2014 to 2018, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

Interpretation of *Salmonella* resistance to individual antibiotics is complicated by the fact that in some subtypes there are well-recognised genetic elements encoding resistance to multiple agents. Thus, the occurrence of resistance to individual antibiotics is not always independent and the apparent prevalence of resistances to different agents can be strongly influenced by the abundance of *Salmonella* sub-types in the sample set for each reporting period.

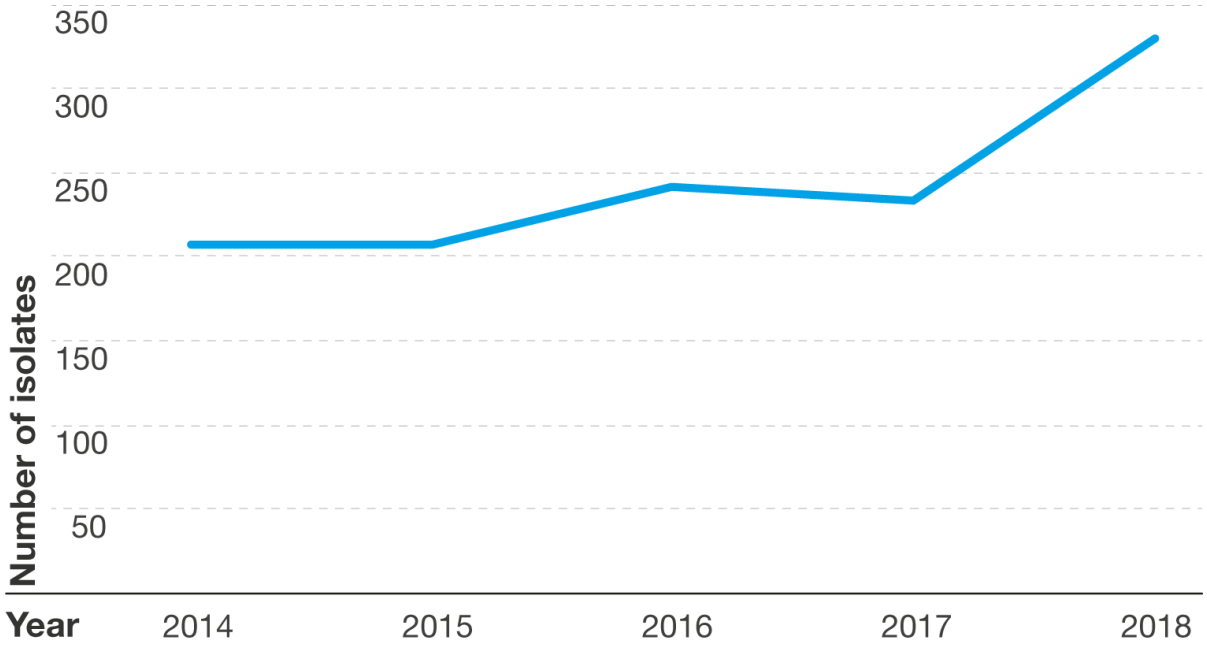
Animal

In Scotland, *Salmonella* is a reportable animal pathogen; all veterinary diagnostic laboratories isolating *Salmonella* spp. from livestock in Scotland are also required to forward suspect isolates for confirmation and typing to the SSSCDRL. No information on prior antibiotic treatment is available for *Salmonella* isolates identified from animal samples. *Salmonella* isolates are tested for susceptibility to the same 15 antibiotic agents of veterinary and human significance (see Appendix). The submission of samples is affected by the willingness of an animal keeper to pay the costs of laboratory testing to inform treatment, in addition to the clinical presentation in the affected animal(s). A number of *Salmonella* spp. are adapted to particular animal host species and are only found rarely in others. Generally, *Salmonella* infection in animals can result in clinical syndromes

suggestive of bacteraemia and systemic illness and, in these cases, antibiotic therapy would often be part of the treatment regimen instituted by an attending veterinarian. Vaccines against some serotypes of *Salmonella* spp. are available for some animal species, and are used to a greater of lesser extent depending on a number of factors including assessed risk of infection in the particular group of animals.

Whilst the number of reports of *Salmonella* in animals has remained relatively stable over the last five years (p=0.3), the number of reports in 2018 was 40% higher than in 2017 (330 versus 233, p=0.001) (Figure 35). The reasons for this apparent increase in isolation are not clear.

Figure 35: Number of laboratory confirmed *Salmonella* isolates from animals in Scotland, 2014 to 2018, by year



[Data source: Electronic Communication of Surveillance in Scotland (ECOSS)]

The majority of reports were from cattle (42.7%), pigs (23.9%) and sheep (21.5%). The remaining reports were from a variety of animals including dogs, birds and wild animals.

Susceptibility of animal non-typhoidal *Salmonella*

In 2018, 64.8% (n=214) of *Salmonella* reported from animals were fully susceptible to all antibiotics against which they were tested. This was not significantly different to 2017 when 72.1% of isolates were fully susceptible (p=0.5).

Non-susceptibility was 30.6% for tetracycline, 28.8% for sulphamethoxazole, 26.1% for streptomycin and 24.5% for ampicillin (see Appendix).

XDR *Salmonella* Typhi

In addition to the risk posed by non-typhoidal *Salmonella*, a clone of XDR *S.* Typhi resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluroquinolones, and third generation cephalosporins has emerged in Pakistan.[75;76] A small number of cases have been identified in the UK among travellers returning from Pakistan, including a case in Scotland, and highlight the need for vigilance for cases returning from the Indian subcontinent.

Whole Genome Sequencing of *Salmonella*

The advent of whole genome sequencing (WGS) for all *Salmonella* in Scotland will bring much greater resolution to the characterisation of isolates and their resistance attributes, so that relationships between isolates and resistance determinants should be easier to decipher going forward. This offers great promise in furthering our understanding of the causation of AMR in the ecosystem.

Antimicrobial Resistance in Animals

Antimicrobial resistance in veterinary clinical isolates

This is the third year that data on resistance in veterinary clinical isolates from Scotland have been reported. Knowledge on AMR in bacterial isolates from animals with disease is necessary to understand more fully the epidemiology of AMR in a ‘One Health’ context.

As previously, some of these data derive from clinical specimens submitted to the farm and companion animal diagnostic services offered by Scotland’s Rural College (SRUC) Veterinary Services and Capital Diagnostics. In addition, for the first time, data were available from samples from animals seen in Scottish veterinary practices that are part of SAVSNET. They were submitted to diagnostic services other than those offered by SRUC/Capital Diagnostics.

The data from veterinary clinical isolates are subject to a number of important biases. Unlike the clinical samples in humans in Scotland, the samples are tested on a ‘charged for’ basis to inform private veterinary treatment of diseased animals. There is a cost to the animal keeper that affects the submission of samples to these services. In addition, the primary purpose of screening for AMR is to inform veterinary treatment and they are tested against a panel of antibiotics relevant for that purpose at, where they exist, species-relevant clinical breakpoints. It is not certain that the microbiological methods applied in the laboratories contributing to SAVSNET are consistent either with one another or with those used by SRUC.

Interpretation of these data in terms of their relevance to public health is difficult beyond the notion of evidence of impact of a selection pressure being applied in another compartment of the ecosystem that humans share closely with animals. The micro-organisms included

are selected based both on their prevalence among all submissions, i.e. their importance as causes of animal morbidity, as well as, in some cases, their similarity to micro-organisms that cause morbidity in people.

AMR in farm and companion animals (Scotland's Rural College)

In 2018, there were 2,117 bacteria isolated from veterinary clinical samples.

***Staphylococcus* spp.**

Staphylococcus spp. are common commensal organisms that can act as important opportunist pathogens of humans and other animals. In humans, *Staphylococcus pseudintermedius* infections are being recognised more frequently, in large part, due to methodology changes in NHS microbiology laboratories. In most cases these human infections will have been transmitted from a pet, most likely a dog,[77] whereas the reverse is likely to apply for *S. aureus*, with canine and perhaps also some feline infections being transmitted by their owners or other human contacts.[78]

The sensitivity patterns for selected *Staphylococcus* spp. for 2014 to 2018 are shown in the Appendix. Non-susceptibility for *S. aureus* and *S. pseudintermedius* isolates from companion animals, for several antibiotics, have fallen, however, relatively high levels to penicillins and the topical agent fusidic acid, are a concern for animal treatment. Fusidic acid is a recommended and commonly used antibiotic for the management of *S. pseudintermedius*-associated otitis externa. Rates of non-susceptibility to first generation cephalosporins and widely used co-amoxiclav remain stable. For *Staphylococcus* spp. from livestock, non-susceptibility was generally unchanged in 2018 and remained low for the majority of antibiotics.

In 2018, meticillin resistance was not found in any *S. aureus* from livestock (38 cattle, 21 sheep, seven pigs, three goats and one each of poultry, pheasant and deer). In coagulase positive staphylococci from companion animals, meticillin resistance was identified in 10/170 *S. pseudintermedius*, 1/18 *S. schleiferi* subsp. *coagulans* recovered from dogs (2.5%) and 1/5 *S. aureus* recovered from cats; meticillin resistance was not detected in *S. aureus* from ten dogs, two horses and a rabbit, nor from a single *S. pseudintermedius* from a cat. Comparison with previous years is difficult due to low numbers assessed previously.

***Streptococcus* spp.**

Streptococcus spp. can be important pathogens or opportunists of livestock and companion animal species, with the potential to cause severe disease of the skin, ear, respiratory tract, body cavities, wounds and urinary tract.

The non-susceptibility patterns for selected *Streptococcus* spp. for 2014 to 2018 are shown in the Appendix.

Pasteurellaceae

Pasteurellaceae are important causes of potentially severe respiratory and soft tissue infections in companion and livestock animals. In livestock animals, high levels of morbidity and mortality can result with consequential significant economic losses. Important bacterial species included in this report are *Pasteurella multocida* (companion animals, cattle, pigs and sheep), *Mannheimia haemolytica* (cattle and sheep), *Bibersteinia trehalosi* (cattle and sheep) and *Actinobacillus pleuropneumoniae* (pigs). Of these, *P. multocida* can cause severe disease in humans.

The non-susceptibility patterns for the selected Pasteurellaceae for 2018 from companion and livestock animals are shown in the Appendix.

Escherichia coli

E. coli are a major constituent of the normal faecal flora of humans and warm-blooded animals. However, some strains cause intestinal and extraintestinal disease. The non-susceptibility patterns for the selected *E. coli* for 2014 to 2018 from companion and livestock animals are shown in the Appendix.

Extended spectrum beta-lactamase producing *E. coli* were identified from two dogs and a bovine animal: CTX-M-15 beta-lactamase was identified in the bovine isolate. Carbapenemases were not detected.

Klebsiella pneumoniae

K. pneumoniae is a cause of significant economic loss to the livestock industry, and is potentially zoonotic. The non-susceptibility patterns for *K. pneumoniae* for 2014 to 2018 are shown in the Appendix. Spectinomycin remains the recommended treatment for *K. pneumoniae* in animals. Extended spectrum beta-lactamases were detected in two *K. pneumoniae* isolates, from a dog's urine and a cow's milk; the latter was CTX-M-32 beta-lactamase. Carbapenemases were not detected.

***Corynebacterium* spp.**

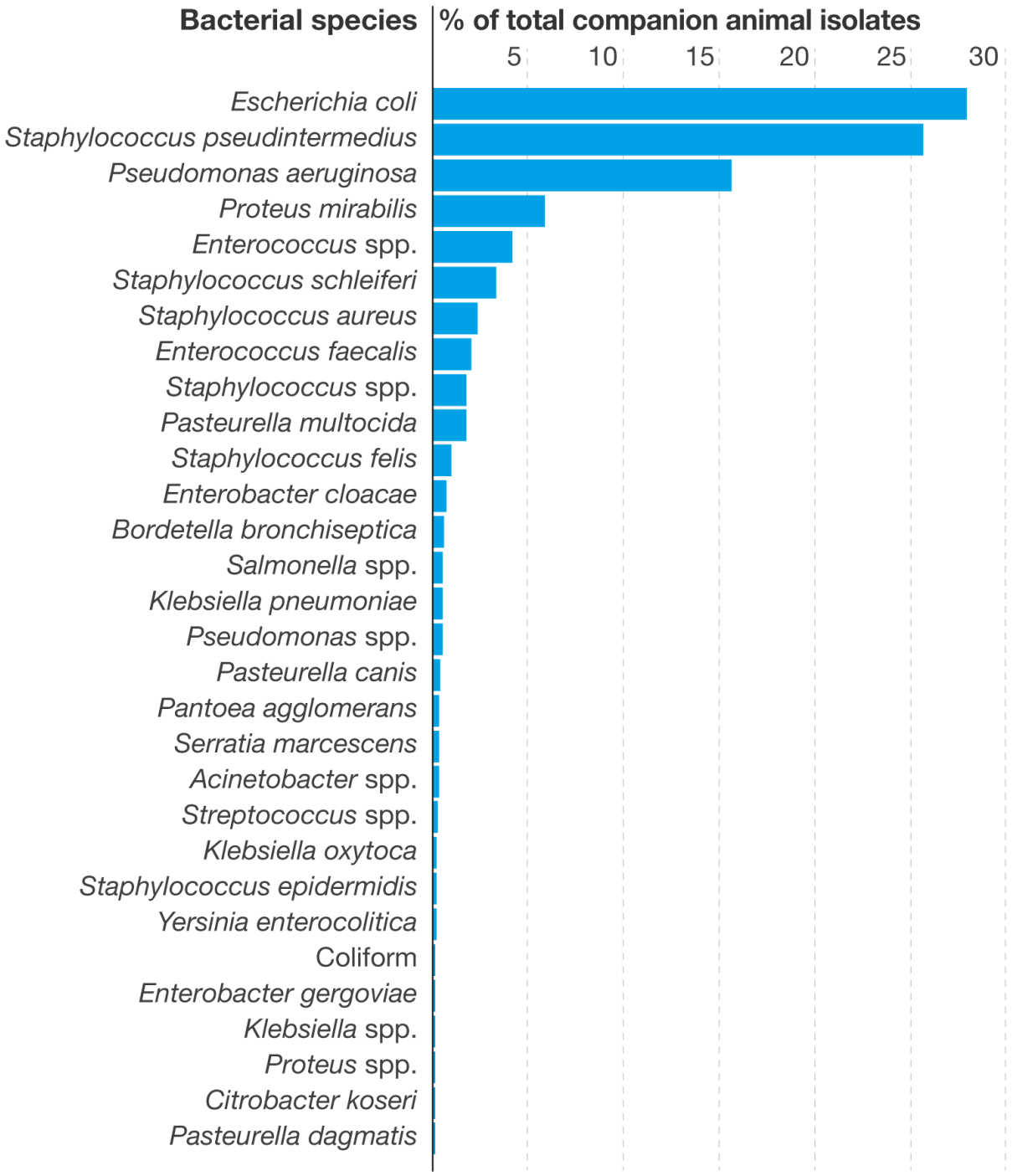
Corynebacterium spp. are associated with serious soft tissue infections and otitis externa in the dog (*Corynebacterium auriscanis*), but invasive corynebacteriosis in companion animals remains rare. *Corynebacterium* spp. are also associated with soft tissue infections in livestock. The non-susceptibility patterns for *Corynebacterium* spp. for 2014 to 2018 are shown in the Appendix.

AMR in small animals (SAVSNET)

For the first time, data on AMR in small companion animals from Scottish veterinary practices that contribute to SAVSNET were available. A total of 8,336 isolates were reported between 2016 and 2018. There were 2,760, 3,487 and 2,089 isolates reported in 2016, 2017 and 2018, respectively. The majority of isolates were reported in dogs (n=84.5%, n=7,043) and the remainder in cats (15.5%, n=1,293).

The distribution of bacterial species isolated is described in Figure 36. *E. coli* was the most frequently isolated bacteria (n=2,332, 28.0%) followed by *S. pseudintermedius (*n=2,141, 25.7%) and *P. aeruginosa* (n=1,303, 15.6%).

Figure 36: Distribution of companion animal isolates, SAVNET, 2016 to 2018, by organism



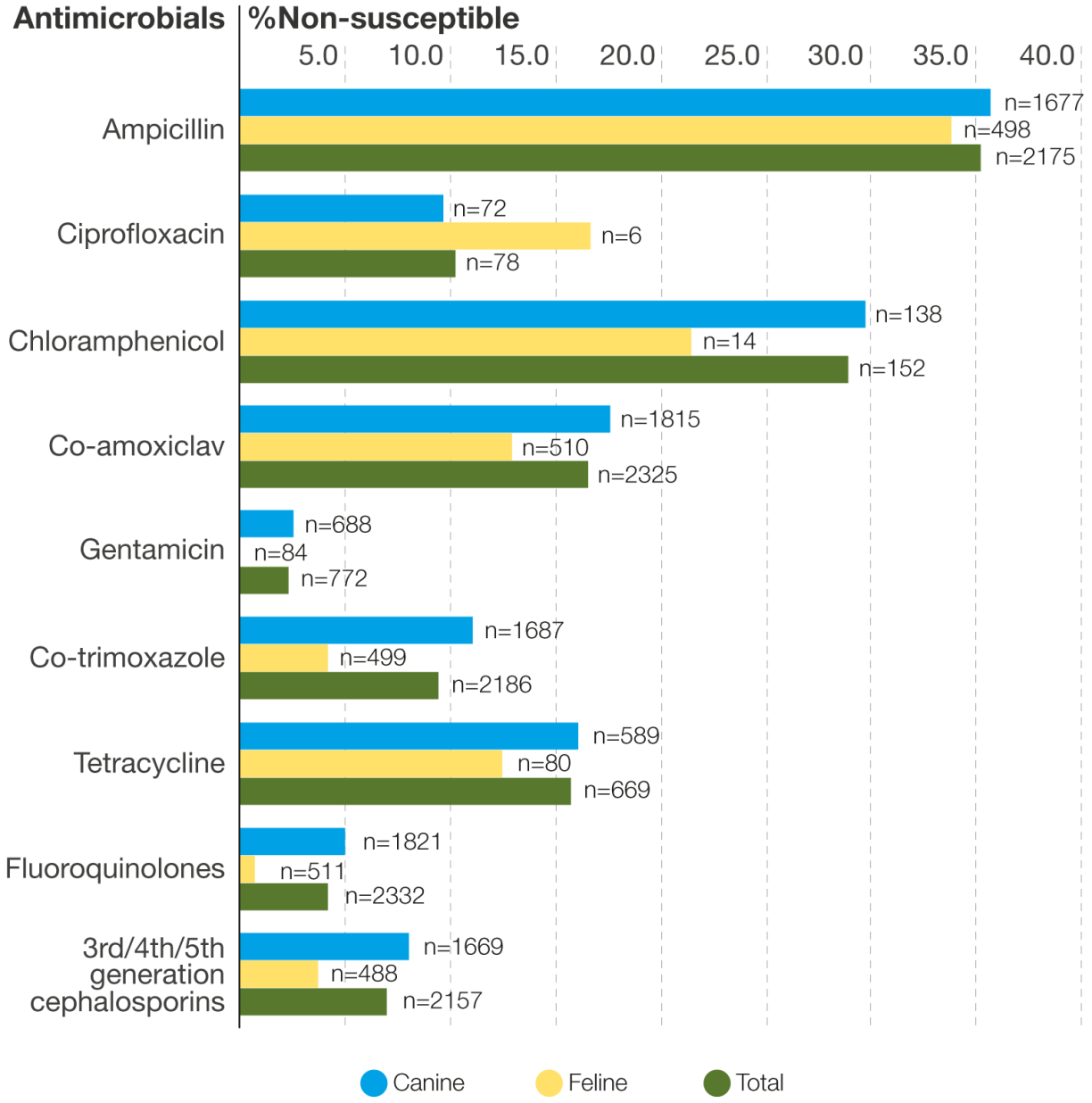
Note: There were a further 66 bacterial species accounting for 175 isolates (2.1%).

[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

AMR in *Escherichia coli* from companion animals

There were a total of 2,332 *E. coli* isolates reported between 2016 and 2018; 1,821 from dogs and 511 from cats. The percentage of isolates that were non-susceptible to selected antimicrobials by animal species is shown in Figure 37. Non-susceptibility was highest to ampicillin with more than a third of *E. coli* isolates non-susceptible (35.2%; 35.6% in dogs; 33.7% in cats).

Figure 37: Non-susceptibility of *Escherichia coli* companion animal isolates to selected antimicrobials, by animal species, 2016 to 2018



[Data source: Small Animal Veterinary Surveillance Network (SAVSNET)]

AMR in *Staphylococcus* spp.

A total of 2,872 *Staphylococcus* spp. isolates were reported between 2016 and 2018; 196 *S. aureus* and 2,141 *S. pseudintermedius.* Non-susceptibility to cefalexin, co-amoxiclav and fusidic acid in *S. aureus* was 10.3% (n=20), 10.3% (n=20) and 12.0% (n=22), respectively. Non-susceptibility to cefalexin, co-amoxiclav and fusidic acid in *S. pseudintermedius* was 6.6% (n=141), 6.8% (n=146) and 17.2% (n=332), respectively.

Streptococcus spp., *Pasteurella* spp., *Corynebacterium* spp. and *Klebsiella* spp. were considered clinically important isolates thought there were insufficient numbers of these isolates to described non-susceptibility robustly.

Antimicrobial resistance in healthy animals

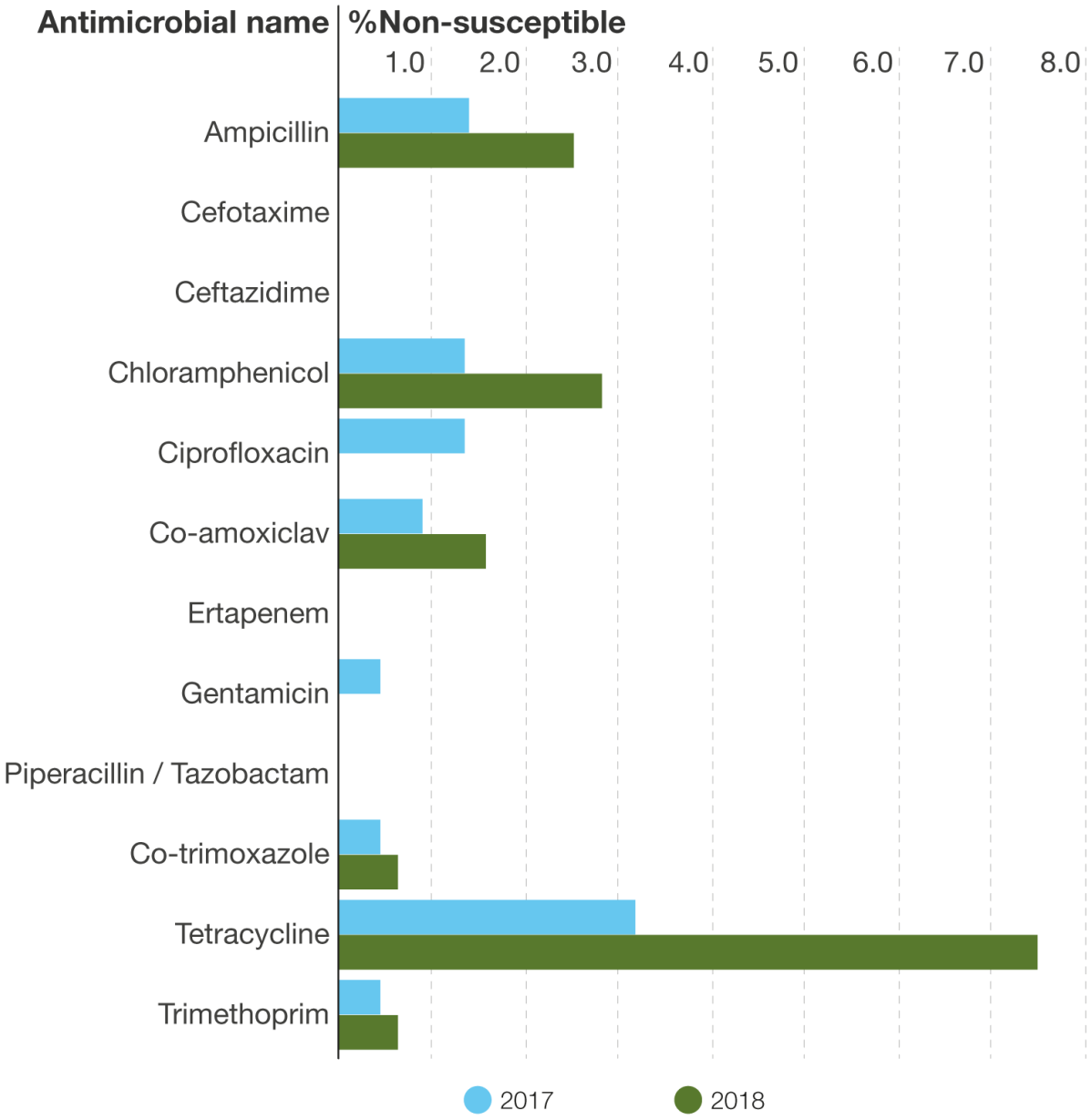
E. coli from healthy animals

In addition to diagnostic isolates, *E. coli* collected from enteric samples of healthy animals are tested as a measure of the background resistance in livestock entering the food chain. Starting in June 2017, a pilot project was set up to estimate and monitor the prevalence of resistance in *E. coli* cultured from cattle, sheep, pigs and poultry presenting at abattoirs for slaughter for human consumption.

The antibiotic sensitivity panel for the isolates from healthy animals were selected specifically for their relevance for human treatment, rather than veterinary practice. Results from the initial pilot study provides a baseline for comparison with 2018 data, collected and tested using the identical protocols to the 2018 results presented in this report, and permits ongoing monitoring of progress for future years.

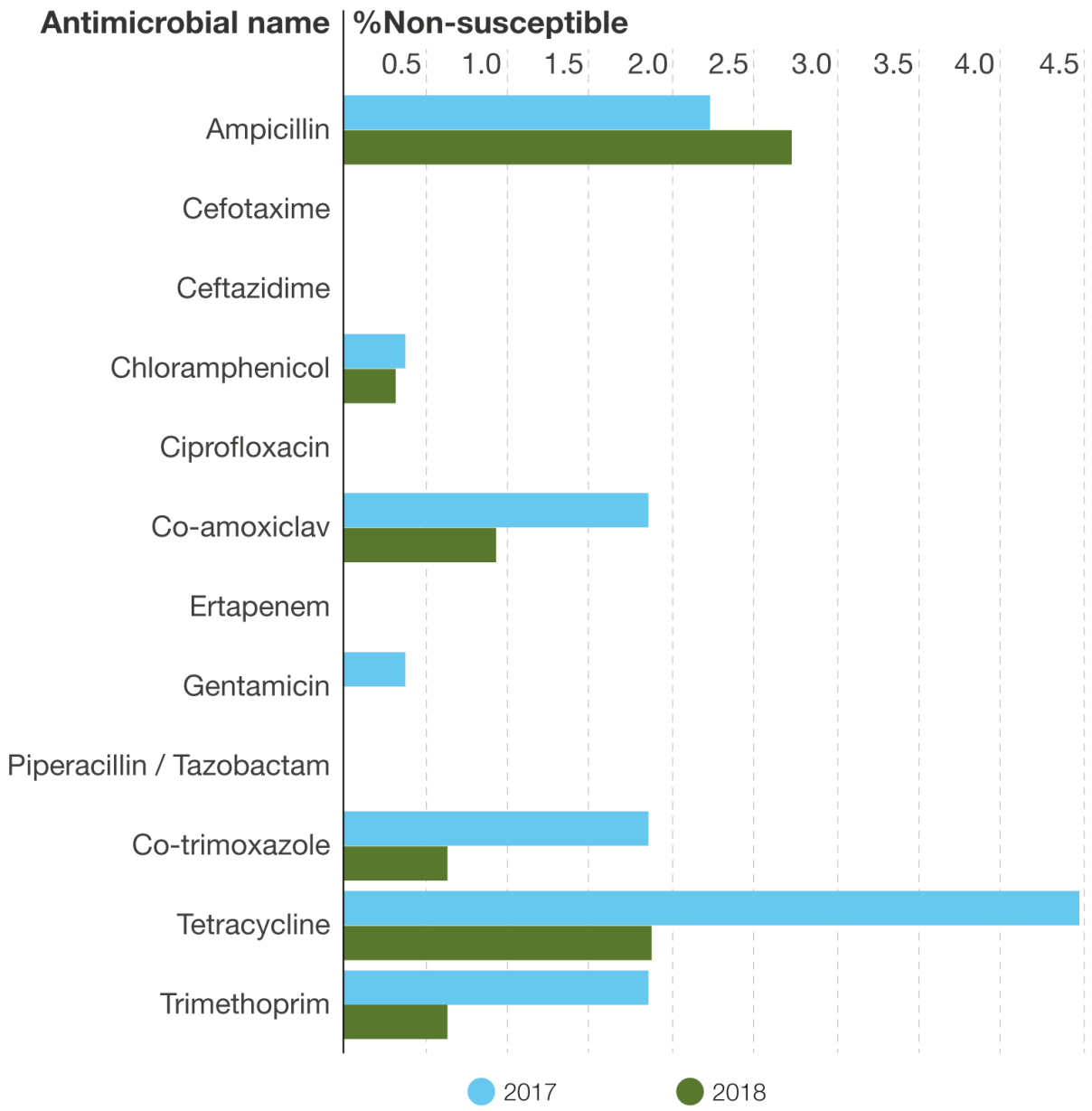
Results are presented for 2017 and 2018 for all livestock hosts are presented in Figure 38, Figure 39, Figure 40 and Figure 41. As for 2017, levels of non-susceptibility in pigs and poultry were higher than those detected for cattle and sheep for which the numbers of non-susceptibility were either absent or very low. Amongst HP-CIA, a single *E. coli* from a pig was non-susceptible to cefotaxime and ceftazidime (1/280, 0.4%) in 2018, while ciprofloxacin non-susceptibility was detected only in poultry (9/193, 4.7%). All isolates were susceptible to ertapenem and piperacillin/tazobactam in 2018. Notable levels of non-susceptibility for a single host were once again evident for poultry with gentamicin and pigs with chloramphenicol.

Figure 38: Percentage of *Escherichia coli* isolates that were non-susceptible to selected antimicrobials in healthy cattle in Scotland, SRUC, in 2017 and 2018, by antimicrobial



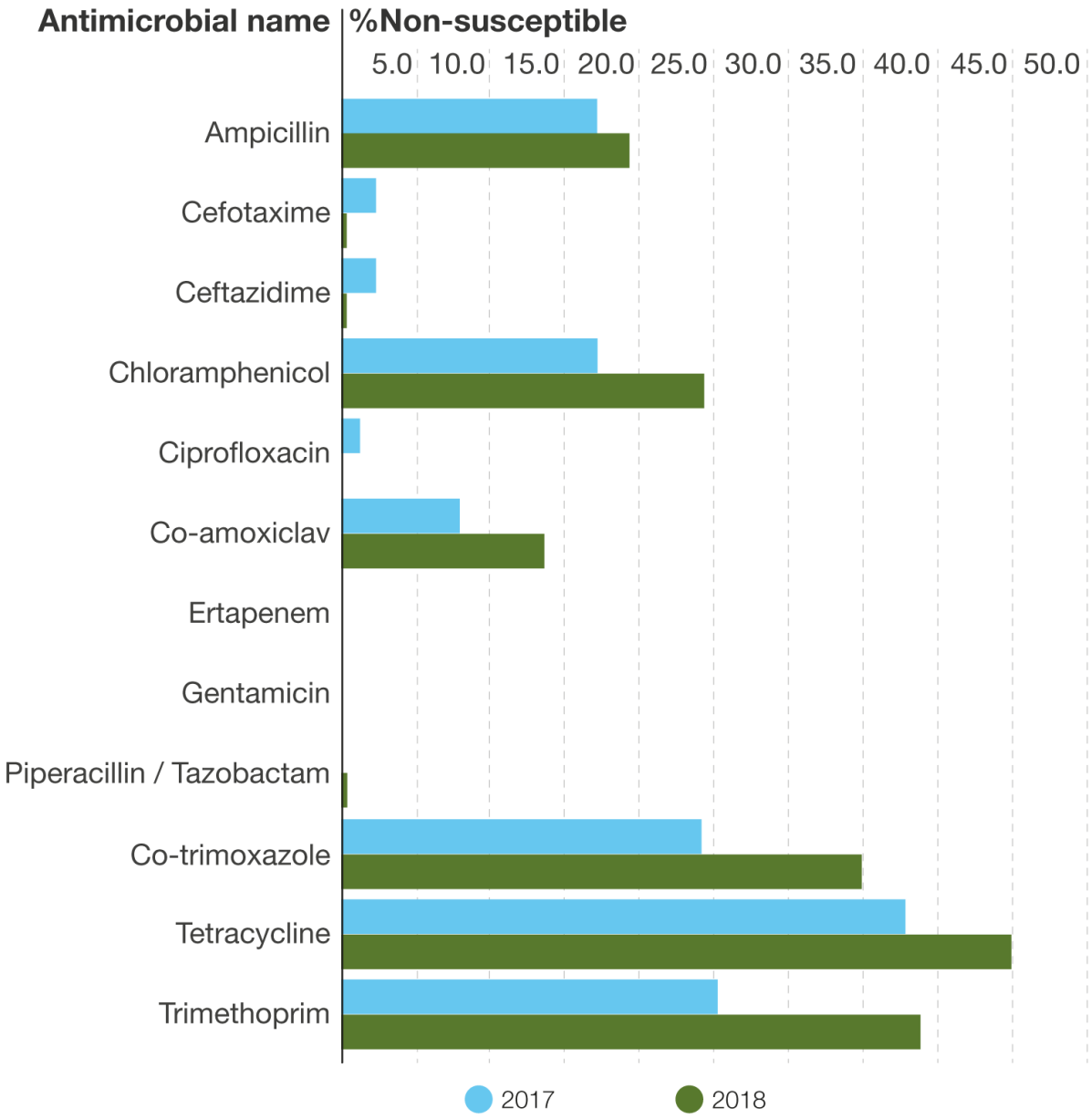
[Data Source: Scotland's Rural College (SRUC)]

Figure 39: Percentage of *Escherichia coli* isolates that were non-susceptible to selected antimicrobials in healthy sheep in Scotland, SRUC, in 2017 and 2018, by antimicrobial



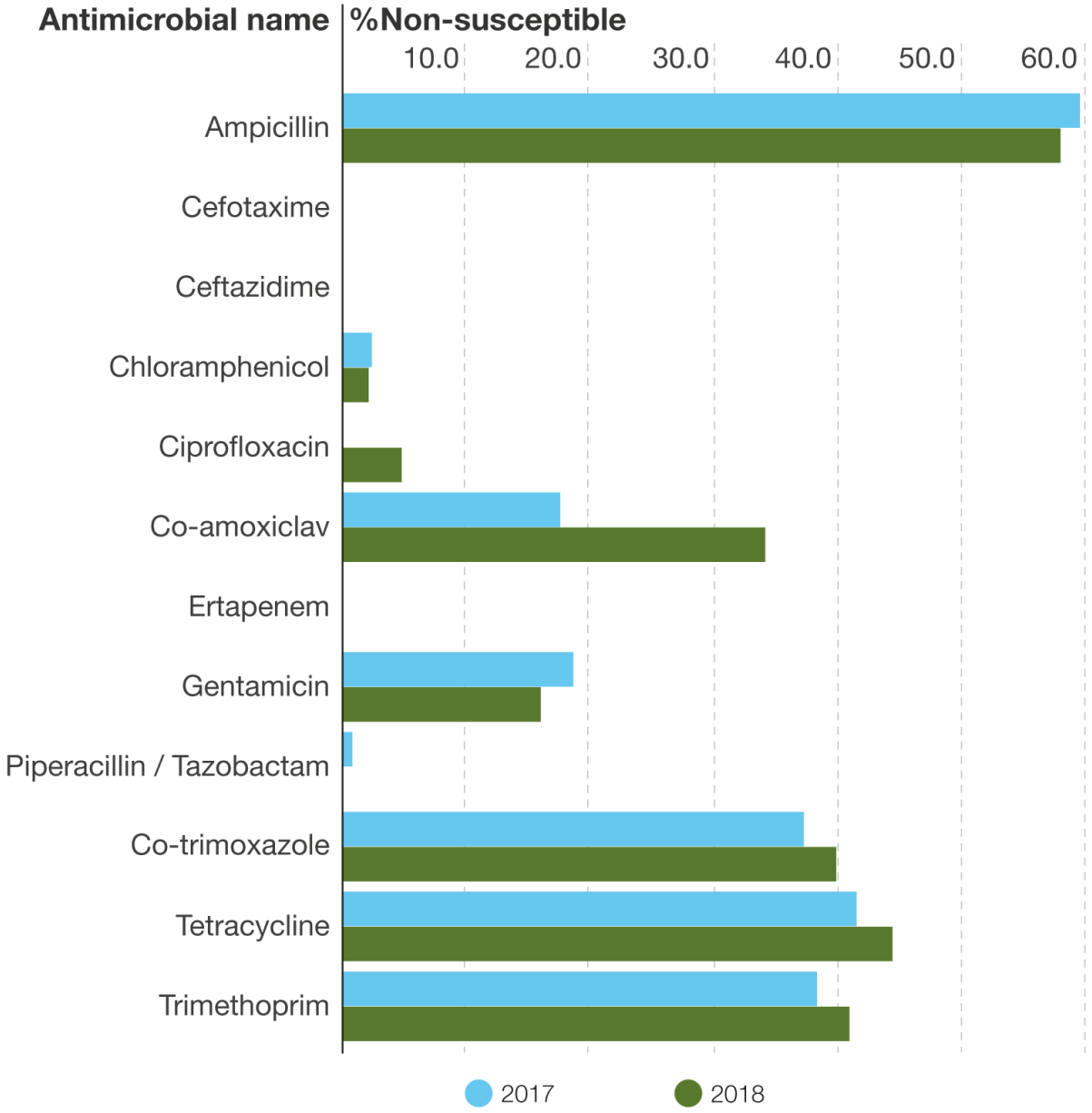
[Data Source: Scotland's Rural College (SRUC)]

Figure 40: Percentage of *Escherichia coli* isolates that were non-susceptible to selected antimicrobials in healthy pigs in Scotland, SRUC, in 2017 and 2018, by antimicrobial



[Data Source: Scotland's Rural College (SRUC)]

Figure 41: Percentage of *Escherichia coli* isolates that were non-susceptible to selected antimicrobials in healthy poultry in Scotland, SRUC, in 2017 and 2018, by antimicrobial



[Data Source: Scotland's Rural College (SRUC)]

Animal AMR Key Points
▶ AMR is a feature of bacterial pathogens affecting all domestic animal species
▶ Non-susceptibility for veterinary clinical isolates is relatively stable over 5 years
▶ AST to support veterinary treatment comes primarily from private laboratories but is not currently part of a formal surveillance system
▶ Monitoring of AMR in animals is a vital component of understanding and mitigation of AMR across the entire ecosystem
▶ Responsible Use of Medicines in Agriculture Alliance (RUMA) Targets Task Force Report of 2018 and Veterinary Antimicrobial Resistance and Sales Surveillance Report of 2018 demonstrate serious commitment to antimicrobial stewardship in UK livestock

Minimising the spread of AMR through the environment

The Tackling Antimicrobial Resistance 2019 to 2024: the UK's 5-year NAP [3] highlights the need for a more focussed effort to minimise the spread of AMR through the environment. This is despite there being no regulatory processes in place to enforce or monitor this. In 2016, Lord O'Neill's AMR review stated that this topic had not received enough attention in the UK. The EU's AMR 2017 action plan[3;79] advocates strategic action on pharmaceuticals in the environment and again in 2017 the United Nations (UN) Environment Assembly reached consensus on the need for environmental surveillance to further understanding on antimicrobial contamination (https://web.unep.org/environmentassembly/documents-third-session-un-environment-assembly). In 2019, the UN Environment Assembly stated that "we are determined to ambitiously scale-up our efforts to tackle common environmental challenges through fostering sustainable and efficient resource management; ensuring the access and use of environmental data; engaging civil society, citizens, private sector and academia."(https://web.unep.org/environmentassembly/fourth-session-un-environment-assembly).

Minimising the spread of AMR through the environment remains a UK priority and the UK's five-year NAP identifies the following areas as key priorities: deeper understanding about AMR in the environment; minimising antimicrobial contamination consistent with the EU environmental quality standards (https://ec.europa.eu/environment/water/water-dangersub/pri_substances.htm); and increased research into AMR in the environment using a One Health approach to identify effective interventions. In order to achieve this, the action plan states that there should be increased activity to identify and assess sources, pathways and exposure risks including their interdependencies that create the opportunity to impact

on the presence and persistence of AMR in the environment. The action plan also advocates the evaluation of existing regulations to evaluate whether they can be applied, and if not amended, to encompass monitoring of AMR in the environment. Engagement at a global level also remains a key priority.

HPS has engaged with environmental and veterinary agencies and academia to scope out collaborative areas of work. Initial work with the Scottish Environmental Protection Agency (SEPA), SRUC and Napier University has centred around *E. coli* cefotaxime resistance in human bacteraemia isolates, healthy animal isolates and bathing water isolates. Cefotaxime was chosen as it is widely used to treat human infection and is currently routinely tested against human, healthy animal and bathing water isolates. Whilst no conclusions can be drawn from these baseline data, it is worth noting that in 2018, the proportion of *E*. *coli* cefotaxime resistance in human bacteraemia and bathing water isolates is broadly comparable (8.0% and 7.9% respectively) whilst it is markedly lower in the healthy animal isolates (0.4%).

HPS will continue to collaborate with SEPA, SRUC and academia to take forward the AMR One Health agenda as without inclusion or consideration of all of the drivers and pathways of AMR into the environment, any action plans are incomplete and at risk of not achieving the desired goals of ensuring and improving the efficacy of existing and future antibiotics.

Emerging diagnostic technologies to support antimicrobial stewardship

One of the main themes addressed within the UK Tackling Antimicrobial Resistance 2019-2024 Five Year National Action Plan relates to the need for development of new diagnostic technologies.[3]

Diagnostic antimicrobial stewardship initiatives currently take many forms including input into laboratory testing policies alongside focused education surrounding appropriate test ordering, interpretation and specimen collection.[80] A variety of rapid diagnostic technologies to identify micro-organisms are now available, which when coupled with antimicrobial stewardship programmes, can influence AMU and improve patient outcomes.[80-82] These technologies enable earlier diagnosis of infections and have been shown to reduce the time to administration of appropriate antimicrobial therapy. In recent years, technology such multiplex PCR have become more routinely used for the diagnosis of micro-organisms from blood, stool and respiratory specimens. This has revolutionised diagnosis due to rapid identification of micro-organisms and resistance profiles, leading to faster de-escalation of antimicrobial therapy.[80]

There has been recent diagnostic stewardship focus diagnosis of UTI in Scotland, since abnormal urinalysis results often lead to unnecessary urine culturing and inappropriate treatment of asymptomatic bacteriuria.[2] In instances where culture is necessary, one NHS laboratory in Scotland has recently implemented combined use of two automated technologies which has led to improvements in the diagnosis of UTI and supported local

antimicrobial stewardship. Within this laboratory the majority of AST on urine isolates is now performed using the VITEK-2 analyser to provide next day AST results. The combined use of this technology and the automated specimen processing instrument; the Walk Away Specimen Processor (WASP) and digital imaging system (WASPLab), allows further automation and has improved test turnaround times, with 95% of results authorised and available to the clinician within 48 hours as opposed to between 48 and 72 hours. Since the VITEK-2 AST card panels contain a large number of agents as standard, this allows clinician's to rapidly assess treatment options and commence directed therapy, particularly for MDR infections, without having to request further agents to be tested.

There are now also various molecular tests available enabling diagnostic laboratories to detect MDR micro-organisms including CPO and MRSA rapidly. This allows information to be provided to local IP&C and antimicrobial stewardship teams, as appropriate, without having to rely on referral to reference laboratories, to initiate early patient management. Currently, within a number of laboratories in Scotland, multiplex PCR assays are employed which facilitate the detection of resistant micro-organisms.

Examples include:

1) An assay to detect the most common carbapenemase enzymes, which provides an indication of whether a carbapenem resistant organism is a CPO
2) An assay to detect MRSA isolates directly from blood culture specimens.

Novel diagnostic technologies that improve the speed of current local testing practices are important to enable rapid patient treatment. However, this does not take away the need for appropriate reference laboratory referral of key resistant micro-organisms. Referral of selected isolates ensures the validity of results obtained by diagnostic laboratory methods, as well as feeding into national epidemiological intelligence. HPS, in conjunction with reference laboratories in the UK have recently developed a reference laboratory AST exceptional resistance referral guide, to ensure that certain isolates found to be resistant by diagnostic laboratories are referred to the appropriate reference laboratory. It is anticipated that this document will assist in the rapid referral of resistant isolates, ensuring that results are obtained and communicated promptly, to influence patient management.

In summary, effective communication and collaboration between microbiology laboratories and antimicrobial stewardship teams is expected to become increasingly important, particularly due to the fact that more novel and complex tests will continue to be developed in the future.[80-82]

New EUCAST susceptibility definitions

In January 2019 EUCAST introduced new definitions for susceptibility test results. This decision was taken in June, 2018, following three general consultations (2015, 2017 and 2018).

The changes in the definitions of ‘S’ and ‘R’ categories are minor. They mostly emphasise the relationship between the susceptibility category and the level of patient exposure to the antibiotic. The changes in the ‘I’ category will have clinical and technical impact. The ‘Intermediate’ susceptibility result has been changed to ‘Susceptible, increased exposure’: A micro-organism is categorised as ‘Susceptible, increased exposure’ when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

Importantly for the surveillance of AMR, the changes may have implications for comparisons with previous years. The changes to the susceptibility definitions and breakpoints will be reflected in the national AMR dataset from 2019 and reported in the Scottish One Health Antimicrobial Use and Resistance report in 2020.

In addition to a change to the definitions there have been changes to some breakpoints. Namely: *Pseudomonas*: aztreonam; *Enterococcus*: trimethoprim and trimethoprim-sulfamethoxazole; *N. meningitidis*: chloramphenicol; *H. influenzae*: cefpodoxime; *Proteus*: imipenem; *Morganella*: imipenem; *Providencia:* imipenem*;* and *Acinetobacter:* ciprofloxacin.

List of Abbreviations and Acronyms

AMEG	Antimicrobial Advice Ad Hoc Expert Group
AMR	Antimicrobial Resistance
AMR-EWS	Antimicrobial Resistance Early Warning System
AMRHAI	Antimicrobial Resistance and Healthcare Associated Infections
AMT	Antimicrobial Management Teams
AMU	Antimicrobial Use
ASP	Antimicrobial Stewardship Programme
AST	Antimicrobial Susceptibility Testing
BASHH	British Association for Sexual Health and HIV
BMD	Broth Microdilution
BSAC	British Society for Antimicrobial Chemotherapy
BSI	Bloodstream Infection
CLSI	Clinical and Laboratory Standards Institute
CPE	Carbapenemase-producing Enterobacteriales
CPO	Carbapenemase-producing Organism
DDD	Defined Daily Doses
ECB	*Escherichia coli* bacteraemia
ECDC	European Centre for Disease Prevention and Control
ECOSS	Electronic Communication of Surveillance in Scotland
EEA	European Economic Area
EMA	European Medicines Agency
ESBL	Extended-spectrum beta-lactamases
EWS	Early Warning System
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FSS	Food Standards Scotland
GASS	Gonococcal Antibiotic Surveillance in Scotland
GP	General Practitioner
HCAI	Healthcare Associated Infection
HIV	Human Immunodeficiency Virus
HL-AziR	High level azithromycin resistance
HP-CIA	High Priority Critically Important Antibiotics
HPS	Health Protection Scotland
HPT	Health Protection Team
IPCT	Infection Prevention and Control Team
IQR	Interquartile range
ISD	Information Services Division
IV	Intravenous
MDR	Multi-Drug Resistant
MRSA	Meticillin Resistant *Staphylococcus aureus*
NAP	National Action Plan
NDM	New Delhi Metallo-beta-lactamases
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIPCM	National Infection Prevention Control Manual
NRS	National Records of Scotland

OBD	Occupied Bed Days
OXA	Oxacillinase
PCR	Polymerase Chain Reaction
PHE	Public Health England
PID	Pelvic Inflammatory Disease
RUMA	Responsible Use of Medicines in Agriculture Alliance
SAC	Scottish Agricultural College
SAPG	Scottish Antimicrobial Prescribing Group
SARIS	Surveillance of Antimicrobial Resistance in Scotland
SAVSNET	Small Animal Veterinary Surveillance Network
SBSTIRL	Scottish Bacterial Sexually Transmitted Infections Reference Laboratory
SCIEH	Scottish Centre for Infection and Environmental Health
SEAG	Scottish Environmental AMR Group
SEPA	Scottish Environmental Protection Agency
SHPN	Scottish Health Protection Network
SMA	Scottish Microbiology Association
SMVN	Scottish Microbiology and Virology Network
SOHNAAP	Scottish One Health AMR Action Plan
SONAAR	Scottish One Health Antimicrobial Use and Antimicrobial Resistance
SRUC	Scotland's Rural College
SSSCDRL	Scottish *Salmonella*, *Shigella* and *Clostridium difficile* Reference Laboratory
STI	Sexually Transmitted Infection
SUTIN	Scottish UTI Network
ICU	Intensive Care Unit
UK	United Kingdom
UN	United Nations
UTI	Urinary Tract Infections
VARSS	Veterinary Antimicrobial Resistance and Sales Surveillance
VRE	Vancomycin-resistant enterococci
WASP	Walk Away Specimen Processor
WGS	Whole Genome Sequencing
WHO	World Health Organisation
XDR	Extensively Drug Resistant

List of Tables

List of Figures

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- Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit at Public Health England (PHE)
- Scottish Antimicrobial Prescribing Group (SAPG)
- Scottish Microbiology and Virology Network (SMVN)
- Scottish Environment Protection Agency (SEPA)
- Scotland's Rural College (SRUC) which includes Scottish Agricultural College (SAC) Veterinary Services and Capital Diagnostics in Scotland
- Small Animal Veterinary Surveillance Network (SAVSNET)
- Scottish Environmental AMR Group (SEAG)
- Food Standards Scotland (FSS)

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Appendices

Appendix 1 – Background information

Additional information is provided in the **SONAAR report 2018 appendix**.

Appendix 2 – Metadata

Metadata indicator	Description
Publication title	Scottish One Health Antimicrobial Use and Antimicrobial Resistance report, 2018 (SONAAR report, 2018)
Description	This annual report provides data relating to antimicrobial use and antimicrobial resistance in Scotland during 2018.
Theme	Health and Care (HPS and ISD)
Topic	Antimicrobial use and resistance in humans and animals.
Format	Online resource (PDF)
Release date	12 November 2019
Frequency	Annual
Relevance and key uses of the statistics	Making information publicly available. The report is intended to support planning, prioritisation and evaluation of initiatives to optimise antimicrobial use and to minimise antimicrobial resistance.
Accessibility	It is the policy of HPS to make its web sites and products accessible according to published guidelines.
Coherence and clarity	This report followed the PHI Graphics guidance for content and accessibility: This report followed the NHS National Services Scotland Code of Practice for publishing official statistics. More information on official statistics is available here.
Disclosure	The HPS protocol on Statistical Disclosure Protocol is followed.
Official Statistics designation	Official Statistics.
UK Statistics Authority Assessment	Not assessed.
Last published	12 November 2019
Next published	November 2020
Date of first publication	14 November 2017
Help email	Juliewilson4@nhs.net
Date form completed	29/10/2019

Metadata indicator	Description
Data item	***(1) Prescribing, antibiotic use in humans,*** *antibiotic use in primary care numerator* ***(2) Prescribing, antibiotic use in animals,*** *antibiotic use in companion animals* ***(3) Human AMR, Bacteraemia,*** *Number of bacteraemia cases and antimicrobial susceptibility data relating to the following: Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Klebsiella oxytoca, Acinetobacter spp., E. faecalis, E. faecium, S. aureus, S. pneumoniae* ***(4) Human AMR, Bacteraemia,*** *Population denominator data: Mid-year population projections for Scotland* ***(5) Human AMR, Bacteraemia,*** *E. coli bacteraemia enhanced data* ***(6) Human AMR, Candidaemia,*** *Number of candidaemia cases and antifungal susceptibility data* ***(7) Human AMR, Candidaemia,*** *Population denominator data: Mid-year population projections for Scotland* ***(8) Human AMR, Urinary Tract Infections,*** *Number of urinary tract positive results and antimicrobial susceptibility data relating to Escherichia coli and Klebsiella pneumoniae* ***(9) Human AMR, Urinary Tract Infections,*** *Population denominator data: Mid-year population projections for Scotland* ***(10) Human AMR, Neisseria gonorrhoeae,*** *Number of cases* ***(11) Human AMR, Neisseria gonorrhoeae,*** *Antimicrobial susceptibility data* ***(12) Human AMR, Neisseria gonorrhoeae,*** *Population denominator data: Mid-year population projections for Scotland* ***(13) Human AMR, Mycoplasma genitalium,*** *Antimicrobial susceptibility data* ***(14) Human AMR, Carbapenemase-Producing Organisms,*** *Number of cases and antimicrobial susceptibility data* ***(15) Human AMR, Carbapenemase-Producing Organisms,*** *Population denominator data: Mid-year population projections for Scotland* ***(16) Human AMR, Salmonella,*** *Number of cases and antimicrobial susceptibility data* ***(17) Animal AMR, AMR in small animal clinical isolates,*** *Number of isolates and antimicrobial susceptibility data* ***(18) Animal AMR, AMR in animal clinical isolates,*** *Number of isolates and antimicrobial susceptibility data* ***(19) Animal AMR, AMR in animal clinical isolates,*** *Staphylococcus aureus animal isolates antimicrobial susceptibility data* ***(20) Animal AMR, AMR in healthy animals (abattoir),*** *Number of isolates and antimicrobial susceptibility data* ***(21) Animal AMR, Salmonella,*** *Number of isolates and antimicrobial susceptibility data*

Metadata indicator	Description
Data sources	(**1**) Prescribing Information System (PIS), ISD. (**2**) Small Animal Veterinary Surveillance Network (SAVSNET). (**3,6,8,10,16,21**) ECOSS (Electronic Communication of Surveillance in Scotland). (**4,7,9,12,15**) National Records of Scotland (NRS) population estimates. (**5**) Enhanced surveillance of E. coli bacteraemia Web Tool. (**11,13**) Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) (**14**) ECOSS (Electronic Communication of Surveillance in Scotland), Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit Public Health England (PHE) and the Scottish AMR Satellite Laboratory. (**17**) Small Animal Veterinary Surveillance Network (SAVSNET, 2015 to 2018. (**18,20**) Scotland's Rural College (SRUC) Veterinary Services and Capital Diagnostics. (**19**) MRSA reference laboratory (via SRUC).
Date that data were acquired	(**1**) Patient-based analysis 08/08/2019 (**1**) UTI analysis 17/06/2019 (**1**) PC Trend data 12/06/2019 (**1**) PC Duration of course analysis 30/07/2019 (**1**) PC Variation analysis 12/07/2019 (**1**) PC Antifungal analysis 02/07/2019 (**2,17**) 31/05/2019 (**3,6,8**) 13/08/2019 (**4,7,9,12,15**) 01/02/2019 (**5**) 04/09/2019 (**10**) May 2019 (**11,13**) August 2019 (**14**) 14/08/2019 (**16,20**) 09/10/2019 (**18,19,20**) 04/10/2019

Metadata indicator	Description
Timeframe of data and timeliness	(**1,3,4,6,7,8,9,12,15,18,20**) Data are for 2014 to 2018 and are timely for this report. (**2**) Data are for 2015 to 2018 and are timely for this report. (**5**) Data are for 2017 and 2018 and timely for this report. (**10**) The data are for 2013 to 2018 (from 2008 in appendix). (**11**) The data are for 2018 (from 2015 in appendix). (**13**) The data are for 2018 (from 2014 in appendix). (**14**) The data are from 2003 to 2018 and are timely for this report. (**16,20**) Number of cases from 1991 to 2018, AMR data 2018 only. Data to end of 2018 presented. (**17**) Data are for 2016 to 2018 and are timely for this report. (**19**) Data for 2018 and timely for this report.
Continuity of data	There are no discontinuities in the reporting period.
Revisions	(**1**) These data are not subject to planned major revisions. However, ISD and HPS aim to continually improve interpretation of data and therefore analysis methods are regularly reviewed and may be updated in future. (**2,3,5,6,8,10,11,13,14,16,17,19,20,21**) These data are not subject to planned major revisions. (**4,7,9,12,15**) As more administrative data sources become available and accuracy improves, changes to the methodology and projections will result. (**18***) These data are not subject to planned major revisions. *An erratum was issued in 2018 relating to a small number of penicillin non-susceptible *Streptococcus* spp. isolates derived from animals from 2012-2016. Careful review of information pertaining to these isolates has identified that they were wrongly classified as non-susceptible; they were in fact all susceptible to penicillin at the relevant break point.
Accuracy	(**1**) A subset of these data are routinely validated by Practitioner Services on a monthly basis. Data are extracted and analysed by two separate analysts. (**2**) Data are checked at HPS before analysed. (**3**) These data are supplied by Scottish Reference and Diagnostic laboratories who are accredited the UK's National Accreditation Body (UKAS). As secondary users of accredited clinical data we assume these data to be accurate. Enhanced ECB ECOSS web tool has built in validation rules. Data are checked at HPS before analysed. (**4,7,9,12,15**) Best available estimate.

Metadata indicator	Description
	(**5**) These data are validated on a quarterly basis. Enhanced ECB ECOSS web tool has built in validation rules. Data are checked at HPS before analysed. (**6,8,10,11,13,14,16,21**) Data are supplied by Scottish Reference and Diagnostic laboratories accredited by UKAS. As secondary users of accredited clinical data we assume these to be accurate. Data are checked at HPS before analysed. (**17**) Accreditation status of laboratories involved is unknown. Data are checked at HPS before analysed. (**18,19,20**) At SRUC bacteriology is accredited by UK Accreditation Service (UKAS) to International Organization for Standardization (ISO) 17025. Data are checked at HPS before analysed.
Completeness	(**1,4,7,9,12,15**) All data for the reporting period have been included in the analysis. (**2**) Database represents a non-random sample of veterinary practices based on voluntary submission of data to SAVSNET. (**3,6,8,14,16**) All data submitted by Scottish Reference and Diagnostic laboratories are included in the analysis. (**5**) Completeness is near to 100%. (**10**) Number of detections of *Neisseria gonorrhoeae*: Data are extracted from ECOSS which contains data from all local laboratories and the reference laboratory so completeness will be close to 100%. (**11**) Available for 52% of gonococcal episodes. (**13**) All isolates tested for genotypic resistance to antibiotic class. 18% of isolates were not able to be tested for fluoroquinolone resistance genes. (**17**) Database represents a non-random sample of veterinary practices based on voluntary submission of data to SAVSNET. (**18,20**) Database represents a non-random sample of veterinary practices and veterinary isolates, based on voluntary submission of data and/or samples to SRUC. (**19**) All data submitted by SRUC are included in the analysis. (**21**) All data submitted by Scottish Reference and Diagnostic laboratories are included in the analysis. All isolates are tested for AMR susceptibility.
Comparability	(**1**) The numerator for antibiotic use includes the number of WHO defined daily doses and is comparable to other antibiotic use surveillance programmes. (**2**) Comparable to prescribing databases from ISD.

Metadata indicator	Description
	(**3**) Data used are reported in the Health Protection Scotland Quarterly epidemiological Reports. Definitions applied to the antimicrobial susceptibility data are aligned with the ECDC EARS-Net definition and can be compared to similar data from Europe. (**4,7,9,12,15**) Standardised population projections comparable with other countries across years. (**5,6,8**) Data used are reported in the HPS Quarterly Reports. Definitions applied to the antimicrobial susceptibility data are aligned with the ECDC EARS-Net definitions. (**10**) ECOSS data were recently compared to the positive tests reported on the National Sexual Health System (NaSH) and are consistent with only very small differences in numbers. (**11**) Data for 2018 were based on EUCAST breakpoints which are used by most laboratories across Europe. (**13**) Data are not routinely collected at UK or international level. (**14**) Standardisation of testing for Carbapenemase Producing Organisms (CPO) in Scotland. (**16**) Salmonella spp. data from isolates from humans and animals are all provided by SSSCDRL, and are therefore tested in an identical manner, and are directly comparable across host species in Scotland. (**17**) Comparable to AMR databases at HPS. (**18**) SRUC data from healthy livestock animals are tested against a panel of antimicrobials, and at breakpoints, relevant to human clinical isolates so that AMR results are comparable (BSAC). (**19**) Standardisation of testing at MRSA reference laboratory. (**20**) SRUC data from healthy livestock animals are tested against a panel of antimicrobials, and at breakpoints, relevant to human clinical isolates so that AMR results are comparable (EUCAST). (**21**) *Salmonella* spp. data from isolates from humans and animals are all provided by SSSCDRL, and are therefore tested in an identical manner, and are directly comparable across host species in Scotland.
Value type and unit of measure	(**1,4,7,9,10,12,15**) Counts, number. (**2**) Counts, number of prescriptions. (**3,5,6,8,11,13,14,16,17,18,19,20,21**) Counts, number; Percentage of non-susceptible isolates over all tested isolates.

Metadata indicator	Description
Concepts and definitions	• (**1,2**) Prescribing data • (**1,2**) Occupied bed days – link 1, link 2 • (**1,2**) Prescribing time period - All trend data are reported for calendar years 2014 to 2018. Data before these time periods may be accessed via older reports. • (**1,2,4,6,7,8,9,12,14,15**) Population projections: to align with HAI Annual report, population projection as was available 02/2019 was used. • (**1,2,4,6,7,8,9,14,15**) Time Period • (**1,2**) Defined Daily Dose (DDDs, World Health Organisation (WHO)) • (**3,17**) SAVSNET website • (**3,17**) Description of the methods used by SAVSNET to capture electronic health records: Sánchez-Vizcaíno, F., et al. (2015) Small animal disease surveillance. Veterinary Record 177, 591-594. • (**3,17**) D.A. Singleton, et al. (2017) Patterns of antimicrobial agent prescription in a sentinel population of canine and feline veterinary practices in the United Kingdom. The Veterinary Journal, Volume 224, Pages 18-24. • (**4**) Health Protection Scotland Quarterly epidemiological data on *Clostridioides difficile* infection*, Escherichia coli* bacteraemia*, Staphylococcus aureus* bacteraemia and Surgical Site Infection in Scotland. The definitions applied to the incidence data can be accessed here. The surveillance methods and caveats can be accessed here. • (**4,8,9**) Definitions applied to the antimicrobial susceptibility data are aligned with ECDC EARS-Net. The definitions applied to the antimicrobial susceptibility data can be accessed here. • (**5**) *E. coli* bacteraemia surveillance. • (**5**) The surveillance methods and caveats can be accessed here. • (**6,7**) The case definition as applied to bacteraemia also applies here: a laboratory confirmed blood sample, counting one positive in every 14 days. More information here. • (**6,7**) Definitions applied to the antimicrobial susceptibility data are aligned with ECDC EARS-Net. The definitions applied to the antimicrobial susceptibility data can be accessed here. • (**6,7,14,15,16,21**) UKAS • (**8,9**) A case or E. coli or K. pneumoniae UTI is defined as a culture positive urine sample, counting one positive in every 14 days aligning with the incidence definition used here. • (**10,11,12**) Further information can be found here. The data associated with the laboratory positive diagnoses are restricted to age, gender and the NHS board where the clinical specimen originated. All positive tests from the same individual in a 6-week period are considered to be from the same episode.

Metadata indicator	Description
	• (**13**) Data are provided by the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory from individuals tested for *M. genitalium* infection which meet strict criteria and therefore represent a small proportion of the true number of infections in Scotland. Macrolide and quinoline resistance in clinical specimens is determined by Sanger sequencing. • (**14,15**) Case definitions can be accessed here. • (**16,21**) Annual summary of Salmonella infections can be found here. • (**18,19,20**) Data presented here represent the percentage of non-susceptible isolates over all tested isolates. These isolates are from healthy livestock animals and are tested against a panel of antimicrobials, and at breakpoints, relevant to human clinical isolates. Database represents a non-random sample of veterinary practices and isolates, based on voluntary submission of data and/or samples to SRUC.

Appendix 3 – Early access details

Pre-Release Access

Under terms of the "Pre-Release Access to Official Statistics (Scotland) Order 2008", HPS is obliged to publish information on those receiving Pre-Release Access ("Pre-Release Access" refers to statistics in their final form prior to publication). The standard maximum Pre-Release Access is five working days. Shown below are details of those receiving standard Pre-Release Access.

Standard Pre-Release Access:

Scottish Government Health Department

NHS Board Chief Executives

NHS Board Communication leads

Appendix 4 – HPS and Official Statistics

About HPS

HPS is a division of NHS National Services Scotland which works at the very heart of the health service across Scotland, delivering services critical to frontline patient care and supporting the efficient and effective operation of NHS Scotland.

HPS was established by the Scottish Government in 2005 to strengthen and coordinate health protection in Scotland. It is organised into three specialist groups with expertise provided by a multi-disciplinary workforce which includes doctors, nurses, scientists and information staff, all of whom are supported by core business teams. The specialist groups are:

- Antimicrobial Resistance Healthcare Associated Infections;
- Blood Borne Viruses and Sexually Transmitted Infections, Immunisation, and Respiratory and Vaccine Preventable Diseases;
- Environmental Public Health, Gastrointestinal and Zoonoses, Travel and International Health.

Official Statistics

Our official statistics publications are produced to a high professional standard and comply with the Code of Practice for Official Statistics. The Code of Practice is produced and monitored by the UK Statistics Authority which is independent of Government. Under the Code of Practice, the format, content and timing of statistics publications are the responsibility of professional staff working within NHS National Services Scotland.

Our statistical publications are currently classified as one of the following:

- National Statistics (i.e. assessed by the UK Statistics Authority as complying with the Code of Practice)
- National Statistics (i.e. legacy, still to be assessed by the UK Statistics Authority)
- Official Statistics (i.e. still to be assessed by the UK Statistics Authority)
- other (not Official Statistics)

Further information on NHS National Services Scotland's statistics, including compliance with the Code of Practice for Official Statistics, and on the UK Statistics Authority, is available on the ISD website.

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