Veterinary Medicines Directorate

UK Veterinary Antibiotic Resistance and Sales Surveillance Report

UK-VARSS 2021

Published November 2022

Suggested citation: UK-VARSS (2022). *Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2021)*. New Haw, Addlestone: Veterinary Medicines Directorate.

This publication is available online. Any enquiries or correspondence regarding this publication should be sent to us at: postmaster@vmd.gov.uk.

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Acknowledgements

This report is issued by the VMD. The veterinary antibiotic resistance and sales data monitoring programmes are commissioned and funded by the VMD. Data for the sales section are produced by the VMD. Data for the antibiotic resistance section are produced and collated by the APHA, Angela Lahuerta-Marin (Agri-Food Biosciences Institute) and Geoff Foster (SRUC Veterinary Services). We are grateful to the following parties for collecting and sharing usage data with the VMD: Agriculture and Horticulture Development Board Pork (pigs), British Poultry Council (meat poultry), British Egg Industry Council (laying hens), Game Farmers' Association/British Veterinary Poultry Association gamebird subcommittee/ Agricultural Industries Confederation (gamebirds), British Trout Association (trout) and Salmon Scotland (salmon). We would also like to thank Starcross laboratory for providing the MIC data. We would like to thank Sannah Malik of the VMD for her support and contribution to the production of this report.

Published on 8th November 2022

Contents

Foreword

Publication of this year's UK-VARSS report comes hot on the heels of the case study "Tackling antimicrobial resistance in food-producing animals: Lessons learned in the United Kingdom of Great Britain and Northern Ireland". This tells the story of how the UK halved its use of antibiotics in animals, the course of which can also be traced in the results published over successive UK-VARSS reports. The UK country case study is the third in a series published by the Food and Agriculture Organisation (FAO) of the UN, and is testament to the drive, ambition and tenacity of dedicated people across the agriculture sector, veterinary profession, and countless other sectors who brought about this remarkable achievement.

While the years of dramatic reductions have passed, this year's UK-VARSS report continues to document downward trends in sales of veterinary antibiotics in the UK. Veterinary antibiotic sales overall, and sales of antibiotic classes which are of critical importance to human health, both reduced by a small amount to reach new lowest recorded levels for the UK at 28.3 mg/kg and 0.12 mg/kg, respectively.

Underpinning this national sales dataset is the usage chapter, which shows more diversity in trends. Nevertheless, there are some impressive results such as the pig sector's reduction in antibiotic usage from 105 to 87 mg/kg since last year. Even where reductions have proved more elusive, measuring and reporting usage data is providing a crucial step for understanding emerging trends and galvanising action where action is needed.

In the resistance chapters, a rise in one parameter in our harmonised monitoring programme stands out against otherwise broadly improving resistance parameters for pigs. While we have seen an encouraging increase in fully susceptible *E. coli* and a decrease in *E. coli* resistant to three or more classes of antibiotics, the percentage of pigs carrying ESBL/AmpC-producing *E. coli*, bacteria which are resistant to third generation cephalosporins, has increased. We haven't seen an increase in resistance to third generation cephalosporins in *E. coli* from pigs in our clinical surveillance programme, where this resistance remains low to very low. It is difficult to explain this ESBL/AmpC *E. coli* result, particularly given the continued year-on-year reductions in antibiotic usage in the pig sector, including further reductions in HP-CIA use, and a downwards trend for this resistance in previous years. We are conducting further investigations in order to better understand it.

Since the last report there have been a number of updates and improvements to the surveillance programmes described in chapters 3 and 4:

One significant change in the harmonised monitoring is the move from taking carcase swabs to measure AMR in *Salmonella* from pigs, to taking samples from caecal contents. Sampling from the gut yields many more isolates, which gives us a much better and more

reliable picture of AMR in *Salmonella* in healthy pigs at slaughter. This is the first year sampling this way, but it will allow us to monitor trends in coming years.

In the clinical surveillance chapter, many more *Salmonella* isolates from dogs were reported, following a legislative change which came into effect in 2021: the Zoonoses Order was amended to make the reporting of *Salmonella* from dogs statutory in England from 22 February 2021 and in Scotland and Wales from 21 April 2021. In this first year, 821 *Salmonella* isolates from dogs were tested for AMR, of which 34.6% were resistant to one or more antibiotics in the panel. Resistance in *Salmonella* isolates from dogs was higher than in several food producing species (cattle, sheep, chickens). This, again, is the first year of reporting at these higher numbers but will allow us to monitor trends in AMR in *Salmonella* in dogs in future years.

Finally, we have continued the expansion of MIC testing of veterinary pathogens from the clinical surveillance programme to *Streptococcus suis* (pigs), *Streptococcus uberis* (bovine mastitis samples) and clinical *E. coli* isolated from chickens.

Surveillance of antibiotic consumption and antibiotic resistance is one of the central pillars of the work we do on AMR. It has the potential to be more valuable still as we strive to continuously enhance our own surveillance programmes, and to link them with similar programmes in people, food, the environment and beyond. There are a several cross-cutting initiatives at present which aim to do just that, and I very much look forward to the publication of the 'Third UK One Health Report' on antibiotic use, sales and antibiotic resistance covering human, animal and food datasets, which will be published next year.

AMR is, and has always been, a threat whose reach extends within and across sectors in complex ways. It is only by working together that we can hope to better understand how our efforts to tackle AMR in one sector affect the whole picture.

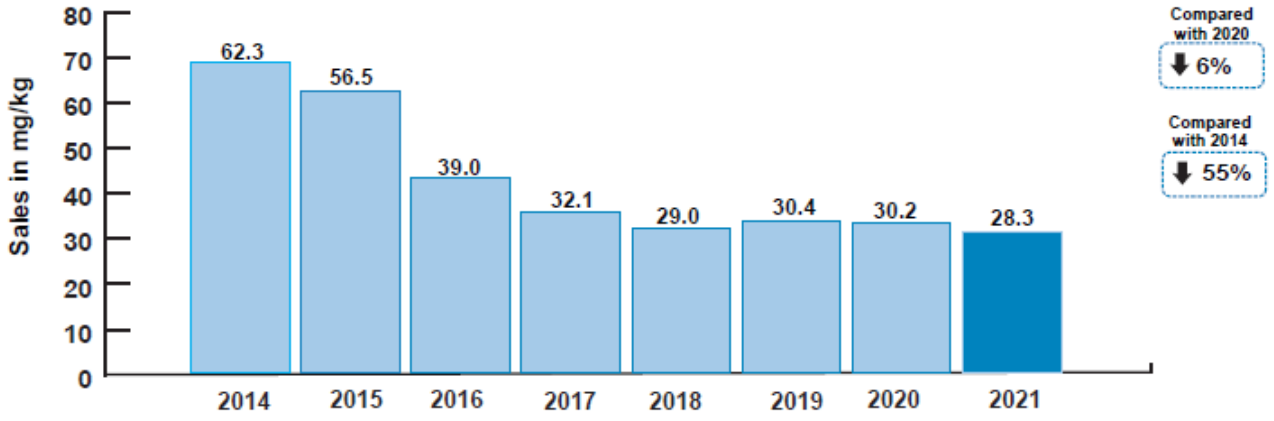
Dr Kitty Healey BVSc PhD MRCVS
Head of Surveillance Division, Head of Antimicrobial Resistance

Highlights

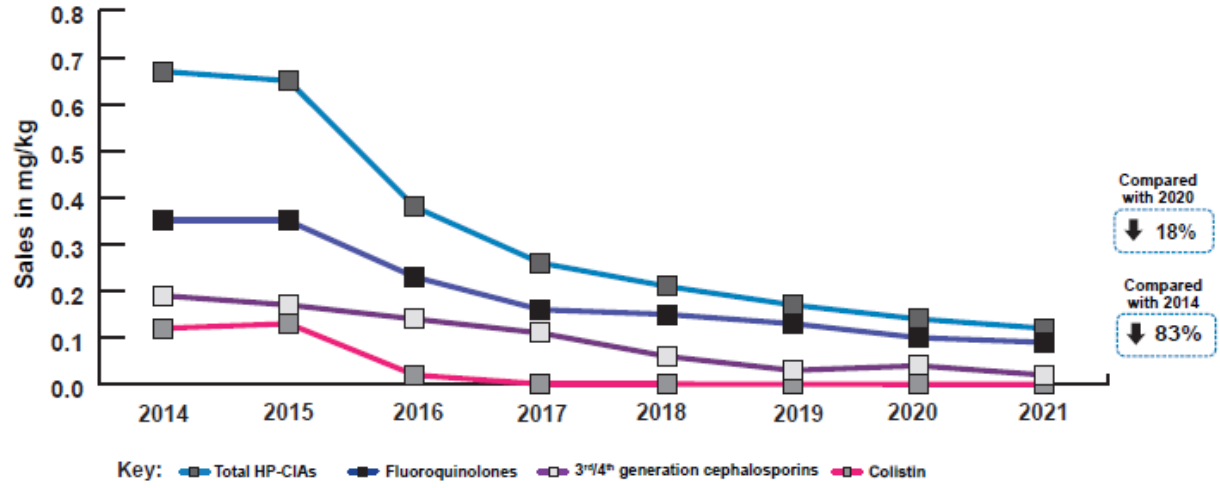
Antibiotic sales

Sales for food-producing animals (mg/kg)

Sales of veterinary antibiotics for use in food-producing animals, adjusted for animal population, were 28.3 mg/kg; a 2.0 mg/kg (6%) decrease since 2020 and an overall 34 mg/kg (55%) decrease since 2014. This represents the lowest sales to date.



Sales of Highest Priority Critically Important Antibiotics (HP-CIAs) in food-producing animals account for 0.4% of total sales and have dropped from 0.14 mg/kg in 2020 to 0.12 mg/kg in 2021; an 18% decrease since 2020.

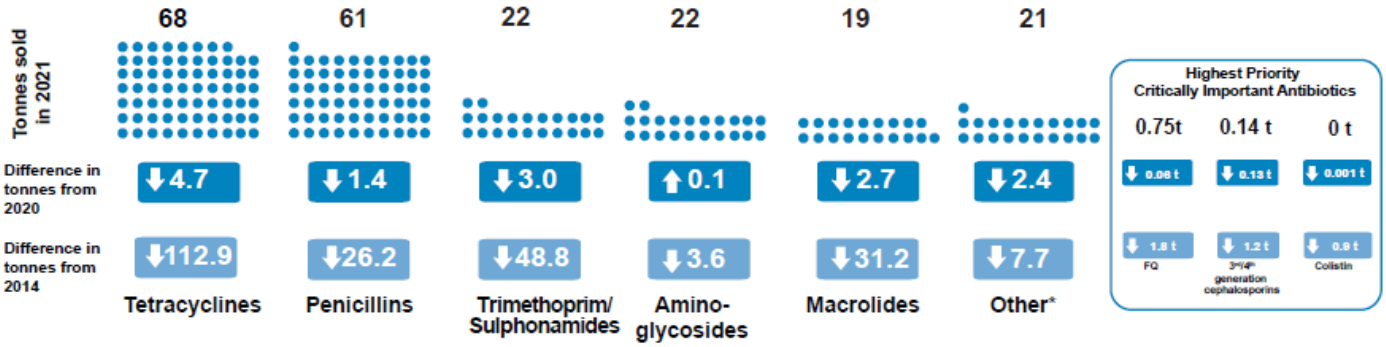


Sales for all animals (tonnes)

In 2021 the total quantity of antibiotic active ingredient sold in the UK was 212 tonnes, the lowest sales to date.

	2014	2015	2016	2017	2018	2019	2020	2021	Compared with 2014	Compared with 2020
Total sales (all animals tonnes)	447	406	293	246	223	229	227	212	⬇ 52%	⬇ 6%

Sales of HP-CIAs reduced by a further 0.19 tonnes (18%) from an already low level; a drop of 3.9 tonnes (81%) since 2014. Tetracyclines remain the most sold antibiotic class (32%), followed by penicillins (29%). Sales of HP-CIAs in all animal species represent a small proportion (0.4%) of total veterinary antibiotic sales.



● = 1 tonne
t = tonnes
FQ = fluoroquinolones
* Includes amphenicols, lincomycins, pleuromutilins, 1st and 2nd cephalosporins, imidazole derivatives and aminocoumarins

Antibiotic Usage

Antibiotic usage refers to the amount of antibiotics prescribed and/or administered per sector. The data have been collected and provided to the VMD by the animal industry on a voluntary basis.

Antibiotic usage by food-producing animal species

	Total coverage %*	2021 Usage**	Change since last year	Trends since data first published
Pigs	>95	87.3 mg/kg	↓ 17.7 mg/kg	↓ 69% since 2015
Turkeys	90	42.6 mg/kg	↑ 16.8 mg/kg	↓ 81% since 2014
Broilers		13.7 mg/kg	↓ 2.6 mg/kg	↓ 72% since 2014
Ducks		1.7 mg/kg	↓ 0.9 mg/kg	↓ 89% since 2014
Laying hens	90	0.33 % bird days	↓ 0.14 % bird days	↓ 50% since 2016
Gamebirds	91	8.9 tonnes	↑ 3.2 † tonnes	↓ 55% since 2016
Salmon	100	43.1 mg/kg	↑ 13.8 mg/kg	↑ 168% since 2017
Trout	90	5.9 mg/kg	↓ 7.9 mg/kg	↓ 69% since 2017

Highest Priority Critically Important Antibiotics by food-producing animal species

	Total coverage %*	2021 Usage**	Change since last year	Trends since data first published
Pigs	>95	0.03 mg/kg	↓ 0.02 mg/kg	↓ 97% since 2015
Meat Poultry	90	0.05 mg/kg	↑ 0.04 mg/kg	↓ 96% since 2014
Gamebirds	90	26.5 kg	↑ 5.0† kg	↓ 59% since 2016
Trout	90	2.1 mg/kg	↓ 2.1 mg/kg	↓ 68% since 2017

* Represents the % animals covered by the data, except gamebirds which represents an estimate of the total % antibiotics sales
** mg/kg relates to the amount of active ingredient standardised by kg biomass and calculated using ESVAC methodology, % doses refers to 'actual daily bird-doses/100 bird-days at risk'
† Note that industry estimates suggest that, due to Covid restrictions, gamebird rearing reduced by 30% during 2020

Antibiotic Resistance in Zoonotic and Commensal Bacteria from Healthy Animals at Slaughter

Resistance in *Escherichia coli* from pigs

The UK can report mostly decreasing trends of AMR in indicator *E. coli* from healthy pigs at slaughter since 2015. Of the HP-CIAs, resistance to third generation cephalosporins is low* and has declined since 2019; resistance to the fluoroquinolone ciprofloxacin has increased since 2015 but remains at low levels; and resistance to the quinolone nalidixic acid has remained low since 2015. No resistance has been detected to colistin over the monitoring period.

In 2021, the percentage of pig caecal samples positive for ESBL- or AmpC- producing *E. coli* on selective media reached the highest level seen so far during this monitoring programme, at 18.1% and 12.0% of samples respectively (30.1% combined). This result is unexpected and is being investigated further. No isolates were positive for both phenotypes, and no carbapenemase-producing *E. coli* were detected during the monitoring period.

* Description of percentage resistance referenced: rare (<0.1%), very low (0.1% to 1%), low (>1% to 10%), moderate (>10% to 20%), high (>20% to 50%), very high (>50% to 70%), extremely high (>70%)

Resistance in *Salmonella* spp. from pigs

This year is the baseline year for testing the resistance of *Salmonella* isolates from caecal samples (rather than carcase swab samples). Of the HP-CIAs, no resistance was detected to third generation cephalosporins or colistin. Resistance to quinolones, including fluoroquinolones, was detected at low levels.

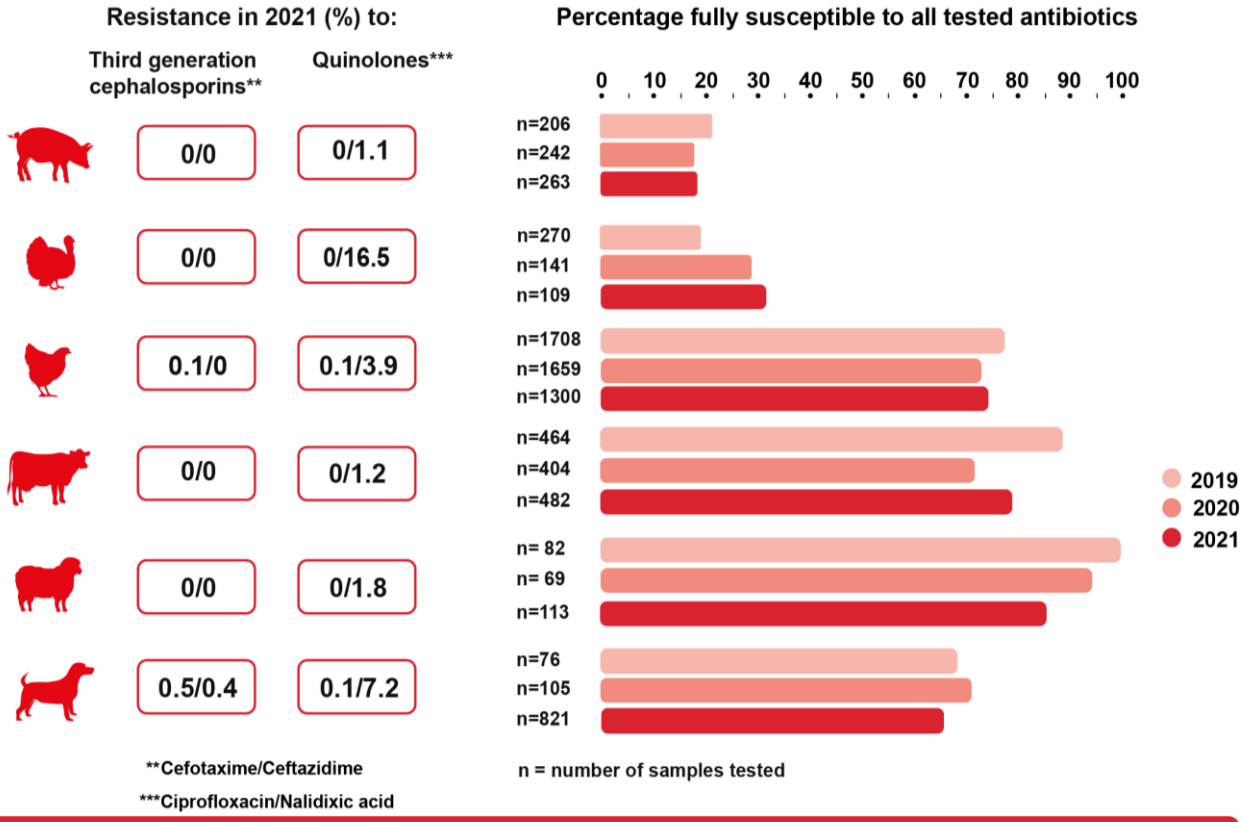
Antibiotic Resistance - Clinical Surveillance

Resistance in *Escherichia coli*

Of the HP-CIAs, resistance to fluoroquinolones and third generation cephalosporins was low or not detected in 2021 for all animal species. Resistance to HP-CIAs has generally not increased for any of the animal species tested.

Resistance in *Salmonella* spp. from animals and their environment

Of the 4,507 *Salmonella* isolates tested, 67.5% were susceptible to all of the antibiotics tested. The number of *Salmonella* isolates from cattle, pigs, chickens and turkeys fully susceptible to the panel of antibiotics tested increased in 2021. No resistance to third generation cephalosporins or fluoroquinolones was detected in cattle, pigs, sheep and turkeys. In chickens, resistance to third generation cephalosporins and fluoroquinolones was very low* (0.1% for both). Resistance to ciprofloxacin was detected in 11 isolates: one from chickens, one from a dog, and nine isolates from feed. A change to legislation in 2021 meant that *Salmonella* isolates from dogs became reportable under the Zoonoses Order in Great Britain. Of the 821 isolates tested, 34.6% were resistant to at least one antibiotic in the panel.



MIC testing of veterinary pathogens

Following the introduction of MIC testing for key veterinary bacterial pathogens against commonly used clinical antibiotics in 2020, as an enhancement of the clinical surveillance programme, additional pathogens have been added to the core range in 2021. This testing improves the usefulness of our AMR surveillance and also helps vets make better prescribing choices. Many isolates were fully susceptible to the panel of antimicrobials tested. Resistance was uncommon or not detected amongst antimicrobials which are often used as second or third line treatment options.

Introduction

The Veterinary Antibiotic Resistance and Sales Surveillance report of the United Kingdom (UK-VARSS) presents combined data on veterinary antibiotic sales and antibiotic resistance in bacteria from food-producing animals in the UK.

The antibiotic sales data from 2014 to 2021 are presented in **Chapter 1** and are based on sales of antibiotic veterinary medicinal products authorised for use in animals in the UK. Sales data are generally used as an estimate for antibiotic usage. The first report on sales figures for antibiotic veterinary medicinal products, collated and published by the Veterinary Medicines Directorate (VMD), covered 1993 to 1998. The figures were provided voluntarily by the veterinary pharmaceutical companies marketing these products. Since 2005, sales data are collected as a statutory requirement (Veterinary Medicines Regulations), and in 2014 the first Veterinary Antibiotic Resistance and Sales Surveillance (VARSS) report was published for the UK (presenting data from 2013).

However, many antibiotics are authorised for use in multiple animal species, and it is not possible to determine from sales data how much is used in each species. The UK-VARSS report has increasingly included data on usage in different animal production sectors and works in partnership with the livestock industry to develop, facilitate and coordinate antibiotic usage data collection systems. These data are reported voluntarily by the livestock sectors and are presented in **Chapter 2**.

While the term antimicrobial resistance (AMR) encompasses resistance of different types of organisms (bacteria, viruses, fungi, and parasites) to the drugs used to treat them, it is used throughout this report to refer to bacterial resistance to antibiotics specifically. The VMD collates data from government laboratories on antibiotic resistance in bacteria obtained from food-producing animals, which are collected under the framework of two surveillance schemes. These include zoonotic bacteria, which are an integral part of our AMR surveillance, due to the potential for resistant bacteria and/or resistance genes found in animals to transfer to people. Results from the harmonised monitoring scheme, which monitors AMR in healthy animals at slaughter, are presented in **Chapter 3.** Results from the scanning surveillance programme, which is based on diagnostic submissions, are presented in **Chapter 4**; these results reflect AMR in bacteria causing disease in animals.

Details on methodology and results not presented in the report are included in the Supplementary Materials. The Supplementary Materials and previous UK-VARSS reports are available to download at https://www.gov.uk/government/collections/veterinary-antimicrobial-resistance-and-sales-surveillance.

For additional context whilst reading the report, please see below 1) a table containing a list of all antibiotics referred to throughout the report split by those authorised and not authorised for use in animals and 2) a table of descriptions used throughout the resistance chapters used when referring to resistance levels.

Table 1: Antibiotics referred to throughout the report, grouped by antibiotic class.

Antibiotic class	Authorised for use in animals	Not authorised for use in animals
Aminoglycosides	Apramycin, gentamicin, kanamycin, neomycin, spectinomycin, streptomycin	Amikacin
Amphenicols	Florfenicol	Chloramphenicol
Beta-lactams: 1st generation cephalosporins	Cefalexin, cefapirin	
Beta-lactams: 3rd generation cephalosporins	Ceftiofur, cefovecin	Cefotaxime, cefpodoxime, ceftazidime
Beta-lactams: Carbapenems		Ertapenem, imipenem, meropenem
Beta-lactams: Penicillins	Amoxicillin, amoxicillin/clavulanate, ampicillin, cloxacillin, phenoxymethylpenicillin	Temocillin
Glycylcyclines		Tigecycline
Lincosamide	Lincomycin, clindamycin, pirlimycin	
Macrolides	Erythromycin, gamithromycin, spiramycin, tildipirosin, tilmicosin, tulathromycin, tylosin	Azithromycin
Polymyxins	Colistin	
Quinolones	Enrofloxacin, marbofloxacin, oxolinic acid	Nalidixic acid, ciprofloxacin
Tetracyclines	Doxycycline, oxytetracycline, tetracycline	
Trimethoprim/ sulphonamides	Sulfamethoxazole, trimethoprim	
Other	Novobiocin, tiamulin	Furazolidone

Table 2: Descriptions of percentage resistance levels referenced in this report (Chapters and 4), using the EFSA definitions.

Description of resistance level	Equivalent percentage resistance range
Rare	<0.1%
Very low	0.1% to 1%
Low	>1% to 10%
Moderate	>10% to 20%
High	>20% to 50%
Very high	>50% to 70%
Extremely high	>70%

CHAPTER 1
Sales of veterinary antibiotics

1.1 Summary

UK sales of veterinary antibiotics for food-producing animals in 2021 were the lowest recorded to date: 28.3 mg/kg, adjusted for animal population. This represents a 6% (2.0 mg/kg) decrease from 2020 and a 55% (34.0 mg/kg) decrease from 2014. Sales of Highest Priority Critically Important Antibiotics (HP-CIAs) for food-producing animals reduced for the seventh consecutive year and were 0.12 mg/kg in 2021, a reduction of 83% (0.6 mg/kg) since 2014 and accounting for 0.4% of the total antibiotic sales.

When considering sales for all animals, the total quantity of antibiotics sold during 2021 was 212.4 tonnes, the lowest recorded. This represents a 6% (14.3 tonne) decrease since 2020, and a 52% (234.2 tonne) decrease since 2014. Sales of HP-CIAs were 0.9 tonnes, representing 0.4% of total sales, and have reduced by 81% (3.9 tonnes) since 2014. For the first time, no colistin was sold for use in animals in 2021.

1.2 Introduction

Pharmaceutical companies have reported the quantity of authorised veterinary antibiotics sold throughout the UK to the VMD since 1993; this has been a statutory requirement since 2005 (see section S1.1 in Supplementary Material 1 for further details). The data reported in this chapter do not take into account wastage, imports or exports of veterinary antibiotics, but they serve as the best currently available approximation of the quantity of antibiotics administered to all animal species within the UK (further details on data limitations can be found in Annex B).

Data have been analysed using European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) methodology.

Note that, for ease of reading, the data has been rounded to one decimal place. However, the percentage changes have been calculated using the exact number. Antibiotics were considered HP-CIAs if they are within “Category B” in the Antimicrobial Expert Group (AMEG) report, i.e. third and fourth generation cephalosporins, polymyxins (e.g. colistin) and quinolones/fluoroquinolones. Data has been presented graphically throughout, but full datasets can be found in Supplementary Material 2.

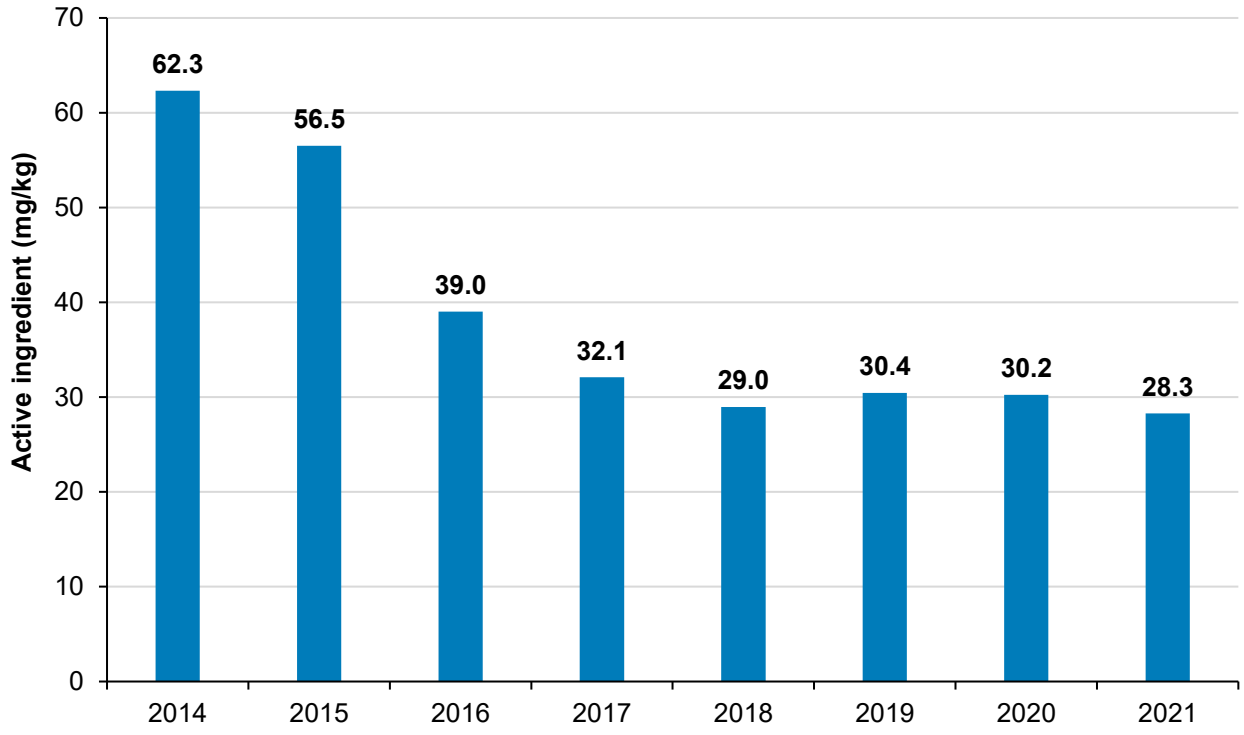
1.3 Results and discussion

1.3.1 Sales of antibiotics for food-producing animal species (mg/kg)

1.3.1.1 Total sales for food-producing animals (mg/kg)

The sales of antibiotics for food-producing animal species in 2021 were 28.3 mg/kg, the lowest recorded figure to date, and a decrease of 2.0 mg/kg (6%) since 2020 and 34.0 mg/kg (55%) since 2014 (**Figure 1.1**).

Figure 1.1: Active ingredient adjusted for population (mg/kg) of antibiotics sold for use in food-producing animals, 2014 to 2021.



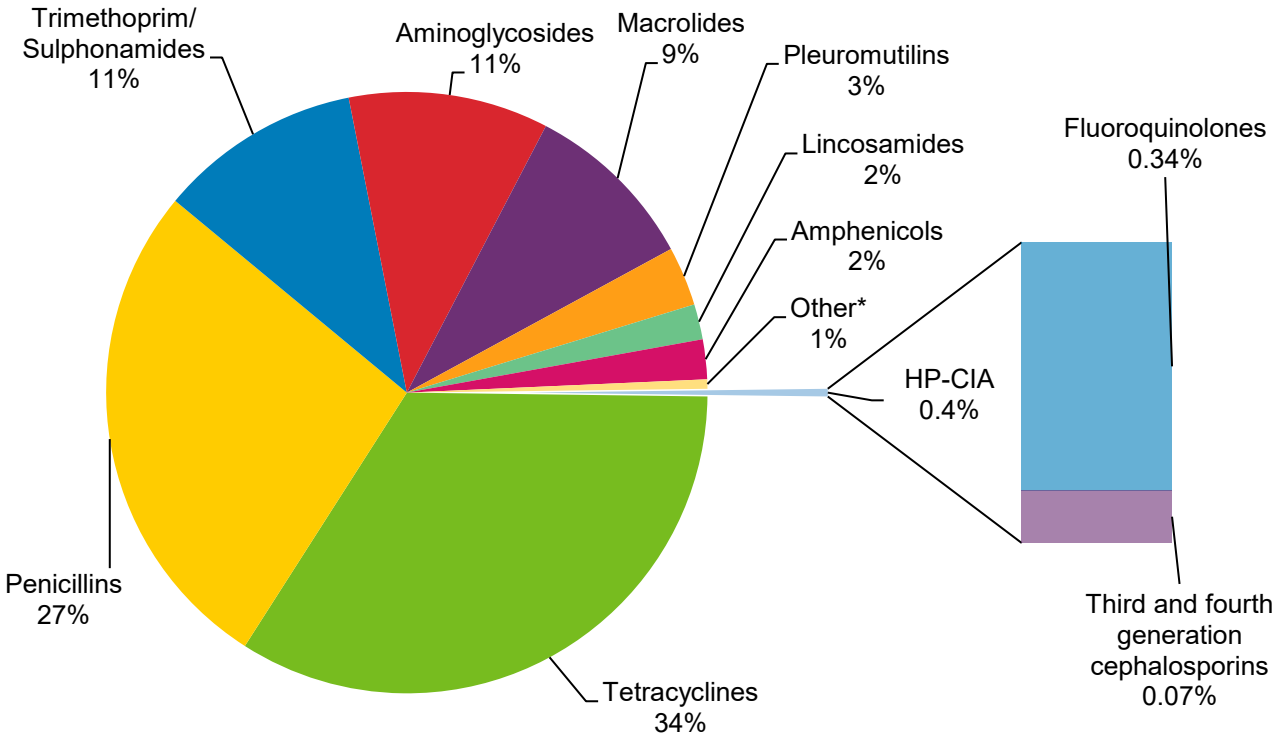
1.3.1.2 Sales by antibiotic class for food-producing animals (mg/kg)

The sales of all antibiotic classes for food producing animals decreased between 2020 and 2021 (**Figure 1.3**), except for aminoglycosides and amphenicols, which remained stable. Tetracyclines and penicillins were the most sold antibiotic classes (**Figure 1.2**) and sales of these classes decreased between 2020 and 2021, by 0.6 mg/kg (6%) and 0.4 mg/kg (4%) respectively. Since 2014, tetracycline sales for food-producing animals have reduced by 16.5 mg/kg (63%) whereas penicillins have fallen to a lesser degree, by 3.8 mg/kg (33%). Since 2018, penicillin sales have increased by 0.9 mg/kg (13%), which has been driven by a 0.8 mg/kg (25%) increase in sales of in-water penicillin products.

Sales of HP-CIAs for food-producing animals are shown in **Figure 1.4**. Sales of HP-CIAs for food-producing animals were 0.12 mg/kg, which represents 0.4% of the overall antibiotic sales, and is a reduction of 0.02 mg/kg (18%) since 2020. HP-CIA sales for food-producing animals have decreased for the seventh consecutive year, with total reductions of 0.6 mg/kg (83%) since 2014.

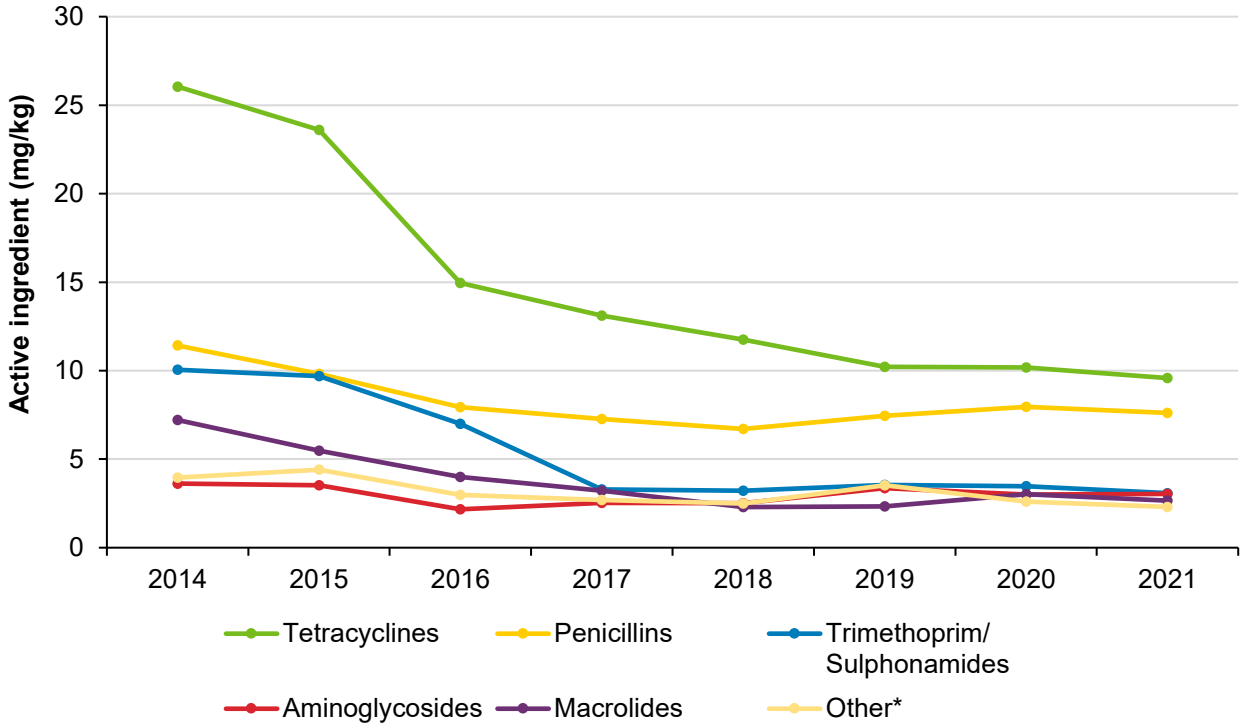
Between 2020 and 2021, third and fourth generation cephalosporin sales reduced by 0.02 mg/kg and fluoroquinolone sales reduced by 0.01 mg/kg, with both at their lowest recorded figures to date. For the first time ever, no colistin was sold in the UK for use in animals in 2021.

Figure 1.2: Active ingredient (% weight) of antibiotics by antibiotic class sold for use in food-producing animals, 2021.



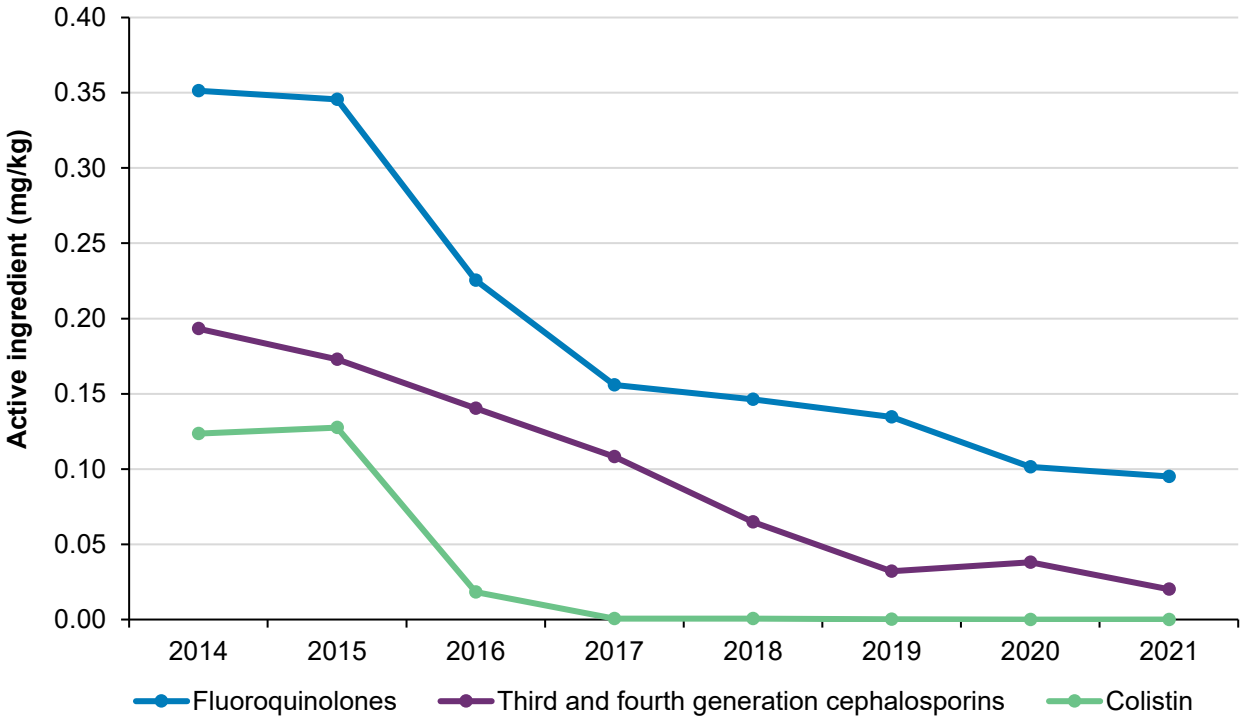
* First and second generation cephalosporins and imidazole derivates

Figure 1.3: Active ingredient adjusted for population (mg/kg) of non-HP-CIA antibiotics by antibiotic class sold for use in food-producing animals, 2014 to 2021.



*Pleuromutilins, lincosamides, amphenicols, first and second generation cephalosporins, imidazole derivates, aminocoumarins.

Figure 1.4: Active ingredient adjusted for population (mg/kg) of HP-CIAs sold for use in food-producing animals, 2014 to 2021.

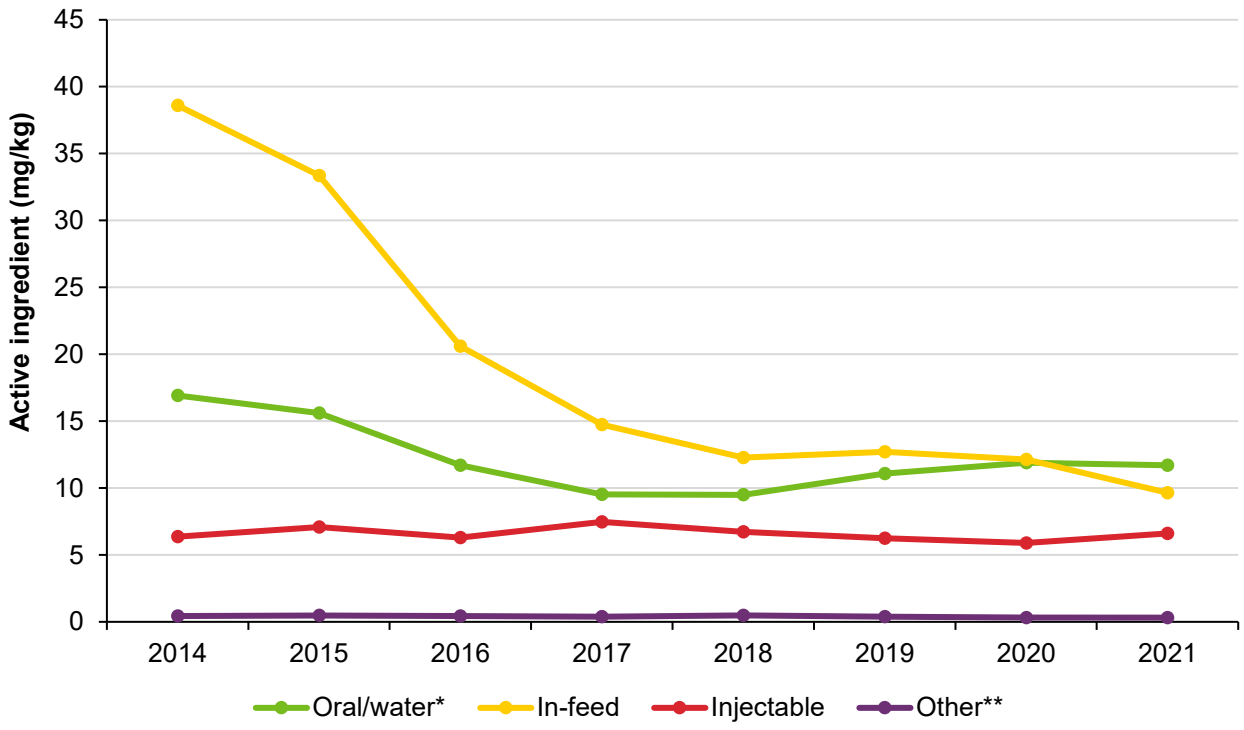


1.3.1.3 Sales by route of administration for food-producing animals (mg/kg)

When considering route of administration for antibiotics for food-producing animals in 2021 (excluding topicals), 41% is indicated for oral/water use and 34% is for in-feed use (**Figure 1.6**). In-feed use refers to premix products, whereas oral/water products refer to oral powders, pastes, solutions, and bolus preparations. Between 2020 and 2021, sales of in-feed products decreased by 2.5 mg/kg (20%) (**Figure 1.5**) whereas sales of oral/water decreased to a lesser degree, by 0.2 mg/kg (2%). Oral/water sales have increased as a percentage of total use every year from 27% in 2014 to 41% in 2021 and, for the first time, oral/water has overtaken in-feed as the most sold route of administration with the highest sales for food producing animals. This change is in line with an industry focus on encouraging more in-water use, which can allow for more targeted antibiotic administration than in-feed.

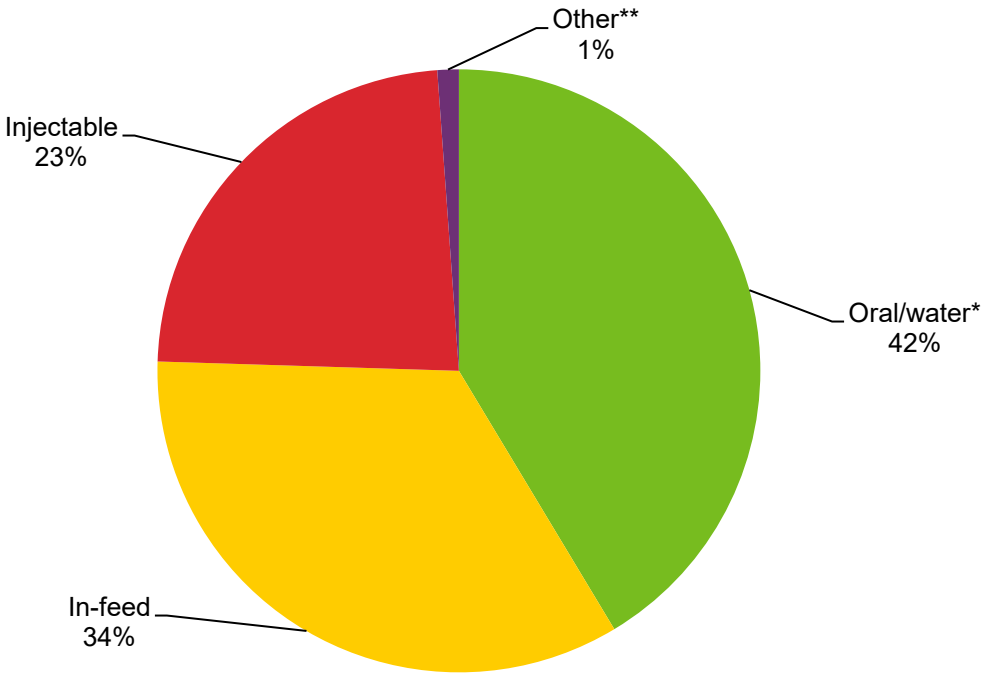
Sales of injectables were 6.6 mg/kg in 2021 (23% of sales for food-producing animals).This has increased by 0.7 mg/kg (12%) since 2020 and 0.2 mg/kg (4%) since 2014, which may reflect a move towards more individual animal treatments. Individual injectable treatments are considered to have a lesser risk of contributing to development of antimicrobial resistance compared to other routes of administration.

Figure 1.5: Active ingredient (mg/kg) of antibiotics by route of administration sold for use in food-producing animals, 2014 to 2021.



* Oral powders, oral pastes, oral solutions, and bolus preparations.
** Includes intramammary dry and lactating cow, and intrauterine preparations.

Figure 1.6: Active ingredient (% weight) of antibiotics by route of administration sold for use in food-producing animals, 2021.



* Oral powders, oral pastes, oral solutions, and bolus preparations.
** Includes intramammary dry and lactating cow, and intrauterine preparations.

1.3.1.4 Sales of intramammary antibiotic products (course doses)

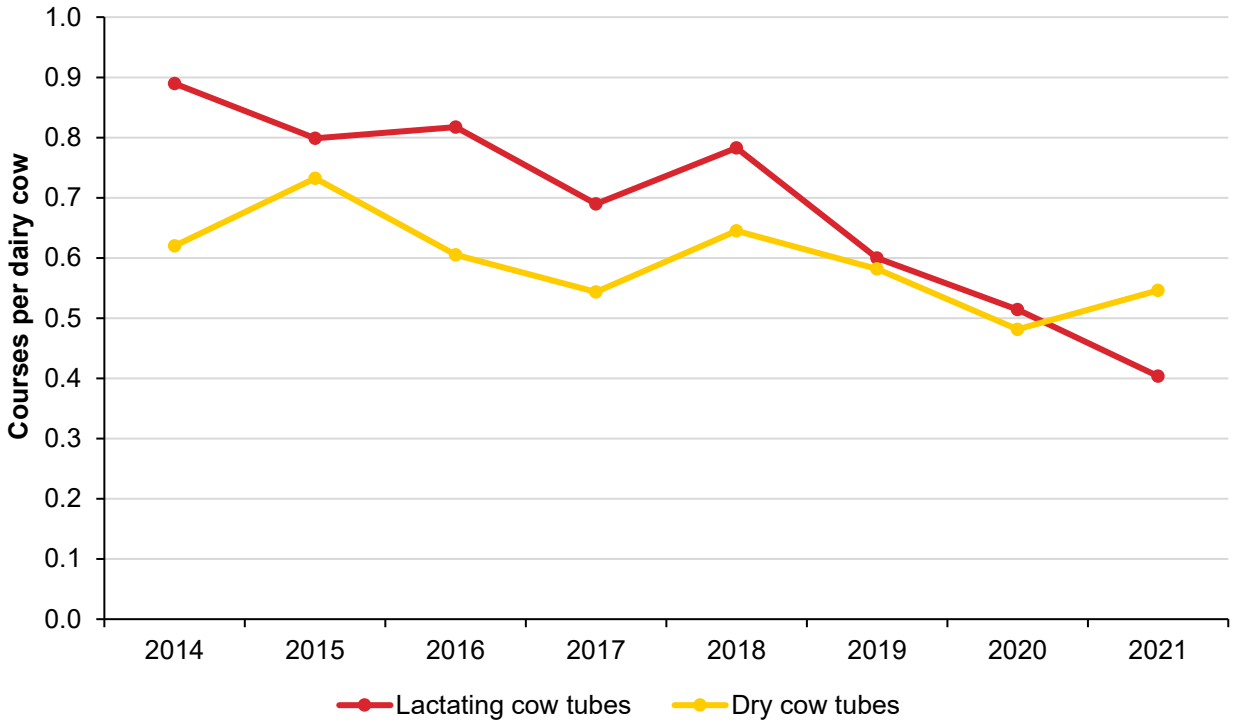
Sales of dry and lactating cow products analysed using the ESVAC defined course dose methodology (DCDvet) are shown in **Figure 1.7**. The DCDvet represents the average number of courses per dairy cow using a standard course dose of four tubes per dry cow and three tubes for lactating cow treatments.

Between 2020 and 2021, sales of lactating cow products reduced by 0.11 course doses (21%). By contrast, sales of dry cow products increased by 0.06 course doses (13%) but remain below the 2019 usage levels. As reported in last year's UK-VARSS report, sales of HP-CIA intramammary products increased by 0.04 course doses between 2019 and 2020; however, between 2020 and 2021 there was a decrease of 0.06 course doses (78%) to 0.02 course doses, the lowest figure to date.

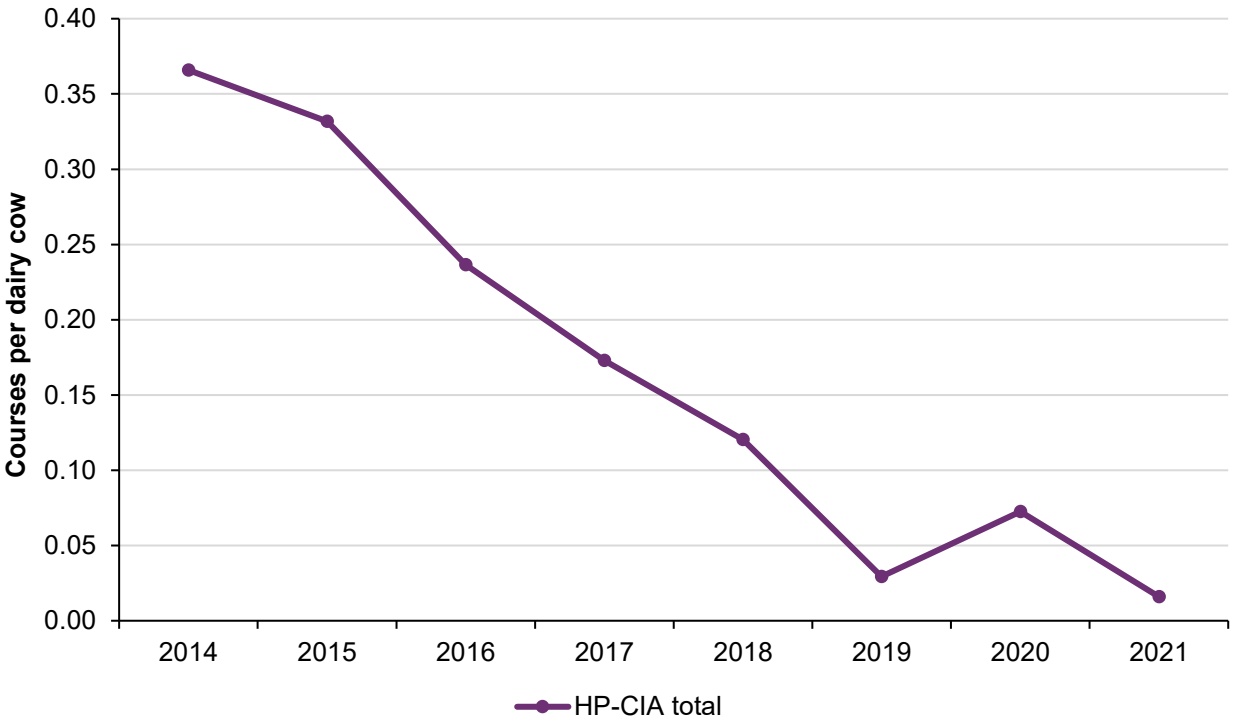
It should be noted that there were availability problems with lactating cow intramammary products in 2021, which may have affected product choice. Additionally, if the available products were considered clinically unsuitable by the veterinary surgeon, alternative products authorised outside the UK can be imported on a case-by-case basis under the Special Import Scheme. These products are not captured in the antibiotic sales data.

Figure 1.7: Sales of (A) dry and lactating cow intramammary products (courses per dairy cow), 2014 to 2021, (B) Sales of HP-CIA intramammary products (courses per dairy cow, 2014 to 2021.

(A)



(B)

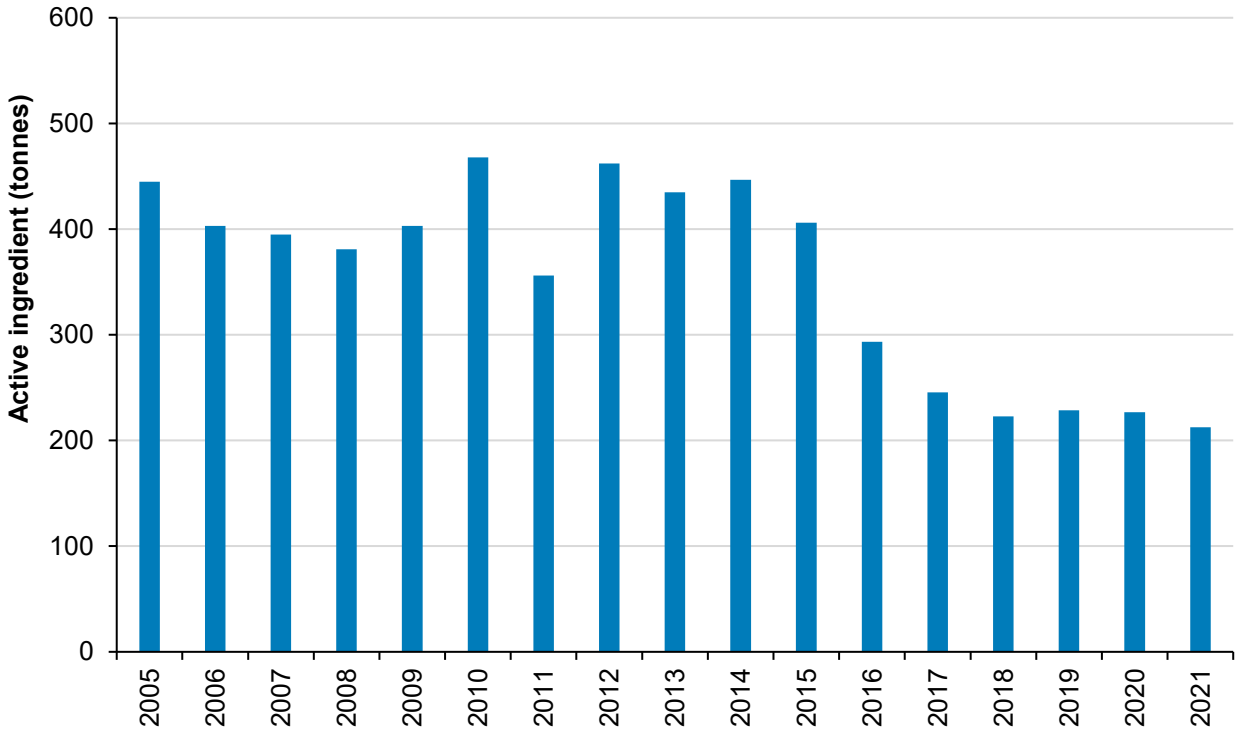


1.3.2 Total sales of antibiotics for all animals (tonnes)

Total sales of antibiotics for all animals (i.e., food-producing animals and companion animals) are shown in **Figure 1.8**.

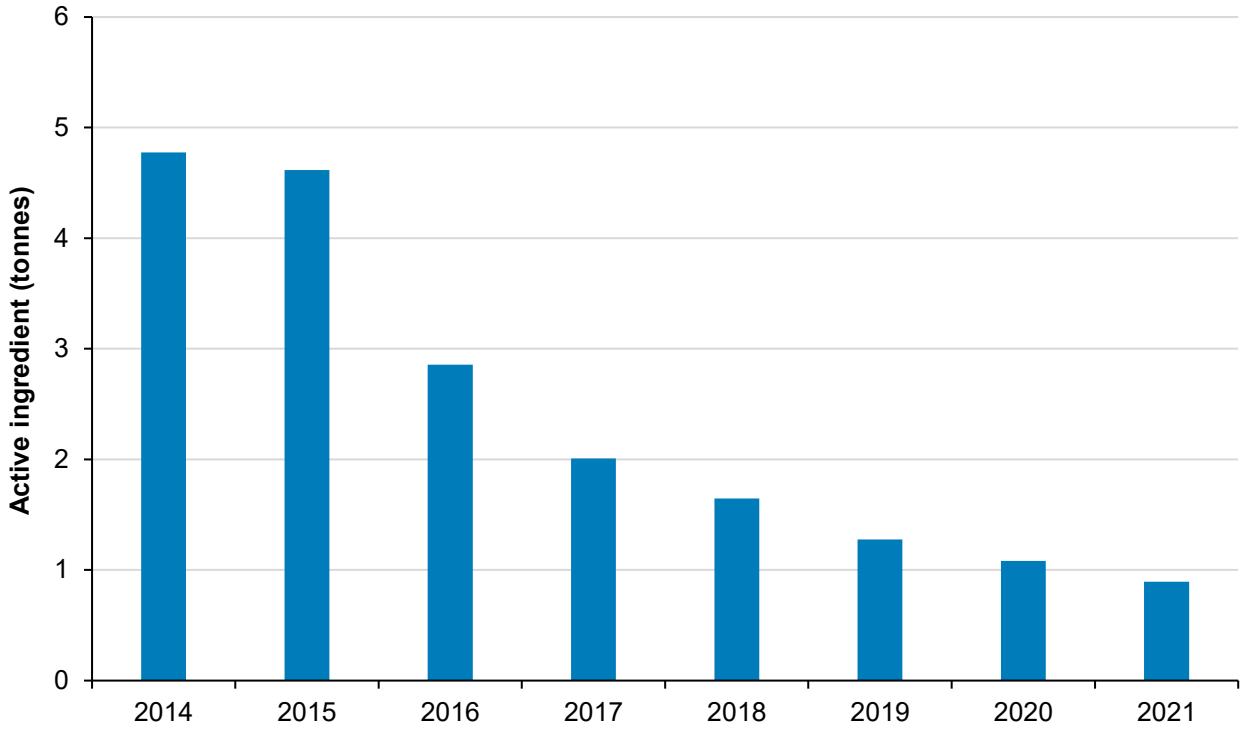
The total quantity of antibiotic active ingredient sold in 2021 was 212.4 tonnes, the lowest recorded figure to date. This is a 14.3 tonne (6%) decrease since 2020, and a 234.2 tonne (52%) decrease since 2014.

Figure 1.8: Active ingredient (tonnes) of antibiotics sold for use in all animals, 2005 to 2021.



Total sales of HP-CIAs for all animals are shown in **Figure 1.9**. HP-CIA sales have reduced every year since 2014, by a total of 3.9 tonnes since 2014 to 0.9 tonnes in 2021 (an 81% reduction). HP-CIA sales accounted for 0.4% of total antibiotic sales in 2021.

Figure 1.9: Active ingredient (tonnes) of HP-CIAs sold for use in all animals, 2014 to 2021.



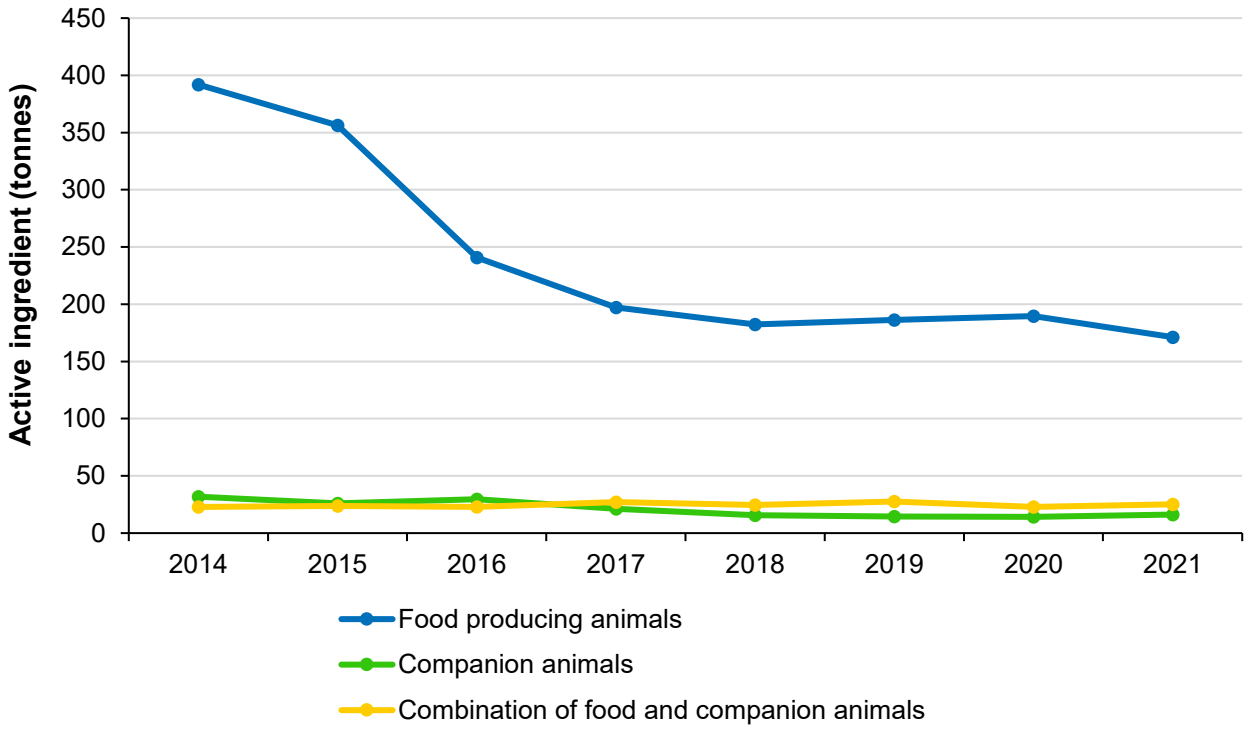
In 2021, 171.3 tonnes of antibiotic sales (81% of the total) were attributed to products licensed for food-producing animal species only (**Figure 1.10**). This is a decrease of 18.3 tonnes since 2020, largely due to a 10.3 tonne decrease in products authorised for pig and/or poultry, and a 4.6 tonne decrease in products authorised for fish only.

Sales of products licensed for companion animals only, accounted for 16.1 tonnes in 2021 (8% of total sales), which has increased by 1.9 tonnes since 2020. This is due to a 1.4 tonne increase in products licensed for cats and/or dogs and a 0.5 tonne increase in products licensed for horses only.

Sales of products indicated for a combination of food and non-food animals also increased by 2.1 tonnes to 25.1 tonnes (accounting for 12% of total sales). This category is comprised of 99.8% injectable products.

Where antibiotic usage data are available per species or sector, and represent a high proportion of the industry (e.g. pigs, meat poultry, laying hens, gamebirds, trout and salmon, see **Chapter 2**), these can be extrapolated and compared with the antibiotic sales of products authorised for those species. For 2021, the sales and use data are very comparable for pigs, meat poultry, laying hens and gamebirds. However, they were not comparable for aquaculture as, due to a temporary availability issue with a licensed product for salmon in 2021, some products were imported for use under the Special Import Scheme, and these are not included in the sales data.

Figure 1.10: Active ingredient (tonnes) of antibiotics sold by species indication, 2014 to 2021.



1.3.2.1 By antibiotic class and route of administration for all animal species (tonnes)

When looking at antibiotic sales for all animal species, tetracyclines accounted for 68.1 tonnes (32% of total sales) (data not shown graphically), 49% of which was in-feed whereas 31% was for oral/water use (**Figure 1.11**). Penicillins sales comprised 60.7 tonnes (29% of total sales), but these were most commonly used for oral/water use (46%) or as an injection (26%).

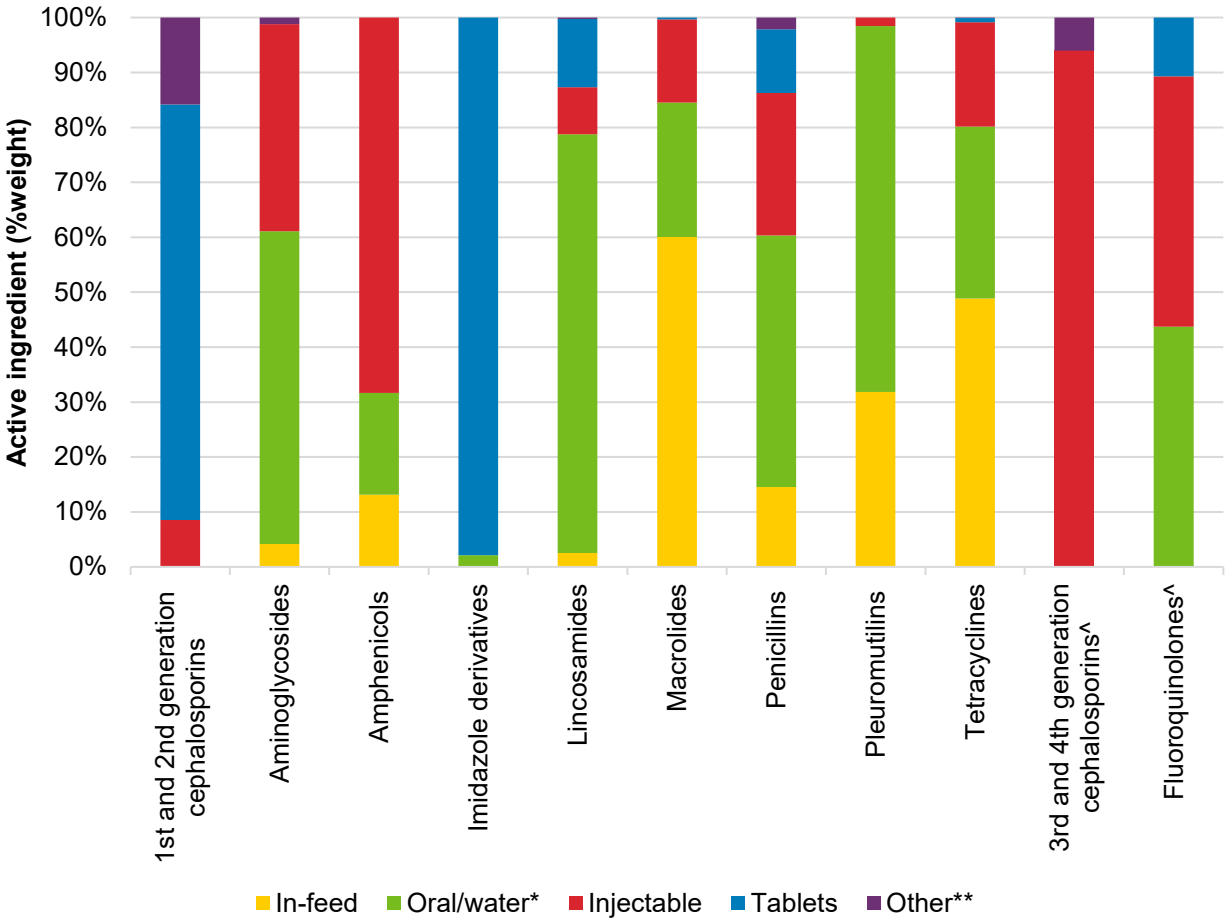
Sales of trimethoprim-sulphonamides, aminoglycosides and macrolides were similar, accounting for 10%, 10% and 9% of total sales respectively (data not shown graphically). However, while trimethoprim-sulphonamides and macrolides were mostly administered in-feed (accounting for 51% and 60% of their use respectively), aminoglycosides were most commonly administered by oral/water (57%) and injection (38%) (**Figure 1.11**).

Sales of pleuromutilins, lincosamides, amphenicols, and first and second generation cephalosporins each represented 2-3% total sales. Both lincosamides and pleuromutilins were most commonly administered by oral/water (accounting for 76% and 67% of their use respectively, **Figure 1.11**), whereas amphenicols were most commonly administered as injectables (68%) and first and second generation cephalosporins as tablets (76%).

Of the HP-CIAs, 94% of third and fourth generation cephalosporins sold were injectables, with the remainder being intra-mammary preparations for cattle. Forty-six percent of

fluoroquinolones were used as injectables, with the remainder used as oral/water (44%) and tablets (11%).

Figure 1.11: Active ingredient (% weight) of antibiotics by antibiotic class and route of administration sold for all animals, 2021.



^ HP-CIA
* Oral powders, oral pastes, oral solutions and bolus preparations
** Intramammary and intrauterine preparations

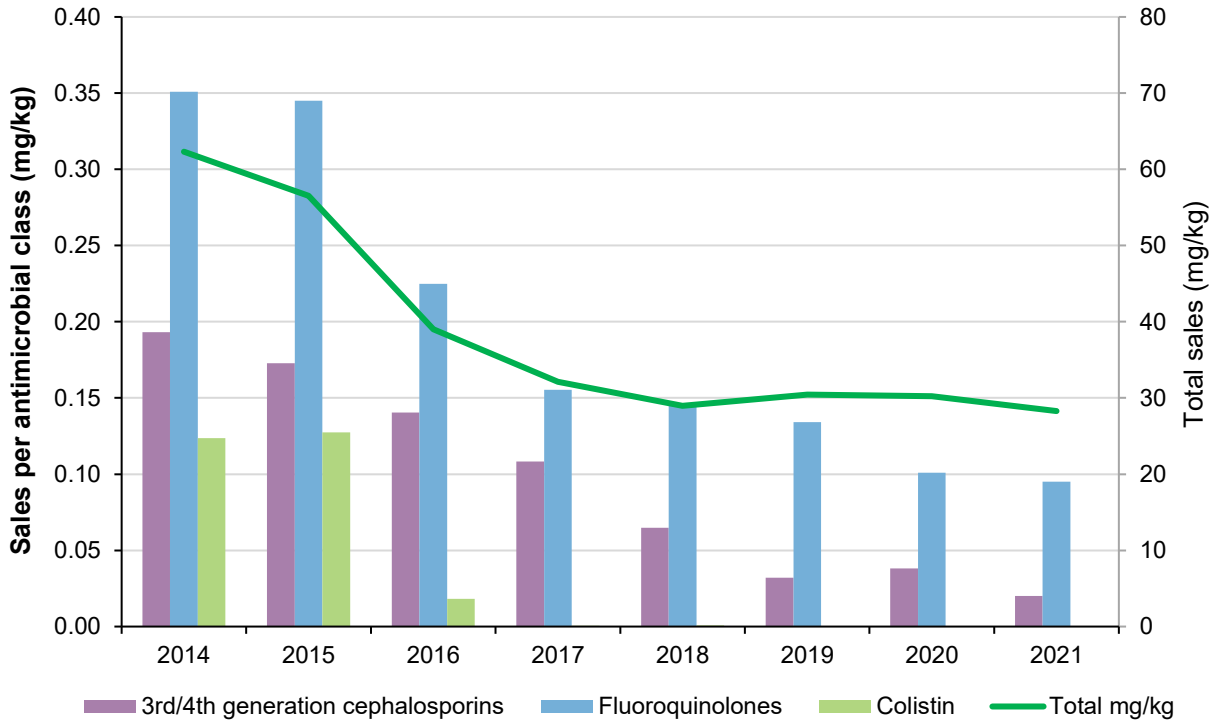
1.3.3 Harmonised outcome indicators for antibiotic use

Harmonised indicators are important in order to monitor trends in a consistent way, and in a way that is comparable across different regions and countries. As explained below, a number of different indicators for monitoring antibiotic sales in animals have been developed globally. However, to allow for consistency with previously published data and harmonisation with other countries in the European region, we are reporting the data using the EU harmonised indicators. These were published by the European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and EMA in 2017.

The primary indicator is "*the overall sales of veterinary antibiotics in milligram of active substance per kilogram of estimated weight at treatment of livestock and of slaughtered*

animals in a country (mg/PCU)" (**Figure 1.1**). Secondary indicators are the sales in mg/PCU of third and fourth generation cephalosporins, quinolones (and percentage of fluoroquinolones) and polymyxins (**Figure 1.4**). In the UK, all quinolones sold for use in food-producing animals are fluoroquinolones (although the quinolone oxolinic acid is imported for use by the fish sector; see **Chapter 2.3.5**), and colistin is the only polymyxin that has been sold for use in food-producing animals. The data show that all indicators have decreased since 2016 (**Figure 1.12**).

Figure 1.12: Harmonised primary outcome indicators for antibiotic consumption in food-producing animal species in the UK; 2014 to 2021.



Harmonised indicators for antibiotic use have also been developed by the Quadripartite (The Quadripartite partnership consist of the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (WOAH) and the United Nations Environment Programme (UNEP)). These include a core indicator measuring total volumes of sales or usage based on a mg/kg biomass metric and the percentage of total sales classified by the World Health Organisation (WHO) as HP-CIAs. The WHO classification differs from AMEG classification used here, in that macrolides are included in the HP-CIA category. This is because the WHO classification assesses AMR risk from a global, rather than a European perspective and does not take into account the indications for and availability of alternative antibiotic classes with lower AMR risk in animal health. The data using these WHO metrics (presented regionally) can be found in the OIE antimicrobial use report.

1.4 Methods

Data collection and validation

Pharmaceutical companies supplied annual sales of all authorised veterinary antibiotics to the VMD in accordance with the Veterinary Medicines Regulations. Upon receipt, data were collated and validated, and product data entries were compared to those submitted in previous years. If there were large discrepancies between data provided in successive years, data validity was investigated and queried with the pharmaceutical company. Sales data contained in returned Periodic Safety Update Reports (PSURs) for antibiotic veterinary medicinal products were also compared to the sales data returned by the pharmaceutical companies, and any discrepancies investigated (further details can be found in Annex E).

Tonnes of active ingredient

The weight of antibiotic active ingredient sold is a measurement obtained by multiplying the quantitative composition of active ingredient for each product, taken from the Summary of Product Characteristics (SPC), by the number of units sold as reported by the pharmaceutical companies. For some active ingredients that are either prodrugs or expressed in International Units (IU), a conversion factor is applied. These conversion factors are recommended by the European Medicines Agency (EMA) in the framework of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project.

Sales data analysed using the ESVAC methodology are available from 2005; the ESVAC project was launched in September 2009 and the first report published aggregated sales data for the years 2005–2009. Prior to these years, data (covering 1993–2005) were analysed using historic UK-VARSS methodology. Since UK-VARSS 2015 (published in 2016), sales data have been reported using ESVAC methodology in recognition of the utility of regional harmonisation of surveillance. Note that data presented in mg/kg for food-producing animals (which equals mg/PCU) do not include tablets or topicals, as, in line with the ESVAC methodology, these are assumed to be exclusively administered to companion animals.

The data reported here are presented according to the ATCvet Classification System for veterinary medicinal products shown in Table S1.1.1 of Supplementary Material 1. Sales of dermatological preparations and preparations for sensory organs (described as ‘other’ route of administration in this and previous UK-VARSS reports) are not included in calculations. Sales of these products have remained stable and account for no more than 3 tonnes of active ingredient (Table S1.1.2 of Supplementary Material 1).

Mg/kg Population Correction Unit (PCU) for food-producing animals

Trends in sales of antibiotics over time are determined by taking into consideration variations in the size and number of the animal population. To achieve this, sales data for food producing animals were analysed using the Population Correction Unit (PCU), which was formulated by the European Medicines Agency and represents the weight of the food

producing animal population (in kg) at risk by using standardised weights that represent the average weight at time of treatment. Using the PCU, overall sales of products authorised for use in food-producing animal species can be presented as mg/PCU.

The mg/PCU can be considered as the average quantity of active ingredient sold per kg bodyweight of food-producing animal in the UK based on an estimated weight at the point of treatment and enables year-on-year comparisons to be made. Further details on these calculations are presented in S1.2.1 of Supplementary Material 1 and full technical details on PCU methodology can be found in the 2011 ESVAC report. Within the sales section of this UK-VARSS report, all references to mg/kg for food-producing animals equate to mg/PCU.

Corrections for historical data

The VARSS methodology changed in 2021, with amendments to International Unit factors and corrections to a number of products active ingredients content and strength. As a result, minor changes can be seen in historical mg/kg figures.

CHAPTER 2

Usage of veterinary antibiotics by animal species

2.1 Summary

The key trends are as follows:

- **Pigs –** Total use reduced by 17.7 mg/kg between 2020 and 2021 to 87.3 mg/kg and has now reduced 69% since data was first published in 2015. HP-CIAs use has reduced by 0.02 mg/kg between 2020 and 2021 to the lowest level recorded (0.03 mg/kg), a 97% reduction since 2015. The sector also continues to demonstrate an ongoing shift away from in-feed medication towards more targeted in-water delivery.
- **Turkeys –** Use increased between 2020 and 2021 by 16.8 mg/kg to 42.6 mg/kg, similar to the levels seen in 2019. Despite this increase, use in turkeys has reduced by 81% since data was first published in 2014. The use of fluoroquinolones (which are HP-CIAs) also decreased from 0.08 mg/kg in 2020 to 0.006 mg/kg in 2021.
- **Broilers –** Antibiotic use reduced by 2.6 mg/kg between 2020 and 2021 to 13.7 mg/kg and use has now decreased by 72% since data was first published in 2014. However, the use of fluoroquinolones (which are HP-CIAs) increased from 0.001 mg/kg in 2020 to 0.05 mg/kg in 2021.
- **Ducks –** Use in the duck sector decreased by 0.9 mg/kg to 1.7 mg/kg between 2020 and 2021 and has now reduced by 89% since 2014. No HP-CIAs were used in 2021.
- **Laying hens –** Use decreased by 0.14% bird days between 2020 and 2021 to 0.33 % bird days and has reduced by 50% since data was first published in 2016. No HP-CIAs were used by the laying hen sector in 2021.
- **Gamebirds –** Use was 8.9 tonnes in 2021, which represents an increase of 3.2 tonnes between 2020 and 2021. However, due to Covid restrictions the industry estimates that gamebird rearing reduced by 30% in 2020, whereas in 2021 gamebird rearing returned to near normal levels. Since data was first published in 2016, antibiotic use has reduced by 55%. HP-CIA use has reduced by 59% since 2016 and accounts for 0.3% of total use. The sector demonstrates an ongoing shift away from in-feed medication towards more targeted in-water delivery.
- **Salmon –** Use increased by 13.8 mg/kg since 2020 to 43.1 mg/kg, over two times (27.0 mg/kg) higher than when data was first published in 2017. There was no use of HP-CIAs in 2021.
- **Trout –** Use decreased by 7.9 mg/kg between 2020 and 2021 to 5.9 mg/kg. This is the lowest use seen in the trout sector since data was first published in 2017 and represents an overall decrease of 69%. Use of the HP-CIA oxolinic acid decreased by 50% between 2020 and 2021 to 2.1 mg/kg.

2.2 Introduction

Many antibiotics are authorised for use in multiple animal species, so it is not possible to determine from sales data how much is used per species. The VMD is working in partnership with all major food-producing animal sectors to develop, facilitate and coordinate antibiotic use data collection systems.

Antibiotic use refers to the amount of antibiotics purchased, prescribed and/or administered. All antibiotics used in UK animals must be prescribed by a veterinarian. Capturing antibiotic use data by animal species provides a baseline against which trends and the impact of interventions, such as those designed to reduce antibiotic use, can be measured. The data can also be used to explore any correlation between changing antibiotic use and antibiotic resistance. Data collection systems also allow for benchmarking, enabling farmers to compare themselves with their peers and encouraging veterinarians and farmers to identify and share good practice and effective stewardship interventions.

This chapter describes the progress achieved so far, with updates provided by the food-producing animal sectors. Data has been presented graphically throughout, but full data sets can be found in Supplementary Material 2. Methodology is outlined in Section 2.4.

2.3 Results

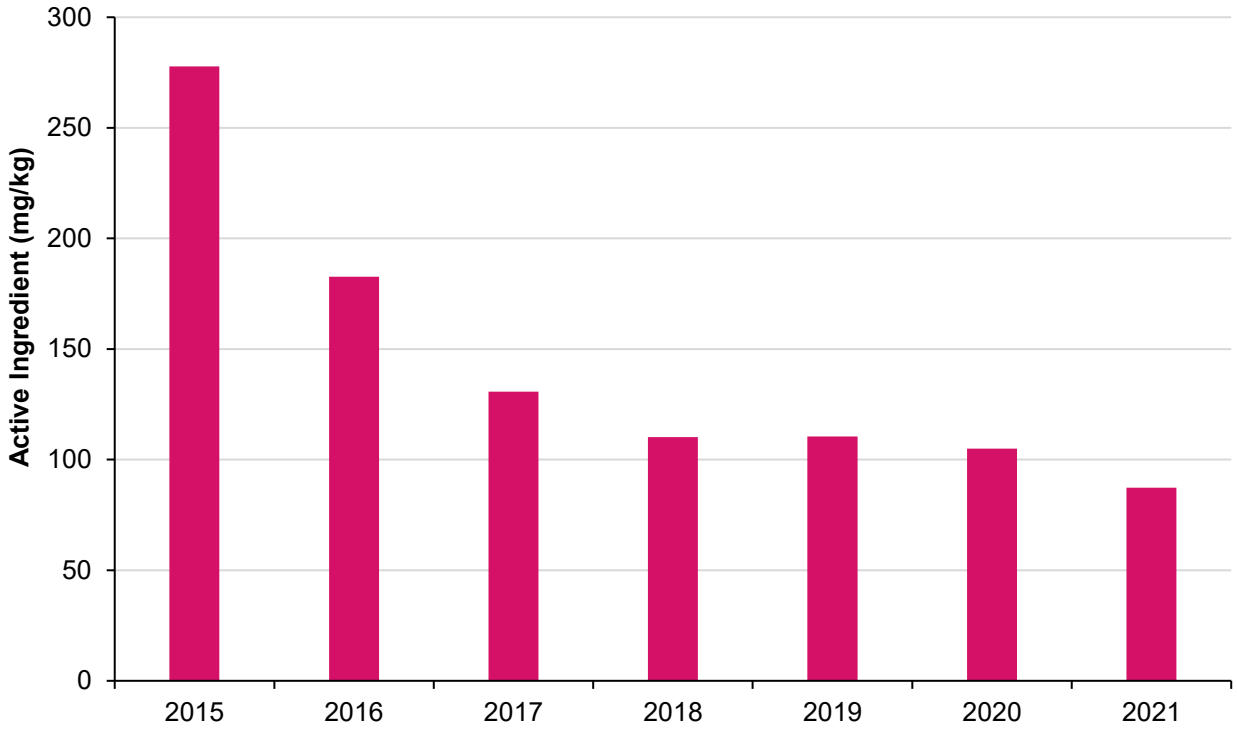
2.3.1 Pigs

2.3.1.1 Antibiotic usage data

Data from the electronic Medicines Book for Pigs (eMB Pigs), representing >95% UK pig production, shows that total antibiotic use in pigs was 69.5 tonnes for 2021, which represents 87.3 mg/kg. This is a decrease of 17.7 mg/kg since 2020, and 69% (190.5 mg/kg) since data was first reported in 2015 (**Figure 2.1**).

The use of antibiotics in pigs is broken down in **Figure 2.1, 2.2 and 2.3.**

Figure 2.1: Active ingredient (mg/kg) of antibiotics reported in eMB pigs, 2015 to 2021.

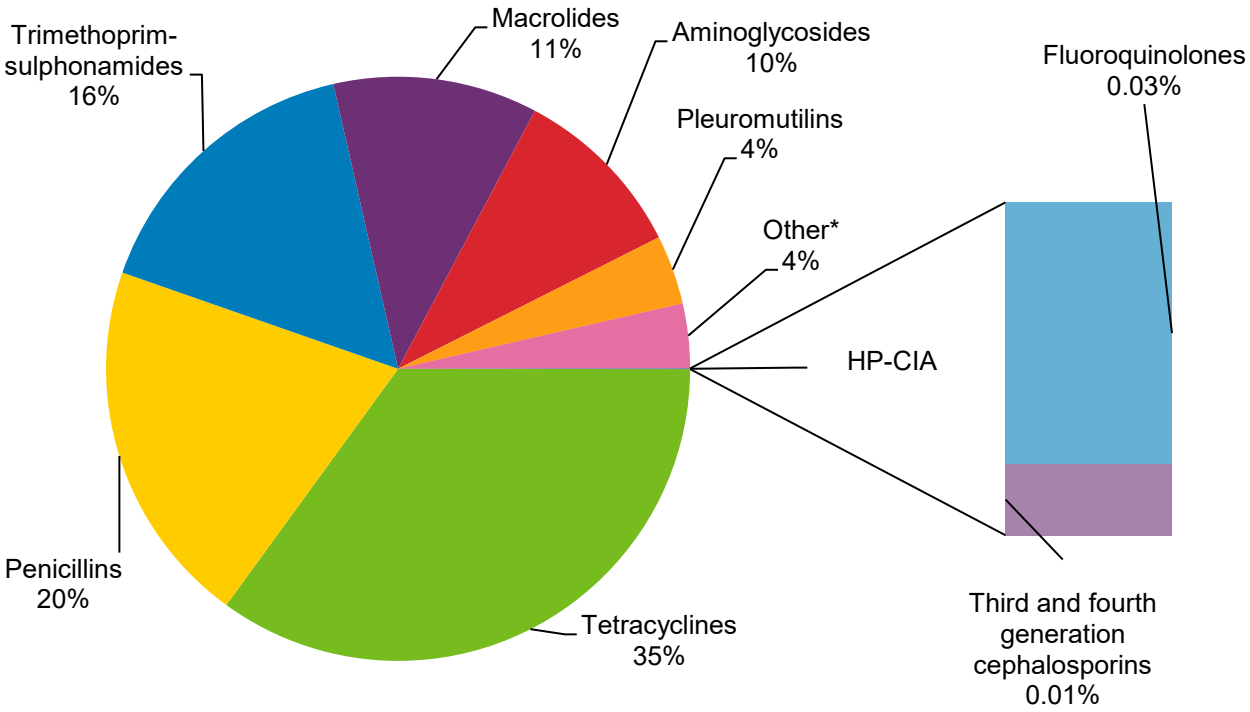


Tetracyclines remain the most used antibiotic class, representing 35% of antibiotic active ingredient used in 2021 (**Figure 2.2**), followed by penicillins (20%) and trimethoprim-sulphonamides (16%). Since data was first published in 2015, tetracyclines, trimethoprim-sulphonamides and penicillins have reduced by 74% (87.2 mg/kg), 52% (19.2 mg/kg) and 79% (52.2 mg/kg) respectively (**Figure 2.3**).

The use of pleuromutilins and macrolides also decreased between 2020 and 2021, whereas aminoglycoside use increased slightly by 3% (0.3 mg/kg) between 2020 and 2021. Aminoglycosides now represent 10% of overall use.

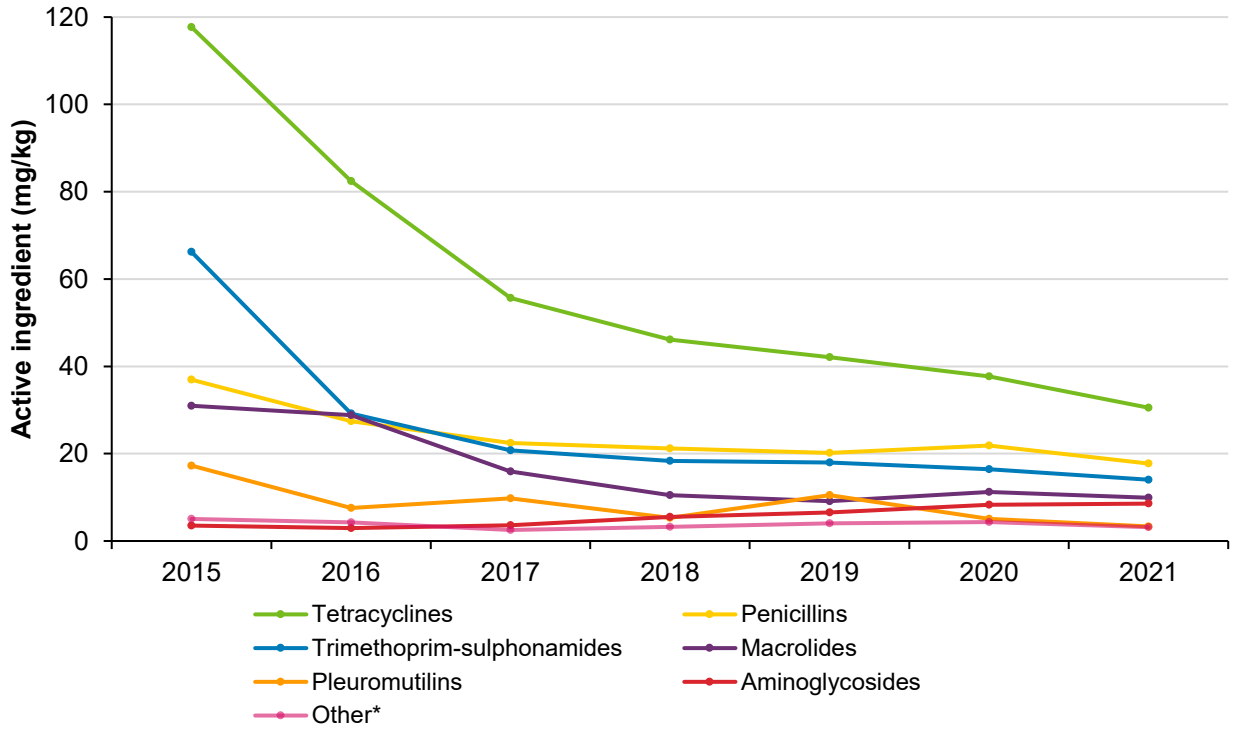
In-feed is the most common route of administration in pigs; however, relative use of in-feed has fallen every year since 2017, representing 78% of total use in 2015 and 59% in 2021. Conversely, in-water administration now accounts for 37% active ingredient used (compared with 19% in 2017) (see **Figure 2.4**). This shift is in line with the pig sector target to encourage producers to move from in-feed to in-water administration of antibiotics, which allows for more accurate targeting and thus more responsible use. The most common antibiotic classes for in-feed use in 2021 were tetracyclines (44% of total in-feed use), trimethoprim-sulphonamides (19%) and macrolides (17%), whereas the most common antibiotic classes for in-water use were penicillins (25% of total in-water use), tetracyclines (25%) and aminoglycosides (22%).

Figure 2.2: Active ingredient (% weight) of antibiotics by antibiotic class reported in eMB pigs, 2021.



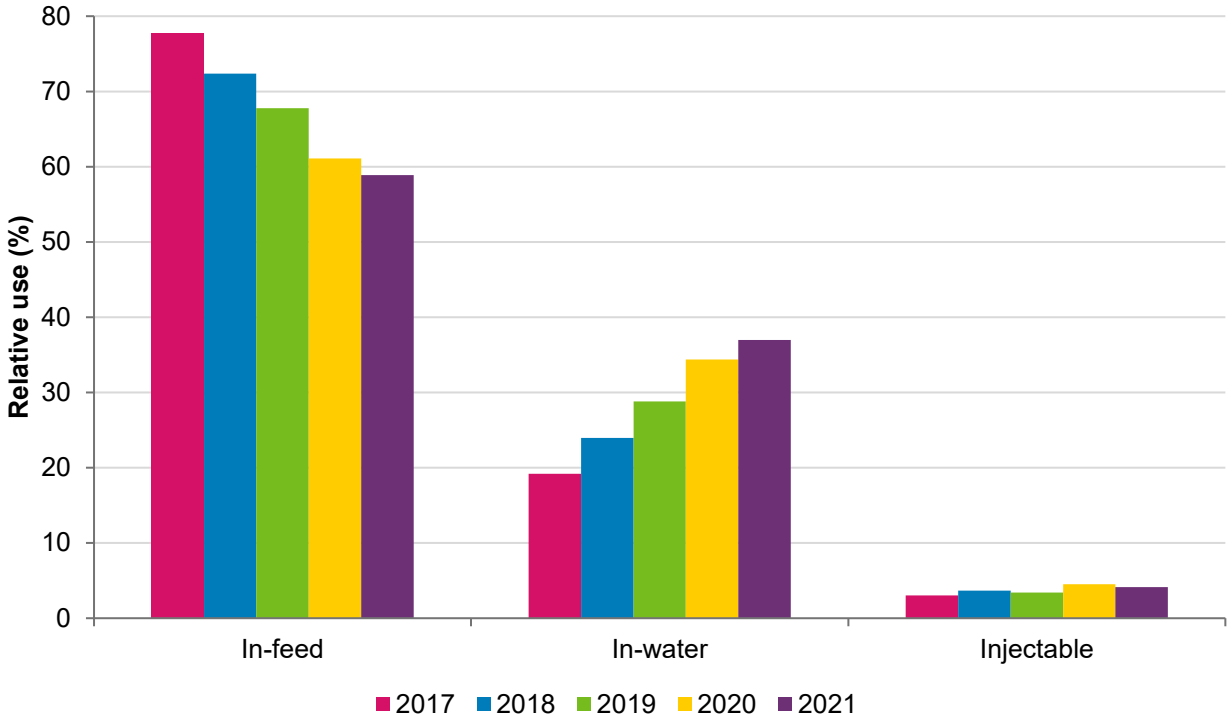
*lincosamides and amphenicols

Figure 2.3: Active ingredient (mg/kg) of antibiotics by antibiotic class reported in eMB Pigs, 2015 to 2021.



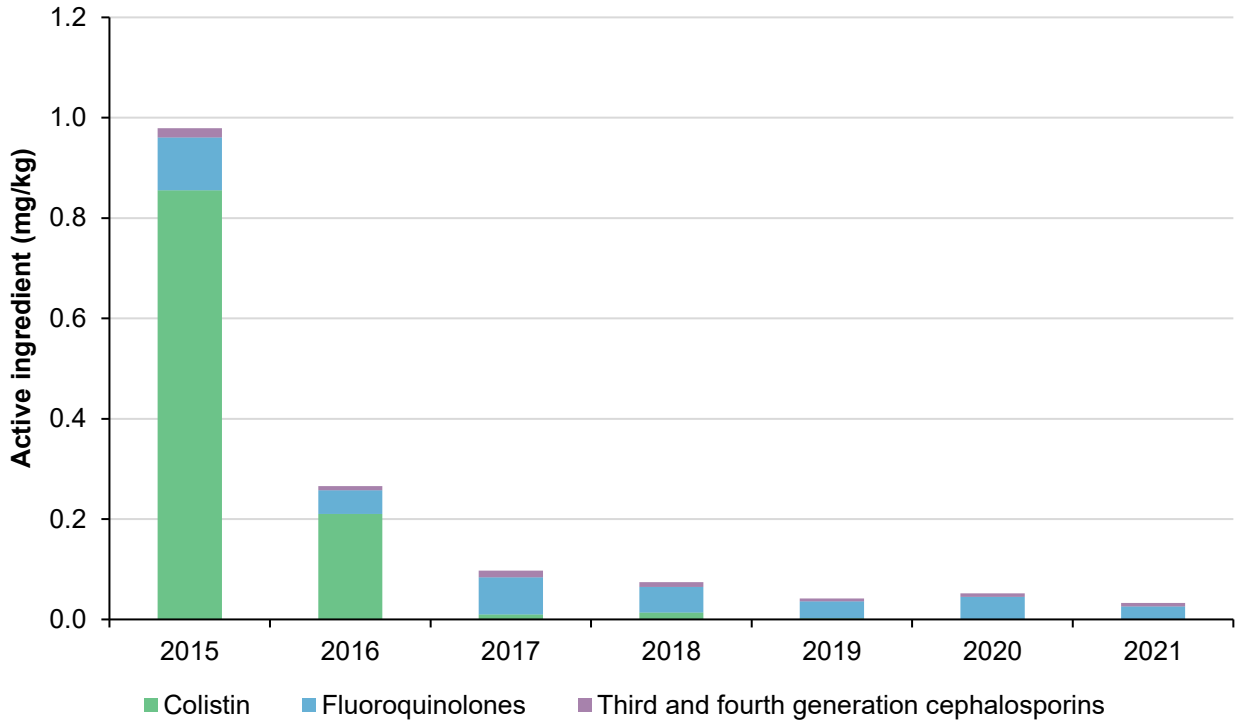
* Lincosamides, amphenicols, polymyxins, fluoroquinolones and third and fourth generation cephalosporins.

Figure 2.4: Active ingredient (% weight) of antibiotics by route of administration reported in eMB Pigs, 2017 to 2021.



The use of HP-CIA in pigs is shown in **Figure 2.5**. The total HP-CIA use in pigs was 26.3 kg for 2021, which represents 0.03 mg/kg. Use of HP-CIAs in pigs returned to a decreasing trend in 2021, reducing by 0.02 mg/kg between 2020 and 2021 to the lowest level recorded to date and accounting for 0.04% of overall use. HP-CIA use has now reduced by 97% (0.95 mg/kg) since 2015. All the third generation cephalosporins and 99.9% of the fluoroquinolones were administered by injection, which means the use is targeted to individual animals. As in 2020, no products containing colistin were used in 2021.

Figure 2.5: Active ingredient (mg/kg) of HP-CIAs reported in eMB Pigs, 2015 to 2021



2.3.1.2 Statement from Pig Health and Welfare Council (PHWC) Antimicrobial Usage Subgroup

"During 2021, the UK pig industry reduced antibiotic use by 17% despite facing a number of significant issues across the supply chain. These included labour shortages in processing plants resulting in a backlog of pigs, with pigs spending longer on farm. The 2021 figure reflects the downward trend in antibiotic use in pigs over the last six years (69% reduction between 2015-2021). The result also demonstrates progress towards the sector target to reduce antibiotic use 30% by 2024 (from the 2020 baseline), an ambition developed by the PHWC AMU group for the RUMA Targets Task Force and which the industry will continue to work towards. The reductions reflect a continued commitment to antibiotic stewardship in the pig sector. Further stewardship initiatives include the Persistently High Users scheme launched in 2021 where, through the farm assurance scheme Red Tractor, farms in the top 5% for antibiotic use per farm type need to produce and action an antibiotic reduction plan with their vet. Overall, the use of all antibiotic classes reduced except aminoglycosides, which increased very slightly (3%) from 8.30mg/kg in 2020 to 8.56mg/kg in 2021. It is thought that this increase may represent responsible prescribing to protect animal health and welfare in the national herd in response to specific disease challenge - aminoglycosides are commonly used for treating gastrointestinal diseases and an increase in enteric colibacillosis in post-weaned pigs was recorded in Q3 2021, and maintained for Q4. The reasons for this are likely to be multifactorial but may include the backlog of pigs described earlier adversely affecting measures taken to control enteric disease as well as some farms moving away from using zinc oxide in anticipation of its withdrawal in June 2022, a treatment widely used to control

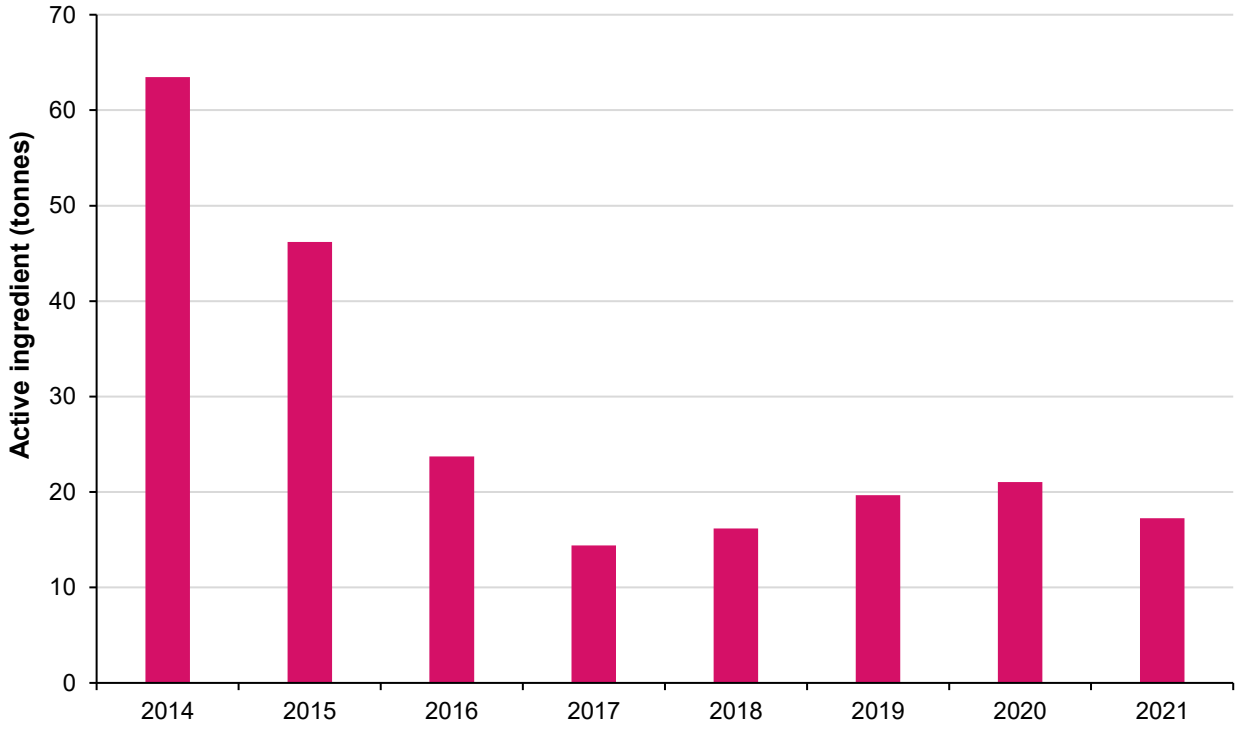
Post-Weaning Diarrhoea (PWD) in pigs. The pig sector will continue to focus on good practice around weaner management to reduce the need for antibiotic treatment post-weaning. The use of Highest-Priority Critically Important Antibiotics (HP-CIAs) in pigs remains at a very low level with a further decrease observed from 0.05mg/kg in 2020 to 0.03mg/kg in 2021. No colistin use was recorded in pigs for the second year running. Finally, 2021 usage data reveals that the total sales of antibiotics administered in water are increasing relative to in-feed. This is important as water-delivery systems have been shown to be more targeted than in-feed administration and therefore present a reduced AMR risk. The pig industry will continue to encourage the administration of antibiotics through water-delivery systems over in-feed where appropriate".

2.3.2 Meat poultry

2.3.2.1 Antibiotic usage data

In 2021, the British Poultry Council (BPC) reported the use of 17.3 tonnes of active ingredient. This is a 3.8 tonne decrease since 2020 and a 73% decrease (46.2 tonnes) since 2014 (**Figure 2.6**).

Figure 2.6: Active ingredient (tonnes) of antibiotics used by members of BPC Antibiotic Stewardship, 2014 to 2021.



When considering the size of the animal population, antibiotic usage in the chicken sector decreased by 2.6 mg/kg to 13.7 mg/kg between 2020 and 2021 (**Figure 2.7**). This represents a 72% decrease (35.1 mg/kg) since data was first published in 2014 and remains below the sector target of 25 mg/kg (**Figure 2.8**). Between 2020 and 2021, antibiotic use in the turkey sector increased by 16.8 mg/kg to 42.6 mg/kg, which is similar

to levels that were seen in 2019. Despite this increase, use in turkeys has reduced by 81% (177.0 mg/kg) since 2014 and remains below the sector target of 50 mg/kg (**Figure 2.8**). Between 2020 and 2021, the duck sector demonstrated a decrease in usage of 0.9 mg/kg to 1.7 mg/kg, and antibiotic use has now decreased by 89% (13.4 mg/kg) since 2014.

Figure 2.7: Active ingredient (mg/kg) of antibiotics by species used by members of BPC Antibiotic Stewardship, 2014 to 2021.

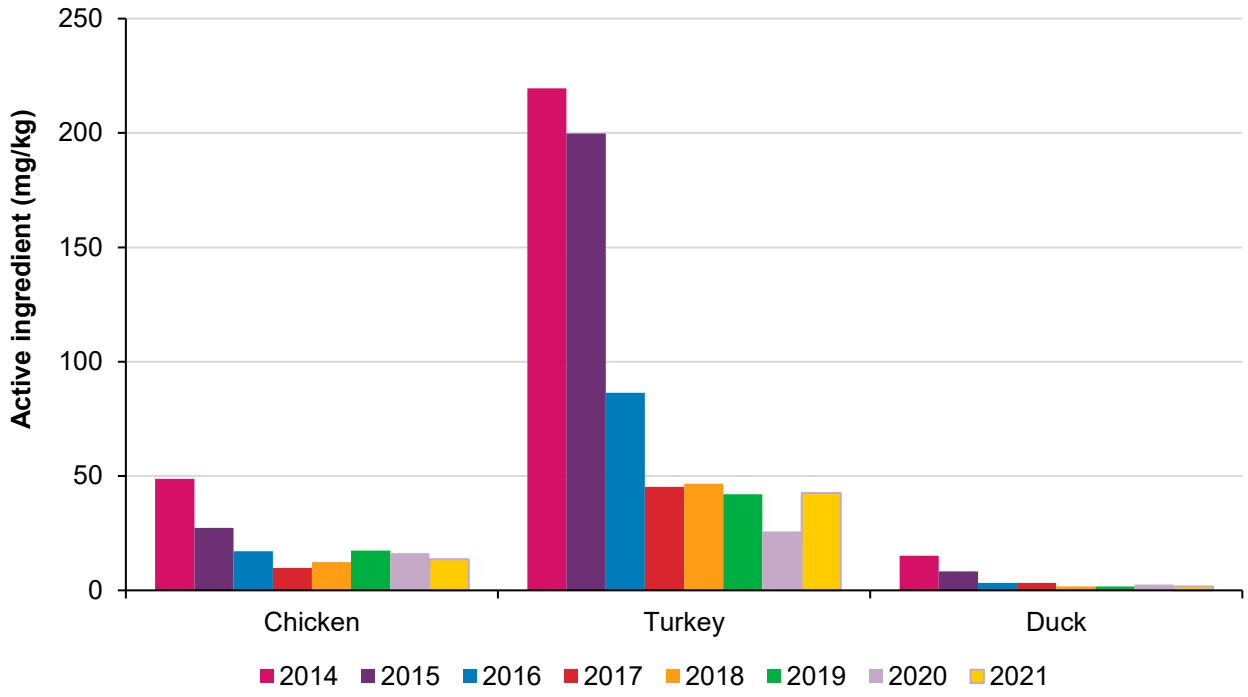
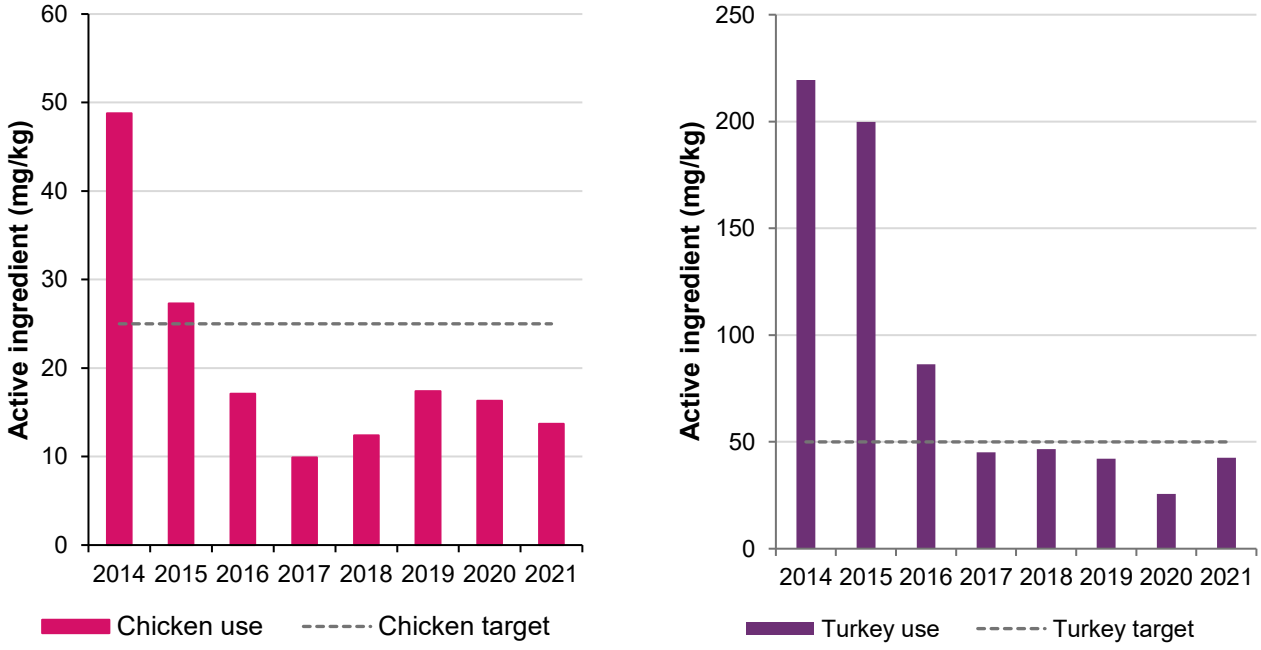


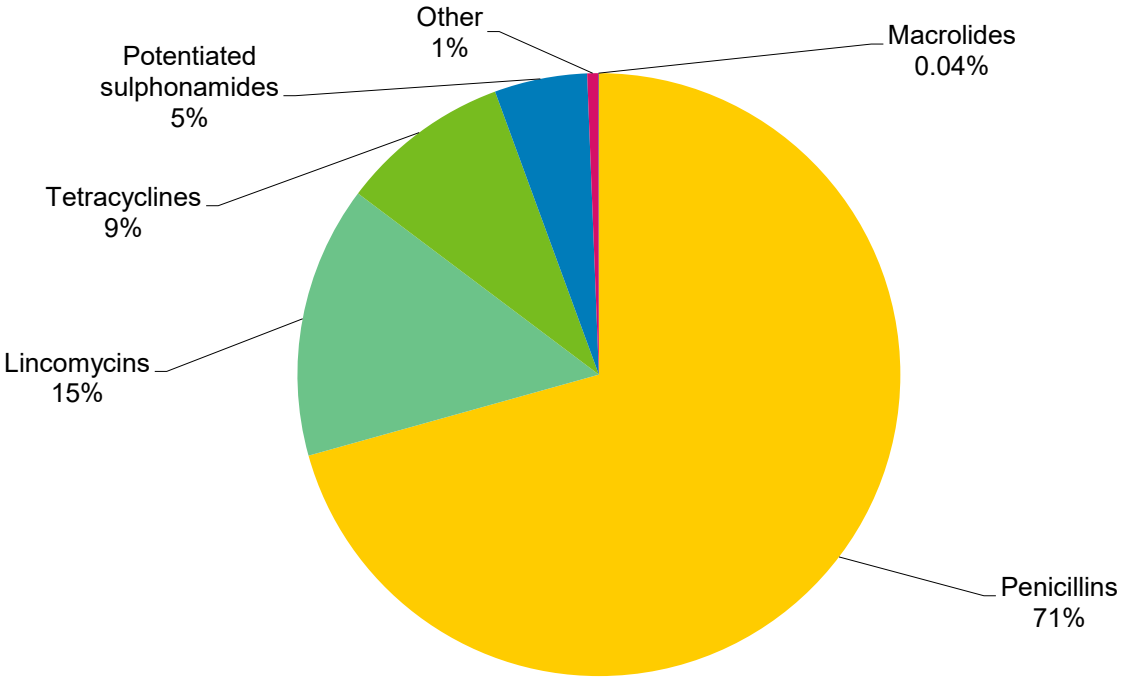
Figure 2.8: Active ingredient (mg/kg) of antibiotics by species used by members of BPC Antibiotic Stewardship and compared with the sector target, 2014 to 2021.



Penicillins remain the most-used antibiotic class in meat poultry. In 2021, 71% of active ingredient use was for penicillins (>99% of which is amoxicillin) (**Figure 2.9**), compared with 31% in 2014. The use of penicillins increased every year between 2017 and 2020, but decreased by 2.8 tonnes between 2020 and 2021. Tetracycline use has now dropped for the second year running (by 2.3 tonnes since 2019). By contrast, use of lincomycins has increased for the second year running (up by 1.0 tonnes since 2019), which means this is now the second-most-used antibiotic class, accounting for 15% of antibiotic use in 2021.

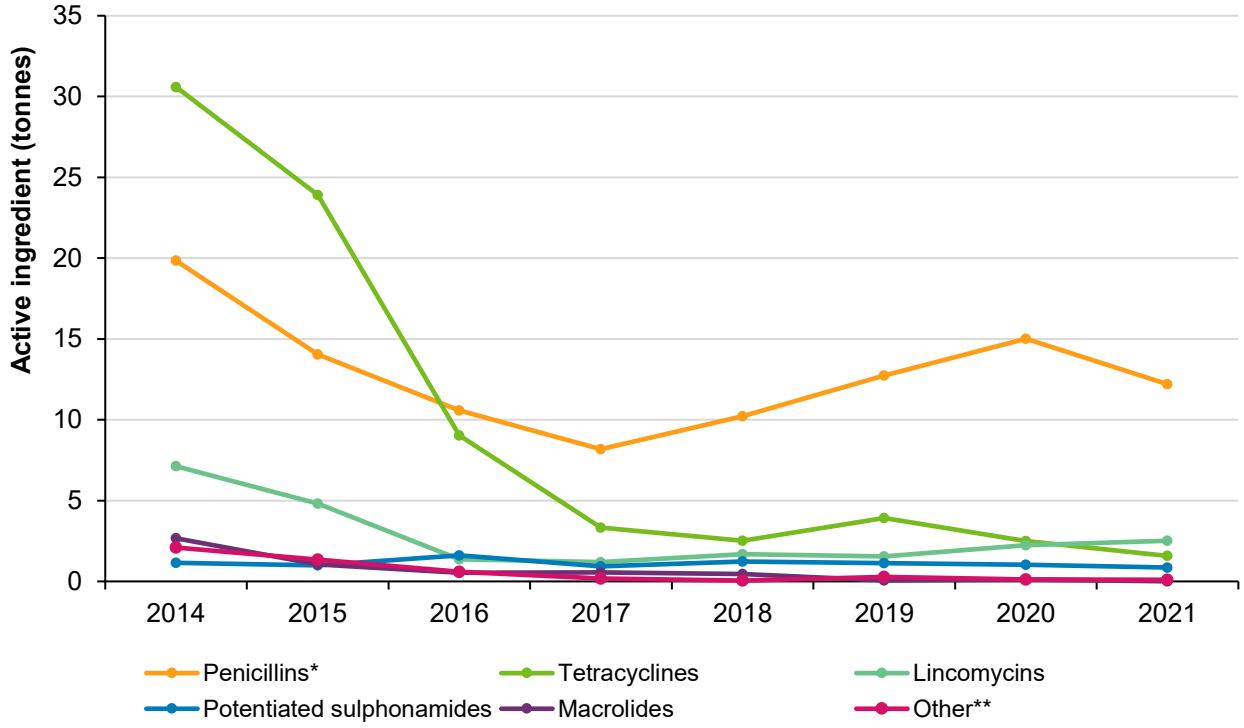
When considering the size of the animal population, use of HP-CIAs increased by 0.04 mg/kg since 2020 to 0.05 mg/kg in 2021. However, HP-CIA use in meat poultry is still 96% lower than when data was first published in 2014. Colistin and third and fourth generation cephalosporins were not used by the meat poultry sectors in 2021. In 2021, the use of fluoroquinolones increased by 44.5 kg since 2020 to 56.6 kg, although this only represents 0.3% of overall use. This is due to an increase in fluoroquinolone use in broilers (from 0.001 mg/kg in 2020 to 0.05 mg/kg in 2021). Fluoroquinolone use in turkeys has reduced (from 0.08 mg/kg in 2020 to 0.006 mg/kg in 2021).

Figure 2.9: Active ingredient (% weight) of antibiotics by antibiotic class used by members of BPC Antibiotic Stewardship, 2021.



* Aminoglycosides, pleuromutilins, fluoroquinolones and products under the cascade.

Figure 2.10: Active ingredient (tonnes) of antibiotics by antibiotic class used by members of BPC Antibiotic Stewardship, 2014 to 2021.



* Amoxicillin and phenoxymethylpenicillin.
** Aminoglycosides, pleuromutilins, fluoroquinolones, colistin and products under the cascade.

2.3.2.2 Statement from British Poultry Council

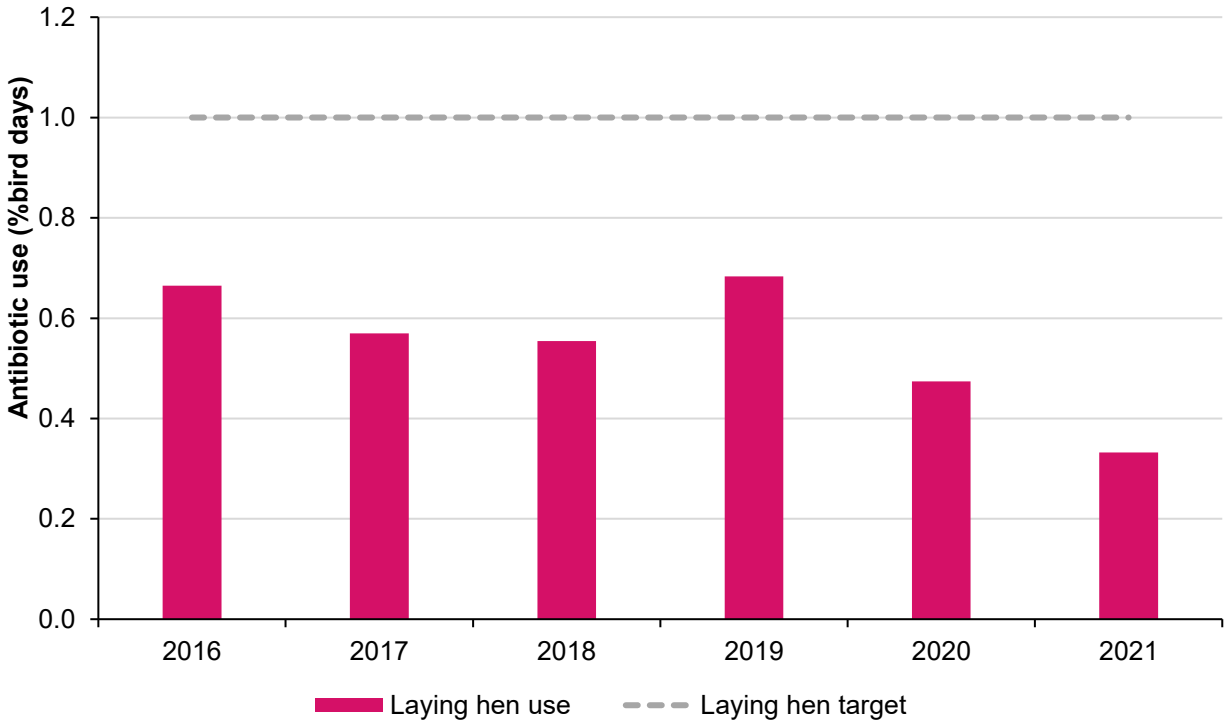
"Once again, the poultry meat sector remained below the sector target of 25mg/kg for broilers and 50 mg/kg for turkeys. This is testament to the work of the poultry meat sector to successfully implement the three R's (Replace, Reduce and Refine antibiotic use), supported by the principles of animal husbandry, hygiene and stockmanship. While remaining below the target, there was an increase in antibiotic use in turkeys between 2020 and 2021 as a result of a lack of availability of a licenced vaccine for *Ornithobacterium rhinotracheale* (ORT), which necessitated the use of antibiotics, albeit not Highest Priority Critically Important Antibiotics (HP-CIAs), to control disease. This illustrates the vulnerability of the poultry industry to the vagaries of commercial vaccine supplies, which is even more acute in minor species like turkeys. Whilst autogenous vaccines are a possibility, the fact they can only be used on the site from which the isolate is made limits their use. Clinical governance means that HP-CIAs are used only as a last resort. Between 2020 and 2021, fluoroquinolones reduced in the turkey sector but increased in broilers, albeit from a low base. BPC Antibiotic Stewardship will investigate the reason for this increase while focusing on continuously reviewing on-farm management practices to ensure antibiotics are only used when appropriate and to safeguard animal health and welfare."

2.3.3 Laying hens

2.3.3.1 Antibiotic usage data

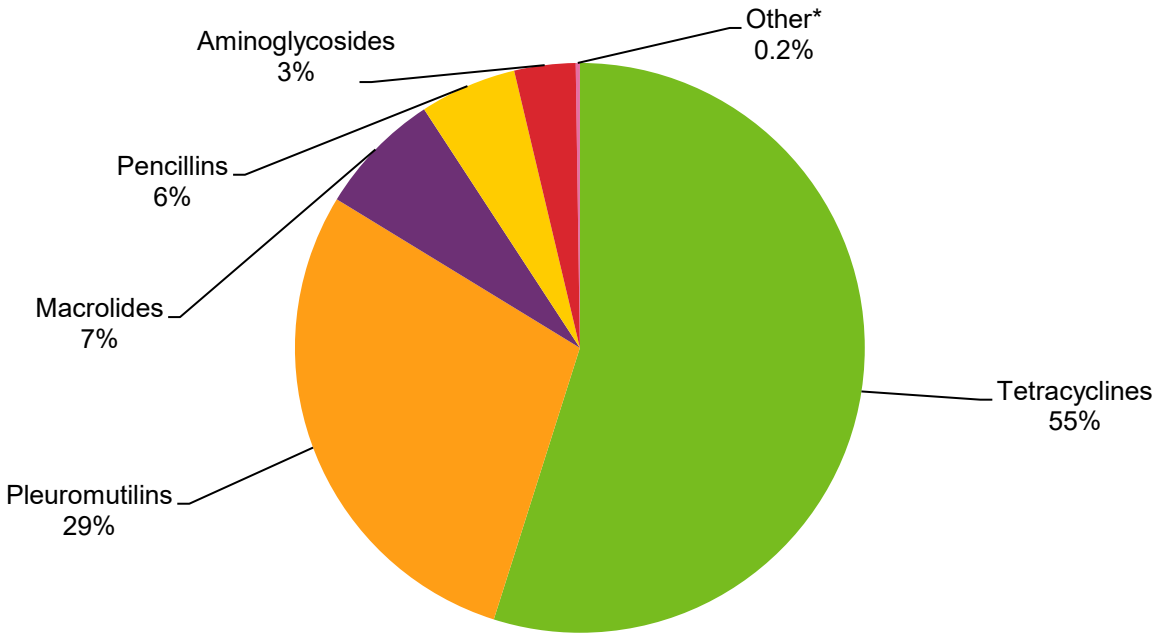
In 2021 data collected by the British Egg Industry Council (BEIC) represented 90% of the laying hen industry. In 2021, a total of 2.5 tonnes of antibiotic active ingredient was used. This represents 0.33% bird days (actual bird days treated/100 bird days at risk), which is below the sector target of 1% and represents a decrease of 0.14% bird days since 2020 and 50% (0.33 % bird days) since data was first published in 2016 (**Figure 2.6**). The methodology for this metric is explained in Section 2.4 of this report.

Figure 2.11: Antibiotic use (% bird days) by members of the BEIC Lion Code alongside the RUMA Targets Task Force sector target, 2016 to 2021.



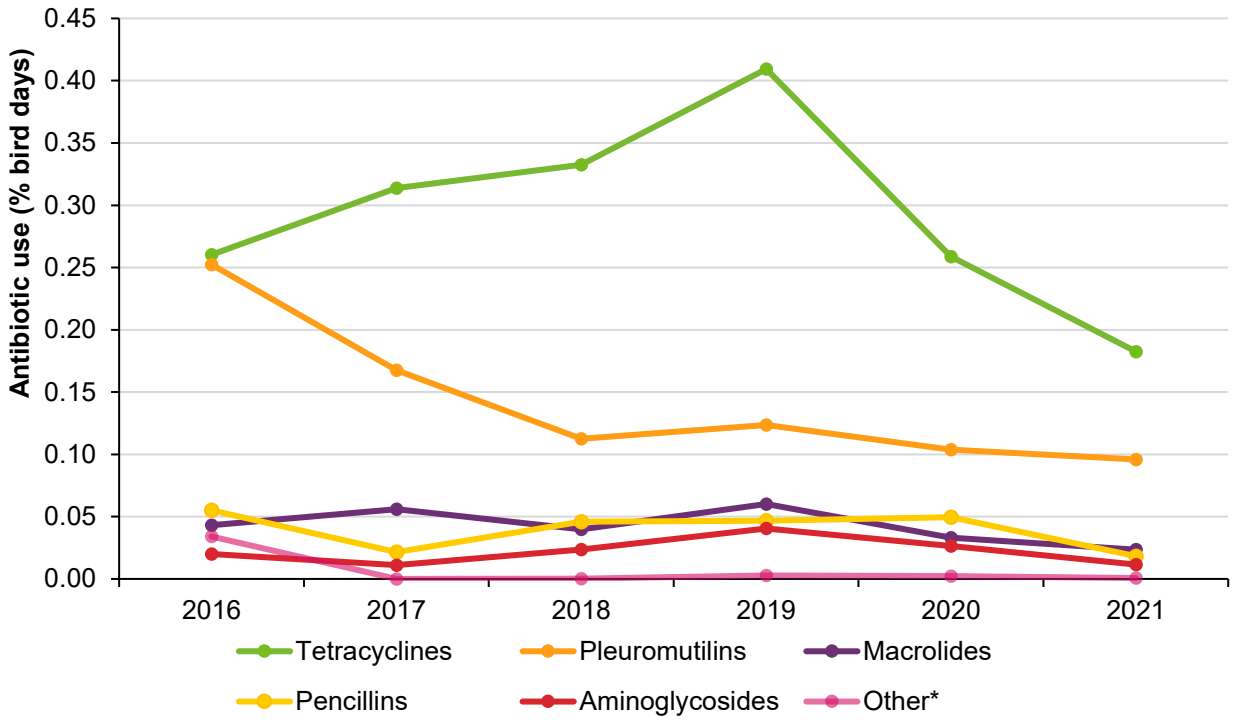
Tetracyclines and pleuromutilins accounted for 84% of total use (**Figure 2.7**) and decreased by 29% (0.08% bird days) and 8% (0.01% bird days) respectively, between 2020 and 2021 (**Figure 2.8**). For the fifth year running there were no HP-CIAs used by the laying hen sector in 2021.

Figure 2.12: Antibiotic use (% of total bird days) by antibiotic class by members of the BEIC Lion Code, 2021.



* Lincosamide/aminoglycoside combination product

Figure 2.13: Antibiotic use (% bird days) by antibiotic class by members of the British Egg Industry Council Lion Code, 2016 to 2021.



*Includes fluoroquinolones, polymyxins, sulphonamides, lincosamides and combination products

2.3.3.2 Statement from the British Egg Industry Council (BEIC)

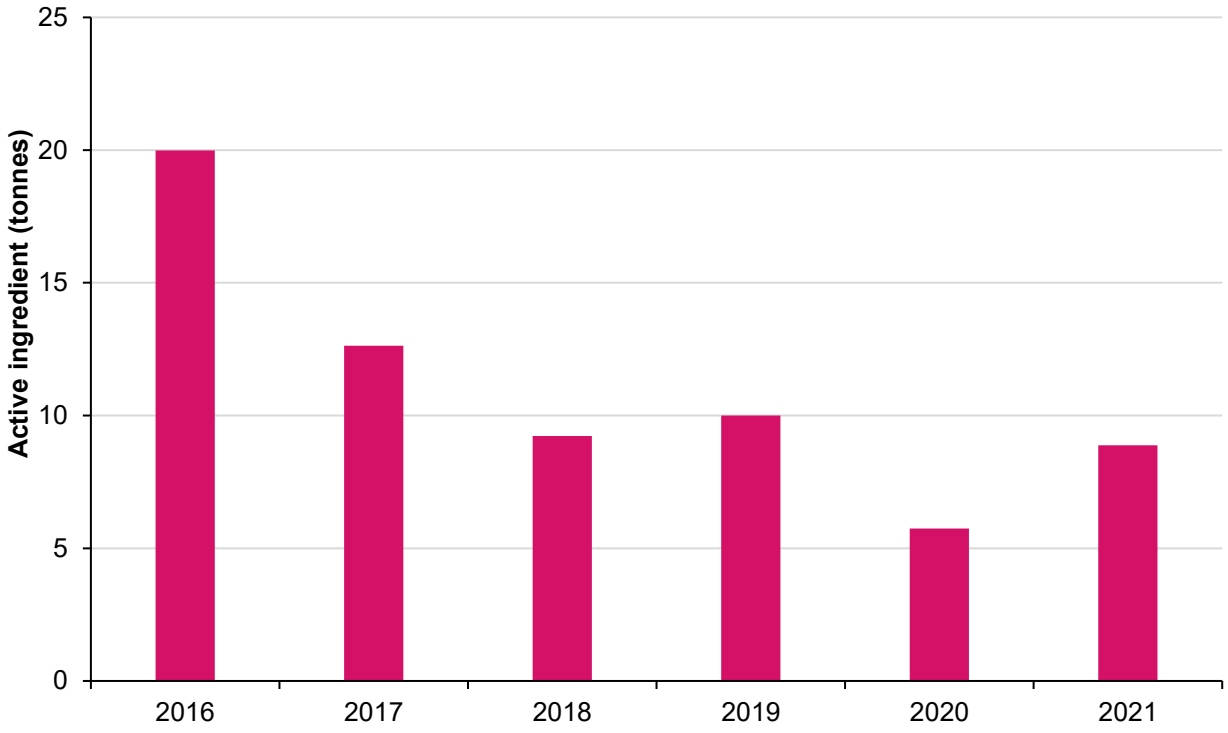
“The antibiotic use data from members of the British Egg Industry Council (BEIC) Lion Scheme for 2021 continues to be below the target of 1% bird days, and for the fifth year running no HP-CIAs were used. In the laying hen sector, there continues to be a focus on disease prevention, including widespread vaccination programmes. It is also a requirement for all farms to have a written biosecurity and veterinary health plan and, in addition, the Lion Training Passport provides a common training standard on key topics, including welfare, biosecurity and medicine usage. From January 2021 the Lion Training Passport, which includes medicine training, has been a required standard for all farms. There are currently some significant structural changes in the industry with a move away from enriched colony cage production for retail supply towards ‘barn’ production. While this will create challenges, we are confident that, through a continued focus on disease prevention and antibiotic stewardship, we will remain below our on-going target of keeping below 1% bird days, and 0.05% bird days for HP-CIAs.”

2.3.4 Gamebirds

2.3.4.1 Antibiotic usage data

In data representing 91% of the gamebird sector, 8.9 tonnes of active ingredient were reported in 2021 through the Game Farmers’ Association (GFA) and British Veterinary Poultry Association (BVPA) gamebird subcommittee data collection programme together with the AIC (Agricultural Industries Confederation) collection of compounded feed data for the first time. This represents an increase of 3.2 tonnes between 2020 and 2021 although, due to Covid restrictions the industry estimates that gamebird rearing reduced by 30% in 2020, whereas in 2021 gamebird rearing returned to approximately 90% of normal levels. If we compare with 2019 then use reduced by 11% (1.1 tonnes) and, since data was first published in 2016, use has reduced by 55% (11.1 tonnes) (**Figure 2.9).**

Figure 2.14: Active ingredient (tonnes) of antibiotics used in gamebirds, collected by the GFA, BVPA and AIC data collection programme, 2016 to 2021.

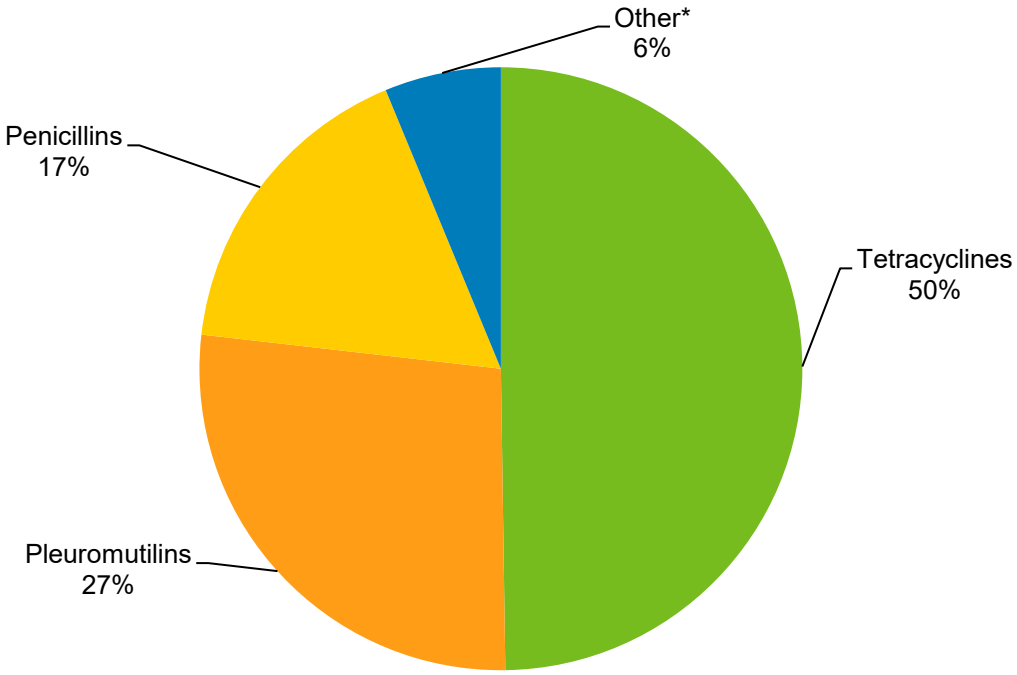


Tetracyclines, pleuromutilins and penicillins represented 95% of antibiotics used in 2021 (**Figure 2.10**). Tetracyclines remain the most commonly used active ingredient, but they have reduced by 69% (9.9 tonnes) since 2016 (**Figure 2.11**). During the same time period, pleuromutilins have reduced by 30% (1.1 tonnes) and penicillins have increased by 30% (0.4 tonnes).

Analysis by route of administration of all antibiotics (not shown graphically) shows that both in-feed and oral/water use decreased by 0.6 and 0.5 tonnes respectively since 2019, with oral/water accounting for 63% of overall use and in-feed 37%. Since 2016, in-feed use has fallen by 78% (11.7 tonnes) whereas oral/water use has increased by 11% (0.6 tonnes).

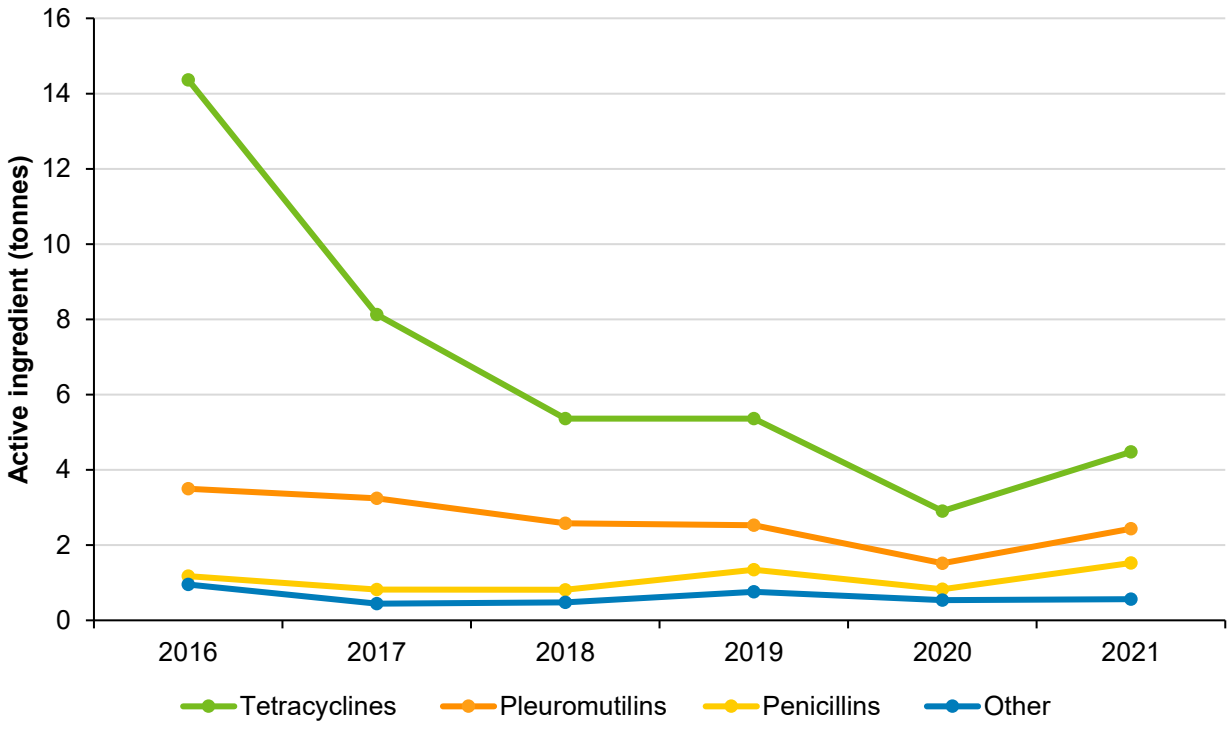
The HP-CIA enrofloxacin accounted for 0.3% of overall antibiotic use in 2021 (compared to 0.4% in 2020 and 0.6% in 2019) and has reduced by 54% (31.3 kg) since 2019. Since 2016, use of HP-CIAs has reduced by 59% (38 kg).

Figure 2.15: Active ingredient (% weight) of antibiotics by antibiotic class used in gamebirds, collected by the GFA, BVPA and AIC data collection programme, 2021.



* Aminoglycosides, amphenicols, fluoroquinolones, lincomycin, trimethoprim/sulphonamides

Figure 2.16: Active ingredient (tonnes) of antibiotics by antibiotic class used in gamebirds, collected by the GFA, BVPA and AIC data collection programme, 2016 to 2021.



* Aminoglycosides, amphenicols, fluoroquinolones, lincomycin, trimethoprim/sulphonamides

2.3.4.2 Statement from the Game Farmers' Association and the British Poultry Veterinary Association gamebird subcommittee

"The 2021 use figure is the lowest figure that has been seen for a year where (unlike 2020) there were near normal levels of gamebird rearing. It is also particularly encouraging to see that the use of the fluoroquinolone enrofloxacin has fallen by over 50% in the last two years.

In 2021, the sector focused on responsible prescribing, ensuring HP-CIAs are only used as a last resort and with good reason, encouraging testing for *Mycoplasma gallisepticum* and for game rearers to monitor their own antibiotic use alongside their vet. Three vet-led BVPA game sector training modules for game hatcheries and rearing farms and shoots were also piloted and a new pen scoring matrix, developed by gamebird vets, was launched and managed to promote better management and welfare through improvements to the environment that birds are released into, since the post release period is responsible for the majority of the sector's antibiotic use.

The Game Farmers Association/ British Game Assurance Independent audit scheme also began in 2021, with the aim to raise standards and help with sustained antibiotic reductions. There is still more work to be done to meet the ambitious target of reducing antibiotic use by 40% (from a 2019 baseline) but by working together, and given the progress so far, we believe that this will be achievable."

2.3.5 Aquaculture

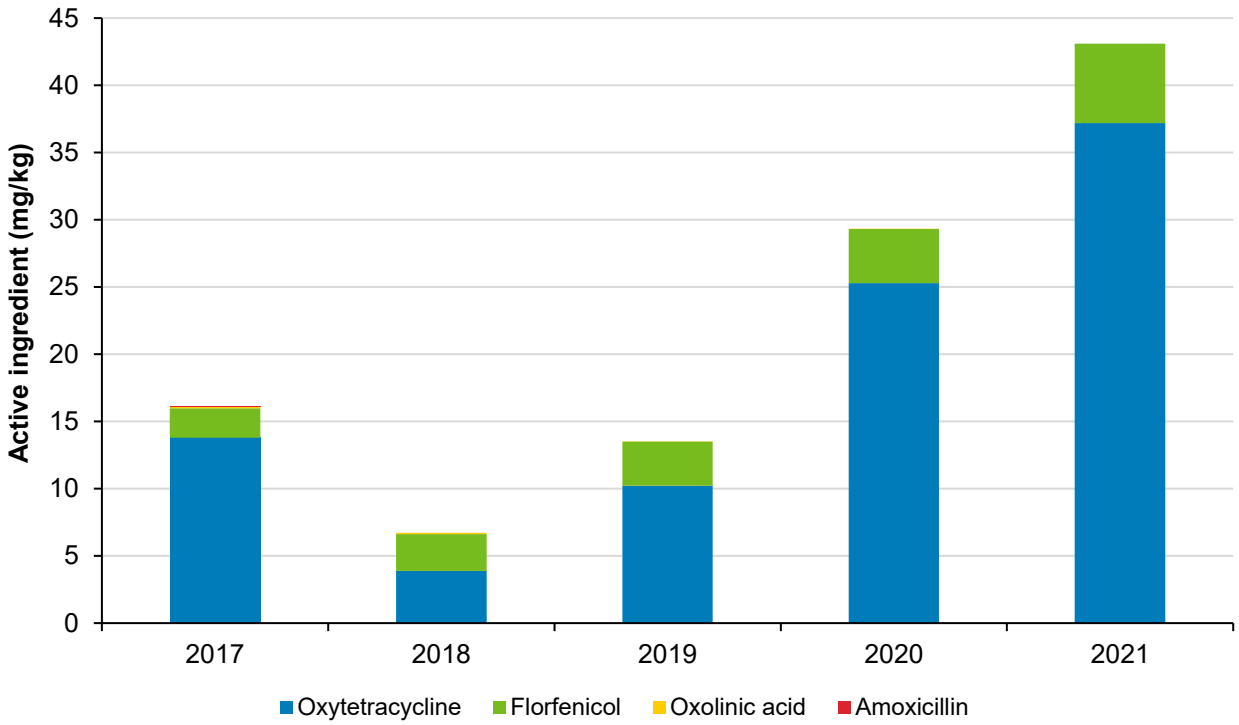
2.3.5.1 Salmon

2.3.5.1.1 Results

In data collected by Salmon Scotland representing 100% of the industry, 8.9 tonnes of antibiotic active ingredient were used in 2021, representing 43.1 mg/kg (**Figure 2.12**), which is 13.8 mg/kg higher than the use reported in 2020, and more than two times (27.0 mg/kg) higher than when data was first published in 2017.

Oxytetracycline remains the most used antibiotic class (accounting for 86% of total use in 2021). The HP-CIA oxolinic acid was not used in 2021 (for the first time since data was first published).

Figure 2.17: Active ingredient (mg/kg) of antibiotics by antibiotic class used in salmon, 2017 to 2021.



2.3.5.1.2 Statement from Salmon Scotland

“The data records an increase in antibiotic use between 2020 and 2021. This relates to an increase in use during the marine phase of production, with a decrease recorded in freshwater. It is important to state that antibiotic treatments are still relatively infrequent in the salmon farming sector, with only 8.5% of freshwater farms and 4.9% of marine farms treated in 2021. Antibiotics are only ever used in response to the clinical presentation of bacterial infection: there is no prophylactic use of antibiotics, and any use is supported by appropriate sensitivity testing. Despite the overall increase, there was no use of the HP-CIA oxolinic acid in 2021.

The salmon sector continues to focus on a holistic and preventative approach to health management, including vaccination, antibiotic stewardship, biosecurity and health and welfare planning. Furthermore, antibiotic use and stewardship are routinely discussed within a dedicated Prescribing Vets forum. It should also be noted that the overall production cycle for salmon is 3 years, so single year mg/kg figures can be difficult to interpret. The sector remains committed to responsible use of antibiotics, balancing a drive to reduce use against the need to safeguard fish health and welfare.”

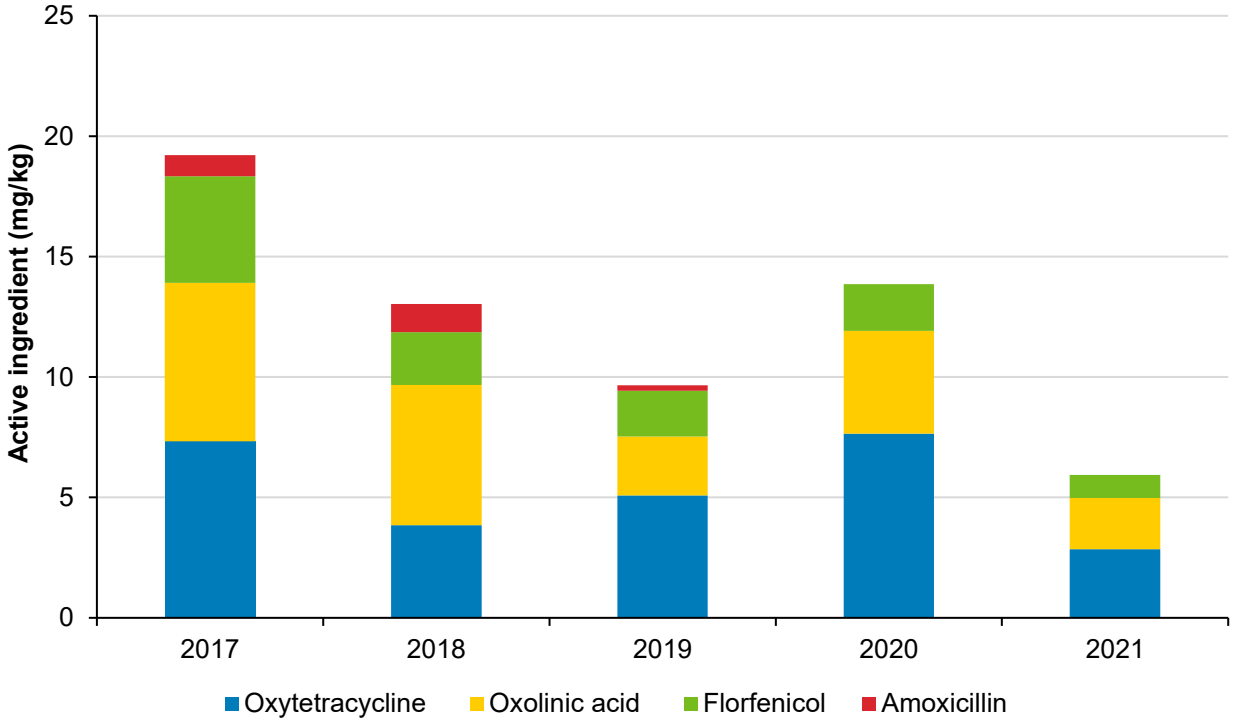
2.3.5.2 Trout

2.3.5.2.1 Results

The data representing 90% of UK trout production demonstrates that a total of 0.08 tonnes of antibiotic active ingredient was used, representing 5.9 mg/kg, a reduction of 7.9 mg/kg since 2020 (**Figure 2.12**). This is the lowest use seen in the trout sector since records began in 2017, representing a 69% (13.3 mg/kg) overall decrease.

When considering use by class, oxytetracycline remains the most used antibiotic (accounting for 48% of overall use) followed by oxolinic acid (36% of overall use) and florfenicol (16% of overall use). In 2021, use of the HP-CIA oxolinic acid was 2.1 mg/kg, a reduction of 2.1 mg/kg since 2020 and 68% (4.4 mg/kg) since 2017.

Figure 2.18: Active ingredient (mg/kg) of antibiotics by antibiotic class used in trout, 2017 to 2021.



2.3.5.2.2 Statement from the British Trout Association

“The trout sector remains below the industry target of 20 mg/kg and the reductions in both overall use and use of the HP-CIA oxolinic acid is testament to the efforts within the trout sector to only use antibiotics when clinically necessary and focus on reducing disease, through biosecurity, farm management and widespread vaccination. This is also aided by the trend towards rearing larger fish, which have lower stocking densities and fewer problems.”

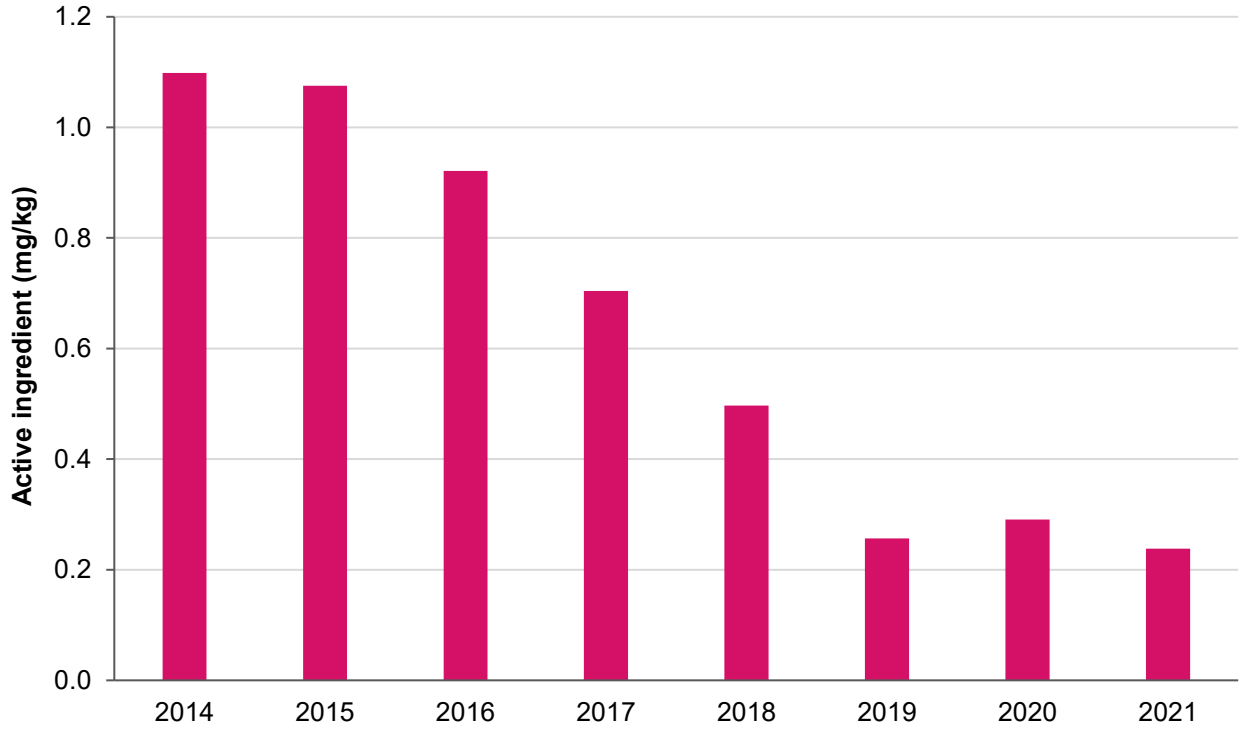
2.3.6 Cattle

2.3.6.1 Cattle update

In the industry sector targets, the cattle sector are aiming for an annual reduction in the rolling three-year average sales from a 2017 to 2019 baseline for both lactating and dry cow intramammary products. Sales of antibiotic intramammary tubes for lactating cows showed an annual reduction in the 3-year rolling average. Between 2018 and 2020, the average yearly sales were 0.63 DCDvet whilst between 2019 to 2021, this had reduced to 0.51 DCDvet. Similarly, sales of antibiotic intramammary tubes for dry cows have also shown a reduction in the 3-year rolling average, decreasing from 0.57 between 2018 and 2020, to 0.54 between 2019 and 2021.

Sales of HP-CIA injectable products licenced for cattle decreased by 0.05 mg/kg between 2020 and 2021, to 0.24 mg/kg. In total, sales of HP-CIA injectables licensed for cattle since 2014 have decreased by 78% (0.86 mg/kg).

Figure 2.19: Active ingredient (mg/kg) of sales of injectable HP-CIA products licenced for cattle, 2014 to 2021.



In the future, overall antibiotic use data from cattle and sheep in the UK will be provided by Medicine Hub, a voluntary industry initiative to collate antibiotic use data. The Hub was launched in 2021 and is the central industry system to record antibiotic use to farm and enterprise level in the ruminant sectors. Medicine Hub have stated that they will not be publishing antibiotic use figures until the dataset has been grown sufficiently to be reflective of the industry as a whole.

Examples of cattle industry data holders

The information below provides information about cattle industry antibiotic data holders within Great Britain. With the relevant farmer permission, data from these data holders will feed into the Medicine Hub.

FarmAssist

FarmAssist is a medicine recording and reporting service run by National Milk Records, which is supported by milk processor clients. Antibiotic data is collected from veterinary practice records and covers 980 dairy herds (approximately 12% of total GB dairy herds in 2021). This data shows a mean use of 19.58 mg/PCU per herd in 2021.

Kingshay

Kingshay Dairy Consultants provide independent consultancy services for a selection of UK dairy farms. Antibiotic data is collected from veterinary practice records and covers 727 dairy herds (approximately 9% of total GB dairy herds in 2021). This data shows a mean use of 16.76 mg/PCU per herd in 2021.

We acknowledge the support of FarmAssist and Kingshay as well as the milk processors, veterinary practices, and farmers who have provided these data. It is important to note that herds within these datasets may not be typical of dairy herds across the United Kingdom as:

- Herd size, production type, or geographic area may vary
- There may be overlap of herds between datasets
- Some farms contain antibiotic use data from 2020 as well as from 2021

Welsh Lamb and Beef Producers AMU calculator

The Welsh Lamb & Beef Producers (WLBP) AMU Calculator went live in 2021 and allows vets servicing Welsh livestock farmers to calculate farm-level antibiotic use in a standardised way. From July 2022, members of the Farm Assured Welsh Livestock (FAWL) scheme are required to have their antibiotic use calculated on the platform during the annual health and welfare review with the vet and, to date, 1009 beef farms and 265 dairy farms have added their data.

FarmVet Systems

FarmVet Systems extracts and analysis data from Vet Practice Management Systems. Antibiotic use data covering 2464 UK dairy farms (representing 25% UK dairy cattle) and 2265 beef farms (representing 5.6% of GB beef cattle) covering the period from 2015 to 2019 is available here.

2.3.6.2 Statement from the Cattle Antibiotic Guardian Group

“Until now, the ruminant sector has not had a central system to record antibiotic use to farm and enterprise level. Medicine Hub was launched in early 2021, as an industry voluntary initiative, to provide this facility for cattle (and sheep) farms. The Hub supports a number of routes for uploading data – direct manual entry by the farmer or vet, or electronic upload from vet practice management software systems, farm software providers or other third-party holders of data, who have the express permission of farmers to upload data on their behalf. These options reflect the greater number of cattle holdings and diversity of enterprise types in comparison to other sectors. The range of options within the system also aims to avoid, wherever possible, the need to duplicate effort by farmers and vets.

The Hub is starting to gain traction and the priority has been to achieve the first-year engagement targets for 2021 datasets agreed by the RUMA Targets Task Force, whilst also using these early datasets to identify and address any technical challenges encountered by users. These targets have been exceeded for beef cattle, uploading over 1200 datasets compared to the target of 1000 for 2021. The dairy sector is also on track, uploading 1100 datasets. Uploads reflect the full range of enterprises, including specialist calf rearers. The Hub will not be publishing any antibiotic usage figures until the dataset has grown sufficiently to be reflective of the industry as a whole.

The engagement targets for 2022 are double those of 2021 and the sectors are working hard to meet those.

The low overall use of injectable HP-CIA products and the further 18% reduction in 2021, demonstrates the sectors commitment to moving away from using antibiotics considered a priority for human medicine. It is also encouraging that intramammary HP-CIA products in 2021 were lowest recorded and represents a 96% reduction since 2014.”

2.3.7 Sheep

2.3.7.1 Statement from the Sheep Antibiotic Guardian Group

“The sheep sector remains committed to using antibiotics as little as possible and as much as necessary. This is a balance between responsible antibiotic use and ensuring sheep health and welfare are protected and to this end, the sheep sector has made substantial progress over the last five years. This includes both efforts to enable national reporting and in targeted action to ensure responsible antibiotic stewardship within the sector.

SAGG worked with the industry to create the metrics that standardise calculations for antibiotic use on sheep farms. These metrics have been widely adopted by industry to ensure consistency in reporting between farms and over time as well as the ability to aggregate data. Medicine Hub, developed and managed by AHDB, was launched in 2021 and provides a central location for the collection of medicine data, including antibiotic use

on farm. There are currently 500 sheep farmer datasets on the Medicine Hub and a further 845 Welsh farmers who have contributed data to the Welsh Lamb and Beef Producer calculator.

The sheep sector has a strong focus on consistent, coordinated, and collaborative communications that is driven by motivating and encouraging teamwork between vets and farmers and the involvement of individuals throughout the supply chain. Industry guidance documents and timely communications have been used to target reduction, refinement, and replacement of antibiotics in focused areas alongside active participation in two annual cross-sector campaigns: Colostrum is Gold and Vaccines Work. A powerful three-word mantra - Plan. Prevent. Protect - has been central to infographics, communication, and activities since 2017. Activity also includes a major collaborative project – Farm Vet Champions – which provides free online training and the capability to set and track goals to unite farm animal vets in establishing good antibiotic stewardship in vet practices and on farm with over 730 registered users. Farm Assurance Schemes have also played an important role in supporting responsible use in sheep through revisions to standards that have included requirements for farmer training in medicine use, improved data recording and increased use of health planning.

Progress is evident and will continue. Annual tracking of oral antibiotic sales and sheep vaccines demonstrated a reduction in oral antibiotic sales by 47.9% between 2016 and 2021 and an increase of 12.6% in total number of vaccine doses sold between 2011 and 2021."

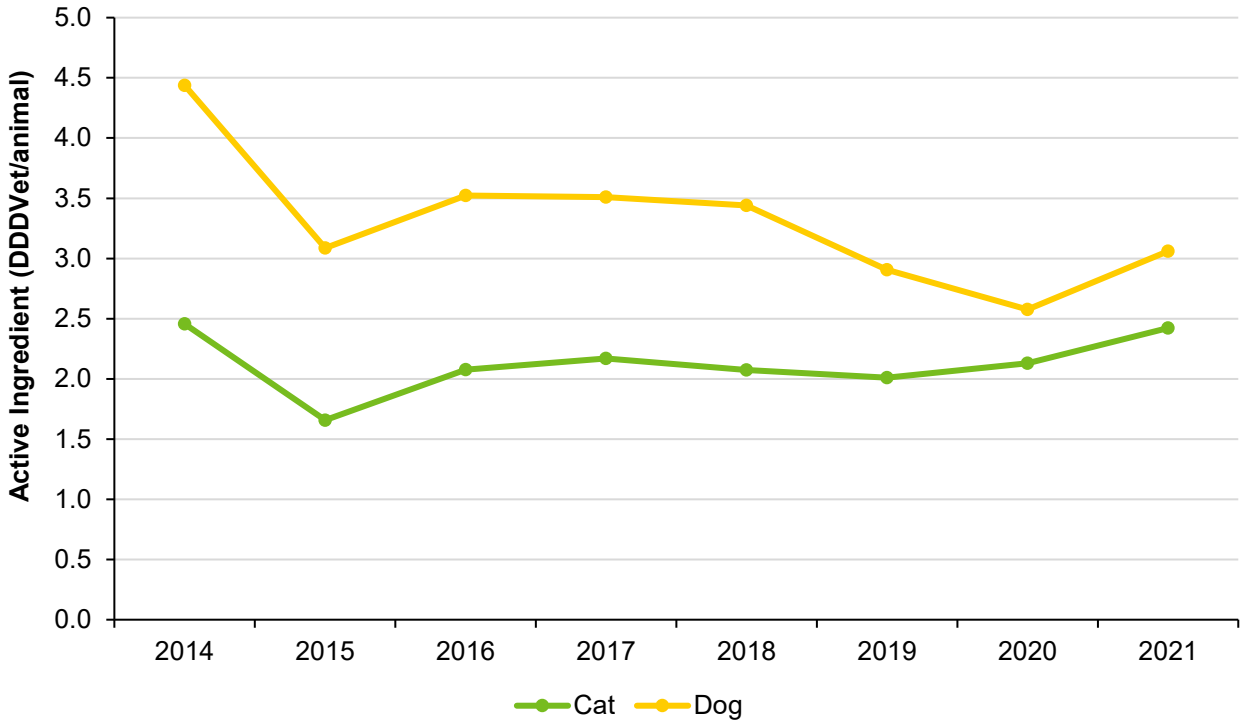
2.3.8 Companion animals

2.3.8.1 Antibiotic use in dogs and cats

In 2021, antibiotic use in dogs and cats has been estimated to be 65.5 mg/kg for dogs and 32.9 mg/kg for cats. This has been calculated by stratifying the sales data and a full methodology can be found in the S.1.4 of this report and the Supplementary Material 1.

When monitoring trends, however, a different metric (DDDVet/animal) is used, which relates to the average number of days that each dog or cat in the UK has received an antibiotic throughout the year. This is considered preferable as it takes into account the length of activity for long-acting products (which are commonly used in dogs and cats) as well as differences in dose rates used. Sales of antibiotic products were 3.1 DDDVet/animal for dogs in 2021, which represents a 0.5 DDDVet/animal increase from 2020 but a 31% (1.4 DDDVet/animal) decrease since 2014 (Figure 2.13). In comparison, sales of antibiotic products for cats were 2.4 DDDVet/animal in 2021, which represents an increase of 0.3 DDDVet/animal since 2020 but a decrease of 1.4% (0.03 DDDVet/animal) since 2014.

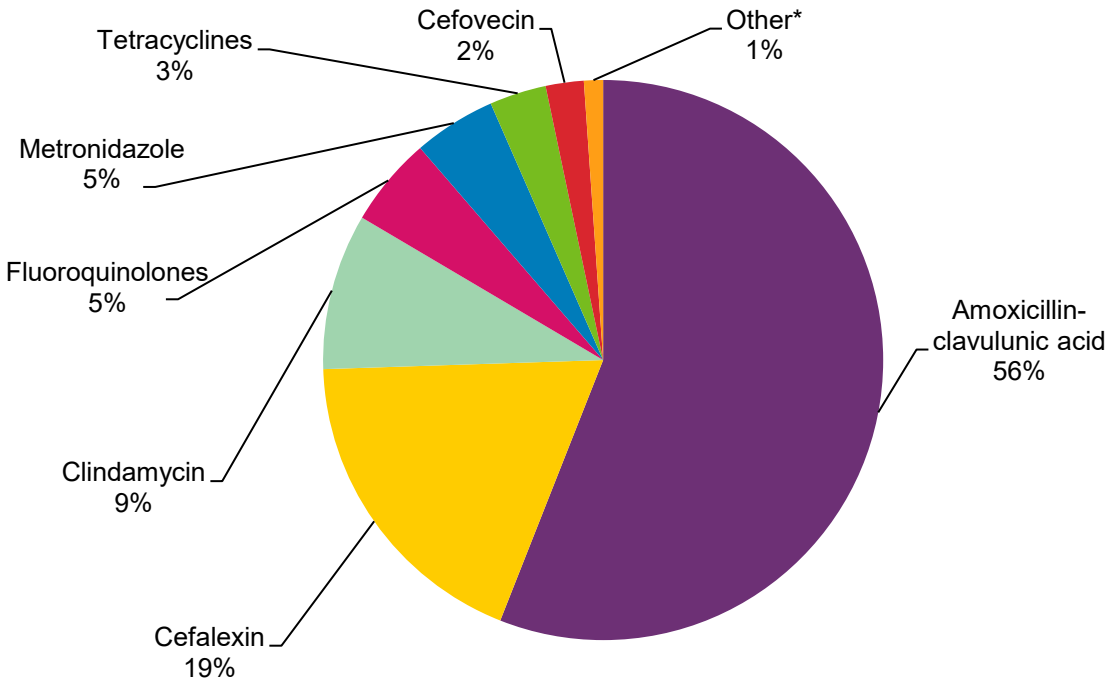
Figure 2.20: Active ingredient (DDDvet/kg) of antibiotics sold for use in dogs and cats, 2014 to 2021



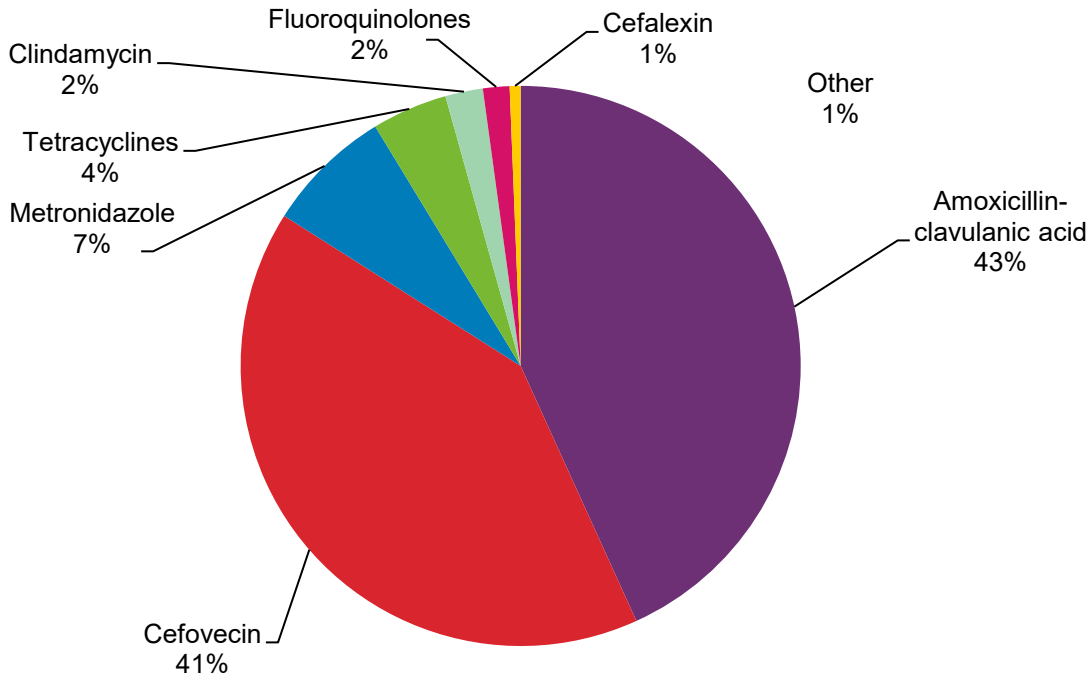
In dogs, amoxicillin-clavulanic acid products were the most sold active ingredient in 2021(**Figure 1.9**), representing 56% of total sales, followed by cefalexin (a first generation cephalosporin), which represented 19% of total sales. In cats, amoxicillin-clavulanic acid products were also the most sold active ingredient in 2021 (**Figure 1.9**), representing 43% of total sales, closely followed by cefovecin (a third generation cephalosporin), representing 41% of total sales.

Figure 2.21: Active ingredient (DDDVet/animal) of antibiotics by active ingredient/antibiotic class sold for use in (a) dogs and (b) cats, 2021.

A)



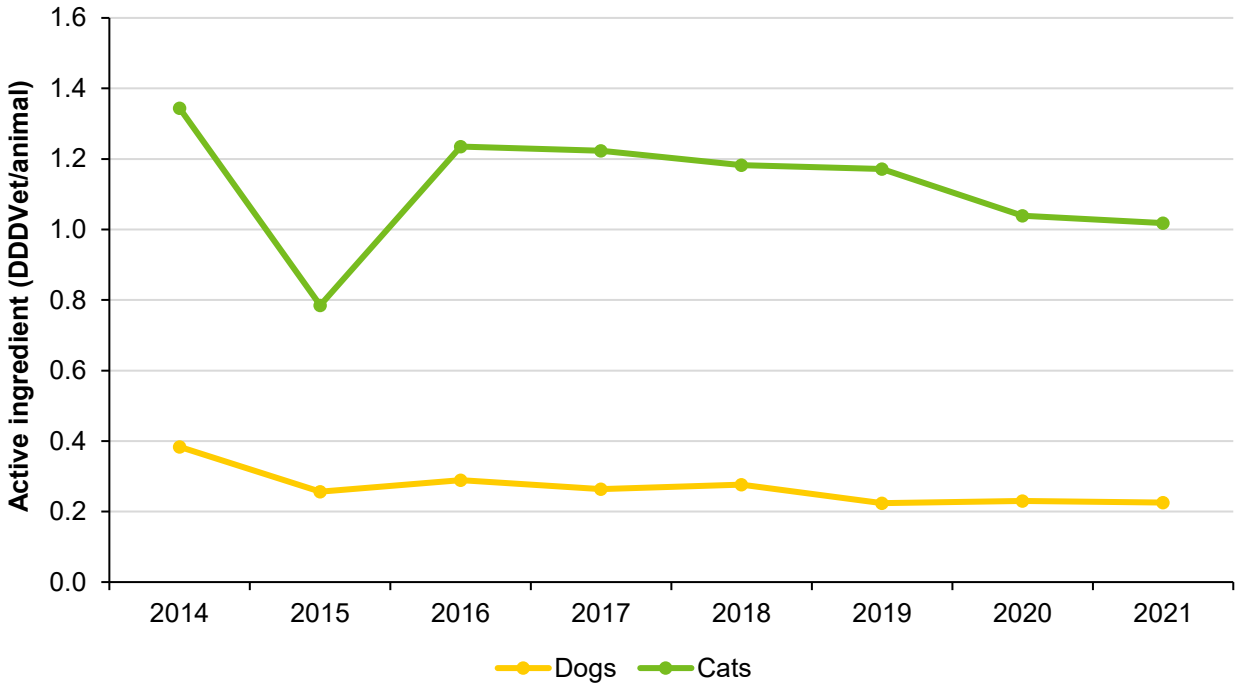
B)



* Aminopenicillins (amoxicillin and ampicillin), trimethoprim-sulphonamides, metronidozole-spiramycin

In dogs, sales of HP-CIAs (**Figure 1.15**) accounted for 7% of total sales (0.23 DDDVet/animal), which represents a reduction of 41% (0.2 DDDVet/animal) since 2014. In cats, however, HP-CIAs accounted for 42% of total sales (1.0 DDDVet/animal), which represents a reduction of 24% (0.3 DDDVet/animal) since 2014. Fluoroquinolones represented 70% of HP-CIA use in dogs, whereas in cats, 96% of HP-CIA sales were for the third generation cephalosporin cefovecin.

Figure 2.22: Active ingredient (DDDVet/animal) of HP-CIAs, sold for use in dogs and cats, 2014 to 2021.



2.3.8.2 Industry updates

RUMA Companion Animal and Equine Group

"There is a big focus in the companion animal and equine sectors on antibiotic stewardship currently. The collaborative, cross-sector Responsible use of Medicines Alliance – Companion Animal and Equine (RUMA CA&E) has met regularly, with a particular focus on developing metrics for monitoring and benchmarking use in dogs and cats in the first instance, with equine to follow, and identifying key areas where antibiotic stewardship can be improved, including how to reduce the high use of HP-CIAs as highlighted by the 2021 antibiotic use data. We will follow this up with the creation of educational case reports and evidence-based and measurable activities that will promote and enhance stewardship. There has also been a focus on how to communicate these messages to the veterinary practice teams, and our website (https://rumacae.org.uk/) has been updated to include links to resources and research about antibiotic stewardship in dogs, cats and horses. RUMA CA&E will also be publishing its first progress report towards then end of 2022, which will summarise all activity to date, as well as future activity plans. This will be available to download from the website."

RCVS Knowledge

"Veterinary charity, RCVS Knowledge is part of the RUMA Companion Animal and Equine Group and leads VetTeamAMR, which champions the responsible use of antimicrobials within companion animal, farm animal, and equine veterinary teams. This major collaborative project, funded by the Veterinary Medicines Directorate, brings together a cross-industry consortium to use and create the evidence base to support continuous improvements in antimicrobial use at the point of care. Part of VetTeamAMR is the Farm Vet Champions project, which launched in May 2021 and provides farm veterinary teams with free online learning to improve knowledge on antibiotic stewardship, infection prevention and control, and behaviour change. The charity will launch an additional online learning course for companion animal and equine veterinary teams. Another area of focus for VetTeamAMR is an audit and national benchmarking tool for companion animal and equine practitioners. The tool will enable veterinary practices to better understand their antibiotic use to identify and promote best practice approaches to antibiotic prescribing. Through the VetTeamAMR project, RCVS Knowledge is providing a means for veterinary teams to network and share lessons on a national scale. RCVS Knowledge is also inviting applications for its antimicrobial stewardship awards, which celebrate practical examples where individuals and/or teams are improving responsible antimicrobial prescribing. The deadline for applications is Friday 13 January 2023 - learn more at rcvsknowledge.org/awards."

2.4 Methods

Pigs

The antibiotic use data in pigs were extracted from the electronic Medicines Book for Pigs (eMB), developed by the pig sector with support from the VMD, and launched by the Agriculture and Horticulture Development Board Pork (AHDB-Pork) in 2016.

The scope and limitations of the data (as provided by AHDB-Pork) are presented below:

- These data are national, aggregated figures for antibiotic use calculated from individual unit data held in the eMB for pig farms across the UK.
- eMB uptake to date has been voluntary and this sample may not be representative for the whole of the UK.
- In terms of pig production, this eMB data covers English slaughter pigs only for 2015 and 2016, and UK slaughter pigs for 2017 to 2021 The eMB data as a percentage of the total clean pig slaughter figures for the relevant region are: 2015 - 61%, 2016 - 70%, 2017 - 87%, 2018 - 89% , 2019 - 95%, 2020 - > 95% and 2021 - > 95%.
- The data are inputted by producers and, although clear outliers have been identified and queried, AHDB is not able to validate every individual producer's data. However, at a national, aggregated level, the data provide an estimation of national use and allow year on-year comparisons to be made.

- The data for 2021 were extracted from eMB on 12th August 2022 and these figures will now be fixed as the reference levels for 2021.
- The eMB database and the calculations within it are subject to a series of quality assurance checks to ensure national aggregated figures are as accurate as possible. As a result of this process, the eMB system is continuing to develop and work to further improve data accuracy is ongoing.
- The calculations used for the eMB data are in-line with the methods used by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, to allow comparisons to be made with European counterparts.

Meat poultry

The British Poultry Council (BPC) provided antibiotic use data for the poultry meat (chicken, turkey and duck) sectors. BPC runs BPC Antibiotic Stewardship, which covers 90% of UK poultry meat production. This process of data collection started in 2012 and producers are responsible for submitting quarterly (chicken, duck) or annual (turkey and all breeders) antibiotic use data in the form of an aggregate spreadsheet. BPC then collate the data and report use by sector in their annual report. This includes the overall annual amount of active ingredient used (in tonnes), which covers both breeders and producers.

For the producers, this is then compared with the population at risk of treatment to create a mg/kg use figure. BPC calculates the population at risk of treatment by using annual slaughter numbers and standardised estimated weights at time of treatment (chickens: 1.0 kg as derived by ESVAC; turkeys: 6.5 kg as derived by ESVAC; ducks: 1.75 kg as derived by BPC based on ESVAC principles).BPC carries out the calculations using ESVAC methodology. The process of calculating the quantity of antibiotic active ingredient has been validated by the VMD.

Laying hens

The collection of antibiotic use data for the laying hen industry is organised by the British Egg Industry Council (BEIC). Sharing these data with BEIC is mandatory through the Lion Scheme, a farm assurance scheme which represents over 90% of the UK laying hen industry.

All egg producers, pullet rearers and breeding companies are required to report any use of an antibiotic to their subscriber. This is then reported to the BEIC on a quarterly basis. The BEIC collated aggregate annual antibiotic pack level data and provided it to the VMD, who carried out the calculations and validation of the use by active ingredient using ESVAC methodology. Denominator data are available from monthly records of the total number of birds in the scheme, averaged over the year.

The data published here as ‘actual daily bird days/100 bird days at risk’ represent the average number of days treatment administered per chicken over a 100-day period.

Note that a ‘mg/kg’ figure has not been included, as ESVAC methodology does not include a standardised method for laying hens.

Gamebirds

The Game Farmers’ Association (GFA) and the British Veterinary Poultry Association (BVPA) gamebird subcommittee coordinated a comprehensive, voluntary data collection exercise to measure the use of antibiotics throughout the sector for 2021. This involved the collection of in-feed medication records from game feed producers (which supply 95% of game farmers and rearers) and prescribing records from specialist gamebird vets (of which 75% of game farmers and rearers are clients).

Each company was asked to provide a spreadsheet showing the amount of antibiotics used in 2018. GFA aggregated the results and provided them to the VMD, who then used ESVAC methodology to calculate the amount of antibiotic active ingredient administered by the game sector.

Note that a ‘mg/kg’ figure has not been included, as ESVAC methodology does not include a standardised method for gamebirds.

Aquaculture

The trout data were collected from the main veterinary practices dealing with trout in England and Scotland and represent approximately 90% of UK trout production. The salmon use data were collected by the Salmon Scotland from all veterinary practices treating salmon in Scotland and therefore represent 100% of Scottish salmon production. The aggregated data were analysed as mg/kg using ESVAC methodology, where kg represents the weight of slaughtered fish as live weight.

It is important to note that around 30% of trout are reared for restocking waters for angling rather than directly for food production. Antibiotic use on these restocking fish will be captured in the weight of active ingredient, but not in the weight denominator, leading to a potential overestimate of the mg/kg. It should also be noted that salmon have a three-year production cycle, so the tonnes of fish produced in any one year do not fully represent the overall salmon population that may require treatment.

Cattle

Total antimicrobial use for each farm in the subsection of dairy farms presented were calculated using mg/kg following the standardised ESVAC methodology. The weight of active antimicrobial product (mg) was obtained from veterinary prescription data. Population data was obtained from vet or farmer reported herd numbers for 2021.

Companion animals

Mg/kg for dogs and cats

In this metric, mg refers to the weight of antibiotic active ingredient sold for use in dogs and cats. As with the mg/PCU metric, topical products (e.g. those for treating eye, ear and

skin infections) are excluded. The denominator is the estimated weight of the whole dog and cat population at risk. The total number of dogs and cats in the UK is estimated using statistics from the PDSA PAW report, which is a survey that is representative of the UK pet-owning population. This is then multiplied by the aggregated mean weight for all adult cats and all adult dogs registered at practices participating in the Small Animal Veterinary Surveillance Network (SAVSNET) between 2013 and 2021 (excluding animals aged under 2 years, over 22.5 years for dogs and 27.5 years for cats and/or with unrealistic weight measurements).

The metric is calculated separately for dogs and cats, with the amount of antibiotic active ingredient separated by dog and cat. For products licensed for more than one species, the relative amount of total product sold which is consumed by dogs and cats have been estimated. Estimates are obtained by the VMD from stratification data provided by the Market Authorisation Holder (MAH) for each product. The stratification data indicates the percentage of each product which is estimated to have been used in dogs and in cats, respectively, in any given year. Only products which were licensed for dogs and/or cats +/- other species commonly seen in small animal practice (e.g. rabbits, rodents and exotics) were considered. Products indicated for dogs and/or cats alongside horses and/or food producing animals were not considered, as it is harder to accurately provide stratification estimates for these products, which are primarily injectables and are used increasingly in food producing animals.

The average number of Daily Defined Doses per animal per year (DDDVet/animal) for dogs and cats

The main issues with using mg/kg for trend monitoring in dogs and cats are that it underestimates the use of long acting injectables (which are very commonly used in cats) and there are also some big variations in dose rate. For example, marbofloxacin has a dose rate of 2 mg/kg/day, whereas metronidazole has a dose rate of 50 mg/kg/day. For this reason, dog and cat (companion animal) trend sales data for systemic antibiotics is presented and calculated using the the average number of Daily Defined Doses (DDDVet) per animal per year(DDDVet/animal). This metric has been developed alongside, and with the support of, the RUMA Companion Animal and Equine group.

The DDDVet is defined as the assumed average dose per kg animal per species per day. These standard daily doses are extracted from the Summary of Product Characteristics (SPC) for each antibiotic product. If there is a dose range, then the lowest dose was chosen, and where the dose rate varies between products with the same active ingredient/ route of administration, then the median dose rate was selected. For long-acting products, the DDDVet is calculated by dividing the daily dose rate with the length of activity for that product. A full list of the DDDVet figures used for each active ingredient/ route of administration can be found in Table S1.3.1 of Supplementary Material 1.

The DDDVet/animal is calculated (for each active ingredient/ route of administration and for both dogs and cats) using the method below:

$$\frac{\text{Total amount of active ingredient (mg)}}{\text{(DDDVet (mg/kg/day) * total animal population weight at risk (kg))}}$$

The results are then added together to get the total figure. The mg of antibiotic active ingredient and total weight of animal population at risk is calculated in the same way as described above for the mg/kg calculation.

CHAPTER 3

Harmonised monitoring of antibiotic resistance

This programme was originally developed to harmonise monitoring and reporting of antimicrobial resistance (AMR) in the food chain across Europe. It involved testing for resistance in zoonotic and commensal bacteria from healthy food-producing animals at slaughter, *Salmonella* isolates from the poultry National Control Programmes and food products at retail. The UK is continuing these surveillance activities in animals at slaughter to ensure the continuity of data outputs, trends, and indicators from this programme. Maintaining regional/international harmonisation in this area also facilitates comparability of AMR data with other countries across Europe. In 2022, we expanded this programme to include monitoring AMR in enterococci; results will be published in next year's VARSS report.

In the UK, key livestock species are monitored in alternating years (poultry in even years, pigs in odd years); the 2021 data presented here originates from healthy pigs at slaughter. The samples collected for this programme are taken from pig caeca and are designed to be representative of the UK pig population. In 2021, we tested for AMR in individual isolates of *E. coli* and *Salmonella* from caecal samples, which gives us an indication of the prevalence of resistance in these bacteria in pigs across the UK. We also used selective media to detect ESBL- and AmpC-producing *E. coli,* which measures the proportion of pigs carrying any *E. coli* resistant to specific HP-CIAs. The samples collected for this programme are designed to be representative of the UK pig population.

The Food Standards Agency (FSA) lead on the testing and reporting of AMR in retail meat, which is published elsewhere.

3.1 Summary

Escherichia coli

- Harmonised outcome indicators have improved substantially compared to the start of the monitoring period (2014/2015). However, there has been an increase in the secondary indicator 'proportion of samples identified as positive for presumptive ESBL-/AmpC-producing indicator *E. coli*' since 2019/2020, from 0.10 to 0.14 (41.1%).
- There was no resistance detected to the aminoglycoside amikacin, the carbapenem meropenem, the glycycline tigecycline or the polymyxin (and HP-CIA) colistin in pigs in 2021.
- Resistance to the HP-CIAs cefotaxime and ceftazidime (third generation cephalosporins) remains low and has declined since 2019 to 1.3% (for both antibiotics).
- Resistance to the HP-CIA ciprofloxacin (fluoroquinolone) has increased since 2015 but remains at low levels (4.6%), and to the HP-CIA nalidixic acid is low (1.7%) and has remained stable since 2015.
- Prevalence of ESBL- and AmpC-producing *E. coli* detected by selective culture is at the highest recorded levels in 2021, at 18.1% and 12.0% of pig caecal samples, respectively, which is affecting the secondary indicator outlined in the first bullet.
- No carbapenemase-producing *E. coli* have been detected over the monitoring period.
- Resistance to all non HP-CIAs remains either stable or in decline.

Salmonella spp.

- This year is the baseline year for testing the resistance of *Salmonella* isolates from caecal samples, rather than carcase swab samples.
- No resistance was detected to the aminoglycoside amikacin, the carbapenem meropenem, the macrolide azithromycin, or the HP-CIAs cefotaxime and ceftazidime (third generation cephalosporins) and colistin in 2021.
- Resistance to the HP-CIAs ciprofloxacin (fluoroquinolone) and nalidixic acid (quinolone) was detected at low levels (6.0% and 5.1% respectively).
- Resistance in *Salmonella* was broadly similar to that seen in *E. coli*.

3.2 Methods

3.2.1 Sample collection

Caecal samples were taken from healthy pigs at slaughter by Food Standards Agency (FSA) personnel. The sampling plan was randomised, stratified, and weighted by slaughter

throughput. Samples were collected from the biggest slaughterhouses, covering over 60% of the UK pig throughput in 2021. Sample collection was randomised and evenly distributed throughout the year. One caecal sample was collected per epidemiological unit sampled. This year the epidemiological unit used was changed to the slaughter batch, rather than pig holding.

3.2.2 Antibiotic susceptibility testing (AST)

AST was carried out by the national reference laboratories (NRLs). Caecal samples were cultured for *E. coli* and *Salmonella* using appropriate media and a single typical colony was selected for speciation and susceptibility testing. Standardised broth microdilution was used to determine the minimum inhibitory concentration (MIC) against a panel of antibiotics. The panel is set out in the EU Commission Implementing Decision 2020/1729.

In addition, caecal samples were cultured for ESBL-/AmpC-/carbapenemase-producing *E. coli*. Whole genome sequencing (WGS) and *in silico* bioinformatic tools were used to detect the antibiotic resistance determinants present in the isolates with ESBL- or AmpC-phenotypes.

Detailed methodology for the susceptibility testing is presented in S3.1 of Supplementary Material 1.

3.2.3 Interpretation of results

This year, epidemiological cut-off values (ECOFFs) were used to assess susceptibility of the bacterial isolates. ECOFFs represent the point at which bacteria have developed a higher level of resistance to an antibiotic than the background level of resistance that exists naturally for that bacterial species. ECOFFs are more sensitive than clinical breakpoints (CBPs) for detecting emerging resistance issues. A 'decreased susceptibility' or 'resistant' result based on ECOFFs does not necessarily imply a level of resistance that would correspond to clinical treatment failure. Measuring resistance using ECOFFs in this report allows the UK's AMR results to be directly compared to those of other European countries.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology for ECOFFs was used in this report. In previous UK-VARSS reports some of the data was interpreted using EUCAST CBPs, rather than ECOFFs. Additionally, some of the ECOFF values used throughout Europe have been updated, and historical data presented in this report has been updated accordingly. The change from CBPs to ECOFFs, and the updates to specific ECOFF values, mean that the trends in data presented here may differ slightly to those presented in previous reports. For instances where no ECOFF is available, EFSA recommended breakpoints have been used instead. This was the case for azithromycin in both *E. coli* and *Salmonella* isolates and for sulfamethoxazole in *Salmonella* only. Results are provided in full for both ECOFFS and CBPs (S1.1 and S1.2) in Supplementary Material 3.

The quinolone nalidixic acid became classified as an HP-CIA in the AMEG guidelines at the end of 2019, and as such is referred to and grouped with other HP-CIA antibiotics within this report.

3.3 Results

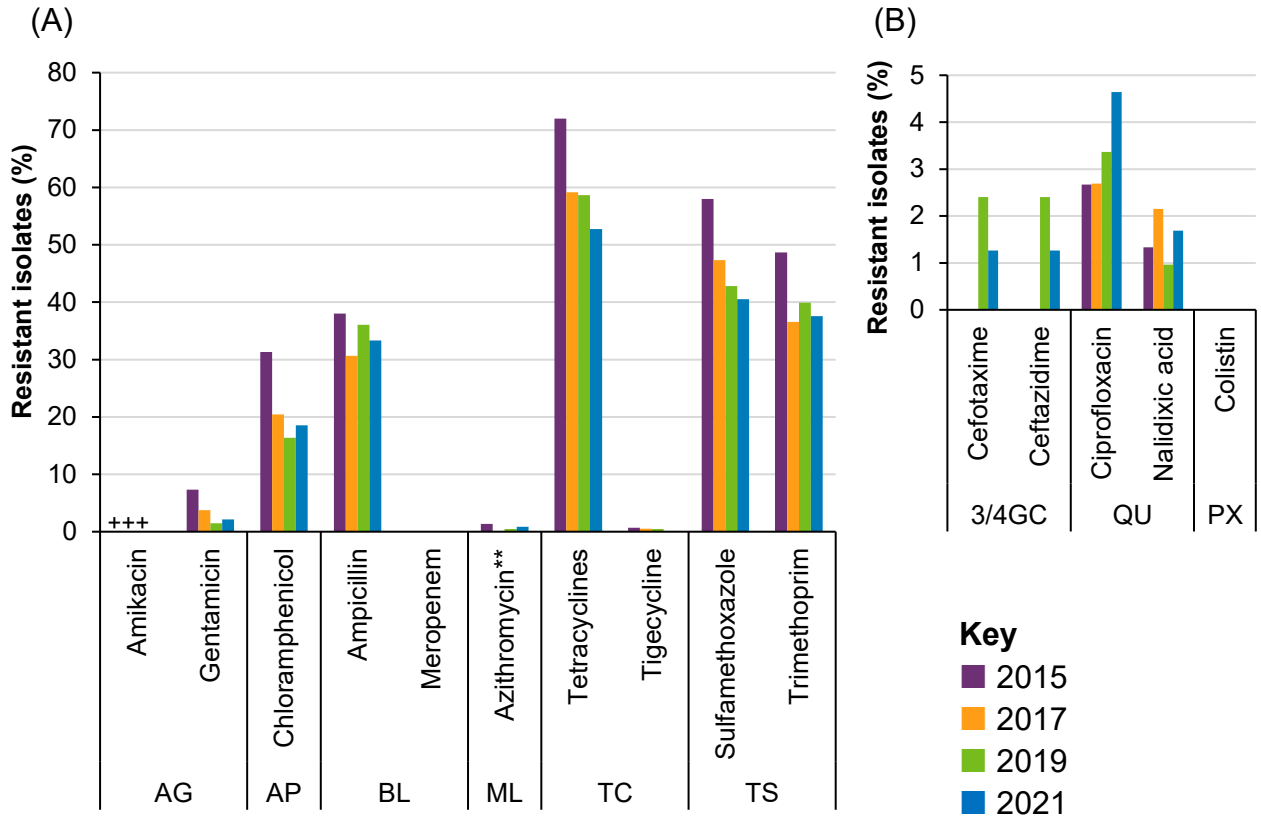
The number of isolates tested are shown in Table S.1.1.1 of Supplementary Material 3. All isolates collected were tested against the full antibiotic panel. Certain active ingredients that were included in the panel are not authorised for use in food-producing animals. These are included to monitor resistances of concern to public health (for example, carbapenem resistance), or because they are representative of an antibiotic class. Please refer to Table S1.4.2 of Supplementary Material 1 to see a table of these compounds. Where a figure in this chapter shows no data for certain antibiotics or years, this is because no resistance was detected.

Classification of resistance as low, moderate, high etc. throughout the report is consistent with EFSA definitions for these terms. A table explaining these definitions can be found in the introduction (Table 2).

3.3.1 *Escherichia coli*

Resistance in indicator *Escherichia coli* isolated from pig caecal samples is shown in **Figure 3.1.** Full susceptibility to the panel of antibiotics tested was exhibited by 34.6% of isolates, whereas 37.1% of isolates were multi-drug resistant (MDR; resistant to three or more classes of antibiotics included in the test panel). The percentage of fully susceptible isolates has increased over the monitoring period from 22.9% in 2015, whereas the percentage of MDR isolates has decreased from 50.6% in 2015.

Figure 3.1: Resistance to non-HP-CIAs (A) and HP-CIAs (B) in *Escherichia coli* isolates from healthy pigs at slaughter. Interpreted using EUCAST ECOFFs unless otherwise indicated. Note scale differs between graphs.



+ Not tested
** Interpreted using an ESFA recommended ECOFF
AG: aminoglycosides, AP: amphenicols, BL: beta-lactams, ML: macrolides, PX: polymyxins, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Of the HP-CIAs, resistance to the third generation cephalosporins cefotaxime and ceftazidime both declined between 2019 and 2021 from 2.4% (the highest resistance noted over the monitoring period) to 1.3%. Resistance to the fluoroquinolone ciprofloxacin remains at low levels (4.6% in 2021). However, moving from CBPs to ECOFFs when determining resistance to this antibiotic means that a new trend has become apparent: increasing departure from the wild type (i.e., decreased susceptibility) over the monitoring period (from 2.7% in 2015 to 4.6% in 2021). Of the 11 isolates resistant to ciprofloxacin, four were also resistant to the quinolone nalidixic acid. Resistance to nalidixic acid is low (1.7%) and has remained stable since 2015. There continue to be no detections of colistin resistance.

For the non-HP-CIA antibiotics, resistance levels are generally stable or in decline. Regarding the aminoglycosides, amikacin was tested for the first time this year; no resistance was detected and resistance to gentamicin has remained low (2.1%). Although resistance levels to gentamicin have slightly increased compared to 2019, they remain lower than those seen in 2015 and 2017. Resistance to chloramphenicol was moderate (18.6%) and shows the same trend. Of the beta-lactams, resistance to ampicillin has

remained high (33.3%) but has dropped to the second lowest levels reported since 2015 and there continues to be no resistance to meropenem. Resistance to the macrolide azithromycin (0.8%) has remained at very low levels since 2017. Resistance to tetracyclines remains very high (52.7%), however resistance has continued to decline since 2015. For the glycycline tigecycline, historically no resistance has been detected over the monitoring period. However due to a recent change in breakpoint, one isolate is now noted as resistant in 2015 (0.7%), 2017 (0.5%) and 2019 (0.5%). No resistance was detected in 2021. Resistance to sulfamethoxazole remains high (40.5%) however, like tetracyclines, resistance has shown a continued decline since 2015. Of the 96 isolates resistant to sulfamethoxazole, 73 were also resistant to tetracyclines, 76 to trimethoprim and 58 to ampicillin. Resistance to trimethoprim also remains high (37.6%) but has dropped to the second lowest levels reported since 2015 (only rising above levels seen in 2017).

3.3.2 ESBL-, AmpC- and/or carbapenemase-producing *E. coli*

The results in Section 3.3.1 and **Figure 3.1** above show that the prevalence of resistance to HP-CIAs in individual *E. coli* isolates from pigs is low. The UK also conducts additional, more sensitive, testing that detects any *E. coli* resistant to third generation cephalosporins and carbapenems, even when they are in the minority amongst the bacterial gut flora of individual pigs. We do this by growing caecal samples in selective culture media, which inhibits growth of susceptible *E. coli* and allows the resistant bacteria to multiply, making them easier to detect. The results in this section therefore represent the percentage of individual pigs carrying *E. coli* resistant to these antibiotics. The results in the previous section represent the percentage of *E. coli* carried by the UK pig population that are resistant to these antibiotics.

In 2021, the percentage of pig caecal samples yielding ESBL- or AmpC-producing *E. coli* increased to 30.1%, the highest levels detected since 2015 (25.1%). This percentage is substantially higher than the prevalence of resistance to third generation cephalosporins shown in the previous section. Taken together, these results indicate that a higher proportion of UK pigs are carrying *E. coli* resistant to these HP-CIAs, although at low levels within individual animals; the majority of *E. coli* isolated from UK pigs remain susceptible (**Figure 3.1**). However, the increase in the prevalence of individual pigs carrying ESBL/AmpC-producing *E. coli* is unexpected, considering the previous downward trend (2015-2019), and the reductions in antibiotic usage recorded by this sector (Section 2.3.1). Further investigations are underway. No carbapenemase-producing *E. coli* were detected over the monitoring period.

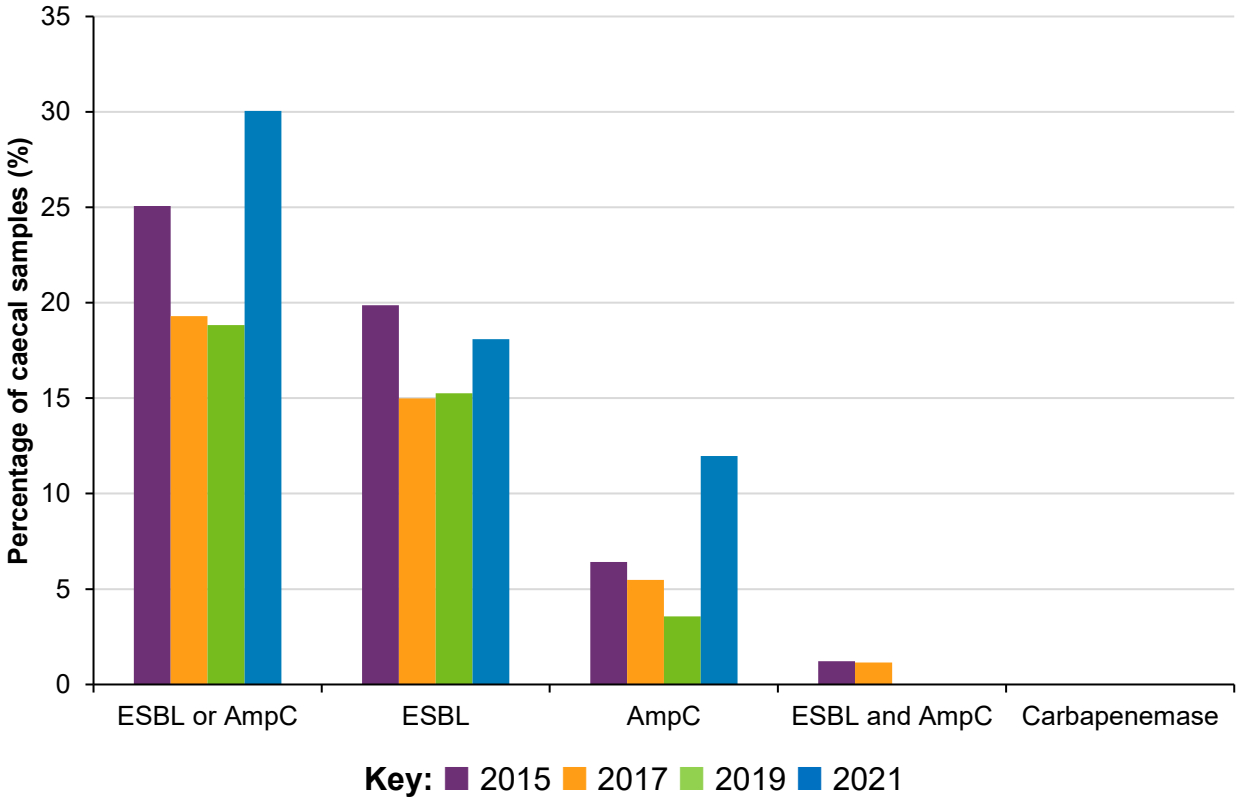
In 2021, of the 376 pig caecal samples tested, 113 (30.1%) yielded growth of *E. coli* on selective MacConkey agar containing the third generation cephalosporin cefotaxime, which normally indicates ESBL or AmpC production. None of the isolates were resistant to the aminoglycoside amikacin, the carbapenems imipenem or meropenem, the penicillin temocillin or the glycycline tigecycline. Of the 113 *E. coli* isolates with an ESBL/AmpC phenotype, 18.1% (68 isolates) had an ESBL phenotype, and 12.0% (45 isolates) had an

AmpC phenotype, increased from 15.3% and 3.6%, respectively, in 2019. The increase in the percentage of pig caecal samples containing AmpC-producing *E. coli* is particularly notable, given that this percentage has historically been low. No isolates were positive for both phenotypes.

Of the isolates with an ESBL phenotype, 25 (36.8%) were resistant to the fluoroquinolone ciprofloxacin, of which 13 were also resistant to the quinolone nalidixic acid, both of which are HP-CIAs. Nine of these isolates had an MIC of ≥64, a phenotype suggesting *gyrA* or *parC* mutations as the underlying mechanism of resistance. Eleven of the 68 ESBL isolates (16.2%) were resistant to gentamicin, two (2.9%) to the macrolide azithromycin, 50 (73.5%) to tetracyclines, 47 (69.1%) to sulphonamides and 42 (61.8%) to trimethoprim.

Of the isolates with an AmpC phenotype, one isolate (2.2%) was resistant to azithromycin, nine (20.0%) to tetracyclines, 32 (71.1%) to sulphonamides and 30 (66.7%) to trimethoprim. An isolate was also resistant to the carbapenem ertapenem but susceptible to other carbapenems imipenem and meropenem. This phenotype can be observed with AmpC production and porin loss. No resistance was detected to gentamicin, nalidixic acid or ciprofloxacin.

Figure 3.2: ESBL-/AmpC- and carbapenemase producing *Escherichia coli* cultured on selective agars, from caecal samples from healthy pigs at slaughter in the UK.



Whole genome sequencing (WGS) was performed on 109 of the 113 ESBL-/AmpC-producing *E. coli* isolates and the underlying genetic mechanism of ESBL or AmpC resistance was determined for 108 these. For one isolate with an ESBL phenotype, the underlying mechanism of resistance was not detected. This likely indicates that resistance in this isolate may be due to a new or novel gene. However, mutations resulting in porin loss or overexpression of efflux pumps can also lead to resistance to beta-lactams in *E. coli*.

The most common ESBL gene detected was *bla*$_{\text{CTX-M-1}}$, which was detected in 31 of 65 ESBL-producing isolates. It was followed by *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{CTX-M-14}}$, which were detected in 11 and seven isolates, respectively. Mutation in the promoter region upstream of the *ampC* gene, leading to overexpression of this gene was the most common resistance mechanism present in AmpC-producing isolates. In total 41 of 44 AmpC-producing isolates harboured the promoter mutation, with only three isolates harbouring the plasmid-mediated *bla*$_{\text{CMY-2}}$.

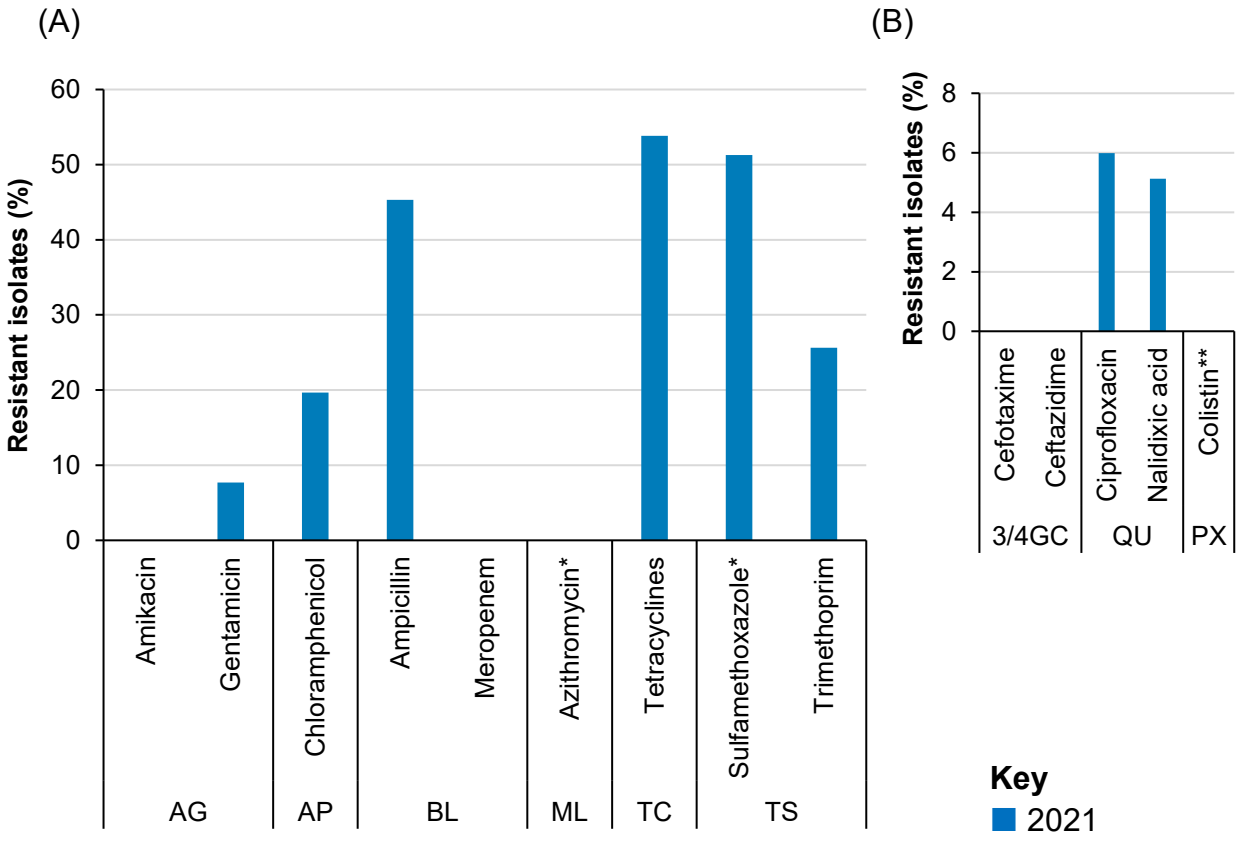
It was also noted from the isolate sequence types (STs) that although the ESBL and AmpC-producing *E. coli* were genetically diverse, the majority of *E. coli* (29 of 41) with mutation in the *ampC* promoter region were from ST23. In contrast, *bla*$_{\text{CTX-M-1}}$-harbouring isolates, which was the most common ESBL type, were represented by multiple STs with ST117 being the most common, indicating its presence on highly mobile plasmid(s).

3.3.3 *Salmonella* spp.

Resistance of *Salmonella* isolated from pig caecal samples is shown in **Figure 3.3.**

For 2021, caecal samples rather than carcase swab samples were used to obtain *Salmonella* isolates. This methodological change not only better aligns with sampling methods used for the other bacterial species; it has also vastly increased the number of *Salmonella* isolations (from nine isolates in 2019, to 117 isolates in 2021). This is due to a much higher level of *Salmonella* in animal gut contents than on carcases, and means that the results presented here give a better reflection of AMR in *Salmonella* in healthy pigs at slaughter.

Figure 3.3: Resistance to non-HP-CIAs (A) and HP-CIAs (B) in *Salmonella* isolates from healthy pigs at slaughter. Interpreted using EUCAST ECOFFs unless otherwise indicated. Note scale differs between graphs.



* Interpreted using an EFSA recommended ECOFF
** Interpreted using EUCAST CBP
AG: aminoglycosides, AP: amphenicols, BL: beta-lactams, ML: macrolides, PX: polymyxins, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

In 2021, 117 *Salmonella* isolates were tested and included monophasic *S.* Typhimurium (42 isolates), *S.* Derby (20 isolates), *S.* Typhimurium (18 isolates), *S.* Panama (13 isolates), *S.* Newport (seven isolates), *S.* Reading (four isolates) and *S.* London (three isolates). Other serovars identified were *S.* Rissen, *S.* Kentucky and *S.* Bovismorbificans (two isolates of each) and single isolates of *S.* Goldcoast, *S.* Infantis, *S.* Kedougou and one incomplete serovar. Of these, 38.5% exhibited full susceptibility to the panel of antibiotics tested which included all *S.* Newport isolates, 12 of the 13 *S.* Panama isolates and 12 of the 20 *S.* Derby isolates.

In 2021, no resistance was detected to the HP-CIAs colistin, cefotaxime or ceftazidime (third generation cephalosporins). Resistance to the fluoroquinolone ciprofloxacin, another HP-CIA, was detected at low levels (6.0%). The ciprofloxacin-resistant isolates comprised two isolates each of monophasic *S.* Typhimurium and *S.* Kentucky, and single isolates of *S.* Typhimurium, *S.* London, and *S.* Derby. The *S.* Kentucky isolates did not show high-level (≥4 mg/l) resistance. Six of the seven ciprofloxacin-resistant isolates were also resistant to the HP-CIA quinolone nalidixic acid. Resistance to nalidixic acid was low

(5.1%). Please note the EUCAST CBP was used for determining resistance to colistin, since no ECOFF is available.

Regarding the non-HP-CIA antibiotics, gentamicin resistance was low (7.7%), chloramphenicol resistance was moderate (19.7%), and ampicillin resistance was high (45.3%). Resistance to tetracyclines and sulfamethoxazole was very high (53.8% and 51.3%, respectively) and trimethoprim resistance was high (25.6%). No resistance was detected to the aminoglycoside amikacin, the carbapenem meropenem or the macrolide azithromycin.

Regarding specific serovars, the typical core pattern of resistance to ampicillin, sulphonamides and tetracyclines was observed in 85.7% of the monophasic *S.* Typhimurium isolates, with or without additional resistance. Streptomycin resistance is also commonly observed as part of this core resistance pattern in monophasic *S.* Typhimurium; however, it is not included in the test panel. *S.* Rissen is an important serovar detected in pigs and humans, particularly in parts of Asia, and was isolated twice. One isolate was resistant only to tetracyclines and the other was resistant to ampicillin, tetracyclines, sulphonamides and trimethoprim.

3.3.4 Harmonised AMR outcome indicators

Indicators are an important tool for interpreting and comparing the results of this AMR monitoring programme. Indicators that are standardised and harmonised between different countries and livestock sectors allow for data to be reported in a consistent way over time, facilitating the assessment of trends, and enabling international comparison in a transparent way.

In 2017, the ECDC, EFSA and EMA recommended harmonised outcome indicators for presenting data on antibiotic resistance in food-producing animal species. These harmonised outcome indicators were developed by panels of experts, including from the UK, and comprise one primary and three secondary indicators. *E. coli* is the indicator organism due to its ubiquitous nature in animals, food and humans and its ability to readily develop or transfer antibiotic resistance between these reservoirs. The indicators are averaged over two years due to the alternating schedule for AMR pig and poultry sampling and are weighted by population size (expressed in PCU). These results therefore give us an indication of the UK's progress as a whole in combatting AMR.

Primary indicator:

- Proportion of indicator *E. coli* isolates from broilers, fattening turkeys, and fattening pigs fully susceptible to the entire panel of antibiotics defined in the Decision 2013/652/EU, weighted by PCU.

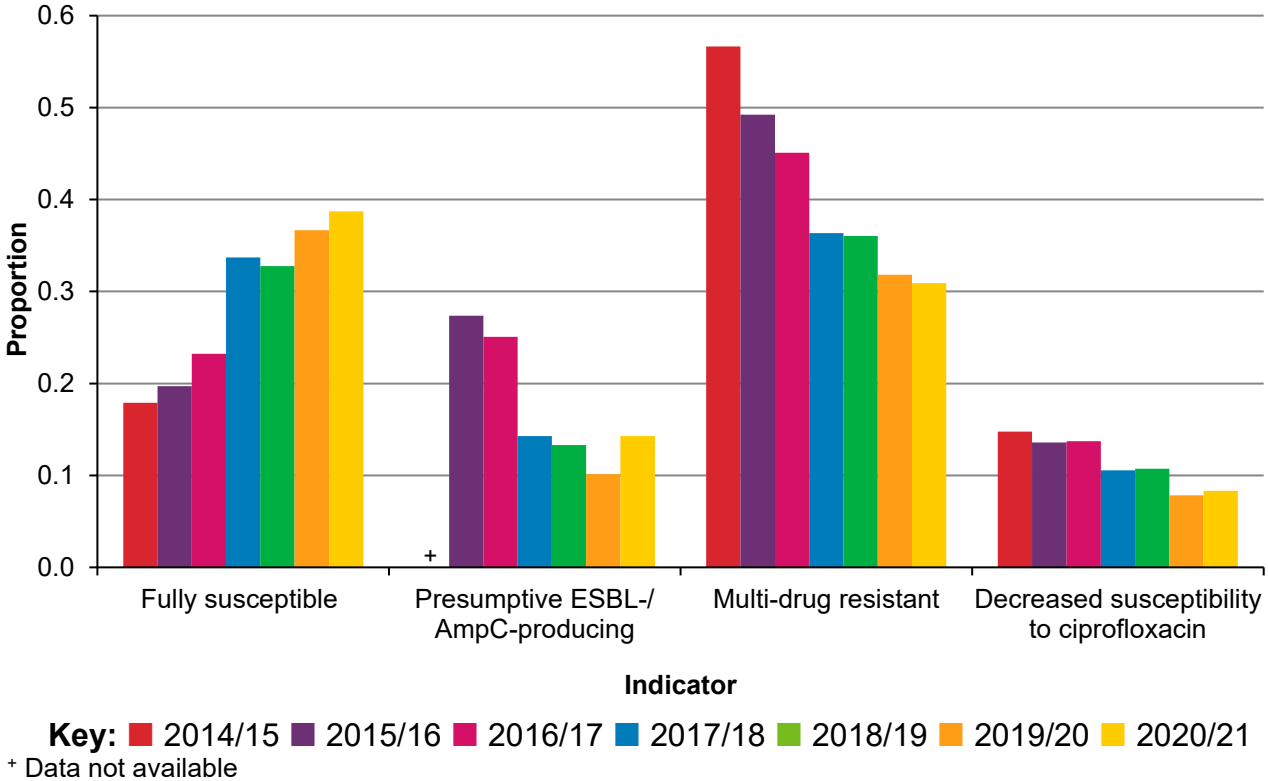
Secondary indicators:

- Proportion of indicator *E. coli* isolates from pigs and poultry, weighted by PCU, showing decreased susceptibility to at least three antibiotics from different classes from the predefined panel of antibiotics (MDR).
- Proportion of indicator *E. coli* isolates from pigs and poultry, weighted by PCU, showing decreased susceptibility to the fluoroquinolone ciprofloxacin.
- Proportion of samples identified as positive for presumptive ESBL-/AmpC-producing indicator *E. coli* from pigs and poultry, weighted by PCU.

For the 2020/2021 monitoring period, all indicators have substantially improved when compared to the start of the monitoring period (2015/2016 for presumptive ESBL/AmpC-producing *E. coli*, and 2014/2015 for all other indicators, **Figure 3.4**). The primary indicator, the proportion of fully susceptible *E. coli*, has continued to increase, and at 0.39, is more than double that reported in 2014/2015.

Of the secondary indicators, levels of presumptive ESBL/AmpC-producing *E. coli* has increased by 41% since 2019/2020, to 0.14. This reflects the increased prevalence of pig caecal samples positive for ESBL/AmpC-producers detected this year (described in Section 3.3.2). However, this indicator remains 48% lower than the proportion observed in 2015/2016 (0.27) and is similar to the proportion reported in 2017/2018 and 2018/2019. MDR has also continued to decline, and at 0.31 is 45% lower than in 2014/2015 (0.57). The proportion of *E. coli* with decreased susceptibility to ciprofloxacin has reduced by 44% since the start of the monitoring period, from 0.15 to 0.08.

Figure 3.4: Proportion of harmonised monitoring *Escherichia coli* from broilers, fattening turkeys and fattening pigs weighted by PCU, averaged over two years. ESBL/AmpC results refer to caecal samples, all other indicators refer to isolates.



+ Data not available

CHAPTER 4

Clinical surveillance of antibiotic resistance

Clinical surveillance is a programme of passive surveillance which evaluates AMR in bacteria of relevance to animal health. These bacteria are isolated from post-mortem carcases or other diagnostic samples submitted by private veterinary surgeons to APHA and partner veterinary laboratories in England and Wales. When a bacterial pathogen is identified, susceptibility testing is performed to provide the practitioner with relevant information for treatment. Similar programmes are conducted by Scottish (SRUC Veterinary Services) and Northern Irish (AFBI-NI) laboratories. This chapter for the majority reports the APHA methods and results; results from SRUC and AFBI-NI are included in S2.6 and S2.7 of Supplementary Material 3.

As this is a passive programme, the results in this chapter should not be considered representative of the UK as a whole and should be interpreted with caution (see Section 4.2 below and S4.1 of the Supplementary Material). The primary aim of the programme is to provide scanning surveillance of animal disease. However, it also helps to identify new and emerging patterns of resistance, particularly since treatment failure is a frequent reason for submission of samples. The programme also incorporates results from the susceptibility testing of *Salmonella* isolates recovered from animals and their environment, as part of the UK Zoonoses Order 1989. Any findings considered to pose a particular risk to human or animal health are reported to the Defra Antibiotic Resistance Coordination (DARC) group and to the VMD for consideration and management in accordance with protocols outlined in the VMD AMR Contingency Plan.

For the second time, this report also presents the results of minimum inhibitory concentration (MIC) testing to assess the susceptibility of important veterinary respiratory pathogens to antibiotics. This year we have expanded this testing to *Streptococcus suis* isolates from pigs, *S. uberis* isolates from bovine mastitis samples, and clinical *E. coli* isolates from chickens. This enhancement of the clinical surveillance programme applies recent recommendations for monitoring AMR from food-producing animals in a way that will generate robust and comparable susceptibility testing outputs for relevant combinations of antibiotics and veterinary pathogens. We aim to continue expanding this

surveillance methodology to a wider range of relevant veterinary pathogens. Results will help inform veterinarians' prescribing choices and support responsible use of antibiotics, as well as increase the ability of clinical surveillance to detect emerging resistance issues in the UK.

4.1 Summary

The resistance levels observed in many veterinary pathogens showed limited change over the monitoring period covered by this report (2019 to 2021). Because scanning surveillance is subject to biases and differences in the intensity of sampling, results in this chapter cannot be extrapolated to the general livestock population.

Respiratory pathogens:

- Major respiratory pathogens (*Pasteurella multocida*, *Mannheimia haemolytica*, *Bibersteinia trehalosi*, *Actinobacillus pleuropneumoniae*) were tested for the second time using a microbroth dilution method to generate MIC results in addition to disc diffusion testing.
- In sheep, all *B. trehalosi* (n=37), *M. haemolytica* (n=123) and 84% (16/19) *P. multocida* (n=19) were susceptible to the panel of antibiotics tested.
- In cattle, 91% (59/65) of *M. haemolytica* and 48% (33/69) of *P. multocida* were susceptible to the panel of antibiotics tested.
- In pigs, 48% (13/27) of *P. multocida* and 61% (11/18) *A. pleuropneumoniae* were susceptible to the panel of antibiotics tested.
- In general, results were broadly similar to last year. Multiple alternative therapeutic options remain available for antibiotic treatment of the main bacterial respiratory pathogens of cattle, sheep and pigs.

Mastitis pathogens:

- *S. uberis* was the most frequently isolated bacteria in bovine mastitis submissions in 2021 (n=49), followed by *E. coli* (n=42), then *Staphylococcus aureus* (n=25) and finally *S. dysgalactiae* (n=13).
- Only one bovine mastitis (*E. coli*) isolate was found to be resistant to an HP-CIA.
- Penicillin resistance was not detected in bovine mastitis streptococci.
- Private lab data (see Section 4.3.2.6) shows resistance to beta-lactams was low or not detected for all pathogens tested, except *E. coli*. Moderate to high resistance to beta-lactams was seen in *E. coli* from bovine mastitis cases, similar to 2020.

LA-MRSA:

- In 2021, LA-MRSA CC398 *spa*-type t108 was recovered in low growth at post-mortem from the heart of a young piglet which had died with no premonitory signs.

Clinical *E. coli*:

- In neonatal and pre-weaning calves, resistance to HP-CIAs was detected at very low to low levels and is mostly decreasing. Isolates from adult cattle were susceptible to all HP-CIAs tested.
- In neonatal and post-weaning pigs, resistance to HP-CIAs was detected at very low to low levels and appears to be stable. Isolates from adult pigs were susceptible to all HP-CIAs tested.
- In neonatal lambs, resistance to HP-CIAs was low and appears to be stable or in decline. No resistance to HP-CIAs was detected in *E. coli* isolated from pre-weaning lambs and adult sheep.
- In chickens, resistance of *E. coli* to HP-CIAs was either not detected or was low and appears to be in decline.
- For the first time, *E. coli* isolates from chickens also underwent MIC testing in 2021. Susceptibility to the full panel of antibiotics tested was detected in 20 (27%) of the 74 isolates, and 51% showed MDR.

Clinical *Salmonella*:

- Of the 4507 *Salmonella* isolates tested in 2021, 2376 were from food-producing animal species, 1019 from non-food-producing animal species, 1090 from feed and 22 from the environment.
- Of the 4507 *Salmonella* isolates tested in 2021, 3044 (67.5%) were sensitive to all antibiotics tested, which is very similar to 2020 (68.3%).
- In 2021 the proportion of *Salmonella* isolates resistant to third generation cephalosporins and fluoroquinolones (HP-CIAs) was very low.
- In 2021, full susceptibility to the panel of antibiotics tested was seen in 77.6% of cattle isolates, 17.5% of pig isolates, 74.3% of chicken isolates, 31.2% of turkey isolates and 68.1% of feed isolates which is higher than last year for all categories.
- In 2021, full susceptibility to the panel of antibiotics tested was seen in 85.0% of sheep isolates and 75.7% of isolates classified as ‘other’, which is a slight decrease compared to last year.
- A change to legislation in 2021 meant that *Salmonella* isolates from dogs became reportable under the Zoonoses Order in Great Britain. Of the 821 isolates tested, 65.4% were fully susceptible to the panel of antibiotic tested.

4.2 Methods

4.2.1 Sample sources

Bacteria were isolated from clinical or post-mortem samples submitted to APHA by practising veterinary surgeons. Submission of diagnostic material may occur more frequently from serious cases of disease or those cases which are refractory to treatment and may therefore be subject to bias. For *Salmonella* spp., any laboratory isolating these

from animals under the UK Zoonoses Order 1989 and their environment in Great Britain is required to notify and submit an isolate to a Defra-approved laboratory for characterisation including antibiotic sensitivity testing.

4.2.2 Susceptibility testing methodology

For the majority of the results presented in this chapter, the method used was that formerly recommended by the British Society for Antimicrobial Chemotherapy (BSAC). The susceptibility tests were performed (unless otherwise stated) by disc diffusion and interpreted using BSAC human clinical breakpoints, where available. Isolates have been classed as either sensitive or resistant; intermediate isolates under the BSAC guidelines are considered resistant. Detailed methodology for the susceptibility testing by disc diffusion and MIC testing is presented in S4.1.1 and S4.1.2 of Supplementary Material 1. However, disc diffusion is limited by the availability of suitable breakpoints for all relevant antibiotic and organism combinations. Assessing the susceptibility of veterinary pathogens by determination of the MIC using a standardised broth microdilution method provides a higher quality, internationally recognised output, which is comparable with other monitoring programmes (such as the harmonised monitoring programme in Chapter 3). VMD and APHA are therefore expanding MIC testing of veterinary bacterial pathogens from clinical surveillance.

MIC testing under the clinical surveillance programme has historically been limited to specific organisms, such as *Brachyspira hyodysenteriae*, which causes swine dysentery. Bacterial susceptibility determined by MIC testing was introduced in UK-VARSS 2020 for key respiratory pathogens (Section 4.3.1), and this year, is expanded to a broader range of veterinary pathogens. Three new additions are *S. suis* isolates from pigs, *S. uberis* isolates from bovine mastitis samples and clinical *E. coli* isolates from chickens, which are presented in Sections 4.3.2.3, 4.3.4.1 and 4.3.5.4 alongside disc diffusion results. The aim for future years is to continue expanding this surveillance methodology to a wider range of relevant veterinary pathogens.

Application of established veterinary clinical breakpoints (CBPs) for relevant antibiotic-pathogen combinations provides useful data for vets to support their prescribing choices. Antibiotics were chosen for the MIC panels according to their clinical importance and licensing in the UK and across Europe, as well as their suitability as representatives or class representatives of resistance. More than one antibiotic could be chosen within a class, for example, on the respiratory panel, tetracyclines were represented by doxycycline and tetracycline. Additionally, antibiotics which are not used in animals but are important indicators of resistance to relevant veterinary antibiotics were also included.

MIC results have been interpreted using available veterinary CBPs from the Clinical and Laboratory Standards Institute (CLSI), and where these are unavailable, veterinary CBPs from the Antibiogram Committee of the French Society of Microbiology (CASFM) and human CBPs from the European Committee on Antimicrobial Susceptibility Testing

(EUCAST). Multi-drug resistance (MDR) was assessed using veterinary CBPs (or human CBPs where a veterinary CBP was not available) and was considered to indicate resistance to any three or more classes of antibiotics. CBPs are used for interpretation of the MIC results as they help to inform veterinarian's prescribing choices, due to their clinical relevance.

This year, EUCAST Epidemiological Cut-off Values (ECOFFs) and tentative ECOFF (TECOFF) values have also been used for interpretation of the MIC results when available. These values allow us to capture emerging resistances below the point of treatment failure, thereby increasing the sensitivity of surveillance for AMR. This is the same approach used in the harmonised monitoring programme, as explained in Section 3.2.3.

Further details on the methods and interpretation criteria can be found in S4.1.2 of the Supplementary Material 1. Data presented in Section 4.3.2.6 (Private Laboratory Initiative) utilised different methods, which are described separately in S4.1.3 of the Supplementary Material 1.

4.3 Results

Classification of resistance as low, moderate, high etc. throughout the report is consistent with EFSA definitions for these terms. A table explaining these definitions can be found in the introduction (Table 2).

Certain active compounds included in the antibiotic testing panels are not authorised for use in food-producing animals. These are included to monitor the emergence or risk of resistance to these antibiotics in bacteria in humans, or because they are representative of an antibiotic class. Panels of antibiotics can vary between years and individual isolates. Where a figure shows no data against specific antibiotics or years as a result of this panel variation, this has been identified in a footnote.

For some bacterial pathogens, very few isolates are recovered in any one year and therefore the prevalence of resistance and any trends need to be interpreted with caution. The complete dataset is available in the Supplementary Material 3 (Section 2.1 onwards), but only those pathogens with test results for more than 20 isolates in 2021 are presented graphically in the main body of the report.

Of the organisms chosen for MIC testing, results are presented for both MIC and disc diffusion methodology. All isolates were tested using disc diffusion methodology, but due to laboratory error, smaller numbers of isolates underwent MIC testing.

4.3.1 Respiratory pathogens

Results presented are for the majority of key respiratory pathogens isolated through the clinical surveillance programme, and are generated using MICs, as outlined in S.4.1.2 of

Supplementary Material 1. Results of disc diffusion testing for these and additional isolates are provided in full in S2.2 to S2.4 of the Supplementary Material 3.

4.3.1.1 *Mannheimia haemolytica*

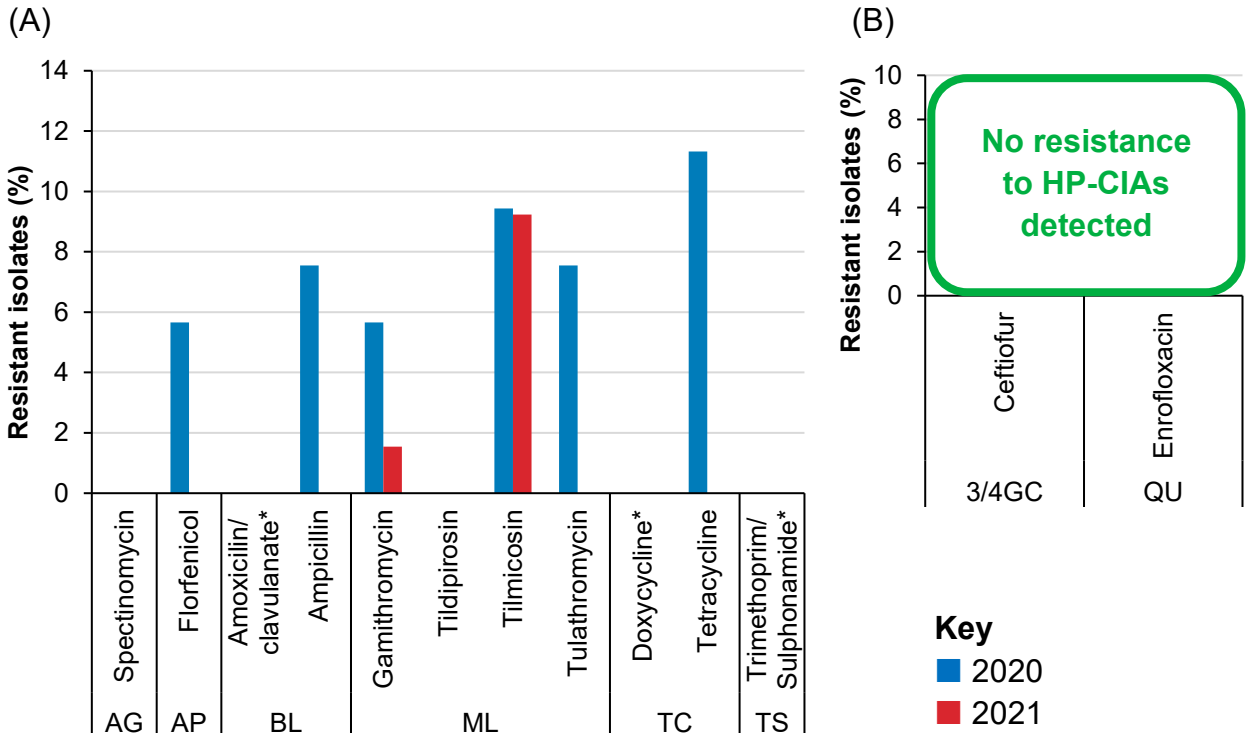
M. haemolytica is a common cause of respiratory disease in both cattle and sheep in the UK although different serotypes predominantly affect each species. Ovine *Mannheimia* strains can also cause mastitis; *M. haemolytica* has been more rarely recorded as causing mastitis in cattle. Healthy animals can carry the bacteria in the upper respiratory tract.

Of the 123 *M. haemolytica* isolates from sheep that underwent MIC testing, all were fully susceptible to the panel of antibiotics tested when applying CBPs, which is higher than the percentage of susceptible isolates for *M. haemolytica* in cattle.

Of the 65 *M. haemolytica* isolates from cattle, 59 (90.8%) were susceptible to the full panel of antibiotics tested, which is more than in 2020. No MDR was detected, nor was resistance to the HP-CIAs ceftiofur (third generation cephalosporin) and enrofloxacin (fluoroquinolone). Resistance was also not detected to the aminoglycoside spectinomycin, the beta-lactams amoxicillin/clavulanate and ampicillin, doxycycline, tetracyclines or trimethoprim/sulphonamides. Resistance was detected to the macrolides gamithromycin (1.5%) and tilmicosin (9.2%).

When applying ECOFF values, which indicate emerging resistance, reduced susceptibility was observed in ovine *M. haemolytica* isolates versus enrofloxacin (3.3% of isolates). For the bovine *M. haemolytica* isolates, when applying the CLSI CBP, no resistance was detected to the fluoroquinolone enrofloxacin, however 13.8% of isolates did have MICs exceeding the ECOFF, indicating reduced susceptibility. Similarly, when applying the CLSI CBP no florfenicol resistance was detected, however 1.5% of isolates had reduced susceptibility when using the ECOFF value. These findings indicate emerging resistance to enrofloxacin in a low number of ovine and bovine *M. haemolytica* isolates, and to florfenicol in a low number of bovine isolates.

Figure 4.1: Antibiotic resistant of *Mannheimia haemolytica* isolates from respiratory infections of cattle (n=65 in 2021) interpreted using cattle CLSI veterinary breakpoints unless indicated otherwise.



* Interpreted using CA-SFM veterinary CBP
AG: aminoglycosides, AP: amphenicols, BL: beta-lactams, ML: macrolides, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

4.3.1.2 *Pasteurella multocida*

P. multocida causes primarily respiratory disease in cattle and (more rarely) sheep in the UK. It can also affect poultry (fowl cholera) and toxigenic strains are responsible for the development of atrophic rhinitis in pigs.

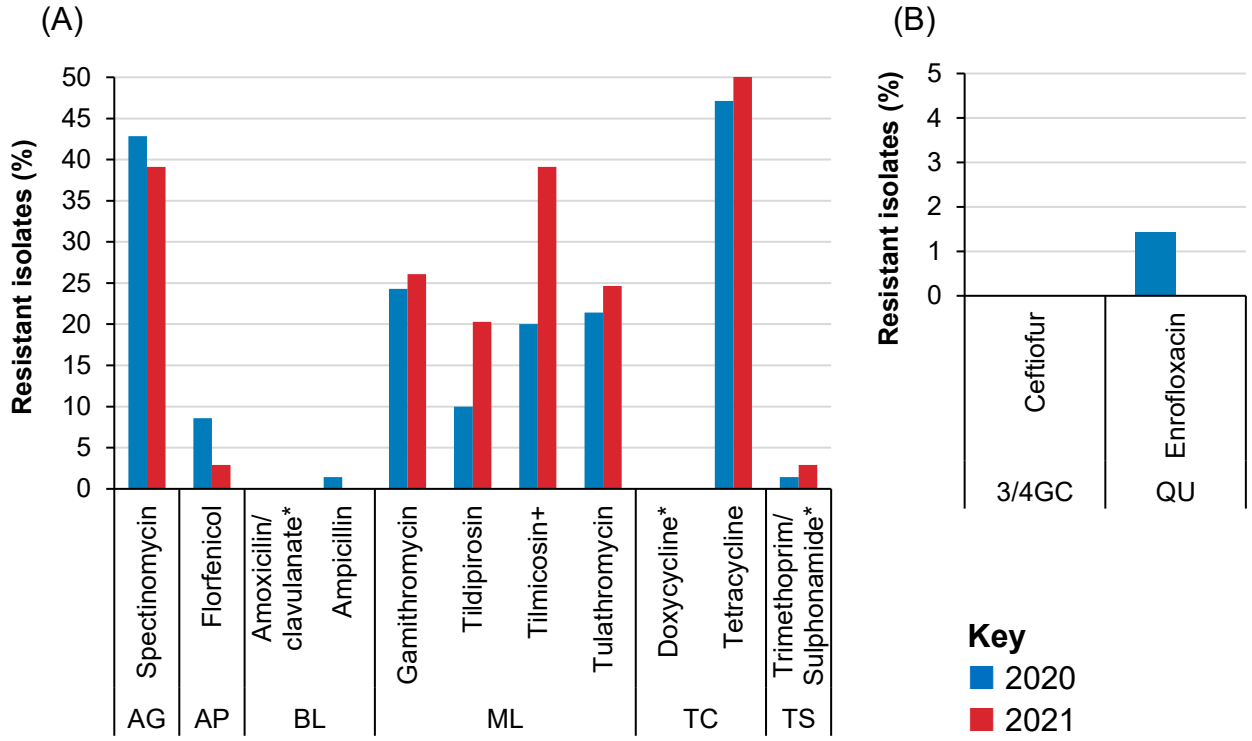
Of the 19 *P. multocida* isolates from sheep, 16 (84.2%) were fully susceptible to the panel of antibiotics tested, with resistance to the macrolide tilmicosin (15.8%) detected in those which were not fully susceptible. The percentage of fully susceptible isolates for *P. multocida* in sheep was higher than for cattle isolates, as seen for *M. haemolytica.*

Of the 69 *P. multocida* isolates from cattle, 33 (47.8%) were susceptible to the full panel of antibiotics tested. MDR was detected in 18.8% of isolates, however no resistance was detected to the HP-CIA and third generation cephalosporin ceftiofur or the beta-lactams amoxicillin/clavulanate and ampicillin. Resistance to the aminoglycoside spectinomycin and trimethoprim/sulphonamide was observed in 39.1% and 2.9% of isolates respectively, which differs to resistance noted in the *M. haemolytica* cattle isolates. Of the macrolides, resistance was detected to gamithromycin (26.1%), tildipirosin (20.3%), tilmicosin (39.1%)

and tulathromycin (24.6%). For tildipirosin and tilmicosin this represents an increase compared to last year. Fourteen (20.3%) isolates were resistant to all four macrolides tested and were also resistant to tetracyclines. Tetracycline resistance was common (53.6%), and reduced susceptibility to doxycycline was noted in 30.4% of isolates.

When applying ECOFF values to detect emerging resistance in ovine *P. multocida* isolates, reduced susceptibility was seen for the HP-CIA and fluoroquinolone enrofloxacin (5.3%), the macrolide tildipirosin (5.3%) and trimethoprim/sulphonamides (10.5%). Regarding bovine *P. multocida* isolates, like the bovine *M. haemolytica* isolates, when applying the CLSI CBP no resistance was detected to enrofloxacin, however 14.5% of isolates had reduced susceptibility when applying ECOFFs. Florfenicol resistance was similar: 2.9% of isolates were classed as resistant when applying the CBP, but 5.8% had reduced susceptibility using ECOFFs. Again, this indicates emerging resistance to these antibiotics in a low number of isolates.

Figure 4.2: Antibiotic resistant of *Pasteurella multocida* isolates from respiratory infections of cattle (n=69 in 2021) interpreted using cattle CLSI veterinary breakpoints unless indicated otherwise.

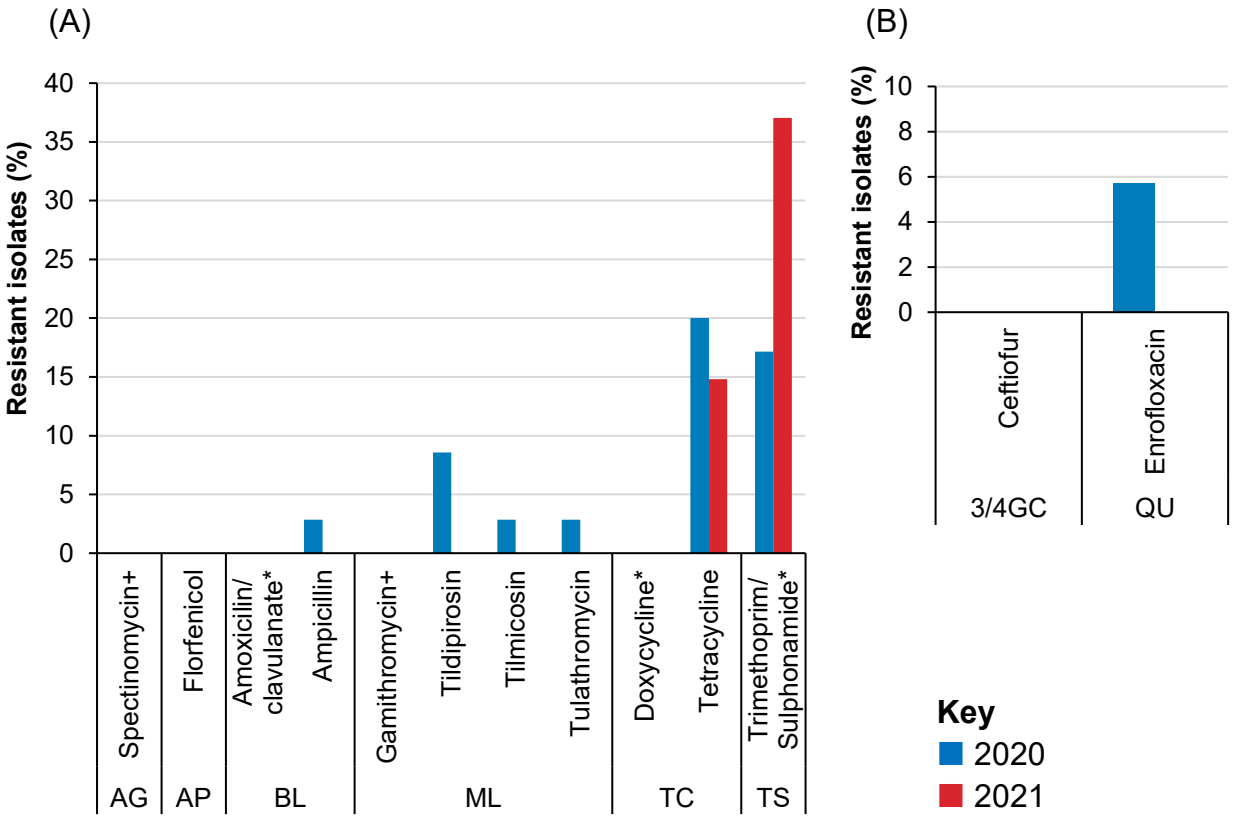


* Interpreted using CA-SFM veterinary CBP
+ Tilmicosin breakpoint for porcine isolates applied
AG: aminoglycosides, AP: amphenicols, BL: beta-lactams, ML: macrolides, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Of the 27 *P. multocida* isolates from pigs, 13 (48.1%) were susceptible to the full panel of antibiotics tested and no MDR was detected. Resistance was also not detected to the HP-CIA and third generation cephalosporin ceftiofur or the beta-lactams amoxicillin/clavulanate

and ampicillin. Additionally, all isolates were also susceptible/did not have decreased susceptibility to the HP-CIA and fluoroquinolone enrofloxacin, the aminoglycoside spectinomycin, florfenicol, or the macrolides gamithromycin, tildipirosin, tilmicosin and tulathromycin when applying both CBPs and ECOFFs. Tetracycline resistance (14.8%) exceeded doxycycline resistance (0%) and resistance to trimethoprim/sulphonamides (37.0%) exceeded the values observed in *P. multocida* from ruminants and was increased compared to last year (17.1%).

Figure 4.3: Antibiotic resistant of *Pasteurella multocida* isolates from respiratory infections of pigs (n=27 in 2021) interpreted using CLSI veterinary breakpoints unless indicated otherwise.



* Interpreted using CA-SFM veterinary CBP
+ Spectinomycin and gamithromycin breakpoint for bovine isolates applied.
AG: aminoglycosides, AP: amphenicols, BL: beta-lactams, ML: macrolides, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

4.3.1.3 *Actinobacillus pleuropneumoniae*

A. pleuropneumoniae is a cause of pneumonia in pigs. Of the 18 *A. pleuropneumoniae* isolates tested, 11 (61.1%) were susceptible to the full panel of antibiotics and no MDR was detected. Resistance to the beta-lactam ampicillin was observed in 38.9% and to tetracycline in 33.3% of isolates. Six isolates were resistant to both antibiotics.

4.3.1.4 *Bibersteinia trehalosi*

B. trehalosi causes septicaemia in growing lambs. Of the 37 isolates tested, all were fully susceptible to the panel of antibiotics tested.

4.3.1.5 Discussion

This is the second report describing the new improved testing protocol for veterinary respiratory pathogens obtained through scanning surveillance in England and Wales. Results were evaluated primarily using veterinary CBPs, which are most useful for practitioners; the recent publication of many relevant ECOFFs and TECOFFs by EUCAST also allowed evaluation using these more sensitive thresholds, which helps us detect emerging resistances. Where appropriate, the panels of antibiotics were designed to include multiple, clinically relevant antibiotics within the same class. This protocol therefore has an important role in improving selection and refinement of possible treatment options.

Many isolates remain susceptible to the panel of antimicrobials tested and when resistance was detected, alternative therapeutic options remain available amongst those antimicrobials authorised for veterinary use. Resistance was uncommon or not detected to those antimicrobials which are often used as second- or third-line treatment options. There are differences between the occurrence of resistance detected by MIC determination compared to disc diffusion susceptibility testing, mainly in relation to tetracycline resistance (in most of the bacterial species studied) and for ampicillin resistance in *A. pleuropneumoniae*. The disc diffusion breakpoint for tetracyclines and *Pasteurellaceae* is a legacy breakpoint from BSAC, correlating to an MIC >1 mg/l indicating resistance. This tetracycline resistance breakpoint is no longer exactly congruent with breakpoints set by other organisations and the results of the MIC determinations are considered the more robust output.

The differences between the occurrence of tetracycline and doxycycline resistance are noteworthy because resistance genes occur which confer resistance to tetracycline but not to doxycycline and thus doxycycline may remain a therapeutic option in these cases. Susceptibility testing may therefore have an important role in selection and refinement of possible treatment options. However, there may also be breakpoint considerations which are relevant in relation to the interpretation of results for tetracycline and doxycycline.

Resistance to the macrolides showed interesting patterns across the bacterial and animal species studied. Tulathromycin and gamithromycin have a 15-membered ring structure, whereas tilmicosin and tildipirosin have a 16-membered ring structure. Isolates with the resistance gene *erm*(42) have been reported to show greatly elevated MICs for the 16-membered macrolides, while smaller MIC increases were seen for the 15-membered macrolides. In contrast, the resistance genes *msr(E) and mph(E)* (which are frequently linked genetically) are associated with large increases in MICs for tilmicosin, tulathromycin, and gamithromycin but not for tildipirosin. Additionally, all three of these genes have been shown to occur on the same mobile genetic element ICEPmu1 (see this and this paper).

All 14 of the *P. multocida* isolates from cattle resistant to tildipirosin were also resistant to gamithromycin, tilmicosin and tulathromycin; tulathromycin resistance was detected in 17 isolates and occurred in conjunction with tilmicosin resistance and gamithromycin resistance. The macrolide resistance phenotype therefore in many cases appears to correlate well with the described mechanisms of resistance; determination of genotype by whole genome sequencing would be useful to confirm predicted genotype and to investigate the phenotypic patterns of resistance.

4.3.1.6 Other respiratory pathogens

The remaining respiratory pathogens were tested under the disc diffusion protocol (see S2.2 to S2.4 in Supplementary Material 3).

Glaesserella (*Haemophilus*) *parasuis* is included in this section because it is a member of the *Pasteurellaceae*. Harmonised susceptibility testing methods and breakpoints for this organism are still being established. Of the five *G. parasuis* isolates recovered in 2021, no resistance was detected to the HP-CIAs cefpodoxime (third generation cephalosporin) or enrofloxacin (fluoroquinolone). Resistance was detected to the aminoglycoside neomycin (60.0%) and trimethoprim/sulphonamides (20.0%) but not to the beta-lactam ampicillin or tetracyclines.

Histophilus somni (formerly known as *Haemophilus somnus*) is a cause of pneumonia and thrombo-embolic meningo-encephalitis in calves. Over the monitoring period the small number of isolates tested were susceptible to the panel of antibiotics tested, with the exception of a single isolate in 2019 which was resistant to ampicillin.

There were no isolates of *Trueperella* (*Arcanobacterium) pyogenes* from respiratory or systemic disease in sheep, cattle or pigs tested in 2021.

Further details on percentage of resistance for respiratory infections are included in Tables S2.2, S2.3 and S2.4 of Supplementary Material 3.

4.3.2 Bovine mastitis pathogens

Bovine mastitis is complex and the patterns of resistance observed vary with time and between farms. The data presented are aggregated at a national level and therefore have limited ability to inform treatment protocols. However, they do highlight that acquired resistance does occur in England and Wales and should be considered when veterinarians and farmers develop mastitis control programs for individual farms.

Note that Gram negative (*E. coli*) and Gram positive (*S. aureus* and streptococci) isolates are tested against different panels of antibiotics and that the number of isolates tested is highly variable, which is likely to impact the interpretation of percentage resistance. Details on the number of tests performed on bovine mastitis pathogens are in S2.1 of Supplementary Material 3.

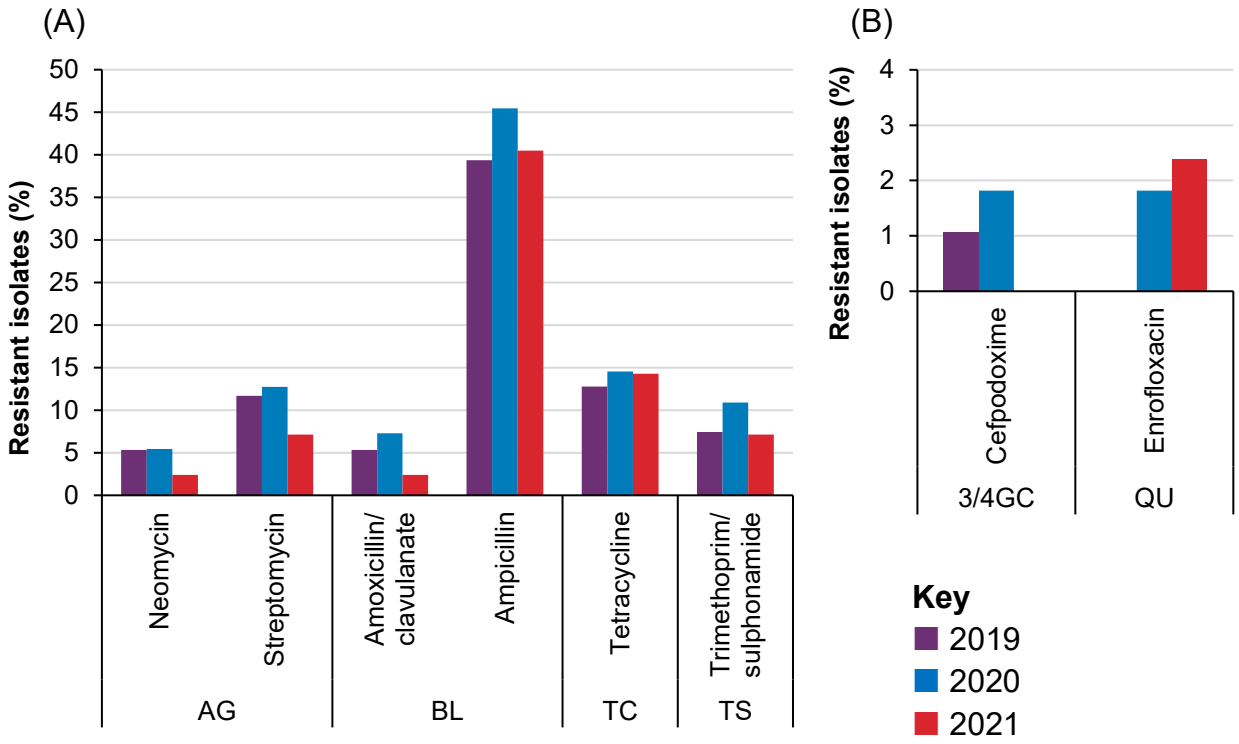
4.3.2.1 *Escherichia coli*

E. coli and other coliforms are major causes of bovine mastitis. Most *E. coli* strains originate from the immediate environment of the cow, and it is thought that no particular virulence factors are required to infect the mammary gland. These *E. coli* isolates therefore mostly represent strains that are present in the environment of adult dairy cattle, particularly cattle sheds and cubicle houses, and are probably mainly of faecal origin.

The percentage of *E. coli* isolates from mastitis infections resistant to different antibiotics are presented in **Figure 4.4**. The number of isolates tested has decreased over the monitoring period and the full results are presented in Table S2.1.1 of Supplementary Material 3.

Of the HP-CIAs tested, resistance remains low; in 2021 no resistance was detected to the third generation cephalosporin cefpodoxime. This can be contrasted with the situation for *E. coli* from neonatal calves in 2021 where the percentage resistance to cefotaxime was 4.7%. This is similar to the situation observed in previous years. Only one isolate was resistant to the fluoroquinolone enrofloxacin (2.4%). Of the non-HP-CIAs, resistance has showed only limited annual fluctuations for most antimicrobials, with the occurrence of resistance tending to be relatively stable, apart from ampicillin where resistance has increased from 22% in 2017/2018 to 39-46% between 2019 and 2021. Resistance to the aminoglycosides tested was low in 2021, as was resistance to the beta-lactam amoxicillin/clavulanate (2.4%). Resistance to the beta-lactam ampicillin remains high (40.5%) and to tetracycline remains moderate (14.3%). Resistance to trimethoprim/sulphonamides was low (7.1%).

Figure 4.4: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolated from mastitis samples from cattle (n=42 in 2021) in England and Wales. Note scale differs between graphs.



AG: aminoglycosides, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides, 3/4GC: third and fourth generation cephalosporins

4.3.2.2 *Streptococcus dysgalactiae*

Streptococcus dysgalactiae is a commensal of the mucous membranes of cattle; it is a cause of mastitis and occasionally other diseases in cattle. It is not considered a zoonosis and Group C streptococci that can cause disease in humans constitute a separate population. The number of *S. dysgalactiae* isolates tested has decreased in 2021 and the full results are presented in Table S2.1.2 of Supplementary Material 3.

In 2021, no resistance was detected to any antibiotics included in the panel – which included beta-lactams and tylosin – except for tetracycline where all thirteen isolates were resistant. This resistance is recognised as being common in *S. dysgalactiae.*

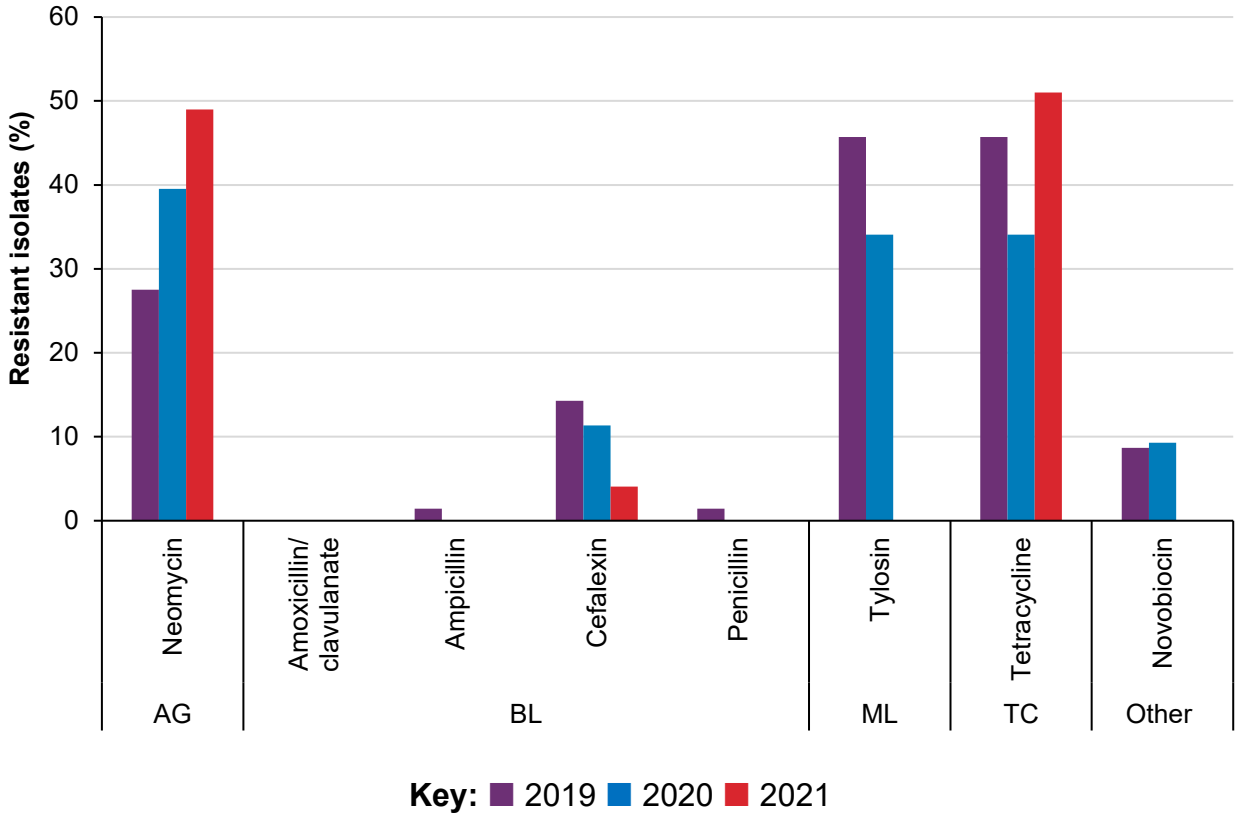
4.3.2.3 *Streptococcus uberis*

Streptococcus uberis is a well-recognised cause of bovine mastitis and is widely distributed in the environment of dairy cows, as well as being a commensal resident of the bovine vagina, tonsil, and skin. It is not regarded as zoonotic.

The percentage of *S. uberis* isolates from mastitis infections resistant to different antibiotics and tested by disc diffusion methods are presented in **Figure 4.5.** The number

of isolates tested via disc diffusion has fluctuated over the monitoring period, with 49 isolates tested in 2021. In 2021, no resistance was detected to the antibiotic panel tested other than to the aminoglycoside neomycin (49.0%), the first generation cephalosporin cefalexin (4.1%), and tetracycline (51.0%). Resistance to neomycin probably reflects the degree of intrinsic resistance shown by streptococci to aminoglycosides and resistance to tetracycline is recognised as being common in *S. uberis.* Resistance was not detected to penicillin or ampicillin.

Figure 4.5: Antibiotic resistance of *Streptococcus uberis* isolated from mastitis samples from cattle (n=49 in 2021) in England and Wales.



AG: aminoglycosides, BL: beta-lactams, ML: macrolides TC: tetracyclines

For the first time, this year ten *S. uberis* isolates obtained from bovine mastitis samples in 2021 underwent MIC testing. No MDR was detected when using veterinary clinical breakpoints (or human CBPs when veterinary were not available). All antibiotics in the panel were interpreted using CBPs; the panel included the HP-CIAs ceftiofur (third generation cephalosporin) and enrofloxacin (fluoroquinolone), florfenicol, penicillin, lincomycin, the macrolide erythromycin, doxycycline, tetracycline and trimethoprim/sulphonamide.

Typically, in *Streptococci*, erythromycin and other 14-membered macrolides are inducers of macrolide resistance whereas 16-membered macrolides (e.g., tylosin) and lincosamides are non-inducers. Isolates were not induced with a suitable macrolide prior to testing. Two

isolates were lincomycin resistant without macrolide resistance. A further isolate had an erythromycin MIC above the ECOFF and (considering the published MIC distributions for tylosin and *S. uberis*) a moderate tylosin MIC. Underlying genetic mechanisms have not been investigated, but lincomycin resistance without macrolide resistance is consistent with acquisition of a lincosamide resistance gene. The lincosamide antimicrobial pirlimycin is used for treatment of bovine mastitis. No resistance was detected to the rest of the antibiotic panel which included the HP-CIAs ceftiofur and enrofloxacin. High-level aminoglycoside resistance (HLAR), which is thought to obviate the synergistic effect of aminoglycosides and penicillins, was not detected.

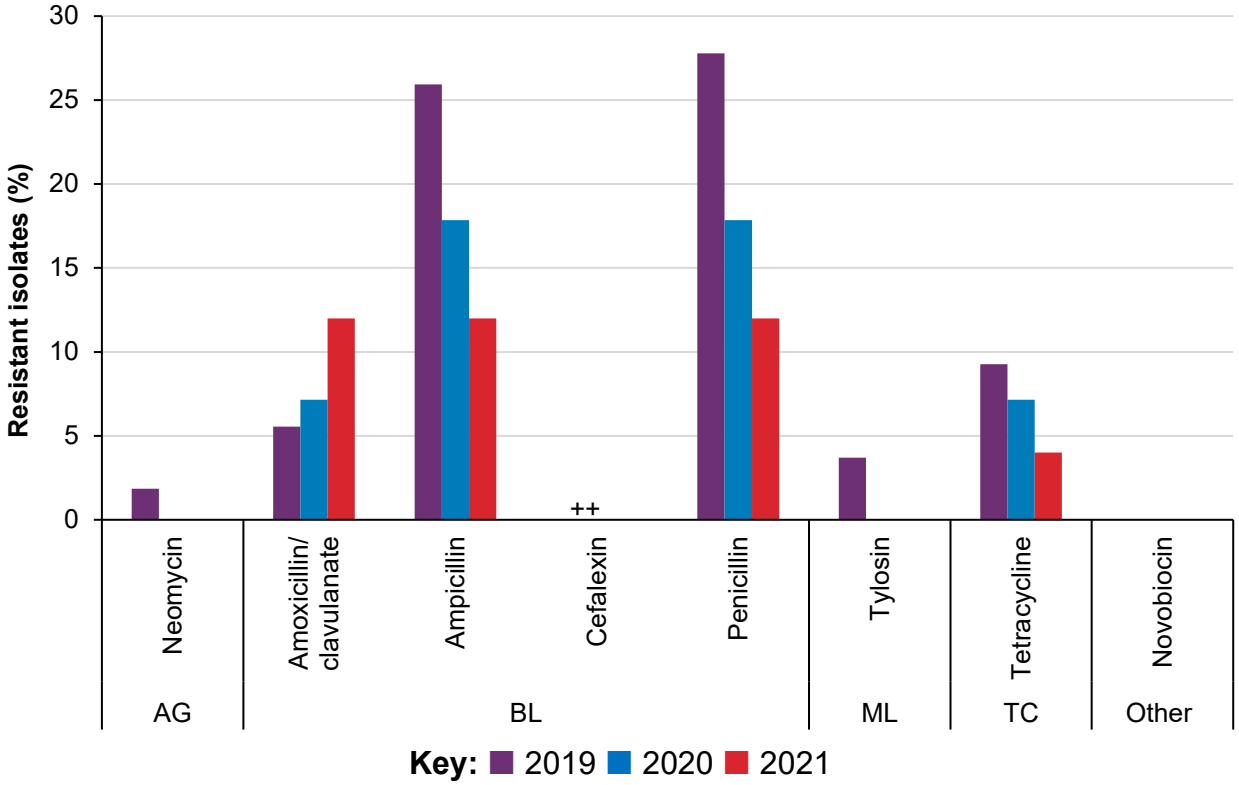
4.3.2.4 *Staphylococcus aureus*

S. aureus is normally resident on the skin and mucous membranes of cattle and is a common cause of mastitis. Bovine *S. aureus* is not generally regarded as zoonotic and although both *mecA* methicillin-resistance *Staphylococcus aureus (*MRSA) and *mecC* MRSA have been detected in cattle (see this and this paper), the possible role of cattle as a source of human infection has not been well-defined.

The percentage of *S. aureus* isolates from mastitis infections resistant to different antibiotics are presented in **Figure 4.6**. The number of isolates tested has decreased over the monitoring period and the full results are presented in Table S2.1.2 of Supplementary Material 3.

Resistance to all antibiotics tested has declined or remained at zero, except for the beta-lactam amoxicillin/clavulanate, which has increased to 12.0% over the monitoring period. Isolates with this resistance are screened to check for the presence of *mecA* and *mecC* MRSA, which was not detected. Resistance to the beta-lactams ampicillin and penicillin declined over the monitoring period, dropping from high to moderate resistance; resistance to the latter declined from 27.8% to 12.0%. Penicillin resistance in bovine *S. aureus* from England and Wales occurs most frequently via the production of beta-lactamases. The genes encoding beta-lactamases can be located on plasmids and often on transposons and may be readily transferable by conjugation. *S. aureus* isolates from bovine mastitis resistant to amoxicillin/ clavulanate are currently screened for susceptibility to cefoxitin and by agglutination tests for altered penicillin binding protein in order to detect *mecA* and *mecC* MRSA. No MRSA isolates were detected from bovine mastitis over the period 2019-2021 at APHA. No resistance was detected to the first-generation cephalosporin cefalexin, which was tested for the first time in 2021. Isolates have remained susceptible to the aminoglycoside neomycin and the macrolide tylosin since 2020. Resistance to tetracycline (4.0%) declined over the monitoring period and remains low. Isolates remained susceptible to novobiocin over the monitoring period.

Figure 4.6: Antibiotic resistance of *Staphylococcus aureus* isolated from mastitis samples from cattle (n=25 in 2021) in England and Wales.



+ Not tested
AG: aminoglycosides, BL: beta-lactams, ML: macrolides TC: tetracyclines

4.3.2.5 Other mastitis pathogens

Very low isolate numbers were available for the testing of additional mastitis pathogens. Full results are available in Table S2.1.3 of Supplementary Material 3.

All five of the *Klebsiella pneumoniae* isolates originating from bovine mastitis cases were resistant to ampicillin. This reflects the intrinsic resistance to ampicillin shown by this organism; most isolates were susceptible to the other antimicrobials reported.

Pseudomonas aeruginosa isolates are commonly resistant to a range of antibiotics and isolates from bovine mastitis proved no exception in this regard. Efflux and impermeability are frequently responsible for resistance to beta-lactams in *P. aeruginosa* and probably accounted for the observed beta-lactam resistance. However, all six isolates were susceptible to the anti-pseudomonal third generation cephalosporin ceftazidime. Efflux pumps can also confer resistance to quinolones in *P. aeruginosa*, however all isolates over the monitoring period were susceptible to enrofloxacin.

One *Streptococcus agalactiae* isolate was recovered in 2021 which was susceptible to the panel of antibiotics tested, other than to tetracycline. No isolates of *Trueperella (Arcanobacterium) pyogenes* were recovered from bovine mastitis in 2021.

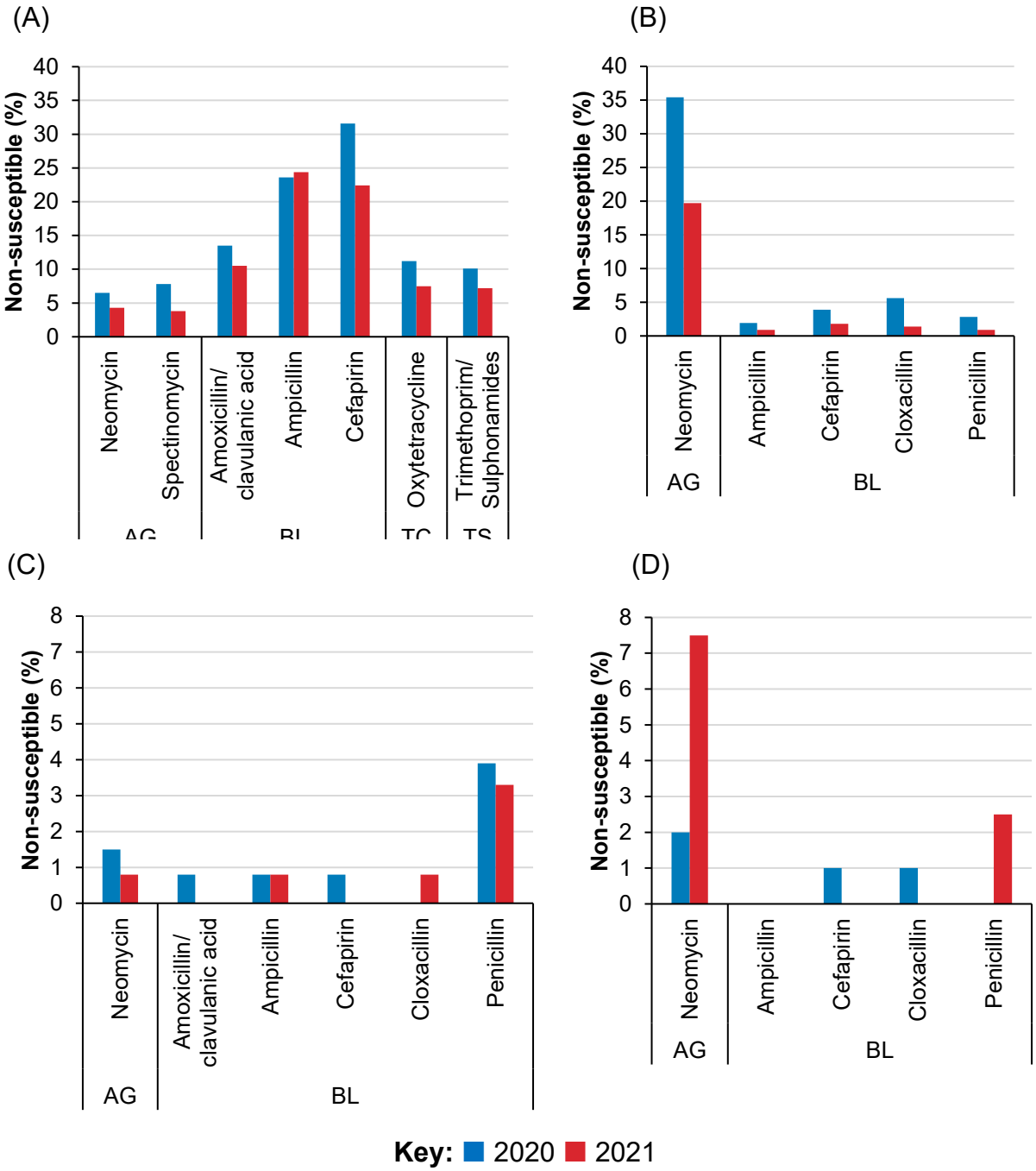
4.3.2.6 Private Laboratory Initiative

The Private Laboratory Initiative (PLI) is a collaborative project between the VMD and APHA. Many veterinarians send mastitis samples to private veterinary laboratories (PVLs) for diagnosis, the results of which do not ordinarily feed into AMR surveillance efforts. The purpose of the project is to routinely collect and analyse data from PVLs to provide an additional source of data for AMR surveillance. This initiative directly supports the UK's ambition to contain and control AMR, by increasing the sensitivity of surveillance and timeliness of detection of potential threats, as well as providing a stronger evidence base for AMR in UK livestock. This project has just concluded its proof-of-concept phase.

We are grateful to the Vale Veterinary Laboratory for providing data for this project. Presented in **Figure 4.7** are the results from antibiotic susceptibility testing of key mastitis pathogens isolated from cattle by the Vale Laboratory in 2020 and 2021. Note that 2020 results have been amended since their inclusion in the previous VARSS report, due to updated data. The changes are minor, except for *S. uberis,* which now includes results from an additional 59 isolates. This data should be interpreted with caution, as there are differences in the laboratory methods, antibiotic panels and interpretation criteria used by government and private laboratories. A summary of the methodology and breakpoints applied can be found in S4.1.3 of Supplementary Material 1.

Overall, resistance to most antibiotics has gone down in both *E. coli* and *S. dysgalactiae.* Similar to 2020, moderate to high resistance to beta-lactams was seen in *E. coli* from bovine mastitis cases, with resistance detected to amoxicillin/ clavulanate (10.5%), ampicillin (24.4%) and cefapirin (22.4%). Resistance to the aminoglycosides and oxytetracycline was low. In *S. uberis,* resistance was low or very low in 2021 to all beta-lactams tested, which is similar to 2020. Resistance to the macrolide tylosin in 2021 was low (1.7%). Resistance to neomycin (19.7%) decreased from high to moderate levels in 2021. For *S. aureus* resistance was either not detected or very low to low, with resistance detected to penicillin (3.3%) and neomycin, ampicillin and cloxacillin (all 0.8%). For *S. dysgalactiae* in 2021, resistance was low and only detected to neomycin (7.5%) and penicillin (2.5%).

Figure 4.7: Non-susceptibility of (A) *E. coli* (n=345 to 353 in 2021), (B) *S. uberis* (n=424 to 437 in 2021), (C) *S. aureus* (n=120 in 2021) and (D) *S. dysgalactiae* (n=39 to 40 in 2021) isolated from bovine mastitis samples submitted to Vale Veterinary Laboratories in 2020 and 2021



AP: amphenicols, BL: beta-lactams, TC: tetracyclines, TS: trimethoprim/sulphonamides

These results broadly align with data presented in Section 4.3.2, with the exception of the slightly lower resistance to ampicillin in *E. coli* and lower resistance to both ampicillin and penicillin in *S. aureus* isolated by Vale compared to APHA. Although, resistance to ampicillin and penicillin in *E. coli* isolated by APHA has decreased since 2020. These

discrepancies could be attributed to population and sampling differences, or variation in laboratory methodology and breakpoints used.

Whilst still in early stages of this project, these early results demonstrate the potential for broadening AMR surveillance by collaborating with the private sector. Bringing together and reporting data from additional sources will both improve representativeness of surveillance through an increased number of samples for testing and provide greater information on AMR at a regional level. This will provide direct benefits to both farmers and vets by creating a more detailed picture of AMR in key veterinary pathogens, and better help inform disease management and treatment.

4.3.3 Other animal pathogens

Brachyspira hyodysenteriae is the causative organism of swine dysentery, an enteric disease of pigs, resulting in serious ill-thrift in its chronic form. A limited range of antibiotics is available for treatment and reliance on ongoing medication without addressing other aspects of disease control, such as hygiene and herd husbandry, risks resistance arising through mutations. Tiamulin is an important antibiotic used in the treatment of swine dysentery and because of the importance of this disease all available *B. hyodysenteriae* isolates are tested for tiamulin susceptibility each year. Two of the twelve *B. hyodysenteriae* isolates tested in 2021 had a high tiamulin MIC of 8 mg/l, which is above the CBP of > 4 mg/l. These isolates were recovered from the same premises at different times throughout the year.

Staphylococcus aureus causes several infections in poultry and game birds including septicaemia, yolk sac infection, arthritis and osteomyelitis. In 2021, a single isolate was recovered from chickens; no resistance was detected. *S. aureus* also causes mastitis and tick pyaemia as well as other infections in sheep and goats. Most of the 30 sheep and 6 goat isolates obtained in 2021 were susceptible to the full panel of antibiotics tested, except for three sheep isolates and one goat isolate with tetracycline resistance. This is assumed to reflect historical usage of this compound in these species. One isolate from each species was also resistant to tylosin.

Streptococcus dysgalactiae is the major cause of infectious arthritis in young lambs and is thought to be carried on the mucous membranes of a small proportion of sheep. Tetracycline resistance remained high for the 17 ovine isolates tested; a similar trend was seen in the bovine (mastitis) *S. dysgalactiae* isolates. No resistance to the beta-lactam ampicillin, penicillin, the first-generation cephalosporin cefalexin, or macrolide tylosin was detected in 2021.

Staphylococcus xylosus is a coagulase-negative *Staphylococcus* which has been reported to cause dermatitis in sheep and mastitis in cattle. The singular sheep isolate was susceptible to all antibiotics as were the four cattle isolates, except for novobiocin for which one isolate was resistant. Resistance to a wider range of antibiotics was noted for

the five chicken isolates which included the beta-lactam ampicillin, lincosamides, macrolides, tetracyclines and trimethoprim/sulphonamides.

Staphylococcus hyicus can cause exudative epidermitis – otherwise known as greasy pig disease – in young pigs. Of the seven isolates tested in 2021, five were resistant to the beta-lactam ampicillin and penicillin, two to tetracycline and one to lincomycin. No resistance was detected to the HP-CIA and fluoroquinolone enrofloxacin, the macrolide tylosin or trimethoprim/sulphonamide.

4.3.4 Zoonotic pathogens

4.3.4.1 *Streptococcus suis*

S. suis causes meningitis, arthritis and pneumonia in pigs and is a zoonosis, though human infections are rare and usually occur following contact with affected pigs. A number of serotypes have been described and the organism is able to colonise the tonsil of healthy pigs, which become carriers.

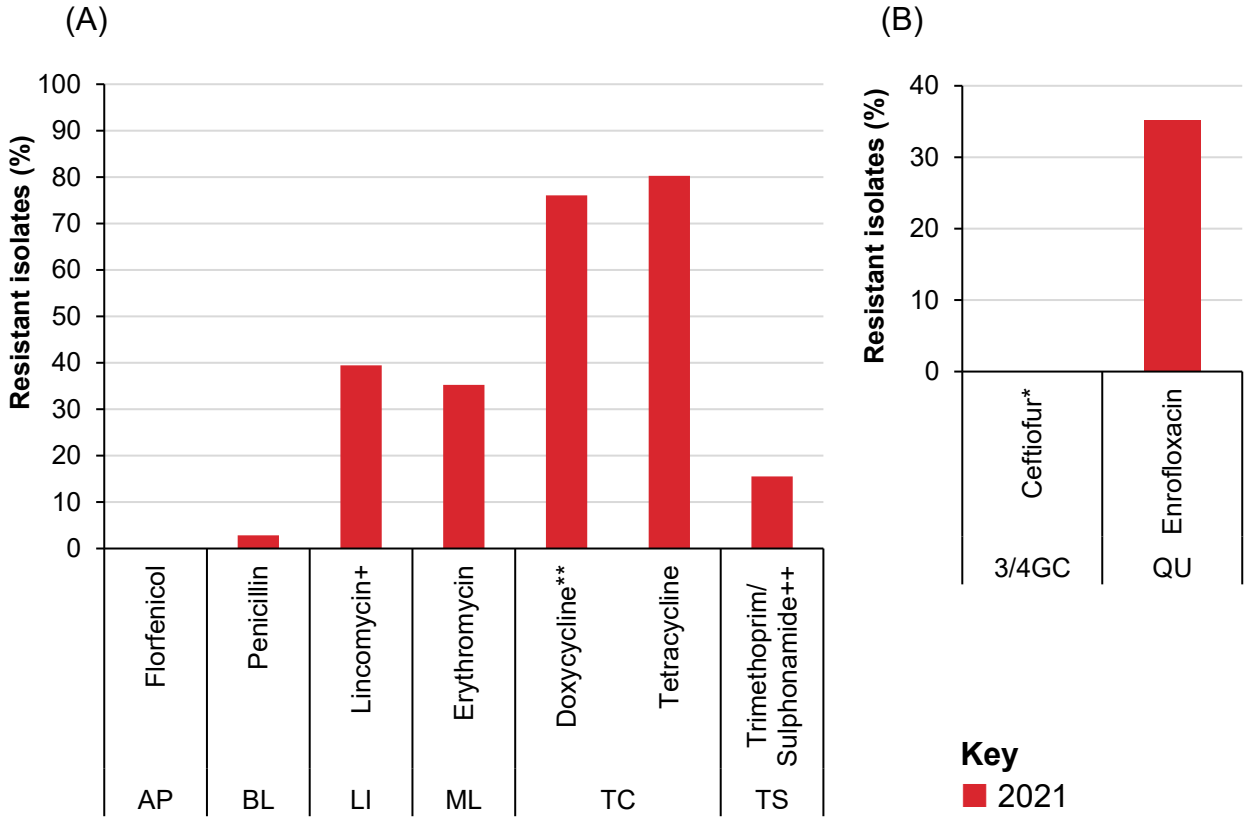
For the first time, 71 *S. suis* isolates from pigs underwent MIC testing in 2021 (**Figure 4.8**). Some breakpoints are not available for *S. suis* and in those cases, breakpoints were applied from other streptococci. Fourteen (19.7%) isolates were susceptible to the full panel of antibiotics tested. MDR was assessed using veterinary CBPs (or human CBPs where a veterinary CBP was not available) and was detected in 25 (35.2%) isolates. Resistance to the macrolide erythromycin, lincomycin and tetracyclines was the most common MDR pattern detected.

Resistance to the HP-CIA and third generation cephalosporin ceftiofur was not detected when applying the CLSI *S. uberis* breakpoint, though two (2.8%) of isolates were in the intermediate category. Of these isolates, one had a penicillin MIC of 0.25 mg/l (susceptible) whereas the other had a penicillin MIC of 2 mg/l (resistant). The MIC distributions for both penicillin and ceftiofur were similar to a previously published study of UK isolates. Penicillin resistance was detected in 2.8% of isolates and is clinically relevant since beta-lactam compounds are important in the treatment of *S. suis* infections in pigs. The effective treatment of meningitis requires adequate levels of antibiotic to cross the blood brain barrier and it is interesting to note that EUCAST breakpoints for *S. pneumoniae* meningitis in humans are set at much lower MIC values than those set for respiratory infection.

EUCAST ECOFFs have not been established for penicillin, however, most isolates had MICs at the lowest tested dilution (0.03 mg/l). ECOFFS have been established for erythromycin and trimethoprim/sulphonamides. Of the 25 isolates resistant to erythromycin, 23 were also resistant to lincomycin and all had tylosin MICs > 64 mg/l. Five isolates were resistant to lincomycin but not erythromycin and in these isolates the tylosin MIC was $\leq$ 2 mg/l. Isolates were not induced with a macrolide (erythromycin) prior to testing. As mentioned previously, typically in streptococci, erythromycin and other 14-

membered macrolides are inducers of macrolide resistance whereas 16-membered macrolides (e.g., tylosin) and lincosamides are non-inducers. The findings are therefore considered to indicate possible constitutive expression of erythromycin resistance in 25 of the *S. suis* isolates. Isolates resistant to lincomycin but not erythromycin may possess lincosamide resistance genes and it is possible these genes were also present in erythromycin resistant isolates. HLAR was not detected to gentamicin but was detected to kanamycin and streptomycin in five (7.0%) and six (8.5%) isolates respectively. Four (5.6%) isolates demonstrated high level resistance to both kanamycin and streptomycin.

Figure 4.8: Antibiotic resistant of *Streptococcus suis* isolates from pigs (n=71) interpreted using CLSI veterinary breakpoints unless indicated otherwise.



* *S. uberis* breakpoint for bovine isolates applied
** Interpreted using EUCAST human CBP for *S. pneumoniae*
+ Interpreted using CA-SFM veterinary CBP
++ Interpreted using EUCAST human CBP for *Streptococci*
AP: amphenicols, BL: beta-lactams, LI: lincosamides, ML: macrolides, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

When looking at the resistance of *S. suis* isolates via disc diffusion, the number of isolates tested has decreased over the monitoring period to 87 isolates in 2021. In 2021, no resistance was detected to the HP-CIA and fluoroquinolone enrofloxacin, or to the antibiotics ampicillin and penicillin. Resistance was detected to tetracyclines (85.1%), trimethoprim/sulphonamides (18.4%), tylosin (28.7%) and lincomycin (29.9%). All resistance detected in 2021 was lower than that seen in 2019 and/or 2020.

4.3.4.2 Livestock Associated-MRSA (LA-MRSA)

LA-MRSA different from other types of MRSA, such as hospital or community associated strains, which are more frequently found in humans. Anyone who has contact with colonised livestock can become colonised with LA-MRSA, although the risk is higher for those in frequent contact with livestock. LA-MRSA usually lives in the nose or on skin and is an opportunist pathogen. Usually this is a local skin infection, but occasionally it can cause diseases such as pneumonia or bacteraemia.

Since the first discovery in 2005, LA-MRSA was found to be prevalent in livestock around the world. It was detected in food-producing animals in the UK for the first time in 2013, and sporadic clinical cases are detected annually. Clonal Complex (CC) 398 is a common LA-MRSA CC group isolated from food-producing animal populations. Isolates are whole genome sequenced and shared with the UK Health Security Agency (UK-HSA) as appropriate to investigate any possible associations with infections in humans.

A summary of all findings identified by UK government veterinary laboratories is provided in Table S2.5.5 of Supplementary Material 3. These reports should not be interpreted as a prediction of prevalence in the animal population, as samples have been collected through differing methods of passive surveillance in animals which are affected with clinical disease. In 2021, LA-MRSA CC398 *spa*-type t108 was recovered in low growth at post-mortem from the heart of a young piglet which had died with no premonitory signs.

4.3.5 *Escherichia coli*

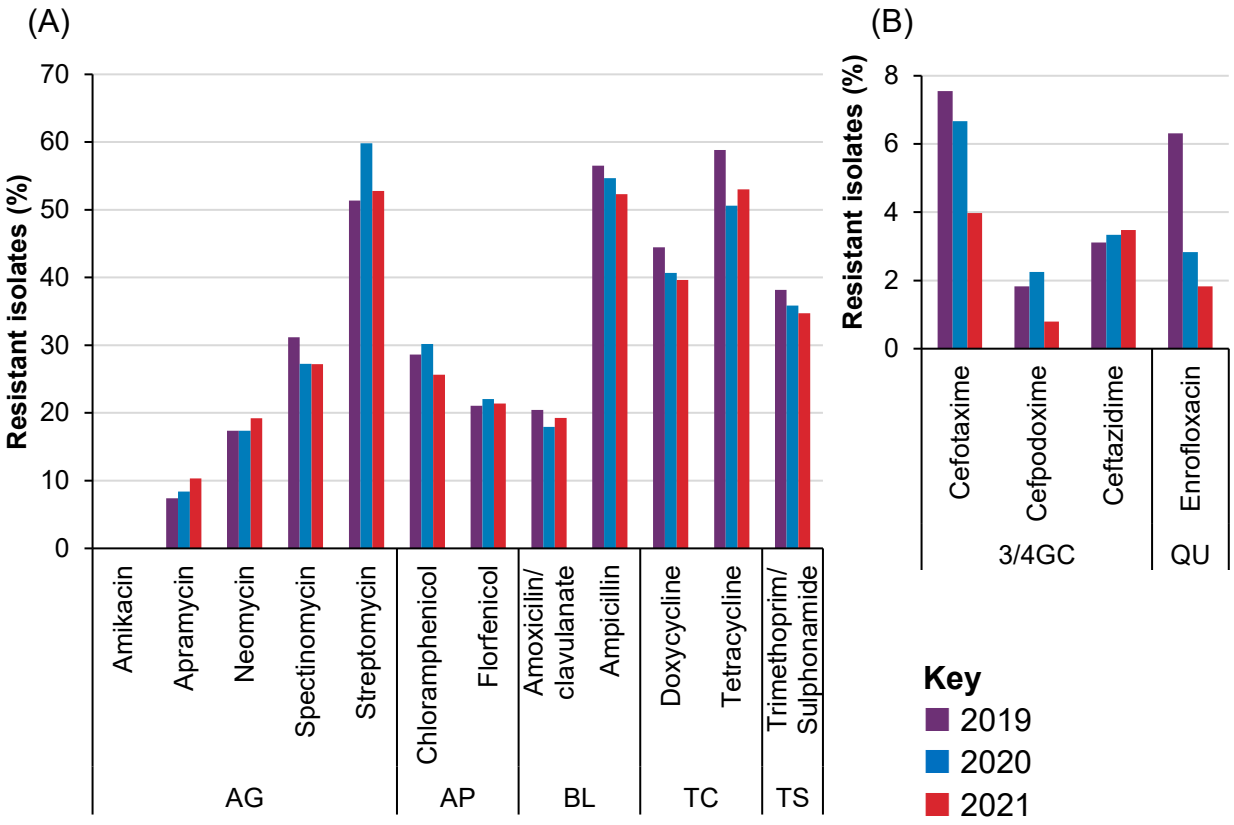
E. coli is an important zoonotic organism and a commensal of animals and humans. The strains affecting animals are often different from those affecting humans but there is some overlap, and *E. coli* can act as a reservoir of transferable resistance genes. *E. coli* can also cause a range of clinical problems in food-producing animals, including diarrhoea and colisepticaemia. Some diseases caused by *E. coli* are related to infection with particular *E. coli* strains which possess recognised virulence factors, whilst opportunistic *E. coli* infections also occur in some circumstances (for example in hypogammaglubulinaemia in neonatal animals).

This section includes all isolates of *E. coli* detected through clinical surveillance in England and Wales, with the exception of isolates recovered from bovine mastitis samples (Section 4.3.2). The isolates reported here will include some strains which are pathogenic for animals, as well as commensal strains. Collated AMR data from England and Wales are presented in the main body of the report, with full data in S2.6 of Supplementary Material 3. Due to differences in methodology, data for Scotland and Northern Ireland are presented in S2.6 and S.7 of Supplementary Material 3.

Overall, resistance in *E. coli* isolated through clinical surveillance is largely unchanged over the monitoring period (**Figure 4.9**), although there are decreases in resistance to

ampicillin, the tetracyclines, and trimethoprim/sulphonamides. An increase in apramycin resistance from 7.4% to 10.3% has also been observed over the monitoring period.

Figure 4.9: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from cattle, pigs, sheep, broilers and turkeys (all ages combined; n=199 to 1,262 in 2021). Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

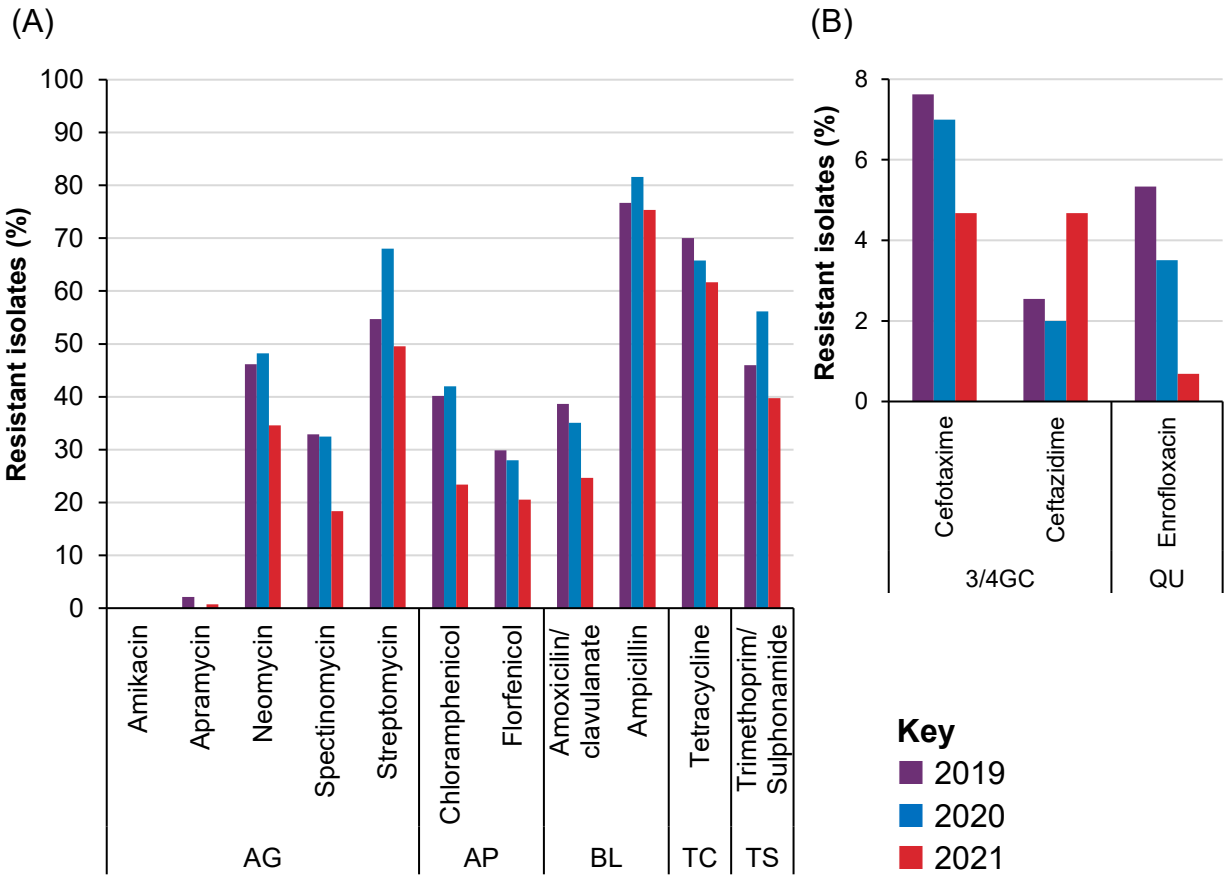
Resistance in *E. coli* is further analysed by livestock species below. For cattle, sheep and pigs the data are analysed by the age categories of neonatal, pre- or post-weaning and adult for each species. Definitions of these age categories can be found in Supplementary Material 3 (Table S2.6.1). There is a general trend towards higher resistance in isolates from younger animals in all species. This is consistent with previous surveillance data and with studies recorded in the literature, and likely reflects the more frequent treatment of young animals with antibiotics.

4.3.5.1 Cattle

The AMR in *E. coli* results from cattle are predominantly from the neonatal age category and are presented in **Figure 4.10**; results for pre-weaning calves are presented in **Figure 4.11** and for adult cattle in **Figure 4.12**. The number of isolates tested are in Table S.2.6.8 of Supplementary Material 3. Overall, 5% *E. coli* from cattle were resistant to the third

generation cephalosporins cefotaxime and ceftazidime; resistance was therefore more frequently observed in this species than in pigs or sheep.

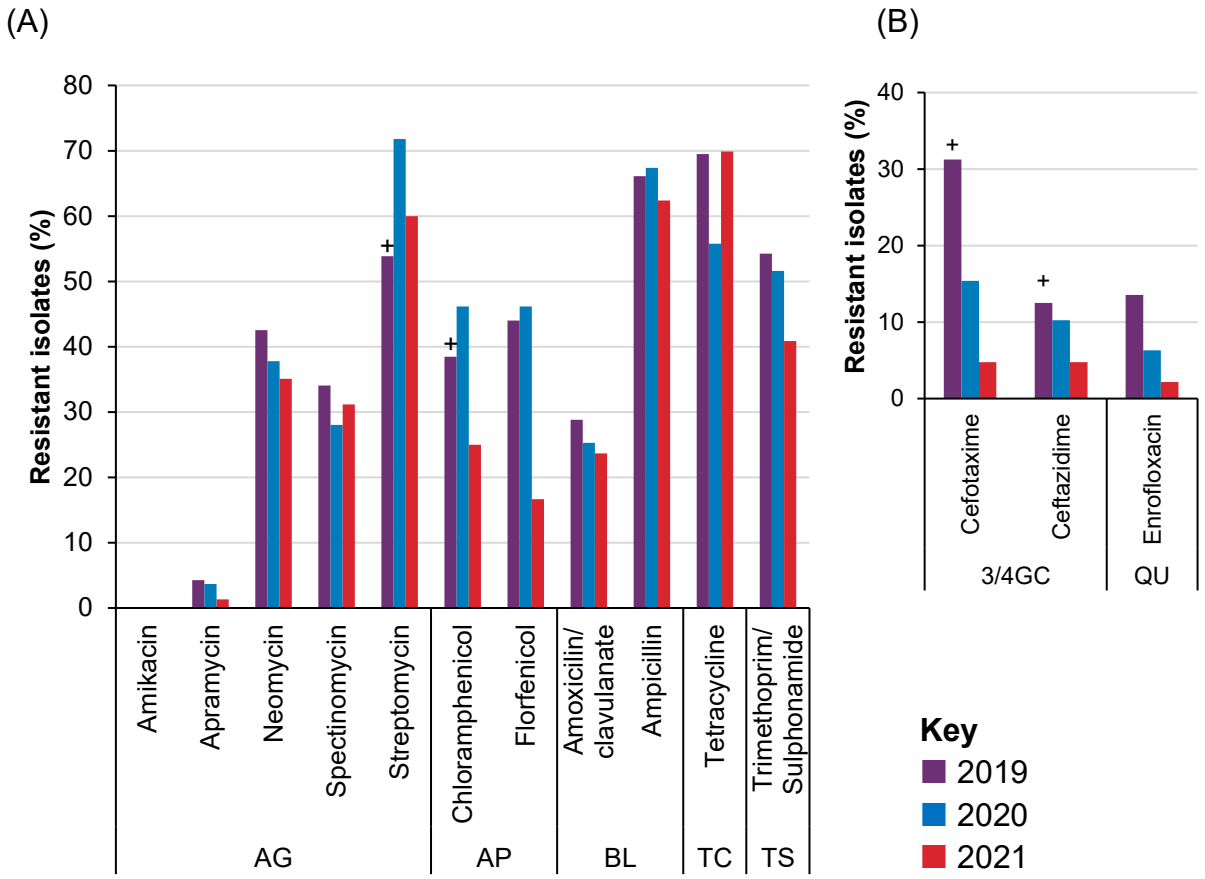
Figure 4.10: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from neonatal calves (n=107 to 146 in 2021). Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

The occurrence of resistance in *E. coli* isolates from neonatal calves was generally similar to that seen in pre-weaning calves, but mostly lower than what was observed in adults. The similar levels of resistance observed in neonatal and pre-weaning calves probably reflects the close proximity in which these age groups are often kept in calf rearing accommodation on farms, as well as similar patterns of antimicrobial usage.

Figure 4.11: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from pre-weaned calves (n=20 to 93 in 2021). Note scale differs between graphs.



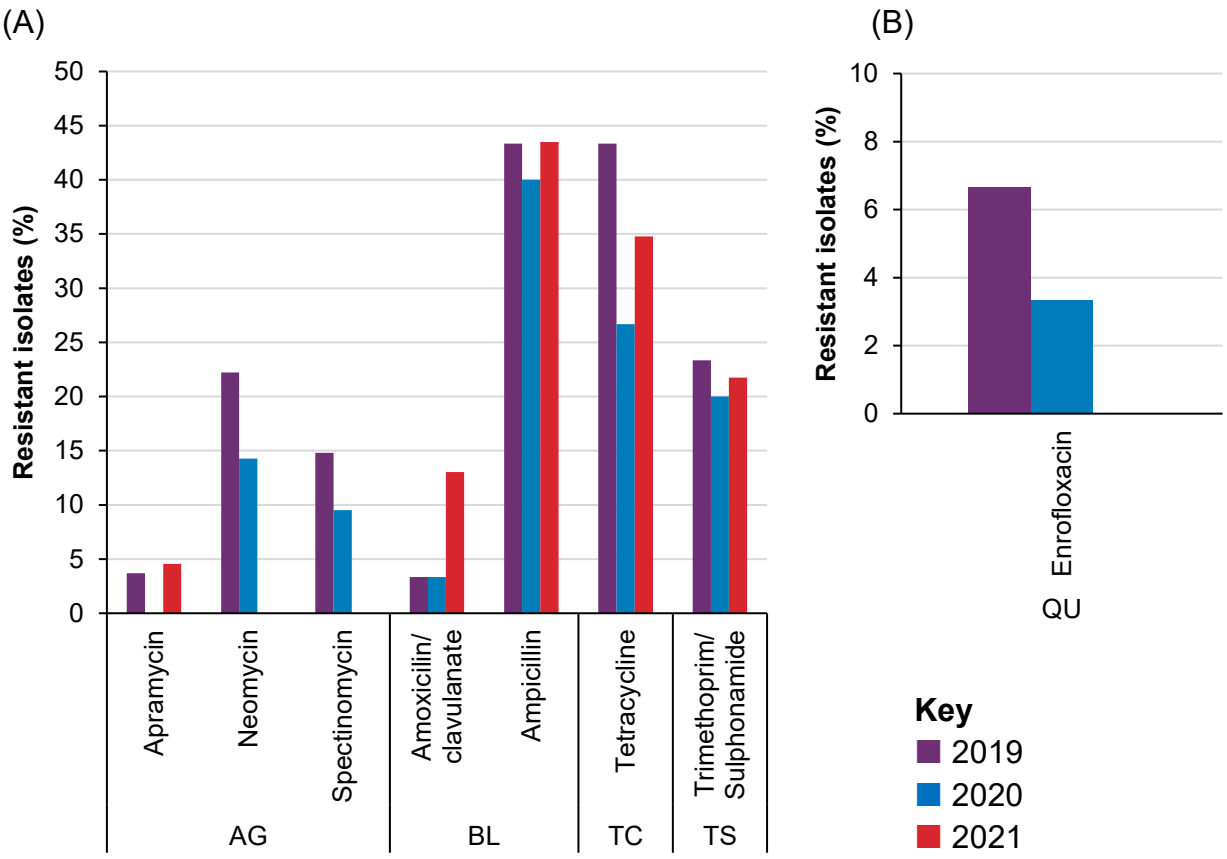
+ less than 20 isolates tested
AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Of the HP-CIAs, resistance of *E. coli* isolates to the third generation cephalosporins appears to be declining for neonatal and pre-weaning calves, except for ceftazidime in neonates, which has seen a minor increase. Resistance to these antibiotics was low for both age groups in 2021 (4.7% for both cefotaxime and ceftazidime in neonatal calves, and 4.8% for both in pre-weaning calves). Similarly, resistance to the fluoroquinolone enrofloxacin appears to be in decline for all age groups, reaching very low (0.7%) and low (2.2%) levels in neonatal and pre-weaning calves, respectively. All adult isolates were defined as susceptible in 2021.

For non-HP-CIA antibiotics, resistance in *E. coli* was predominately high in neonatal calves; however, resistance to all antibiotics has declined since 2019. Resistance to most non-HP-CIAs was also high in *E. coli* from pre-weaning calves. In both age groups, no amikacin resistance was detected over the monitoring period. In 2021, resistance of *E. coli* isolates from adult cattle were lower than those in calves, and similar to or lower than

those seen in previous years, except for the beta-lactam amoxicillin/clavulanate (13.0%), where resistance has increased from low to moderate levels.

Figure 4.12: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from adult cows (n=22 to 23 in 2021). Note scale differs between graphs.

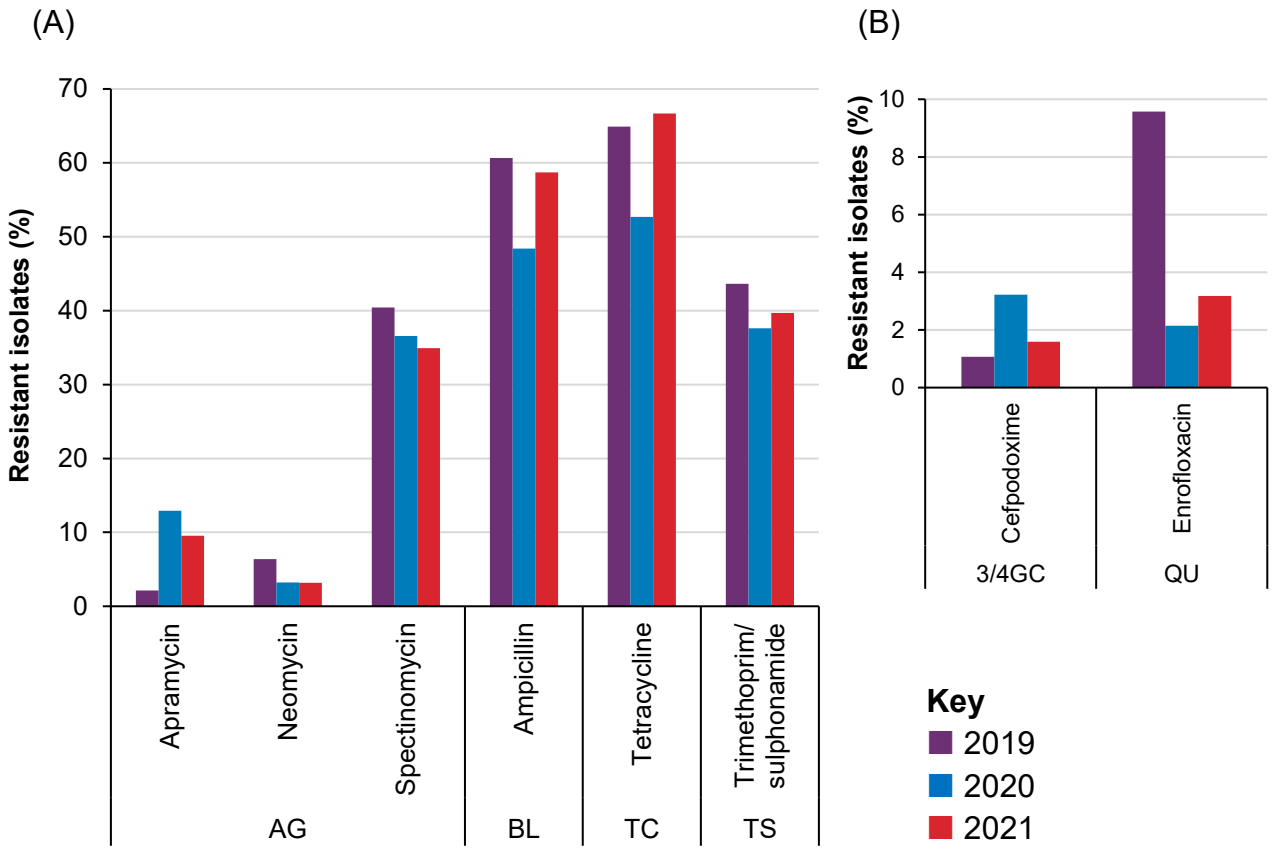


AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides

4.3.5.2 Pigs

Isolations of porcine *E. coli* are predominantly from the post-weaning age category and are presented in **Figure 4.14**. Results for neonatal pigs are presented in **Figure 4.13** and for adult pigs in **Figure 4.15**. The number of isolates tested are in Table S2.6.9 of Supplementary Material 3.

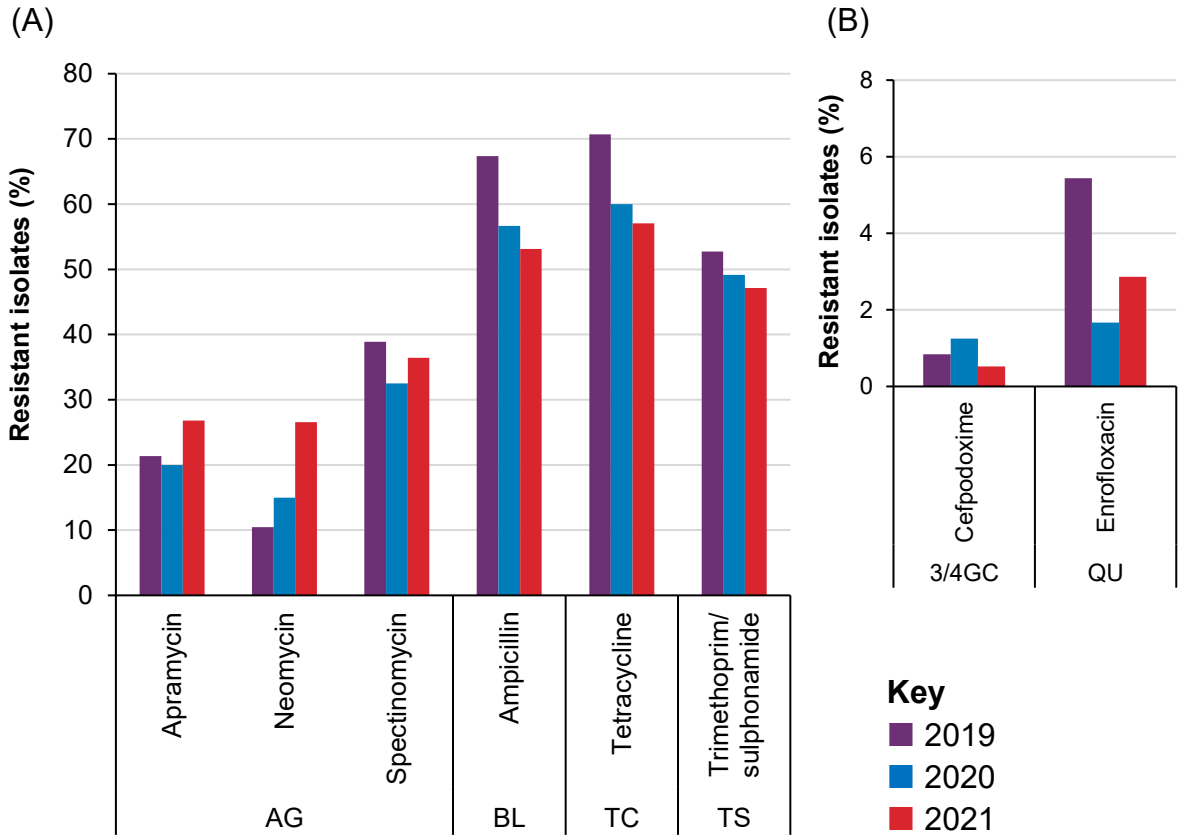
Figure 4.13: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from neonatal piglets (n=63 in 2021). Note scale differs between graphs.



AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides, 3/4GC: third and fourth generation cephalosporins

Of the HP-CIAs, resistance of *E. coli* isolates to the third generation cephalosporin cefpodoxime was uncommon: for neonatal (1.6%) and post-weaning piglets (0.5%) resistance appears to be stable at low and very low levels respectively. Resistance to the fluoroquinolone enrofloxacin also remained low for both neonatal (3.2%) and post-weaning piglets (2.9%). No resistance to HP-CIAs was detected in adult pigs in 2021.

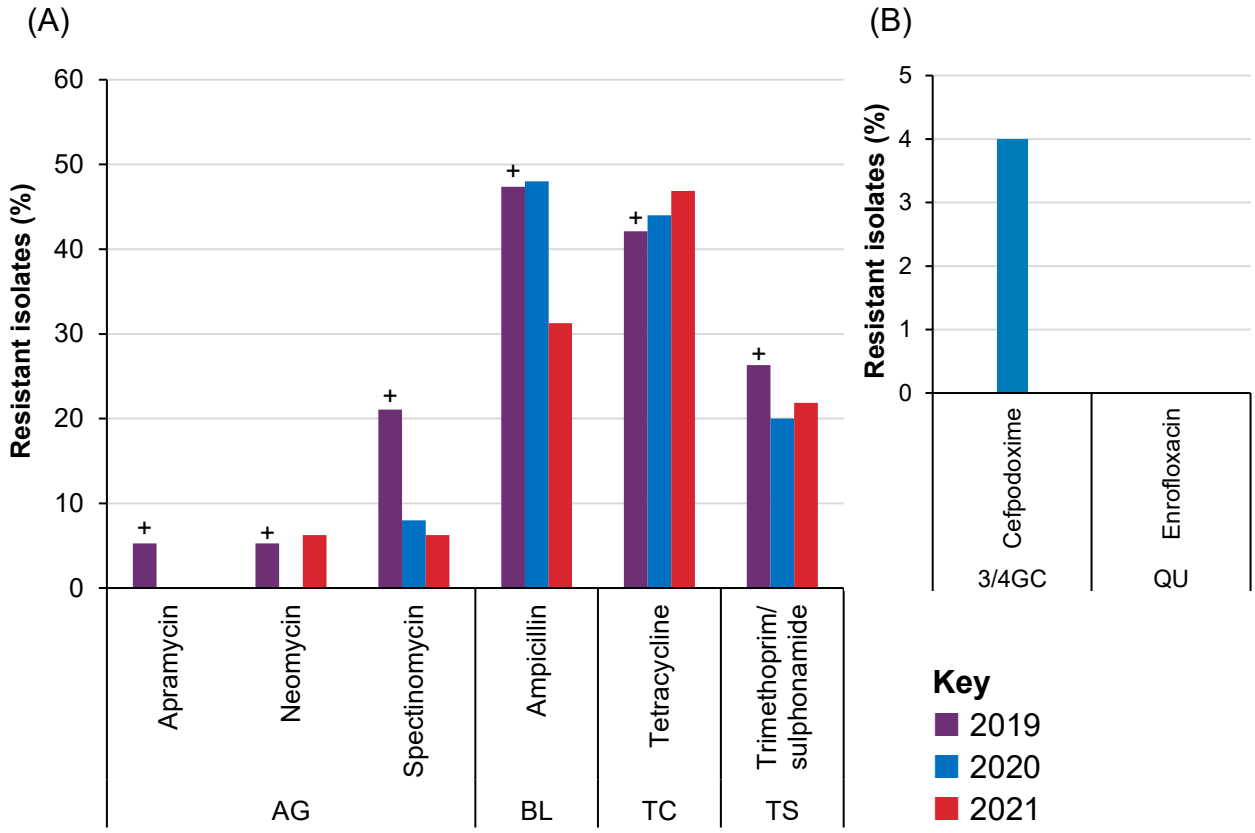
Figure 4.14: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from post-weaning piglets (n=384 in 2021). Note scale differs between graphs.



AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides, 3/4GC: third and fourth generation cephalosporins

Resistance of *E. coli* from neonatal pigs to non-HP-CIAs is broadly stable. For post-weaning piglets, resistance is predominately high but has declined since 2019, except for the aminoglycosides apramycin (26.8%) and neomycin (26.6%). The occurrence of resistance to apramycin, neomycin and trimethoprim/sulphonamides was higher in post-weaning piglets than in neonates; the increased occurrence of aminoglycoside resistance in weaners probably reflects the frequent use of aminoglycosides for post-weaning diarrhoea. Resistance to non-HP-CIAs in adult pigs was fairly fluctuant, likely reflecting the smaller number of isolates tested. Resistance to tetracycline in this age group has increased over the monitoring period.

Figure 4.15: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from adult pigs (n=32 in 2021). Note scale differs between graphs.



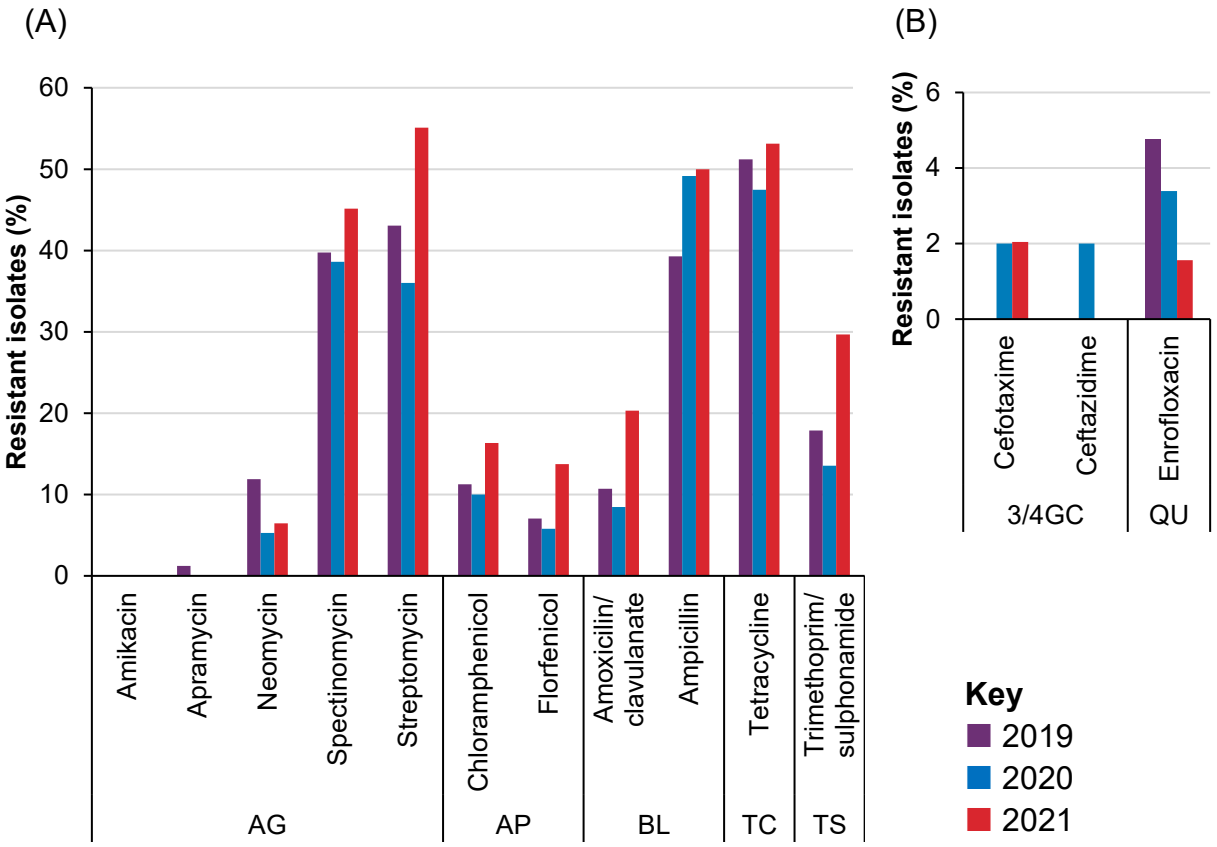
+ less than 20 isolates tested
AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides, 3/4GC: third and fourth generation cephalosporins

4.3.5.3 Sheep

The AMR results for *E. coli* isolated from sheep are predominantly from neonatal lambs and presented in **Figure 4.16**; results for pre-weaning lambs are presented in **Figure 4.17** and for adult sheep are presented in **Figure 4.18**. The number of isolates tested are in Table S2.6.10 of Supplementary Material 3.

In *E. coli* isolated from neonatal lambs, resistance to the HP-CIAs third generation cephalosporins was low or not detected (2.0% and 0% for cefotaxime and ceftazidime, respectively) in 2021. No resistance to either antibiotic was detected in *E. coli* from pre-weaning lambs. No resistance was detected in 2021 to the fluoroquinolone enrofloxacin in *E. coli* from pre-weaning lambs or adult sheep, and in neonates, decreased to 1.6%. Resistance noted in *E. coli* isolates from lambs and sheep is lower than that observed in cattle.

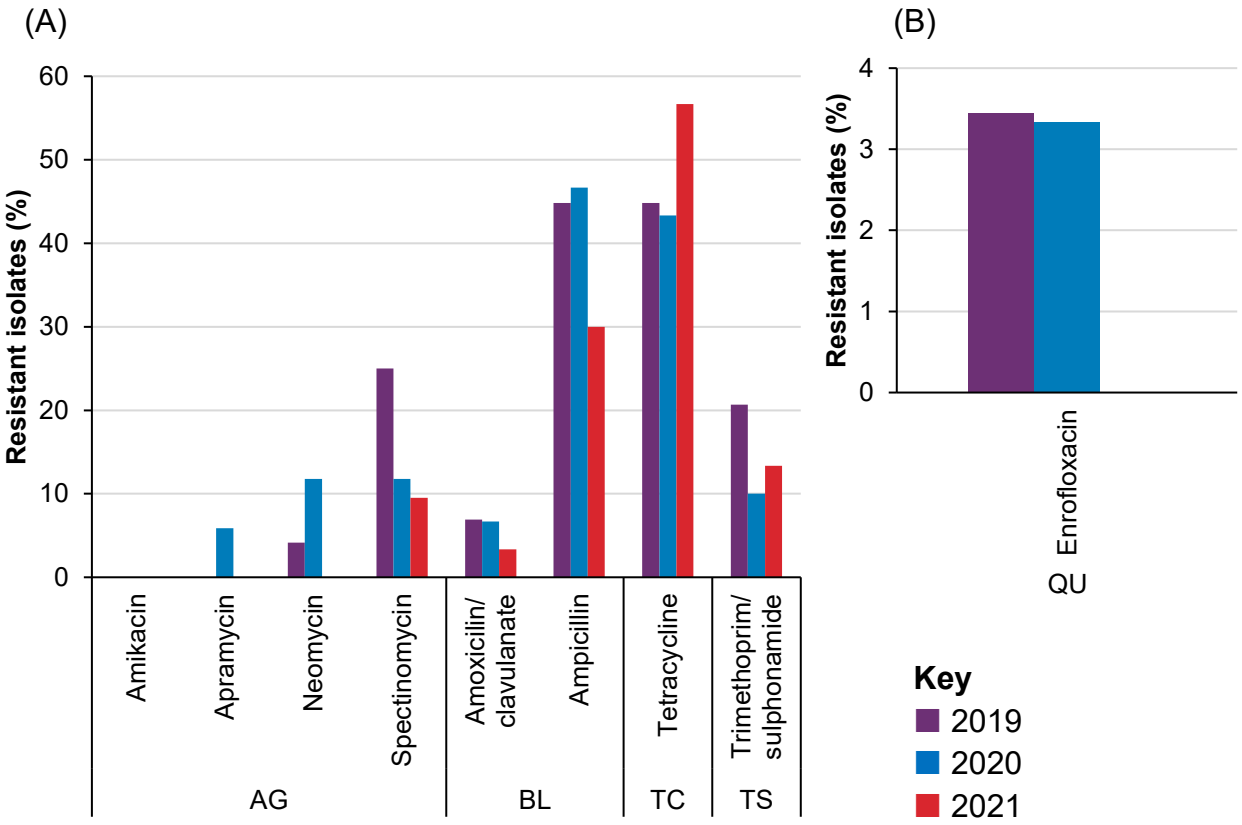
Figure 4.16: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from neonatal lambs (n=49 to 64 in 2021). Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

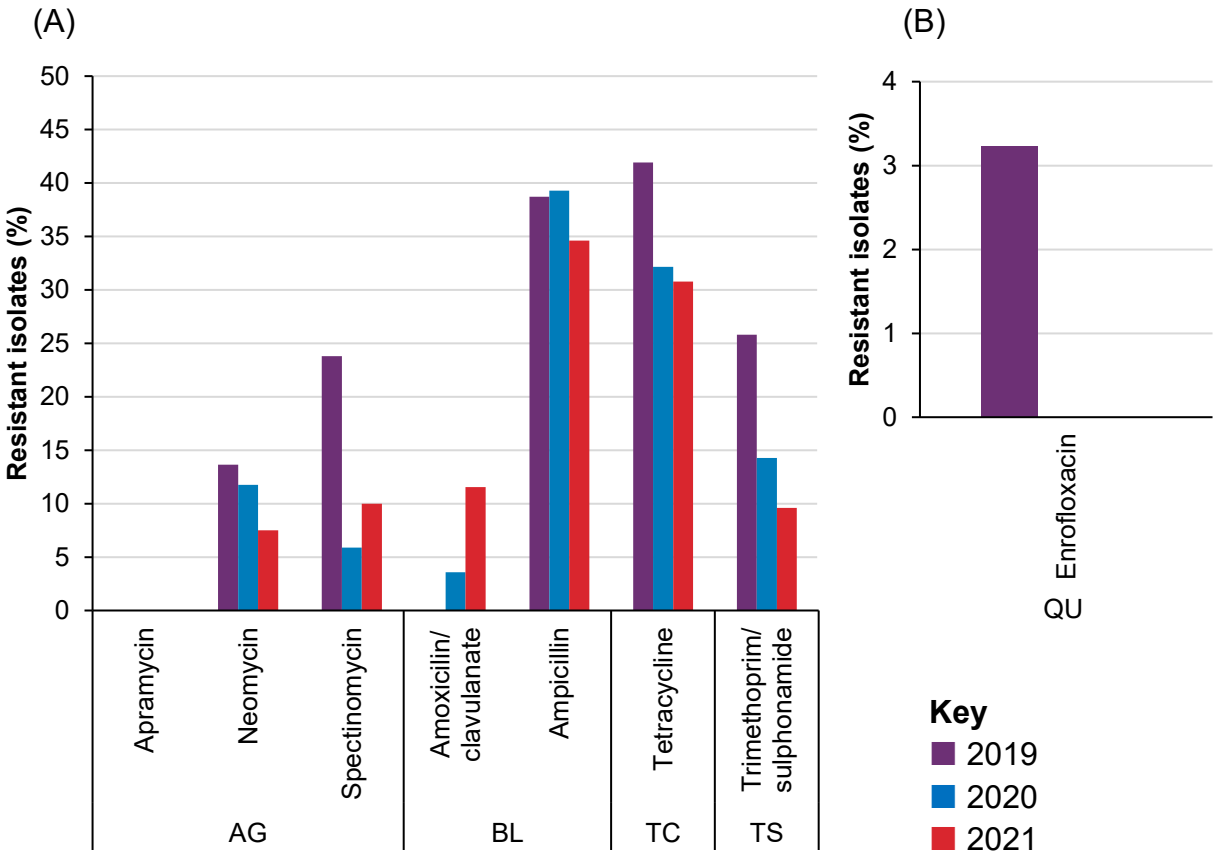
In sheep, resistance in *E. coli* isolates to most of the non-HP-CIA antibiotics tested was generally highest in neonates and declined with age, except for tetracycline resistance which was higher in pre-weaning lambs. For neonatal lambs, resistance to non-HP-CIAs appeared to be slightly higher than those observed in previous years, except for the aminoglycosides neomycin (6.5%), and amikacin and apramycin, to which no resistance was detected. In contrast, for pre-weaning and adult sheep, there appears to be less resistance detected in 2021 compared to 2019 and/or 2020. Exceptions are tetracyclines (56.7%) in pre-weaning lambs and florfenicol (7.1%) and the beta-lactam amoxicillin/clavulanate (11.5%) in adults.

Figure 4.17: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from pre-weaned lambs (n=21 to 30 in 2021). Note scale differs between graphs



AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides

Figure 4.18: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from adult sheep (n=40 to 52 in 2021). Note scale differs between graphs.



AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides

4.3.5.4 Chickens and turkeys

In 2021, for the first time, 74 *E. coli* isolates from chickens underwent MIC testing (**Figure 4.19**). Isolates were recovered from diagnostic submissions of carcases or other diagnostic material from field cases of disease in all types of chickens, including commercial production, pet birds and small-scale poultry enterprises. Susceptibility to the full panel of antibiotics tested was detected in 20 (27.0%) isolates, and 51.4% showed MDR.

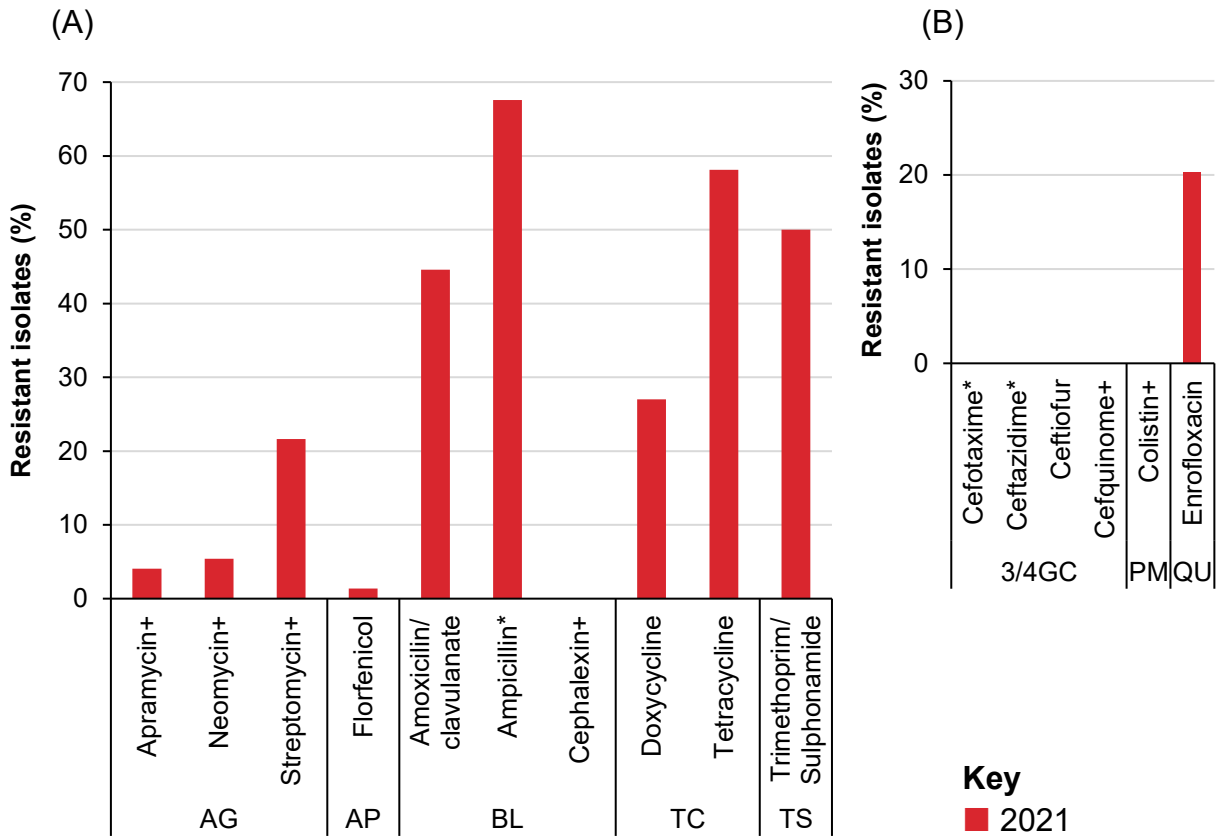
Of the HP-CIAs, no resistance was detected to third or fourth generation cephalosporins or colistin. Of these, only colistin is authorised for use in poultry. Resistance to the fluoroquinolone enrofloxacin was detected in 20.3% of *E. coli* isolates with 13.5% showing high-level fluoroquinolone resistance (MIC $\geq$ 8 mg/l). Fluoroquinolones are rarely used in commercial broiler flocks and scanning surveillance includes submissions of pet and backyard poultry. However, the two *E. coli* isolates with enrofloxacin MIC at 16 mg/l originated from the same flock of broilers and both showed MDR.

Of the aminoglycosides, resistance to apramycin, neomycin, and streptomycin were assessed using CBPs; spectinomycin, for which a CBP is not available, was assessed using ECOFFs. Sixteen *E. coli* isolates were resistant to streptomycin, 14 of which were resistant to spectinomycin, as expected since genes conferring resistance to both compounds are relatively common. Four isolates were resistant to neomycin, spectinomycin and streptomycin with two (2.7%) of these also resistant to apramycin; 2.7% of isolates were therefore resistant to all aminoglycosides tested. The 16S rRNA methyltransferases are an emerging group of enzymes conferring broad-spectrum resistance to aminoglycosides. High-level resistance to amikacin (which is used as an indicator of the possible presence of 16S rRNA methyltransferases) was not detected.

Of the remaining non-HP-CIAs, resistance to the beta-lactam ampicillin (67.6%) was common, and a component of the most common core MDR pattern observed in *E. coli* from chickens. This pattern comprised resistance to ampicillin, tetracyclines and trimethoprim/sulphonamides, occurring (with or without additional resistance) in 36 (48.6%) of isolates. Amoxicillin/clavulanate resistance was detected in 44.6% of isolates; although amoxicillin is widely used to treat poultry, amoxicillin/clavulanate is not authorised. Resistance to the first generation cephalosporin cefalexin was not detected, however, cefalexin susceptibility testing is known to be influenced by inoculum effects. The cefalexin MIC can rise dramatically as the density of the test inoculum increases for TEM-1 beta-lactamase producing *E. coli* and narrow-spectrum cephalosporins have shown poor efficacy against infections caused by ampicillin resistant *E. coli* in human medicine. For these reasons, *E. coli* resistant to ampicillin should generally be considered resistant to cefalexin, unless the infection is at a site where cefalexin reaches high concentrations. The beta-lactamase enzyme OXA-1 hydrolyses clavulanate but doesn't affect cefalexin; the occurrence of this enzyme may also contribute to the observed beta-lactam resistance phenotypes.

Resistance to tetracyclines (58.1%) exceeded resistance to doxycycline (27.0%), indicating doxycycline may remain a therapeutic option in some cases of tetracycline resistance. Although the underlying resistance mechanisms have not been determined, this difference in resistance may reflect the occurrence of the different efflux mechanisms in *E. coli*, some of which confer resistance to both compounds, whilst others confer resistance to tetracycline but not doxycycline. Further investigation would be required since the breakpoints applied may also have a role in the observed differences in resistance prevalence.

Figure 4.19: Antibiotic resistant isolates of *Escherichia coli* isolates from poultry (n=74) interpreted using CLSI veterinary breakpoints unless indicated otherwise.



* Interpreted using EUCAST human CBP
⁺ Interpreted using CA-SFM veterinary CBP
AG: aminoglycosides, AP: amphenicols, BL: beta-lactams, PM: polymyxins, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

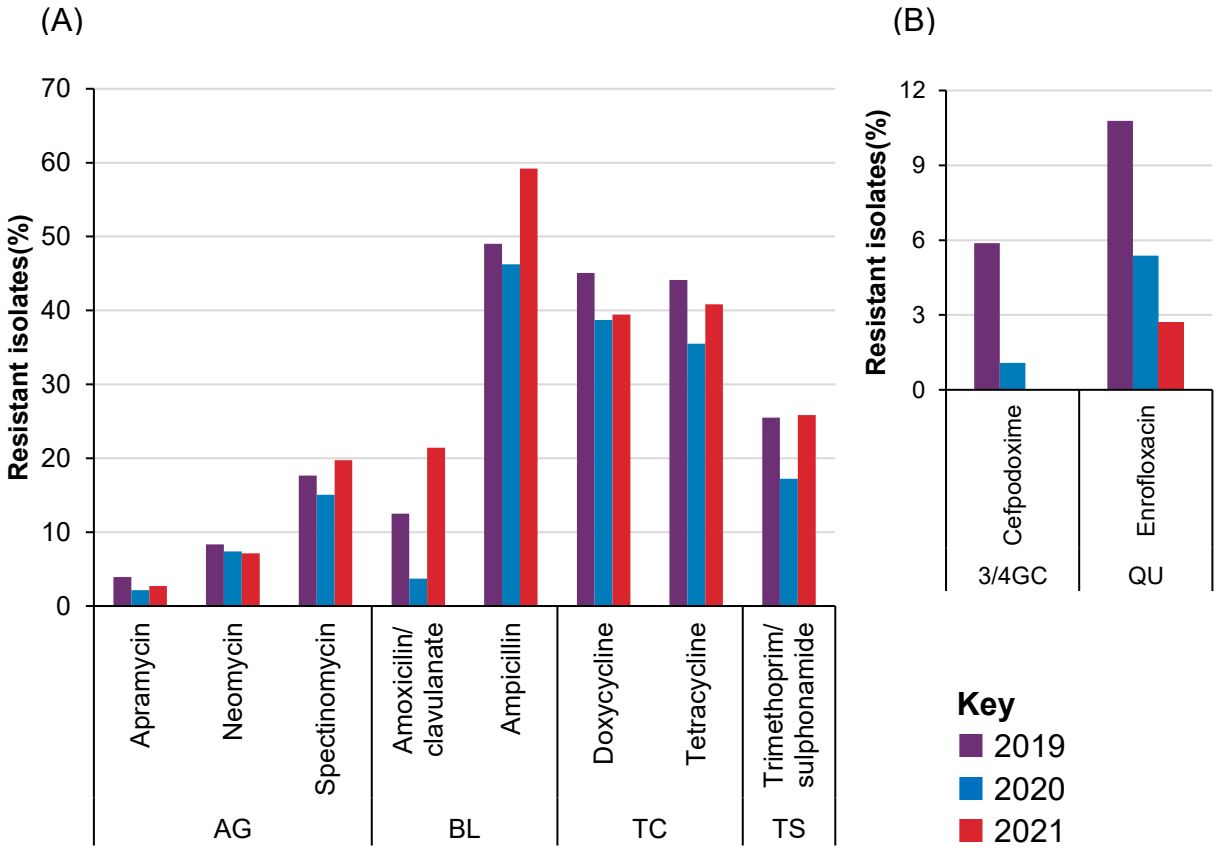
The population of chickens and turkeys sampled and tested by disc diffusion methods includes flocks of various types and sizes, including small scale poultry keepers. Much larger numbers of chicken isolates were obtained compared to turkey isolates over the monitoring period; as such, resistance in *E. coli* isolates from turkeys is shown in Table S2.6.7 of the Supplementary Material 3.

Resistance to the third generation cephalosporin cefpodoxime was not observed in *E. coli* from chickens or turkeys in 2021. Resistance to the fluoroquinolone enrofloxacin declined to 2.7% in chickens and was detected in 5.9% turkeys; it's worth noting this only reflects a single turkey isolate.

The occurrence of resistance to the beta-lactam ampicillin, the aminoglycoside spectinomycin, doxycycline, tetracyclines and trimethoprim/sulphonamides was remarkably similar in *E. coli* from chickens and turkeys, despite resistance within each species having shown fluctuations to each of these antimicrobials in previous years. The reason for this congruity is not known. For chickens, resistance to non-HP-CIAs is varied

(**Figure 4.20**). Resistance detected in *E. coli* isolates in 2021 appears to be lower or similar to that seen in 2019 and/or 2020, with the exception of the beta-lactams amoxicillin/clavulanate (21.4%) and ampicillin (59.2%). Resistance to these antibiotics has increased to high and very high levels respectively.

Figure 4.20: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Escherichia coli* isolates from chickens (all ages; n=56 to 147 in 2021). Note scale differs between graphs.



AG: aminoglycoside, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/ sulphonamides, 3/4GC: third and fourth generation cephalosporins

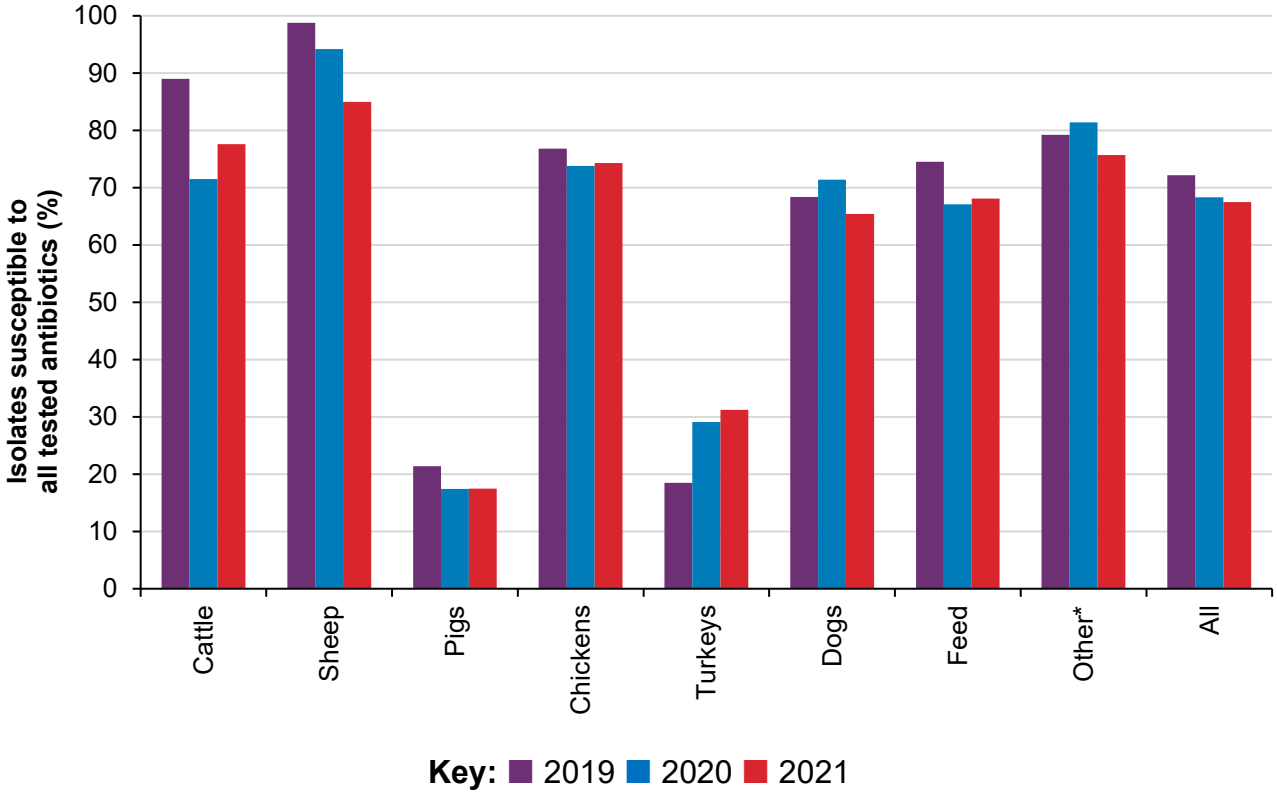
4.3.6 *Salmonella* spp.

Salmonella is an important cause of foodborne disease in people and can cause disease in animals. *Salmonella* isolations are reported on a statutory basis and a culture of the organism must be provided to government laboratories when detected by private veterinary laboratories. Data on *Salmonella* is published annually in the '*Salmonella* in Livestock Production in Great Britain' report. As such, this report presents a condensed summary of *Salmonella* data.

4.3.6.1 Summary

Of the 4507 *Salmonella* isolates tested in 2021, 3044 (67.5%) were sensitive to all the antibiotics tested (**Figure 4.21**), which is very similar to 2020 (68.3%). Additionally, the proportion of isolates resistant to the HP-CIAs ciprofloxacin (0.2%) cefotaxime (0.1%) and ceftazidime (0.1%) remained low, especially in serovars considered of particular public health relevance.

Figure 4.21: *Salmonella* spp. isolates susceptible to all tested antibiotics, from different sources and animal species (n=4,507 in 2021.



* Ducks, horses, other non-avian species, other avian species and farm environment.

Of the most common *Salmonella* serovars, 88.3% of *S.* Dublin isolates from cattle were sensitive to the full antibiotic panel; although the majority of isolates remain sensitive, an increase in resistance was observed in 2020 and 2021 which is mostly due to neomycin and/or chloramphenicol and tetracycline resistance. For *S.* Typhimurium, 44.3% of isolates were sensitive. Three *S.* Typhimurium isolates (two from dogs, one from a horse) were resistant to cefotaxime and ceftazidime. Monophasic *S.* Typhimurium was mostly isolated from dogs and pigs and is often resistant to multiple antibiotics. Amikacin resistance was detected in two *Salmonella* 4,12:i:- DT193 from pigs; a resistance which is rarely detected in livestock.

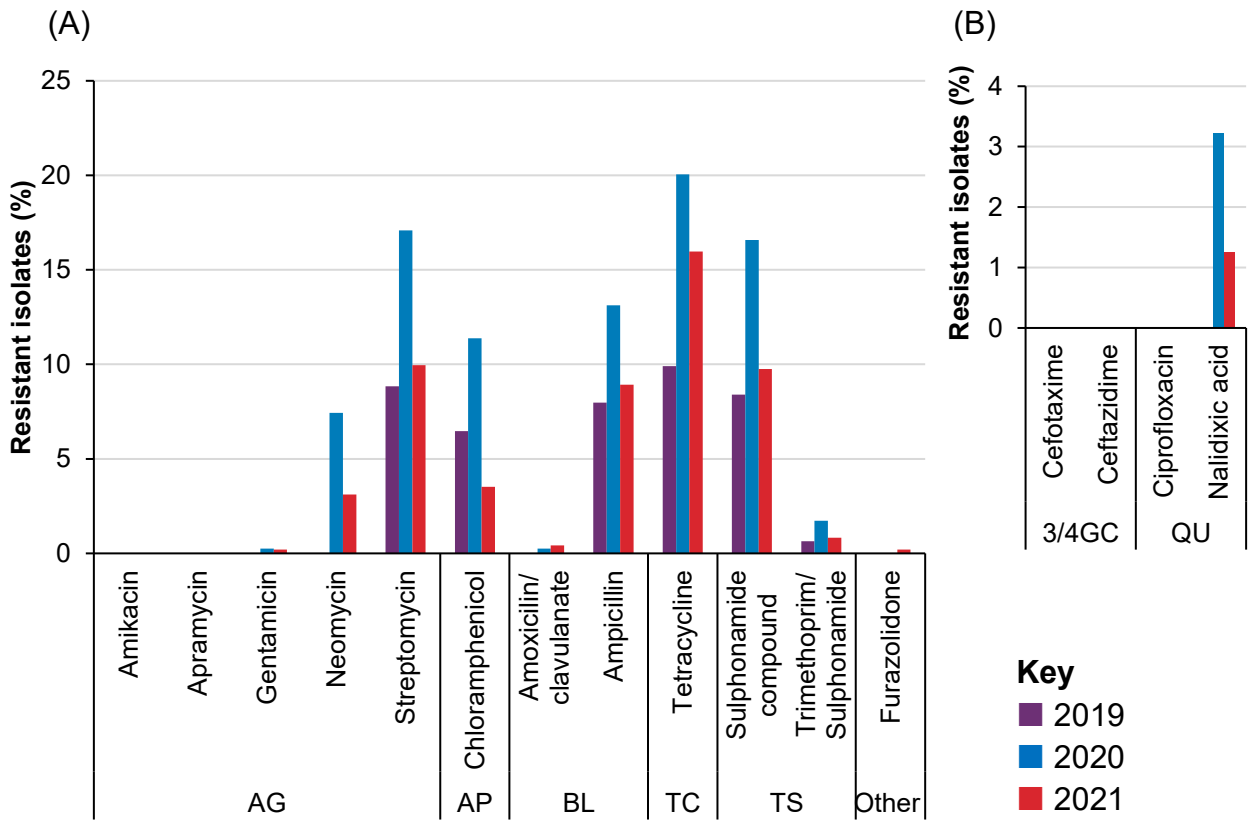
Other findings of note include a MDR *S.* Infantis isolated from a poultry flock in 2021. The MDR included resistance to cefotaxime. *S.* Infantis is known to be established in poultry in continental Europe and to is linked to human cases related to the consumption of contaminated poultry meat. Advisory visits were offered to the affected premise to help

control and manage the infection. Additionally, two *S.* Kentucky isolates were obtained from raw pet food. These isolates were sequence type 198 and were highly resistant to ciprofloxacin. This *S.* Kentucky clone is known to be established in the poultry industry of several countries outside the UK.

4.3.6.2 *Salmonella* by animal species

Cattle: over the monitoring period no resistance to the HP-CIAs cefotaxime, ceftazidime and ciprofloxacin was detected, or to the aminoglycosides amikacin and apramycin. Resistance to nalidixic acid remained low. The highest levels of resistance were detected to tetracycline (16.0%), the aminoglycoside streptomycin (10.0%), sulphonamide compounds (9.8%) and the beta-lactam ampicillin (8.9%). All detections of resistance in 2021 were lower than those detected in 2020, except for furazolidone (0.2%) and the beta-lactam amoxicillin/clavulanate (0.4%) where a single isolate and two isolates were found to be resistant respectively.

Figure 4.22: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from cattle (n=482 in 2021). Note scale differs between graphs.

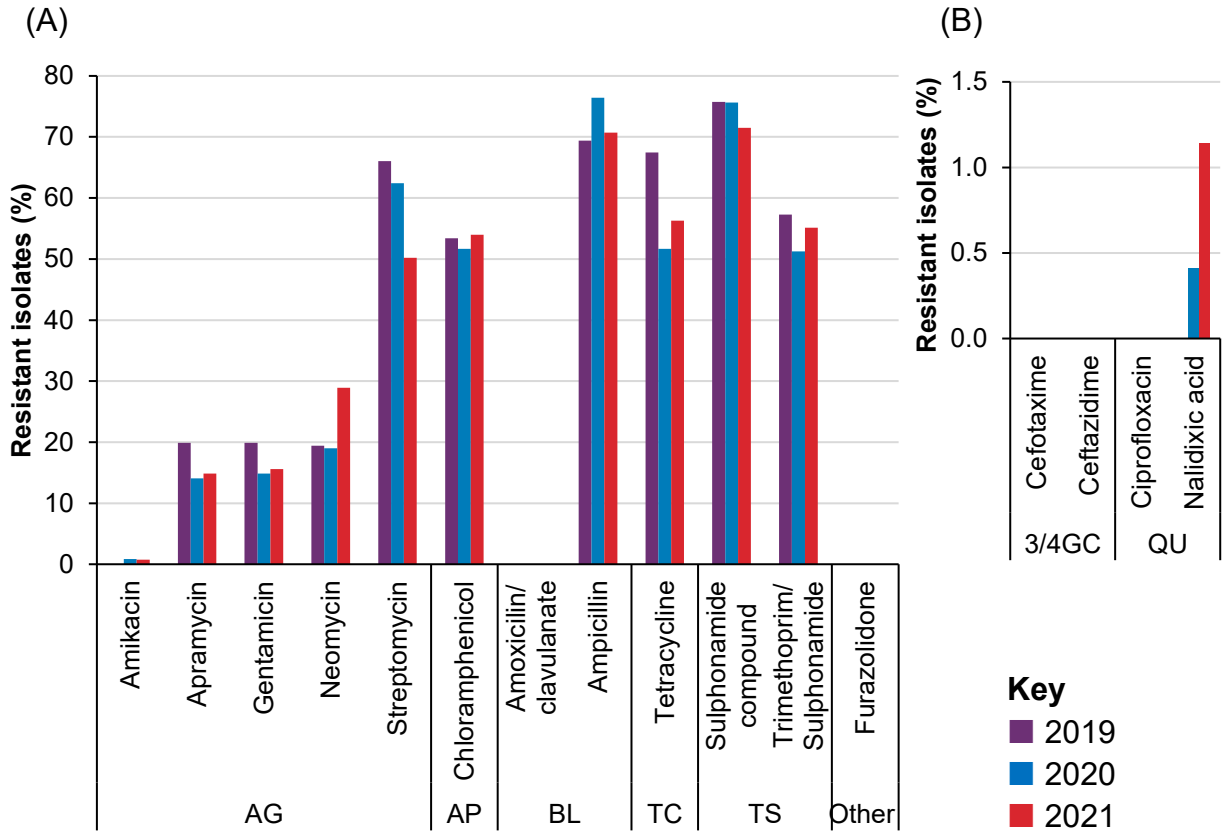


AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Pigs: over the monitoring period no resistance to the HP-CIAs cefotaxime, ceftazidime and ciprofloxacin was detected, or to the antibiotics amoxicillin/clavulanate and furazolidone. Resistance to nalidixic acid was low. The highest levels of resistance were detected to

sulphonamide compounds (71.5%), the beta-lactam ampicillin (70.7%), tetracycline (56.3%) and trimethoprim/sulphonamides (55.1%). All detections of resistance in 2021 were lower than or equal to those seen in 2019 and/or 2020 except for the aminoglycoside neomycin (28.9%) and chloramphenicol (54.0%).

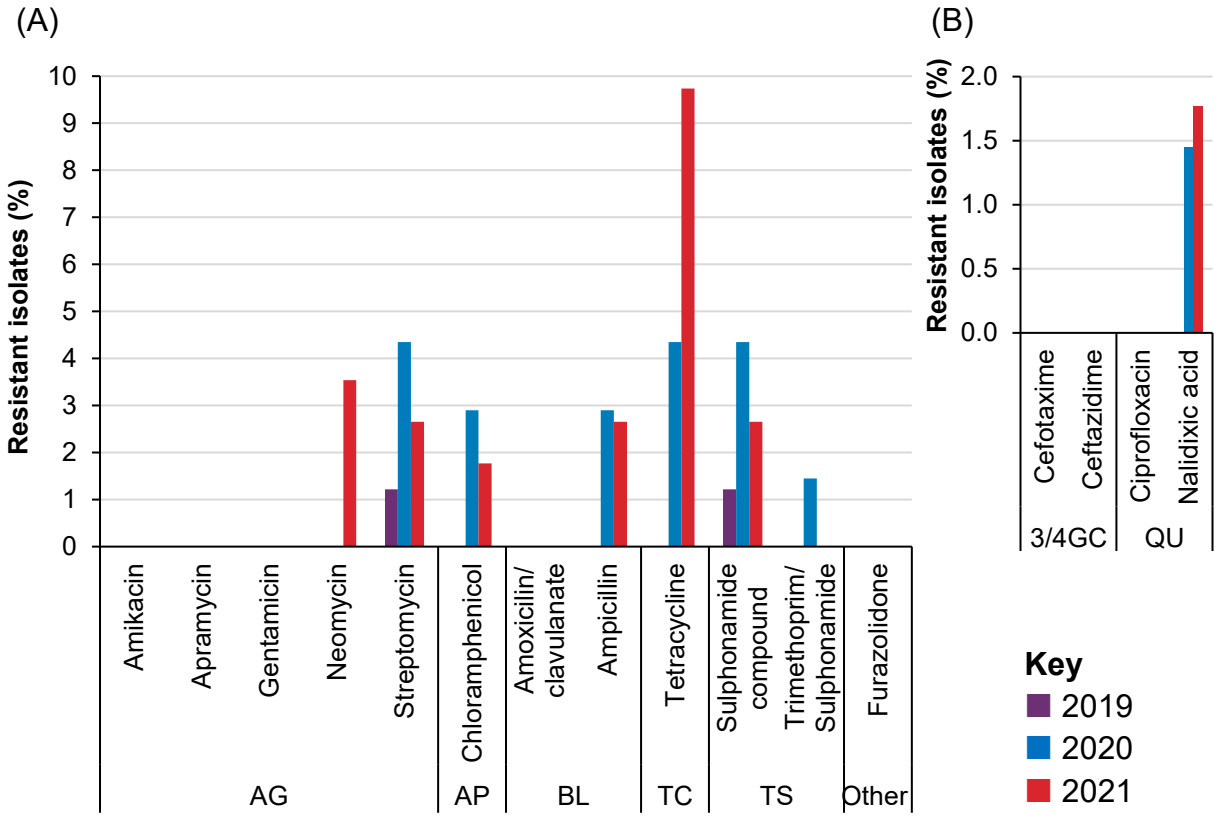
Figure 4.23: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from pigs (n=263). Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Sheep: over the monitoring period no resistance to the HP-CIAs cefotaxime, ceftazidime and ciprofloxacin was detected, or to the antibiotics amikacin, apramycin, gentamicin and amoxicillin/clavulanate. Resistance to nalidixic acid was low. The highest levels of resistance were detected to tetracycline (9.7%), the aminoglycoside neomycin (3.5%) and sulphonamide compounds, the beta-lactam ampicillin, and the aminoglycoside streptomycin (all 2.7%). Although some detections of resistance in 2021 were higher than those seen in previous years, all resistance detected is still classed at low levels.

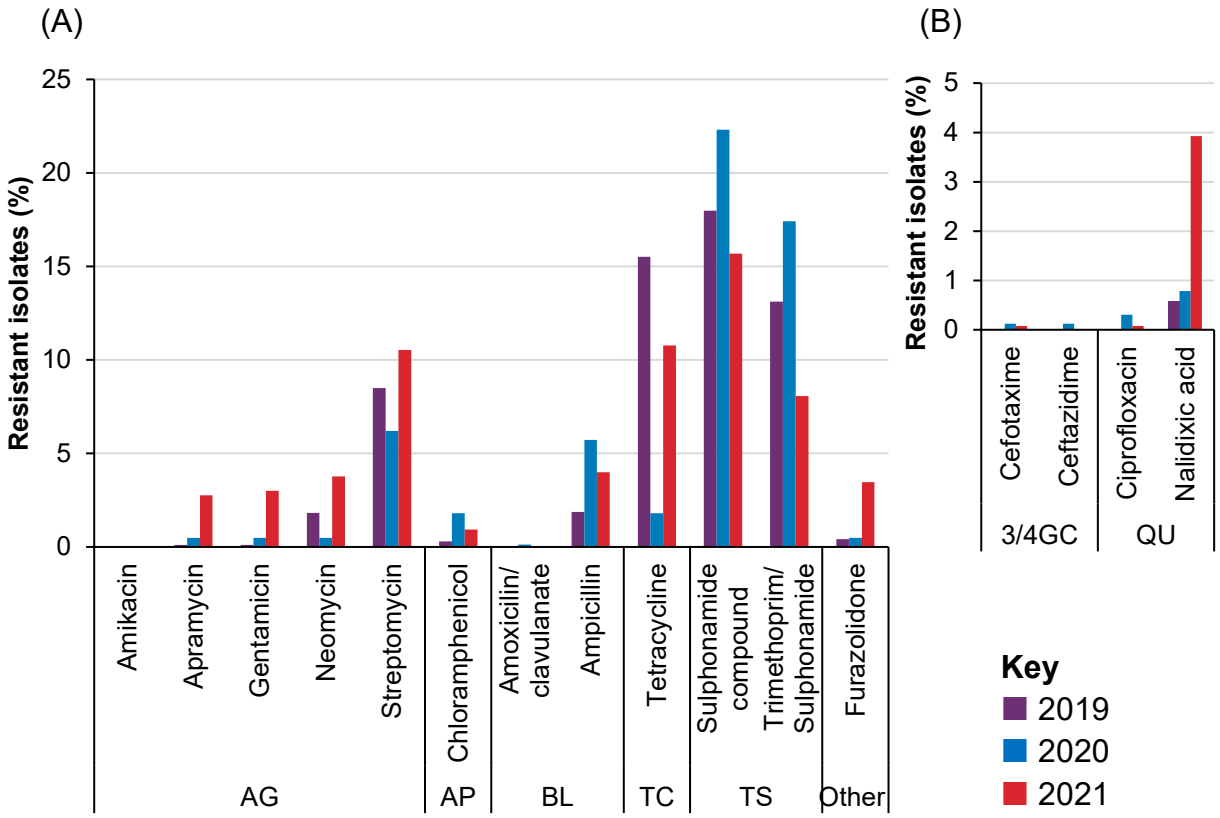
Figure 4.24: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from sheep (n=113 in 2021). Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Chickens: in 2021, singular isolates were resistant to cefotaxime (0.1%) and ciprofloxacin (0.1%) and resistance to nalidixic acid was low; no resistance was detected to ceftazidime. The highest levels of resistance were detected to sulphonamide compounds (15.7%), tetracycline (10.8%), the aminoglycoside streptomycin (10.5%) and trimethoprim/sulphonamides (8.1%). Resistance to the aminoglycosides tested (except amikacin) as well as nalidixic acid and furazolidone was highest in 2021. Resistance to the other antibiotics was lower than that seen in 2019 and/or 2020.

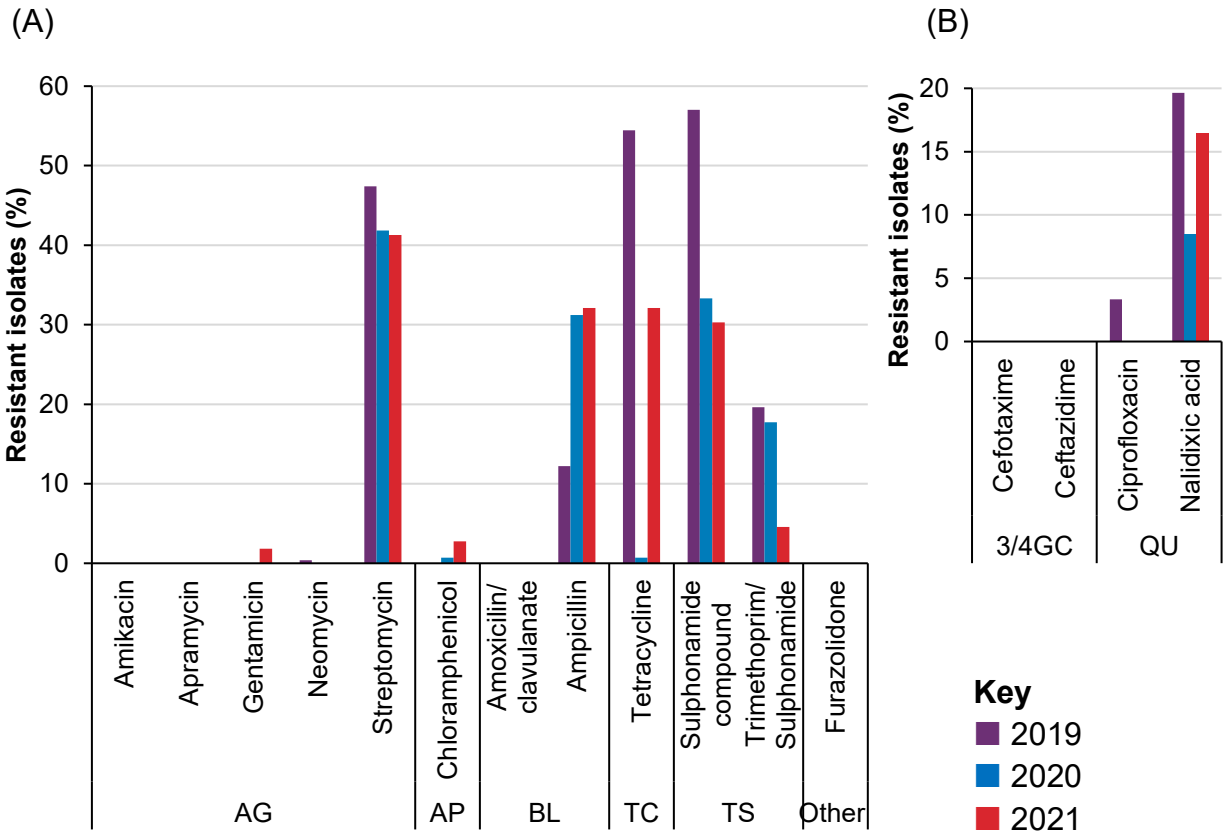
Figure 4.25: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from chickens (n=1300 in 2021). Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

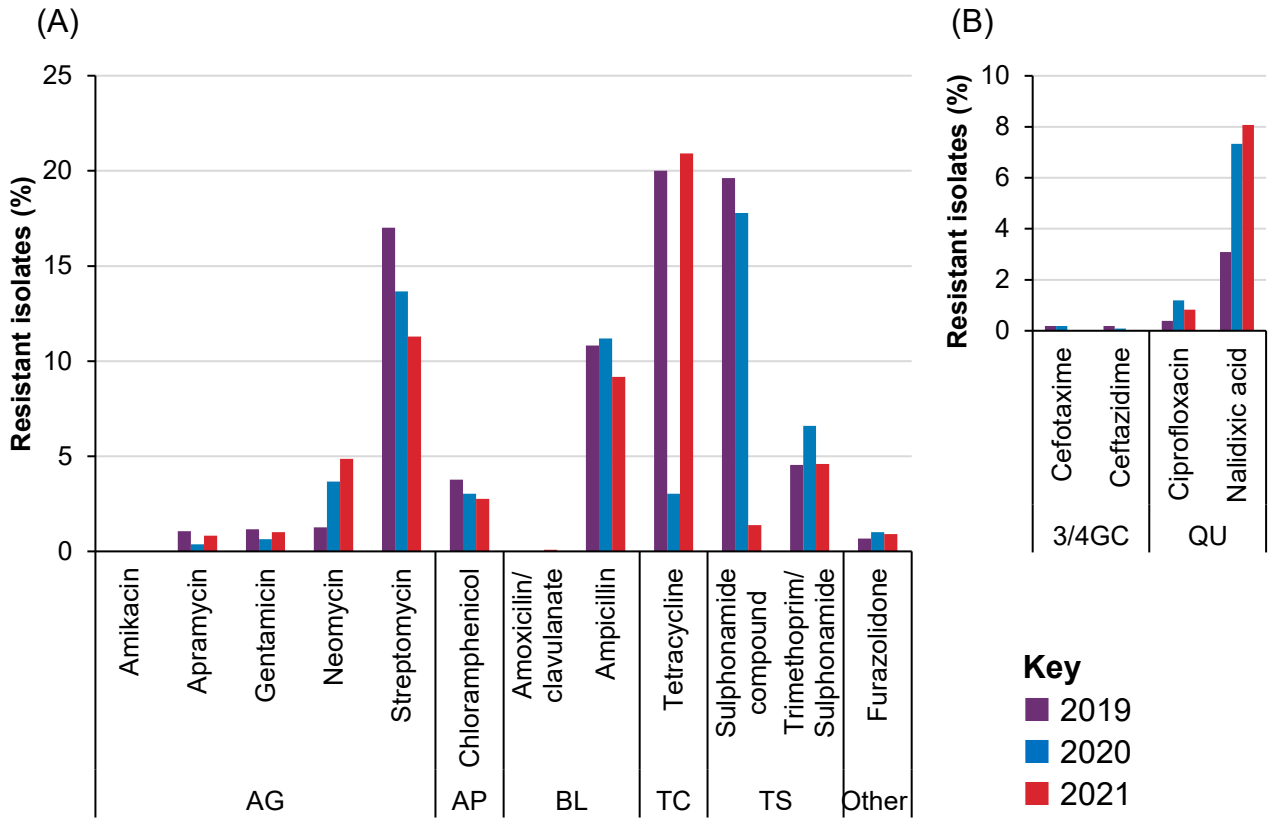
Turkeys: over the monitoring period no resistance was detected to the HP-CIAs cefotaxime or ceftazidime (third generation cephalosporins) and no resistance was detected to the fluoroquinolone ciprofloxacin since 2019. Resistance to nalidixic acid was moderate. Additionally, no resistance was detected to the aminoglycosides amikacin and apramycin, the beta-lactam amoxicillin/clavulanate or furazolidone over the monitoring period. The highest levels of resistance were detected to the aminoglycoside streptomycin (41.3%), the beta-lactam ampicillin (32.1%), tetracycline (32.1%) and sulphonamide compounds (30.3%). In 2021 resistance was lower than that seen in 2019 and/or 2020, except to the aminoglycoside gentamicin (1.8%), chloramphenicol (2.8%) and the beta-lactam ampicillin (32.1%).

Figure 4.26: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from turkeys (n=109 in 2021) . Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

Figure 4.27: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from feed (n=109 in 2021) . Note scale differs between graphs.

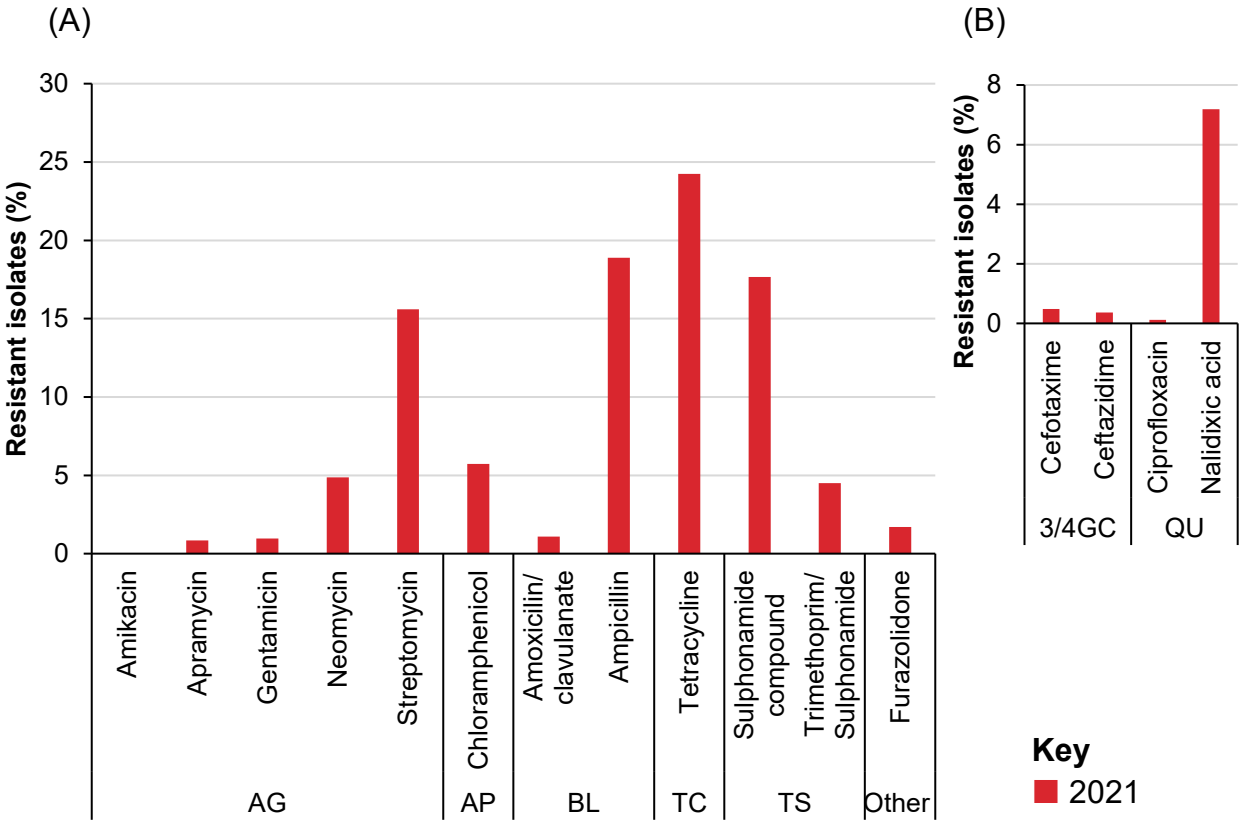


AG: aminoglycoside, AP: amphenicols, BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

4.3.6.3 Changes to surveillance

In 2021, a change to legislation meant that *Salmonella* isolates from dogs became reportable under the Zoonoses Order in Great Britain. Of the 821 isolates from dogs subjected to sensitivity testing, 34.6% were resistant to at least one antibiotic in the panel. Resistance to third generation cephalosporins in *S*. Typhimurium from dogs was identified. Furthermore, strains of MDR *S*. Infantis that are endemic in poultry outside of the UK were also isolated from dogs.

Figure 4.28: Resistance to non-HP-CIAs (A) and HP-CIAs (B) of *Salmonella* isolates from dogs in 2021. Note scale differs between graphs.



AG: aminoglycoside, AP: amphenicols BL: beta-lactams, QU: quinolones, TC: tetracyclines, TS: trimethoprim/sulphonamides, 3/4GC: third and fourth generation cephalosporins

4.3.7 Other zoonotic pathogens

Erysipelothrix rhusiopathiae is widely distributed in nature and occurs as a commensal or pathogen of a very wide range of vertebrate and invertebrate species. The main reservoir amongst the domestic species is probably pigs, though infection of birds and rodents is said to be common. A low number of isolates were tested from pigs (nine), sheep (two) and turkeys (two) and the main resistances detected were to tetracyclines or trimethoprim/sulphonamides. All isolates, irrespective of the species from which they were isolated, were susceptible to penicillin and ampicillin, which are the usual treatment option.

Listeria spp. are widely distributed in the environment and can be isolated from soil, decaying vegetation and poorly fermented silage. Asymptomatic faecal carriage occurs in humans and in many species of animal. Only low numbers of *Listeria monocytogenes* isolates from cattle and sheep were tested. The singular cattle isolate tested showed resistance to cefalexin, reflecting the intrinsic resistance of *Listeria* spp. to this compound. Three *Listeria ivanovii* isolates from sheep were also recovered in 2021 and were susceptible to the antibiotic panel.

Three *Klebsiella pneumoniae* isolates were recovered from avian species; two were resistant to ampicillin reflecting the intrinsic resistance of this organism. No other resistance was detected.

A single *Yersinia pseudotuberculosis* isolate from a sheep was reported in 2021 and was susceptible to the antibiotics tested. No isolates of *Corynebacterium pseudotuberculosis* or *Yersinia enterocolitica* were reported in 2021.

Annexes

Annex A: Glossary of terms

Active ingredient

The part of an antibiotic medicine that acts against the bacterial infection. Alternatively called ‘active substance’.

AMEG

Antimicrobial Advice *ad hoc* Expert Group; AMEG is an *ad hoc* group established by the European Medicines Agency jointly under the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee for Medicinal Products for Human Use (CHMP). The AMEG was set up to provide guidance on the impact on public health and animal health of the use of antibiotics in animals, and on the measures to manage the possible risk to humans.

ATC vet

Anatomical Therapeutic Chemical classification system for veterinary medicinal products

AHDB

Agriculture and Horticulture Development Board

Antibiotic

A large group of antibacterial substances capable of destroying or inhibiting the growth of bacteria, used for treatment or prevention of bacterial infections.

Antimicrobial

Naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of micro-organisms). Used for treatment or prevention of infections. Antimicrobials include antibacterials (antibiotics), antivirals, antifungals and antiprotozoals.

Antibiotic/antimicrobial resistance

The ability of a bacterium/micro-organism to grow or survive in the presence of an antibiotic at a concentration that is usually sufficient to inhibit or kill bacteria/micro-organisms of the same species.

BEIC

British Egg Industry Council

BPC

British Poultry Council

Broiler

A broiler is any chicken that is bred and raised specifically for meat production

BVPA

British Veterinary Poultry Association

CAGG

Cattle Antibiotic Guardian Group

CBP

Clinical Break Point: relates the laboratory results to the likelihood of clinical treatment success or failure.

CHAWG

Cattle Health and Welfare Group

Critically Important Antibiotics

These are antibiotic classes, which are the sole or one of limited available therapies, to treat serious bacterial infections in people and are used to treat infections caused by bacteria that may be transmitted to humans from non-human sources or, bacteria that may acquire resistance genes from non-human sources (WHO definition).

DCDVet

The Defined Course Doses represents the average number of courses per dairy cow using a standard course dose of four tubes per dry cow and three tubes for lactating cow treatments.

DDDVet

The Defined Daily Doses is the assumed average dose per kg animal per species per day. These standard daily doses are extracted from the Summary of Product Characteristics for each antibiotic product

Defra

Department for Environment, Food and Rural Affairs

ECDC

European Centre for Disease Prevention and Control

HP-CIAs

Highest Priority Critically Important Antibiotics. In this report the classification according to the AMEG has been used; therefore the following classes of antibiotics are included under HP-CIAs: fluoroquinolones; third and fourth generation cephalosporins and polymyxins (including colistin).

Defra

Department for Environment, Food and Rural Affairs

ECOFF

Epidemiological cut-off value: represents the point at which bacteria have developed a higher level of resistance to an antibiotic than the background level of resistance that exists naturally for that bacterial species. A ‘resistant’ (or ‘non-susceptible’) ECOFF does not necessarily imply a level of resistance which would correspond with clinical treatment failure.

EFSA

European Food Safety Authority

EMA

European Medicines Agency

eMB Pigs

Electronic Medicines Book for pigs

ESVAC

European Surveillance of Veterinary Antimicrobial Consumption

Food-producing animal (species)

Animals used for food production including (but not limited to): cattle, sheep, pigs, poultry, salmon, trout and bees.

GFA

Game Farmers Association

Injectable product

A product which is administered to animals via injection.

Intramammary product

A product which is administered into the udder.

IU

International Units. A conversion factor used for the calculation of the mass of the active substance.

Medicated feeding stuff

Feeding stuffs that contain a veterinary medicine and that are intended for feeding to animals without further processing.

MIC

Minimum Inhibitory Concentration: the lowest concentration of an antibiotic that inhibits visible growth of a bacterium after overnight incubation.

Non-food-producing animal (species)

Animals not reared for food. These are mainly companion animals including (but not limited to): dogs, cats, horses, small mammals, rabbits and birds.

OIE

Office International des Epizooties (now known as World Organisation for Animal Health)

PHWC

Pig Health and Welfare Council

Oral/water product

A product that is administered to animals orally. In this report this includes boluses, topdressings, powders, dissolvable powders, solutions.

Population Correction Unit (PCU)

This is a technical unit of measurement which is used to represent the estimated weight at treatment of livestock and slaughtered animals. It takes into account a country's animal population over a year, along with the estimated weight of each particular species at the time of treatment with antibiotics. 1 PCU = 1 kg of different categories of livestock and slaughtered animals.

Premix

Veterinary medicinal products intended for incorporation into medicated feeding stuffs.

Prodrug

Ingredient that after administration is metabolized (that is to say, converted within the body) into the pharmacologically active drug.

PSUR

Periodic Safety Update Report. Pharmacovigilance documents submitted by marketing authorisation holders (MAHs) at defined time points post-authorisation. These documents are intended to provide a safety update resulting in an evaluation of impact of the reports on the risk-benefit of a medicinal product.

RCVS

Royal College of Veterinary Surgeons

Red Tractor

Red Tractor Assured Food Standards is a UK company which licenses the Red Tractor quality mark, a product certification programme that comprises a number of farm assurance schemes for food products, animal feed and fertilizer.

RUMA

The Responsible Use of Medicines in Agriculture Alliance

SAGG

Sheep Antibiotic Guardian Group

SAVSNET

Small Animal Veterinary Surveillance Network

SPC

Summary of Product Characteristics

TRACES

The 'TRAde Control and Expert System' (TRACES) is the European Commission’s online management tool for all sanitary requirements on intra-EU trade and importation of animals, semen and embryo, food, feed and plants.

VMD

Veterinary Medicines Directorate, an Executive Agency of the Department for Environment, Food and Rural Affairs (Defra).

WOAH

World Organisation for Animal Health

WHO

World Health Organization

Annex B: Data background and limitations

Antibiotic sales data

- Sales data do not permit accurate analysis of antibiotic consumption by animal species or production category. Some formulations of antibiotics are authorised with indications for use in more than one species, for example pigs and poultry. It is not possible to ascertain from sales data in which species the product was used.
- A given quantity of antibiotic may represent many doses in small animals or few doses in large animals. It is not possible to predict the number of doses represented by the quantity sold.
- Changes in quantities of veterinary antibiotics sold should be considered in parallel with changes in the UK animal population over the corresponding time period. The populations of animal species are an important denominator and may vary quite markedly from year to year depending on market conditions for animal derived food. Similarly, variations in the size of the animals being treated should be taken into consideration as larger animals will require a larger relative quantity of antibiotics over a treatment period.
- To try and address the variation in animal populations and demographics, over time and between countries, the ESVAC project has developed a Population Correction Unit (PCU), a calculation that estimates the weight of the animal (or group of animals) receiving an antibiotic at the most likely time of administration. This unit is now used across EU Member States and is currently the best approximation of consumption. We have used this form of analysis in this report.
- Sales data in general over-estimate use, as not all antibiotics sold will be used. There is natural wastage resulting from pack sizes that do not meet dose need, and from drug expiry. In addition, a product could be sold one year and used, for example, the next year.
- Some products may be sold to UK feed mills for inclusion in feed which is then exported outside of the UK; currently there is no method for separating these sales from the total UK sales data, resulting in an over-estimate of use in UK feed.
- Some products may be imported into the UK on a Special Import Certificate; currently there is no method for including these data in the total UK sales data, resulting in an under-estimate of use in the UK.
- Medication sold for use in humans may be used in animals under certain circumstances, according to the prescribing Cascade; figures on such use are not included in the data presented. Further information on Cascade prescribing can be found in section S1.4 of Supplementary Material 1.

Resistance data, harmonised monitoring scheme

- The sampling size and strategy are designed to provide a sample which is representative of the wider population for each food-producing animal species (pigs,

broiler chickens, and turkeys) in the UK. However, pigs and poultry are monitored on alternating years, therefore not providing annual data

- The organisms monitored are of direct relevance to human health.
- Antibiotics are considered HP-CIAs if they are within "Category B" in the Antimicrobial Expert Group (AMEG) report; these have been included in the panel of antibiotics against which these organisms are tested.
- The sampling methodology used is standardised and harmonised to produce robust susceptibility data that is comparable across species, years, and internationally.
- This year, European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cut-off values (ECOFFs) were used to assess susceptibility of the bacterial isolates. ECOFFs represent the point at which bacteria have developed a higher level of resistance to an antibiotic than the background level of resistance that exists naturally for that bacterial species. A 'decreased susceptibility' (or 'resistant') result based on ECOFFs does not necessarily imply a level of resistance that would correspond to clinical treatment failure. Minimum inhibitory concentrations (MICs) are also recorded and will enable any future changes in CBPs or ECOFFs to be taken into account.
- It should be noted that when using selective culture methods, the occurrence of ESBL-, AmpC- or carbapenemase-producing *E. coli* is assessed with much greater sensitivity than when using non-selective culture methods. The difference is most likely due to the population of ESBL-, AmpC- or carbapenemase-producing *E. coli* being a minority among the *E. coli* populations in the gut flora of these food-producing animals, so the probability of randomly picking a resistant phenotype from a non-selective agar plate is low for most samples tested. Therefore, these selective methods are not able to quantify the risk which these bacteria may potentially pose to human or animal health.

Resistance data, clinical surveillance (including MIC testing of veterinary pathogens)

There are a number of limitations associated with the AMR data and they should be borne in mind when interpreting results from the veterinary clinical surveillance programme. Samples from this programme arise from diagnostic submissions in mostly diseased animals. This results in a biased sample of bacteria and cannot be considered to accurately reflect AMR within the general animal population in the UK. To note, the respiratory veterinary pathogen, *Streptococcus suis, Streptococcus uberis* and avian *E. coli* samples that undergo MIC testing are the same of those that undergo disc diffusion testing in the clinical surveillance program. Therefore, the same sampling limitations as those listed for the clinical surveillance program apply here.

Scanning surveillance limitations:

- Samples arise from diagnostic submissions, which involve mostly diseased animals, and don't reflect UK animal populations as a whole.
- Veterinary surgeons have the option to submit samples to private laboratories rather than Government laboratories/Veterinary Investigation Centres. The proportion of samples that Government laboratories test compared to other laboratories is not known, and therefore we cannot know how representative the samples processed by APHA, SRUC Veterinary Services and AFBI are of total diagnostic submissions.
- Furthermore, geographical proximity of a farm or veterinary practice to a Government diagnostic laboratory may have an impact on the submission rate of samples; clinical surveillance may therefore, naturally, over-represent the animal populations within certain geographical areas.
- Other factors can also influence the submission rate of samples to veterinary diagnostic laboratories. These can include the severity of disease, impact on production or the value of the animals involved.
- The clinical surveillance performed on chickens includes a range of types of bird (layers, broilers, breeders and others) as well as both commercial and backyard flocks. The occurrence of resistance can be influenced by a number of factors, including the types of chickens examined, degree of epidemic spread of resistant bacterial clones the emergence, dissemination and transfer of resistance determinants between and amongst bacteria as well as by the selective pressure exerted by the use of antibiotics.
- The veterinary clinical surveillance data detail the number of bacterial isolates that underwent sensitivity testing, but not the numbers of animals for which samples were submitted for examination. Several bacteria may have been cultured from an individual animal or from a group of animals on the same farm. This type of clustering is not accounted for in the report, although since only low numbers of bacteria are usually subjected to susceptibility testing from the same outbreak of disease, its importance is probably limited.
- The diagnostic tests performed on any sample received through the clinical surveillance programme are dependent on the individual case; that is to say, isolates of the same bacterial species are not always tested against the same panel of antibiotics. Therefore, if resistance is not detected in one isolate, it may not mean that resistance is not present, but that it was not tested for. This is especially true of commensal organisms.
- The levels of resistance demonstrated by the clinical surveillance isolates presented in this report may be higher than those seen in the wider bacterial populations present within animals in England and Wales. This is because samples from diseased animals can include submissions from animals that have been unresponsive to initial antibiotic therapy, and thus the isolates recovered may have already been exposed to antibiotic pressure(s).
- APHA does not provide a veterinary diagnostic service for companion animals, with the exception of *Salmonella* isolated from dogs, which is now encompassed under

the Zoonoses Order. Therefore, bacteria from these animal groups are under-represented in this report.

- With regards to *E. coli*, each organisation in the UK sets their own criteria for testing AMR in *E. coli* from clinically sick animals and these criteria are not uniform. For example, AMR testing on *E. coli* isolates in Northern Ireland is mainly performed if samples are coming from less than 2-week-old calves and animals with bovine mastitis. This is pertinent to highlight as the selection of isolates for susceptibility testing based on age or other criteria can influence the result obtained. Bacterial isolates recovered from young animals can often be more resistant than those from older animals and this relates to the fact that antibiotics are in general more frequently administered to young animals than to older animals.

Laboratory methodology:

- Criteria for the susceptibility testing of some veterinary pathogens are not well-established; this document presents the data which have been collected and acknowledges their limitations and shortcomings. Resistances of particular importance or significance are wherever possible subject to confirmatory testing. The disc diffusion test can be regarded as a screening test, enabling the rapid testing of large numbers of isolates in a cost-effective way and providing a timely result for veterinarians which can assist them in the selection of antimicrobial chemotherapy.
- The breakpoints used for determining resistance for isolates recovered under the veterinary clinical surveillance programme in GB are those recommended by BSAC. These breakpoints were originally determined for human medicine and their use in veterinary medicine is based on the assumption that the concentration of antibiotic at the site of infection is approximately the same in animals as it is in humans. Currently it is not known if this assumption is always correct, especially as different dosing regimens may be used in different animals and pharmacokinetics may vary between species. Currently, there is insufficient data available to apply animal species specific breakpoints to all organism/ antibiotic combinations where these are required.
- For antibiotic susceptibility testing done by APHA, in the case of some veterinary drug-bug combinations a BSAC CBP value may not exist. In this case, APHA may have derived a tentative or suggested breakpoint or the historical veterinary breakpoint (zone size cut-off of resistant: ≤13 mm) may have been used to define resistance. The breakpoints used are set out in S4.1 of Supplementary Material 3.
- Different antibiotic susceptibility testing methodologies are used in England and Wales (APHA), Scotland (SRUC Veterinary Services), and Northern Ireland (AFBI). APHA and SRUC Veterinary Services use BSAC methodology to determine resistance/susceptibility based on human clinical breakpoints, whilst AFBI use CLSI. **In light of the different methodologies and breakpoints used, the amalgamated results of UK wide monitoring should be interpreted with caution.**

- The disc diffusion methodology used to date for assessing susceptibility of veterinary pathogens from scanning surveillance are limited in the availability of breakpoints for all relevant antibiotic and organism combinations. Assessing the susceptibility of veterinary pathogens by determination of the MIC using a standardised broth microdilution method provides a higher quality, internationally recognised output, which is comparable with other monitoring programmes.

Annex C: Sources for reporting of sales data

To enable calculation of sold quantities of active ingredient of antibiotics, data were supplied by:

Marketing Authorisation Holders (MAHs)
It is mandatory for Marketing Authorisation Holders of manufactured antibiotics to provide the Veterinary Medicines Directorate with total annual sales data for each antibiotic product sold within the UK. Data were collected, verified and analysed to calculate the total weight, in tonnes, of each active ingredient sold for each antibiotic. Antibiotic sales data are collected as a proxy for antibiotic use.

Periodic Safety Update Reports (PSURs)
Sales figures submitted by MAHs in PSURs, for the purpose of Pharmacovigilance, were used to validate sales data published in this report. Where a PSUR had been returned to the VMD Pharmacovigilance team in the 2019 calendar year, reported sales were compared to those returned to the AMR team and any discrepancies were queried.

To enable calculation of the Population Correction Unit, data were supplied by:

Defra Statistics division
The live weights of animals slaughtered for food are calculated by Defra. The population numbers of food-producing animals were supplied by Defra via the ‘Agriculture in the UK’ report.

CEFAS
The annual live weight of fish at slaughter for the UK was supplied by CEFAS (Centre for Environment, Fisheries and Aquaculture Science).

TRACES
Import and export figures obtained from TRACES were provided by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project and used in the calculation of the PCU.

Annex D: Contributors

Contributing Pharmaceutical Companies and Other Marketing Authorisation Holders (compiled by the VMD):

- Alfamed
- Alfasan Nederland B.V.
- Alivira Animal Health
- Alpha-Vet Allatgyogyaszati kft
- Andres Pintaluba S.A.
- Animalcare Limited
- aniMedica GmbH
- Audevard
- Avimedical B.V.
- Bela-Pharm GmbH & Co. KG
- Bimeda Animal Health Ltd
- Boehringer Ingelheim Animal Health Ltd
- Ceva Sante Animale
- Ceva Animal Health Ltd
- Chanelle Animal Health Ltd
- CP Pharma Handelsgesellschaft
- Cross Vetpharm Group Ltd
- Dechra Ltd
- Divasa Farmavic S.A.
- Dopharma Research B.V.
- ECO Animal Health
- Ecuphar Veterinaria S.L.U.
- Ecuphar N.V
- Elanco Europe Ltd
- Eli Lilly & Company Ltd
- Emdoka bvba
- Eurovet Animal Health B.V.
- Fatro S.P.A.
- Franklin Pharmaceuticals Ltd
- Global Vet Health S.L.
- Harkers Ltd
- Huvepharma SA
- Huvepharma N.V.
- I.C.F. Sri Industria Chimica Fine
- Industrial Veterinaria S.A.
- Intervet Ltd,
- Kela N.V.
- Kernfarm B.V.
- Krka Dd
- Labiana Life Sciences
- Laboratorios Calier S.A.
- Laboratorios e Industrias IVEN S.A.
- Laboratorios Maymo S.A.
- Laboratorios Hipra S.A.
- Laboratorios Karizoo S.A.

- Laboratorios SYVA S.A.U
- Lavet Pharmaceuticals Ltd
- Le Vet Beheer B.V.
- Livisto Int.'I.S.L
- Lohmann Pharma
- Nimrod Veterinary Products Ltd
- Norbrook Laboratories Ltd
- Orion Corporation
- Oropharma N.V.
- Pharmanovo Veterinararzneimittel GmbH
- Pharmaq Ltd
- Pharmsure International Ltd
- Phibro Animal Health S.A.
- Richter Pharma AG
- SP Veterinaria S.A.
- TVM UK
- Univet Ltd
- Vetcare Oy
- Vétoquinol SA
- Vétoquinol UK Ltd
- Vetpharma Animal Health S.L.
- Virbac S.A.
- VMD N.V.
- Zoetis UK Ltd