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Assessment of animal diseases caused by bacteria resistant to antimicrobials: Poultry

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Abstract

In this opinion, the antimicrobial-resistant bacteria responsible for transmissible diseases that constitute a threat to poultry health have been assessed. The assessment has been performed following a methodology based on information collected by an extensive literature review and expert judgement. Details of the methodology used for this assessment are explained in a separate opinion. A global state of play is provided for: *Avibacterium (Haemophilus) paragallinarum, Bordetella avium, Clostridium perfringens, Enterococcus faecalis* and *Enterococcus cecorum, Erysipelothrix rhusiopathiae, Escherichia coli, Gallibacterium* spp., *Mycoplasma synoviae, Ornithobacterium rhinotracheale, Pasteurella multocida, Riemerella anatipestifer* and *Staphylococcus aureus*. Among those bacteria, EFSA identified *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus cecorum* with ≥ 66% certainty as being the most relevant antimicrobial resistant bacteria in the EU based on the available evidence. The animal health impact of these most relevant bacteria, and their eligibility for being listed and categorised within the Animal Health Law Framework, will be assessed in separate scientific opinions.

Keywords: antimicrobial resistance, Animal Health Law, extensive literature review, poultry

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1. Introduction

EFSA received a mandate from the European Commission to investigate the global state of play as regards resistant animal pathogens that cause transmissible animal diseases (Term of reference (ToR) 1), to identify the most relevant bacteria in the EU (first part of ToR 2), to summarise the actual or potential animal health impact of those most relevant bacteria in the EU (second part of ToR 2) and to perform the assessment of those bacteria to be listed and categorised according to the criteria in Article 5, Annex IV according to Article 9 and 8 within the Regulation (EU) 2016/429 on transmissible animal diseases ('Animal Health Law')[1] (ToR 3).

This scientific opinion presents the global state of play as regards resistant animal pathogens that cause transmissible animal diseases (ToR 1) and the results of the assessment of the most relevant bacteria in the EU (first part of ToR 2) for poultry following the methodology described in EFSA AHAW Panel (2021).

1.1. Background and Terms of Reference as provided by the requestor

The background and ToR as provided by the European Commission for the present document are reported in sections 1.1 and 1.2 of the scientific opinion on the *ad hoc* method to be followed for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the Animal Health Law (AHL) framework (EFSA AHAW Panel, 2021).

1.2. Interpretation of the Terms of Reference

The interpretation of the ToR is as in Sections 1.3.1 and 1.3.2 of the scientific opinion on the ad hoc method to be followed for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021).

The present document reports the results of the assessment of bacterial pathogens resistant to antimicrobials in poultry.

2. Data and methodologies

The methodology applied for this opinion is described in a dedicated document, which details the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021). Additional methods specific to this opinion (data collection by an extensive literature review) are detailed below.

2.1. Extensive literature review

The process to identify the bacterial species to focus on in the extensive literature review (ELR) is described in Section 2.1.2 in the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL (EFSA AHAW Panel, 2021). According to that methodology, the following target bacterial pathogens for poultry had been agreed upon by the EFSA working group: *Avibacterium (Haemophilus) paragallinarum, Bordetella avium, Clostridium perfringens, Enterococcus faecalis* and *Enterococcus cecorum, Erysipelothrix rhusiopathiae, Escherichia coli, Gallibacterium* spp., *Mycoplasma synoviae, Ornithobacterium rhinotracheale, Pasteurella multocida, Riemerella anatipestifer, Staphylococcus aureus*. The ELR was carried out by the University of Copenhagen under the contract OC/EFSA/ALPHA/2020/02 – LOT 1.[2] On 16 April 2021, two different search strings (Appendix A) were applied in PubMed and Embase, respectively, resulting in the identification of 2,549 unique abstracts published since 2010. Upon importation into Rayyan software (https://rayyan.ai/terms/show), these abstracts were screened by a senior scientist who followed the criteria described in the protocol for the inclusion and exclusion of studies. When available, the full text of the articles was downloaded into EndNote software. In addition, the most recent national antimicrobial resistance (AMR) monitoring reports reporting data for the target pathogens and written in English or German were downloaded. Only the latest version of the surveillance reports was included in the review, as isolates included in these reports can be assumed to originate from the same sampled populations and most recent versions would therefore include the most up-to-date AMR data. AMR data in the full texts and national reports were evaluated for eligibility applying the exclusion criteria as described in the ad hoc method followed for the assessment of animal diseases

[1] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0429&rid=8
[2] https://ted.europa.eu/udl?uri=TED:NOTICE:457654-2020:TEXT:EN:HTML

caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021), with the following changes of the standard methodology:

- Exclusion criterion 1: Not possible to differentiate between antimicrobial drugs (e.g. a study reports antimicrobial classes 'fluoroquinolones'). One exception is if the study lists the antibiotic tested in the Material and Method section (e.g. 'enrofloxacin') but reports data at class level ('fluoroquinolone').
- Exclusion criterion 8: the minimum number of isolates in a study to be considered acceptable was set at 50 for *E. coli* and at the default of 10 or more for the other bacterial species.

Information extracted from the eligible assessed full-text reports/publications is described in the scientific opinion describing the ad hoc method applied in the assessment (EFSA AHAW Panel, 2021).

Information on all the full-text studies that were assessed, including the reason for exclusion for those that were excluded at the full-text screening, is presented in Annex II.

AMR was assessed for clinically relevant antimicrobials according to the method detailed in Section 2.1.3 of the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL (EFSA AHAW Panel, 2021). The list of clinically relevant antibiotics for each target bacterial species in poultry considered in this opinion is shown in Annex III. When more than one antimicrobial from a given class was considered eligible for inclusion in the report, the following order of preference for each antimicrobial class and bacterial pathogen was considered:

- For fluoroquinolone data, the order of preference was enrofloxacin > ciprofloxacin.
- For tetracycline, the order of preference was tetracycline > oxytetracycline > doxycycline > chlortetracycline.
- For aminopenicillin, the order of preference was ampicillin > amoxicillin.

For each study, when clinical breakpoints were used, AMR data were extracted as percentages of resistant isolates (%R) and/or as percentages of non-susceptible isolates by combining resistant and intermediate (I) isolates (%R + I). For some drugs (e.g. sulfonamide-trimethoprim), there is no I category; therefore, only %R was reported.

For each study, resistance data were extracted as resistance (%R) alone and/or including the intermediate category (%R + I). The following assumptions and decisions were made when evaluating data sets:

- When no information on the I category was provided in a study, we considered that the reported %R only considered resistant isolates (i.e. I isolates had not been included in the R category).
- When the percentage of susceptible isolates (%S) was reported with no information on I, it was not possible to calculate %R. Instead, we calculated %R + I as 100% − %S.
- When %I was reported separately, we extracted that along with %R and calculated %R + I.
- When %I was reported separately, we extracted that along with %R and calculated %R + I (see Annex II).
- When epidemiological cut-offs (ECOFFs) were used, proportions of non-wild-type isolates were reported as %R + I as the I category is always part of the non-wild-type population.

3. Assessment

3.1. ToR 1: global state of play for resistant bacterial animal pathogens that cause transmissible animal diseases

3.1.1. General overview of studies included and excluded

After screening 2,549 abstracts, 192 publications (including five national AMR surveillance reports) were selected for full-text evaluation as they were considered eligible according to the criteria described above and in the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL (EFSA AHAW Panel, 2021). Of these, 131 (68%) publications were excluded due to one or more of the exclusion criteria listed in Section 2.1.4 of the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL (EFSA AHAW Panel, 2021). The reasons for exclusion of studies are listed in Table 1. The most common reason for exclusion was 'other' (21 studies), with several reasons within this category, e.g.

that resistance was investigated in a subset of resistant isolates. The second most common reason (18 studies) was that isolates were not of clinical origin or it was not possible to distinguish between data from healthy and sick birds. The third most common reason for exclusion was that AMR was reported together for multiple animal (= poultry) species (17 studies).

Table 1: Main reasons for exclusion of studies after full-text evaluation affecting more than one study (a study could be excluded for more than one reason)[(a)]

Reason	Code in Appendix B	Number of studies
Inclusion of non-clinical isolates that cannot be distinguished from clinical isolates	5	19
AMR data from multiple host species (other than poultry) reported together	2	17
Fewer than the minimum number of isolates are included in the study	8	15
Percentage of resistant isolates not reported	7	14
Minimum inhibitory concentration data reported without interpretation	12	14
Full text not available at server of the University of Copenhagen	10	9
Study does not follow a standard for antimicrobial susceptibility testing or a standard is not reported	4	7
AMR assessed genotypically	16	7
Antimicrobials tested are not among the ones of interest for this scientific opinion	13	5
Criteria for selection of isolates unclear and/or high risk of data duplication	14	4
Study investigating AMR in a subset of resistant clinical isolates	17[(b)]	3
Same animals sampled repeatedly	6	3
AMR data reported at bacterial genus level or above	3	2
AMR data included in another included study	9	2
Language (non-English)	11	2
Case study	17[(b)]	2

(a): Other 14 reasons for exclusion affecting one study each are not reported in this table and are listed in Appendix B.
(b): Specified in column E, Appendix B.

After the exclusion of these references, 60 studies and the five national reports from Finland, France, Germany, Sweden and UK were found eligible and were subsequently used to extract the data of interest. An overview of the number of eligible studies for each target bacterium is shown in Table 2.

Table 2: Number of eligible studies from which AMR data were extracted, by target bacteria species

Bacteria species	Number of eligible studies for data extraction (n = 65)[(a)]
Escherichia coli	46
Enterococcus faecalis or *Enterococcus cecorum*	6
Staphylococcus aureus	5
Riemerella anatipestifer	4
Clostridium perfringens	3
Avibacterium (haemophilus) paragallinarum	2
Bordetella avium	1
Mycoplasma gallisepticum	1
Pasteurella multocida	1
Gallibacterium anatis	1
Mycoplasma synoviae	0
Ornithobacterium rhinotracheale	0
Erysipelothrix rhusiopathiae	0

(a): A study can provide information on more than one bacterial species.

Figure 1 provides an overview of the 66 studies included (some with data on more than one bacterial species) sorted by year of publication. Most included studies were published in 2020, which is partly due to the inclusion of only the most recent national reports.

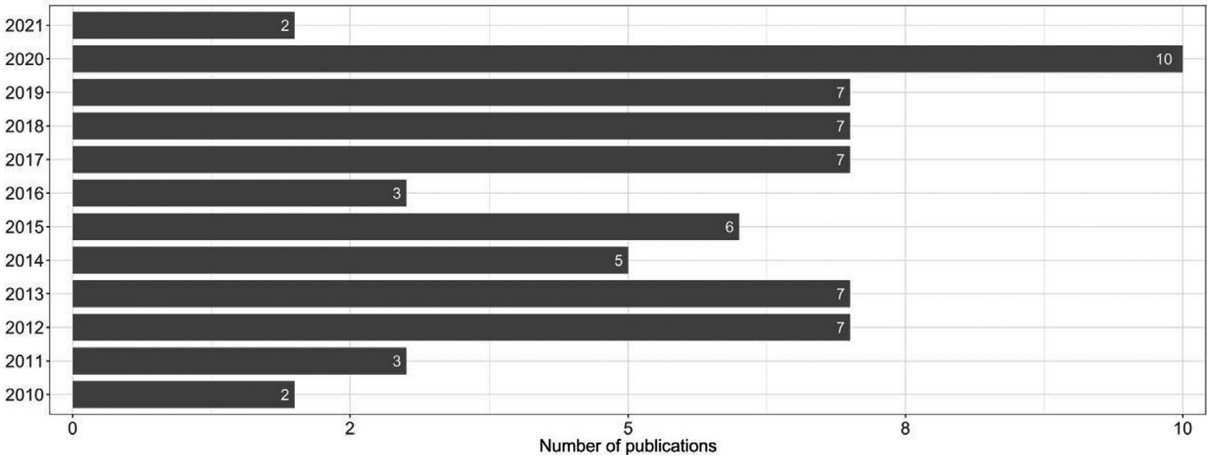


Figure 1: Date of publication of the 66 studies included in the extensive literature review

Considering geographical distribution, data from 27 countries in five continents were included: 32 studies reported AMR data from Asia, 11 from Europe, 10 from Africa, 8 from North America, 5 from South America, 1 from Oceania (one study included data from two continents) (Figure 2). The most represented country was China (16 studies) followed by Egypt (six studies) and Brazil (five studies), with all the remaining countries being represented by one to four studies.

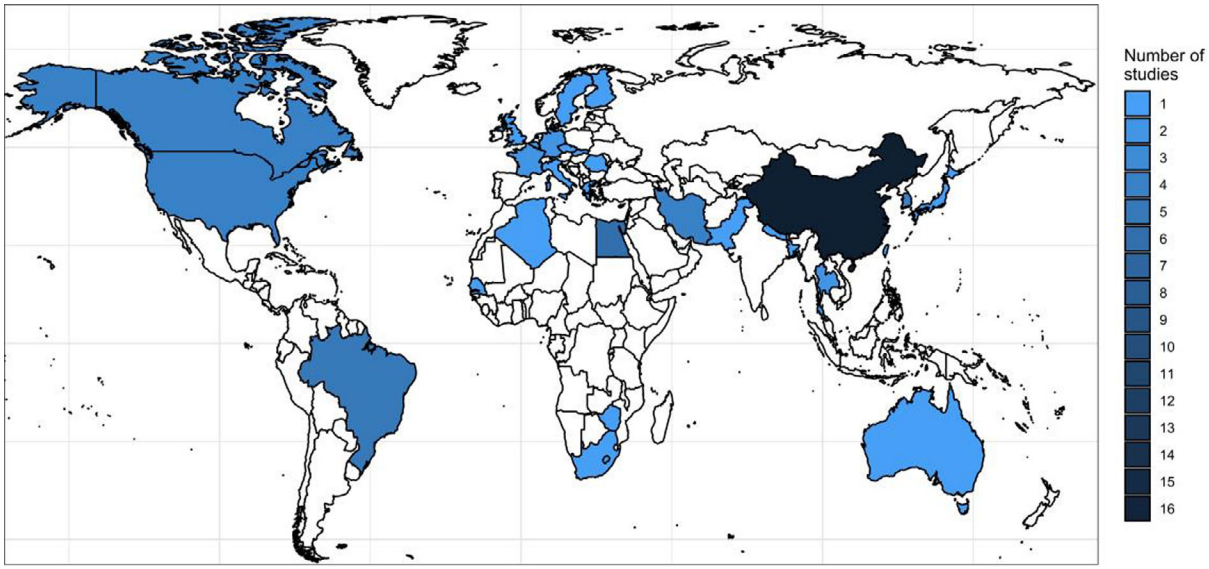


Figure 2: Geographical distribution of the 66 studies included

Isolates originated mostly from two main types of collections: (i) those generated through the analysis of samples collected from a clearly defined population of poultry farm (48 studies), and (ii) those coming from a diagnostic laboratory without or with limited background information on isolates: 12 studies had isolates from diagnostic laboratories and one from a slaughterhouse, without further specification (the origin was unclear for the remaining five studies).

Information about previous antimicrobial treatment in the animals from which isolates were retrieved was only found in one of the included studies. This study (study ID 110; Hasan et al. (2011)) was about resistance in *E. coli* from layers in Bangladesh, and the following was explained: 'Most farmers (215 out of 260) chose antibiotics without getting a prescription and used them regularly as growth-promoting agents as well as for disease prevention. The most commonly used compounds were tetracycline, doxycycline, ampicillin, colistin sulfate, nalidixic acid, neomycin, ciprofloxacin and sulfonamides with trimethoprim'. Without being specified, it is likely that some of the animals from other included studies had also been treated with antibiotics before sampling. So, it is very difficult to relate the observed AMR patterns to prior drug usage.'

3.1.2. AMR frequency data

The figures and tables in the following pathogen-specific sections summarise AMR frequency data reported for poultry from six continents.

The AMR frequency data are extremely difficult to compare, as study design, study populations, methods, interpretive criteria, etc. vary considerably between studies. The number of antimicrobial susceptibility testing (AST) results for any given antimicrobial extracted from the selected references (total of 102.526, Appendix B) was mostly due to results found for *E. coli* (90,994, 88.8% of all data retrieved). The following bacteria for which more AST results were retrieved were *E. caecorum* (3,258), *P. multocida* (2,070), *C. perfringens* (1,860), *S. aureus* (1,410) and *E. faecalis* (1,210), while less than 600 AST results were found for the remaining bacterial species. The laboratory method most commonly used to determine the AST result was disk diffusion (80,968 determinations) followed by broth microdilution (19,853 determinations) and agar dilution (1,580) (Appendix B).

Furthermore, the definition of AMR differed across studies, as the intermediate category defined by clinical breakpoints was included in the calculation of AMR frequencies in some studies, whereas it was omitted in others. So, in the figures with resistance data, we have illustrated for each study whether %R or %RI was reported, therefore this should be taken into account when comparing studies. It is also important to mention that almost no infection-specific and host-specific clinical breakpoints (CBPs) exist for avian pathogens. This complicates interpretation of data, as for several studies it was unclear if the CBPs used were adapted from other bacterial or animal species, from humans, or even 'self-invented'. Also, it was not always clear if the CBPs were specific for the relevant organ or body site. Taken together, the outcomes of the present report should be interpreted and cited with caution, as all specificities of individual studies cannot be taken into consideration. To support conclusions made from the figures or tables (e.g. a high proportion of resistance in a certain country/continent), it is strongly recommended to consult individual papers and check if results may be biased by sampling of animals in a certain environment, the use of certain diagnostic methods or breakpoints, or other factors.

The data found in the last published versions of the five national AMR monitoring programmes that included AMR information on clinical isolates from one or more of the pathogens of interest (FINRES-Vet – Finland, SWEDRES-Svarm – Sweden, GERM-VET – Germany, RESAPATH – France and UK-VARSS – United Kingdom) are included in the tables and figures presenting the outputs of the ELR for each bacterium in the following section. Additional details/data provided in previous versions of the reports from these monitoring programmes (up to the previous 5 years) were extracted and are presented at the end of each bacterium's specific section to assess the existence of changes over time in the proportion of resistant isolates when possible. Nevertheless, assessment of changes in AMR levels over time in the pathogens under evaluation based on the data in the reports is hampered in certain cases by the lack of consistent reporting over the years (i.e. only data from specific years were reported) and/or because data on isolates retrieved over several years were presented together. Furthermore, for poultry, most of the reports included information on isolates only from laying hen and broiler, and the number of isolates tested annually in each country was in general very limited with the only exception of RESAPATH (Table 3). Between-country comparisons must be performed carefully as different methodologies are applied to obtain the results presented in each report, and results provided here are those presented in the reports (e.g. without accounting for the use of different breakpoints).

Table 3: Data from last published versions of the national AMR monitoring programmes included in the literature review

Programme	FINRES-Vet	GERM-Vet	RESAPATH	SWEDRES-Svarm	UK-VARSS
Country	Finland	Germany	France	Sweden	United Kingdom
Laboratory method	Broth microdilution	Broth microdilution	Disk diffusion	Broth microdilution	Disk diffusion
AST interpretation	ECOFFs/CBPs	ECOFFs/CBPs	ECOFFs	ECOFFs	CBPs
E. coli	Yes	Yes	Yes	Yes	No
Origin (number of isolates)	Broiler (colibacillosis) 17–27/year	Broilers, young hens and laying hens, turkey (255–473)	Broiler, laying hen, duck, turkey 108–4,262/year	Laying hen 100 (overall)	
Years covered	2016–2019	2014–2018	2014–2018	2017–2018	
S. aureus	Yes	Yes	Yes	No	Yes
Origin (number of isolates)	Broiler (tenosynovitis) 8–26/year	Broilers, young and laying hens, turkeys	Laying hen and broiler 144–457/year		Chicken 26–33 (overall)
Years covered	2016–2019	2014–2018	2014–2018		2015–2019
E. cecorum	No	No	Yes	No	No
Origin (number of isolates)			Laying hen and broiler 124–445/year		
Years covered			2014–2018		

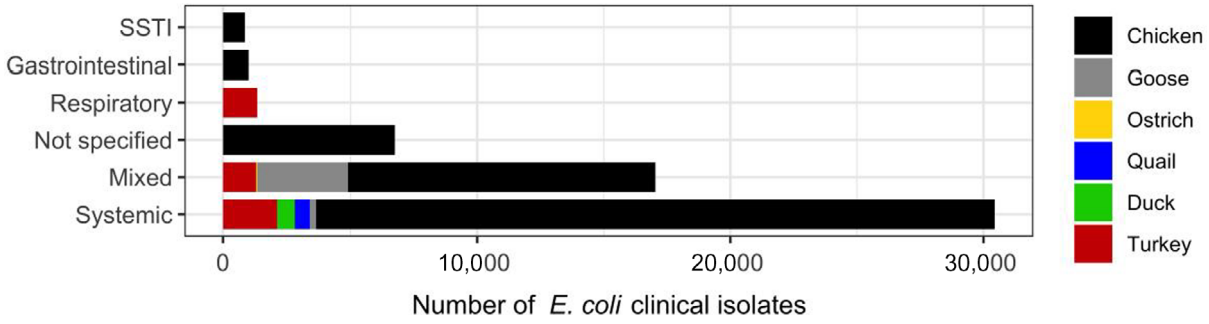
3.1.3. *Escherichia coli*

3.1.3.1. Results of the extensive literature review

Escherichia coli is a commensal and an opportunistic pathogen residing in the intestinal microbiota of animals and humans. It can cause a variety of infections, but in birds it is most known for causing systemic infection referred to as colibacillosis. Following septicaemia, various manifestations such as airsacculitis or pericarditis may develop. Avian-pathogenic strains are commonly, but not exclusively, of serotypes O1, O2 and O78.

In total, 46 studies with ≥ 50 *E. coli* isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, colistin, polymyxin B, enrofloxacin/ciprofloxacin, gentamicin, neomycin, spectinomycin, streptomycin, sulfonamide-trimethoprim, tetracycline/oxytetracycline/doxycycline/chlortetracycline) were included. Those studies were distributed as follows: Africa (8), Asia (24), Europe (8), Oceania (1), North America (2) and South America (4). One study included isolates from two continents.

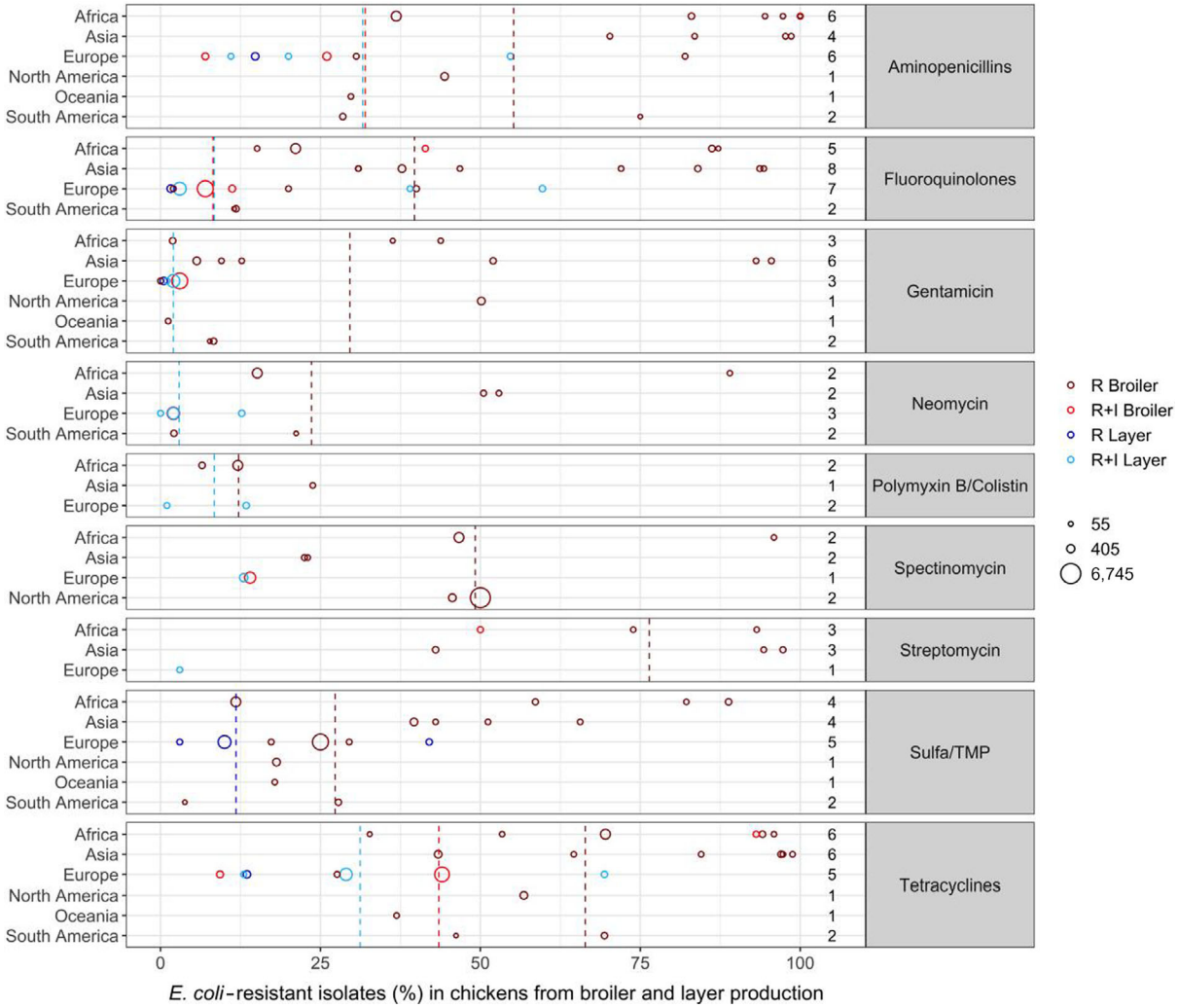
The distribution of *E. coli* isolates by site of infection is shown in Figure 3. Systemic infections were the most common category, generally referred to as colibacillosis in the papers.



SSTI: skin and soft tissue infections.

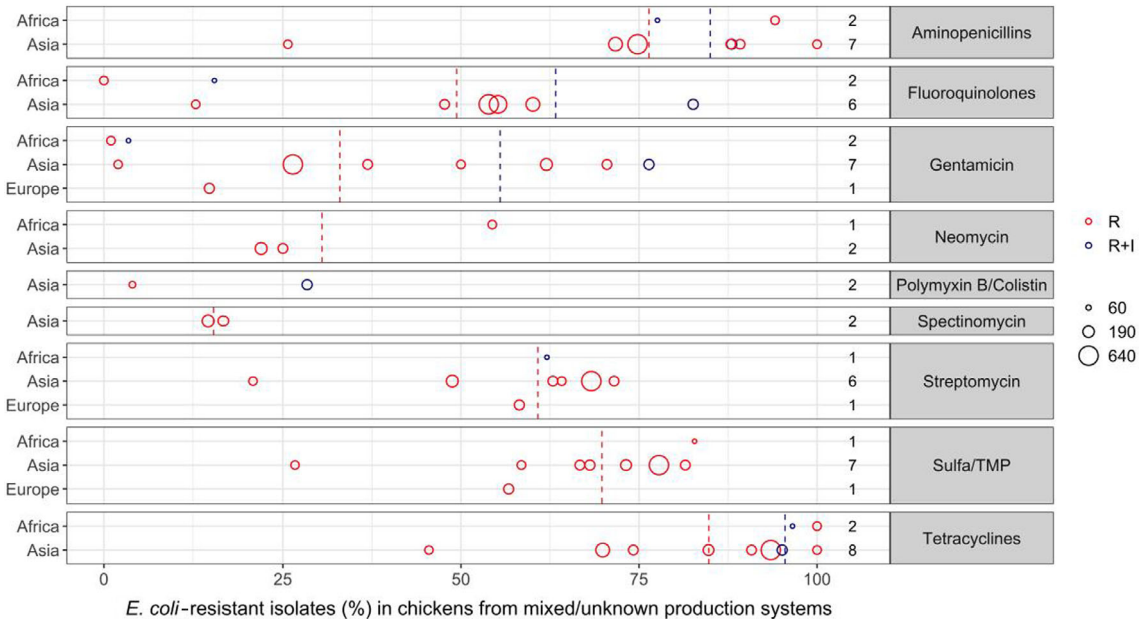
Figure 3: Distribution of *E. coli* isolates per site of infection

The following three figures show the proportion of resistance reported in individual studies with at least 50 *E. coli* isolates in chickens of known production type (laying hens or broilers; Figure 4), those considering isolates from both production types or unknown (Figure 5) and other target poultry species (Figure 6). For chickens, information on proportion of resistance sorted by country is in Appendix D. Table 4 shows weighted arithmetic means, min/max proportions of resistance and weighted standard deviation (SD) for each antibiotic in chickens sorted by production type and continent. Table 5 shows weighted arithmetic means, min/max proportions of resistance and weighted SD for each antibiotic in other poultry species sorted by continent. A number of studies available were much higher for chickens than for other species, and although estimates from the different studies varied largely regardless of population sampled and region considered, high levels of resistance were observed in multiple studies from more than one region for several antimicrobial classes.



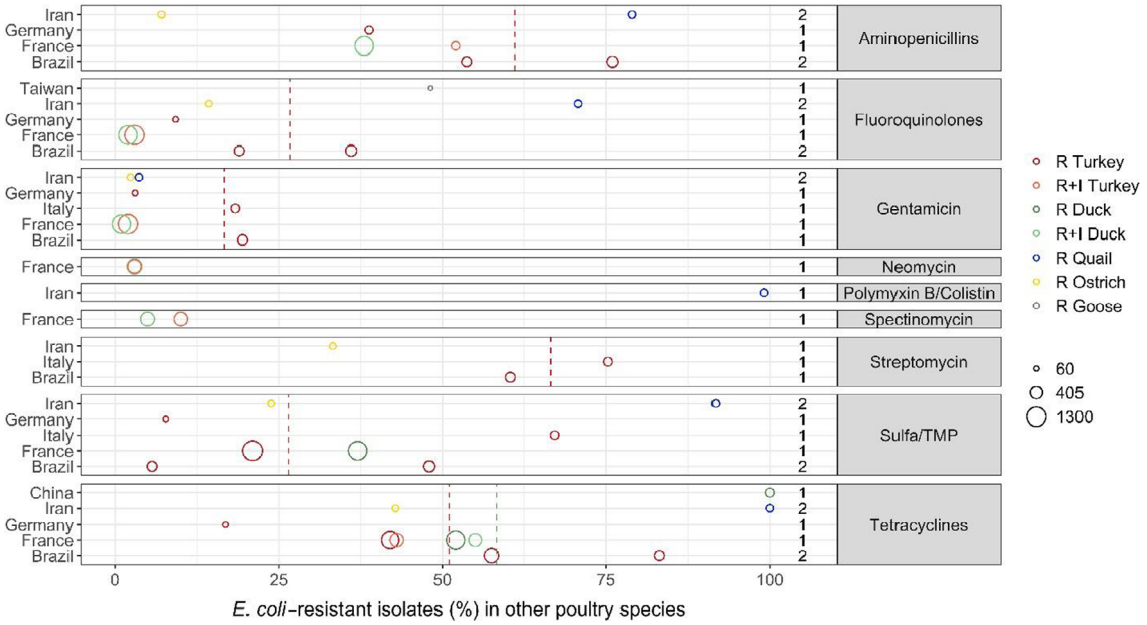
Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates the chicken production type and whether a study reports resistance only (R) or resistance merged with intermediate (R + I). The dashed lines indicate the weighted arithmetic mean with the same colour code as the circles. The exact percentages these lines represent are listed in Appendix E. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/continent combination.

Figure 4: *Escherichia coli* resistance data for each included study on chickens (broiler or laying hens) sorted by continent



Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates the chicken production type and whether a study reports resistance only (R) or resistance merged with intermediate (R + I). The dashed lines indicate the weighted arithmetic mean with the same colour code as the circles. The exact percentages these lines represent are listed in Appendix E. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/continent combination.

Figure 5: *Escherichia coli* resistance data for each included study in chickens from mixed or unknown chicken populations sorted by continent



Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates the poultry species and whether a study reports resistance only (R) or resistance merged with intermediate (R + I). The dashed lines indicate the weighted arithmetic mean with the same colour code as the circles. The exact percentages these lines represent are listed in Appendix E. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 6: *Escherichia coli* resistance data for each included study on poultry species other than chickens (turkey, duck, goose, quail and ostrich), sorted by country

When assessing data on *E. coli*, it should be noted that the only internationally recognised poultry-specific breakpoint for this bacterium that exists is for enrofloxacin (CLSI, 2020). Therefore, any interpretation of AST results for other drugs must be carried out in a different way. The problem here is that such a 'different way' is typically unclear from the studies on poultry *E. coli*, meaning: (i) either it is unknown exactly which breakpoint from a certain reference was used, or (ii) the reference referred to has no breakpoint for the antibiotic reported. An example of the latter is neomycin. Four studies referred to the human CLSI M100 documents (Saidi et al., 2013; Wang et al., 2013; Zhang et al., 2014; Theobald et al., 2019), whereas two studies (Zhang et al., 2012; Koutsianos et al., 2020) referred to veterinary M31 documents for interpretation of neomycin susceptibility data (Appendix B). However, none of these documents have neomycin breakpoints, and studies do not report if e.g. another aminoglycoside was used as surrogate for neomycin. A more transparent way of interpreting data would be to follow the example of the Swedish surveillance system using the EUCAST ECOFF for neomycin in *E. coli* (Swedres-Svarm, 2019).

Disregarding the above-mentioned problem of breakpoints, resistance levels varied considerably, both within and between countries and continents (Figures 4–6, Tables 4 and 5, Appendix B). In the following, selected data are assessed separately for chicken and other poultry species.

Chickens

One way to analyse data is to look at broiler vs. layer production in chickens. Unfortunately, data on layers were somewhat under-represented compared with broilers and only available from Europe. Also, some of the layer and broiler AST data originated from different studies meaning factors other than production type could have influenced results. One exception was the French surveillance system Resapath (2020) reporting data for both layers and broilers. This French report showed that resistance proportions for *E. coli* were similar in the two production systems or higher in broilers than in layers. The most pronounced differences were for tetracycline (44% for broilers vs. 29% for layers) and sulfonamide-trimethoprim (25% for broilers vs. 10% for layers). Another exception was the German surveillance system Germ-Vet (2020) reporting the same general trend of higher resistance levels in *E. coli* of broiler origin. The most pronounced differences were observed for ampicillin (30.6% for broilers vs. 14.8% for layers) and tetracycline (27.6% for broilers vs. 13.5% for layers).

Another way to analyse data is to assess geographical trends. When assessing broiler AST data from the continents most represented in the data set (Asia, Africa and Europe), the trend is the same for almost all antibiotics with Asia having by far the highest mean proportions of resistance followed by Africa and Europe (Table 4). The only exceptions are for tetracyclines and spectinomycin for which mean proportions of resistance were higher in Africa than in Asia. Data from other continents (North America, South America and Oceania) are more difficult to assess with only a single or two studies available for each antibiotic.

Looking closer at enrofloxacin, the only drug for which a poultry-specific breakpoint exists, Europe also stands out with the lowest mean resistance levels. The highest proportion of enrofloxacin resistance in Europe (58.7%) was reported in layers in Greece (Koutsianos et al., 2020). The authors presented no specific explanation for this finding, except that the study's overall high resistance levels to several drugs seemed to reflect a relatively high antibiotic consumption in Greece compared with other countries in Europe. It should be noted that this result for enrofloxacin was %R + I, therefore not directly comparable with most other studies reporting %R for this drug. This is important, as the I category for enrofloxacin in some studies comprised nearly 30% isolates (see Appendix B).

Other poultry species

Resistance levels for poultry species other than chickens are shown in Figure 6 and Table 5. For poultry species represented by only one or two studies (duck, geese, quail, ostrich), it is noticeable that some of the highest resistance levels were observed in a study of 109 *E. coli* isolates from quail in Iran (Salehi and Ghanbarpour, 2010). In that study, resistance proportions varied from 70.7% to 99.1%, except for gentamicin (3.7%). There was no direct explanation for such a high level of resistance, but the authors speculated that this might be related to 'abusive antibiotic use in poultry'.

Five studies (three from Europe and two from Brazil) reported susceptibility data for *E. coli* from turkey. Resistance levels varied a lot between studies, but an overall trend was that higher resistance levels were seen in Brazil compared with Europe (Table 5, Appendix B). One exception however concerned the Italian study (Cavicchio et al., 2015) reporting some of the highest levels of resistance to gentamicin (18.4%) and sulfonamide-trimethoprim (67.1%).

Table 4: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation in *E. coli* for the target antimicrobials in *chickens* from broiler and layer productions in each continent included in the studies. NA means that the standard deviation cannot be calculated as only one study is included

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Aminopenicillins	Africa	Broiler	6	1,299	57.2	36.8	100	27.4
Aminopenicillins	Asia	Broiler	4	334	87.7	70.2	98.6	11.7
Aminopenicillins	Europe	Broiler	4	822	28.1	7	82	21.3
Aminopenicillins	Europe	Layer	4	681	24	11	54.7	16.6
Aminopenicillins	North America	Broiler	1	331	44.4	44.4	44.4	NA
Aminopenicillins	Oceania	Broiler	1	84	29.8	29.8	29.8	NA
Aminopenicillins	South America	Broiler	2	196	40.8	28.5	75	20.6
Fluoroquinolones	Africa	Broiler	5	1,226	33.8	15.1	87.2	24.6
Fluoroquinolones	Asia	Broiler	8	995	58.3	30.9	94.3	25.3
Fluoroquinolones	Europe	Broiler	5	4,252	8.4	2	40	6
Fluoroquinolones	Europe	Layer	4	2,559	7.6	1.6	59.7	14.8
Fluoroquinolones	South America	Broiler	2	196	11.7	11.5	11.8	0.1
Gentamicin	Africa	Broiler	3	281	19.5	1.9	43.8	19.5
Gentamicin	Asia	Broiler	6	827	36.3	5.7	95.5	36.6
Gentamicin	Europe	Broiler	2	3,727	2.9	0	3	0.5
Gentamicin	Europe	Layer	3	2,402	1.8	0.5	2	0.5
Gentamicin	North America	Broiler	1	331	50.1	50.1	50.1	NA
Gentamicin	Oceania	Broiler	1	84	1.2	1.2	1.2	NA
Gentamicin	South America	Broiler	2	196	8.1	7.7	8.3	0.3
Neomycin	Africa	Broiler	2	902	21.1	15.1	89	20.2
Neomycin	Asia	Broiler	2	198	51.6	50.5	52.9	1.2
Neomycin	Europe	Broiler	1	1,787	2	2	2	NA
Neomycin	Europe	Layer	3	1,620	2.9	0	12.7	3.2
Neomycin	South America	Broiler	2	196	7.2	2.1	21.2	8.5
Polymyxin B/ Colistin	Africa	Broiler	2	982	11.2	6.5	12.1	2
Polymyxin B/ Colistin	Asia	Broiler	1	84	23.8	23.8	23.8	NA
Polymyxin B/ Colistin	Europe	Layer	2	250	8.4	1	13.4	6.1
Spectinomycin	Africa	Broiler	2	902	50.6	46.7	95.9	13.4
Spectinomycin	Asia	Broiler	2	198	22.7	22.5	23	0.2
Spectinomycin	Europe	Broiler	1	1,267	14	14	14	NA
Spectinomycin	Europe	Layer	1	436	13	13	13	NA
Spectinomycin	North America	Broiler	2	7,078	49.8	45.6	50	0.9
Streptomycin	Africa	Broiler	3	262	68.7	50	93.2	18.2

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Streptomycin	Asia	Broiler	3	346	73.3	43	97.3	26.3
Streptomycin	Europe	Layer	1	100	3	3	3	NA
Sulfa/TMP	Africa	Broiler	4	1,171	30.9	11.8	88.8	30.6
Sulfa/TMP	Asia	Broiler	4	565	45.7	39.6	65.6	9.2
Sulfa/TMP	Europe	Broiler	3	3,912	24.9	17.3	29.5	1.4
Sulfa/TMP	Europe	Layer	3	2,248	11.8	3	42	8.2
Sulfa/TMP	North America	Broiler	1	331	18.1	18.1	18.1	NA
Sulfa/TMP	Oceania	Broiler	1	84	17.9	17.9	17.9	NA
Sulfa/TMP	South America	Broiler	2	196	21.4	3.8	27.8	10.6
Tetracyclines	Africa	Broiler	6	1,299	73.6	32.7	95.9	14.7
Tetracyclines	Asia	Broiler	6	797	71.3	43.4	98.8	24.7
Tetracyclines	Europe	Broiler	3	3,273	41.2	9.3	44	8.9
Tetracyclines	Europe	Layer	4	2,305	28.9	13	69.4	12.2
Tetracyclines	North America	Broiler	1	331	56.8	56.8	56.8	NA
Tetracyclines	Oceania	Broiler	1	84	36.9	36.9	36.9	NA
Tetracyclines	South America	Broiler	2	196	63.2	46.2	69.4	10.3

Table 5: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation in *E. coli* for the target antimicrobials in *chickens* from mixed/unknown productions in each continent included in the studies. NA means that the standard deviation cannot be calculated as only one study is included

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Aminopenicillins	Africa	Mixed/ Unknown	2	161	88.2	77.6	94.1	8
Aminopenicillins	Asia	Mixed/ Unknown	7	1,543	76.3	25.7	100	15.8
Fluoroquinolones	Africa	Mixed/ Unknown	2	161	5.6	0	15.5	7.5
Fluoroquinolones	Asia	Mixed/ Unknown	6	1,820	54.8	12.9	82.6	12.9
Gentamicin	Africa	Mixed/ Unknown	2	161	1.9	1	3.4	1.2
Gentamicin	Asia	Mixed/ Unknown	7	1,462	41.3	2	76.4	21.7
Gentamicin	Europe	Mixed/ Unknown	1	141	14.8	14.8	14.8	NA

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Neomycin	Africa	Mixed/ Unknown	1	103	54.4	54.4	54.4	NA
Neomycin	Asia	Mixed/ Unknown	2	337	23.1	22	25	1.5
Polymyxin B/ Colistin	Asia	Mixed/ Unknown	2	216	20.3	4	28.4	11.5
Spectinomycin	Asia	Mixed/ Unknown	2	337	15.4	14.6	16.7	1
Streptomycin	Africa	Mixed/ Unknown	1	58	62.1	62.1	62.1	NA
Streptomycin	Asia	Mixed/ Unknown	6	1,318	61.1	20.8	71.5	13.6
Streptomycin	Europe	Mixed/ Unknown	1	141	58.2	58.2	58.2	NA
Sulfa/TMP	Africa	Mixed/ Unknown	1	58	82.8	82.8	82.8	NA
Sulfa/TMP	Asia	Mixed/ Unknown	7	1,421	70.5	26.7	81.5	13.6
Sulfa/TMP	Europe	Mixed/ Unknown	1	141	56.7	56.7	56.7	NA
Tetracyclines	Africa	Mixed/ Unknown	2	161	98.8	96.6	100	1.7
Tetracyclines	Asia	Mixed/ Unknown	8	1,707	84.7	45.5	100	13.9

Table 6: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation in *E. coli* for the target antimicrobials in *poultry species other than chickens* in each continent included in the studies. NA means that the standard deviation cannot be calculated as only one study is included

Antibiotic	Continent	Poultry species	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Aminopenicillins	Asia	Ostrich	1	84	7.1	7.1	7.1	NA
Aminopenicillins	Asia	Quail	1	109	78.9	78.9	78.9	NA
Aminopenicillins	Europe	Duck	1	1,179	38	38	38	NA
Aminopenicillins	Europe	Turkey	2	275	45.7	38.8	52	6.6
Aminopenicillins	South America	Turkey	2	532	66.6	53.7	76	11
Fluoroquinolones	Asia	Goose	1	56	48.2	48.2	48.2	NA
Fluoroquinolones	Asia	Ostrich	1	84	14.3	14.3	14.3	NA
Fluoroquinolones	Asia	Quail	1	109	70.7	70.7	70.7	NA
Fluoroquinolones	Europe	Duck	1	1,179	2	2	2	NA
Fluoroquinolones	Europe	Turkey	2	1,366	3.3	3	9.2	1.3
Fluoroquinolones		Turkey	2	532	28.8	19	36	8.4

Antibiotic	Continent	Poultry species	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
	South America							
Gentamicin	Asia	Ostrich	1	84	2.4	2.4	2.4	NA
Gentamicin	Asia	Quail	1	109	3.7	3.7	3.7	NA
Gentamicin	Europe	Duck	1	1,153	1	1	1	NA
Gentamicin	Europe	Turkey	3	1,524	3.7	2	18.4	5
Gentamicin	South America	Turkey	1	225	19.5	19.5	19.5	NA
Neomycin	Europe	Duck	1	672	3	3	3	NA
Neomycin	Europe	Turkey	1	527	3	3	3	NA
Polymyxin B/Colistin	Asia	Quail	1	109	99.1	99.1	99.1	NA
Spectinomycin	Europe	Duck	1	564	5	5	5	NA
Spectinomycin	Europe	Turkey	1	524	10	10	10	NA
Streptomycin	Asia	Ostrich	1	84	33.3	33.3	33.3	NA
Streptomycin	Europe	Turkey	1	158	75.3	75.3	75.3	NA
Streptomycin	South America	Turkey	1	225	60.4	60.4	60.4	NA
Sulfa/TMP	Asia	Ostrich	1	84	23.8	23.8	23.8	NA
Sulfa/TMP	Asia	Quail	1	109	91.7	91.7	91.7	NA
Sulfa/TMP	Europe	Duck	1	1,179	37	37	37	NA
Sulfa/TMP	Europe	Turkey	3	1,525	25.2	7.7	67.1	14.5
Sulfa/TMP	South America	Turkey	2	532	30.1	5.7	48	20.9
Tetracyclines	Asia	Duck	1	170	100	100	100	NA
Tetracyclines	Asia	Ostrich	1	84	42.8	42.8	42.8	NA
Tetracyclines	Asia	Quail	1	109	100	100	100	NA
Tetracyclines	Europe	Duck	1	1,591	52.9	52	55	1.4
Tetracyclines	Europe	Turkey	2	1,571	41.3	16.9	43	5.1
Tetracyclines	South America	Turkey	2	839	64.4	57.5	83.1	11.3

3.1.3.2. Results from the national AMR monitoring reports

Information on AMR in poultry clinical *E. coli* isolates was included in all five national reports, although numbers of isolates and antimicrobials used for testing varied widely depending on the country. The base population represented in these data will also vary according to the source material for these tests. In some countries, the great majority of clinical antimicrobial sensitivity is carried out in industry and private practice laboratories.

The **FINRES-Vet** reports provide information on AMR in between 17 and 27 isolates retrieved from broiler flocks with clinical colibacillosis and tested each year using four antimicrobials of interest for this opinion. Of note, colibacillosis is not currently treated with antimicrobials in Finland. Because of the very limited sample sizes, the proportion of resistance varied in certain cases between years, although remained below 20% for tetracyclines and ampicillin, < 6% for ciprofloxacin and always 0% for colistin (not shown in Figure 7).

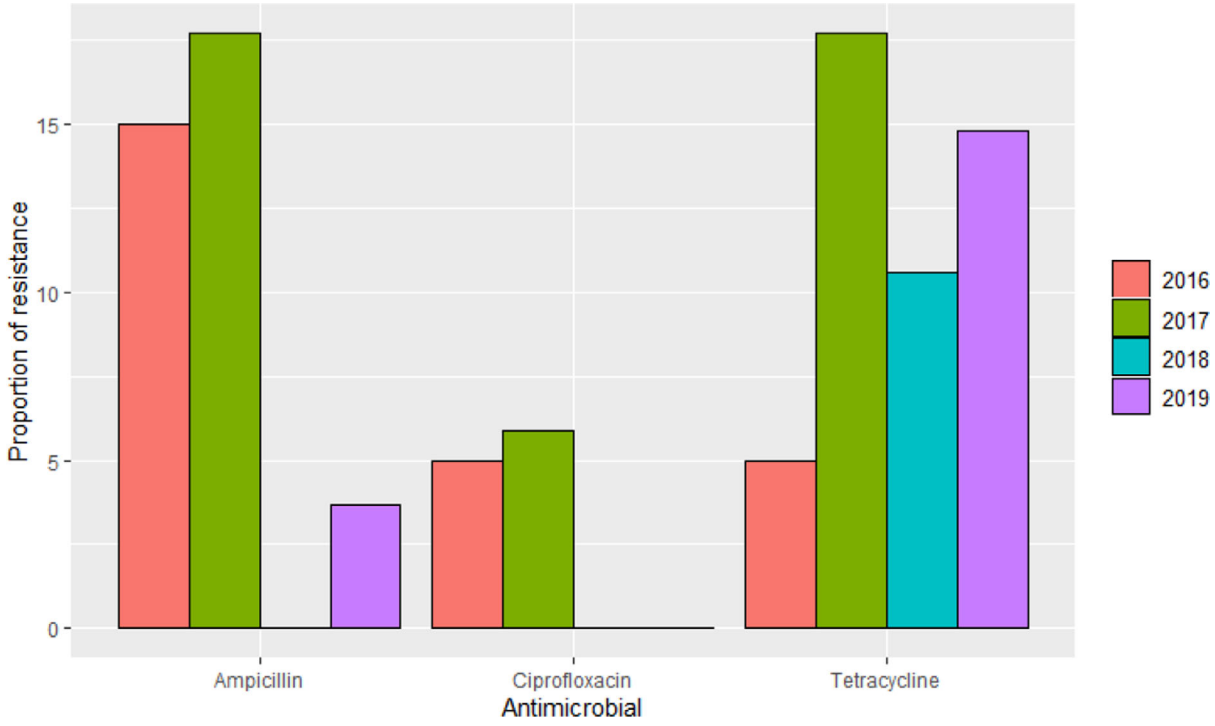


Figure 7: Proportion (%) of clinical poultry *E. coli* isolates retrieved from colibacillosis in broilers to three antimicrobials of interest reported by the FINRES-Vet monitoring programme

The **GERM-Vet** reported between 2014 and 2018 resistance data for poultry clinical isolates from different clinical disease from the following bacterial species of interest *Enterococcus faecalis* (from 2016 onwards), *E. coli* (all years for laying hens, broilers and turkeys) and *S. aureus* (all years). Isolates were sampled in different laboratories according to a national sampling plan on diseased animals. Resistance was determined according to the CLSI standards using the broth micro dilution method. *E. faecalis* was sampled from septicaemic poultry, *E. coli* and *S. aureus* from different indications. Resistance data on *E. coli* were provided from different groups/animal species: turkeys, young and laying hens and broilers. Even though AMR testing included a variety of different antimicrobial substances only those stated as resistant/intermediate resistant in the report according to published clinical break points are mentioned here.

In 2014 in total 317 *E. coli* isolates were tested for AMR; 31 isolates from broilers with different indications, 110 from turkeys with different indications and 176 from young and laying hens with septicaemia. In 2015, of the *E. coli* isolates tested, 114 and 109 isolates came from turkeys and broilers with different indications, respectively, and 116 from young and laying hens with septicaemia. In 2016, sample numbers for turkeys, broilers and young and laying hens were 96, 77 and 132, respectively. In 2017, isolate numbers included 70, 136 and 49 and, in 2018, isolate numbers were 65, 98 and 310. Intermediate and resistant isolates are cumulated and shown in Figure 8 for all years from 2014 to 2018.

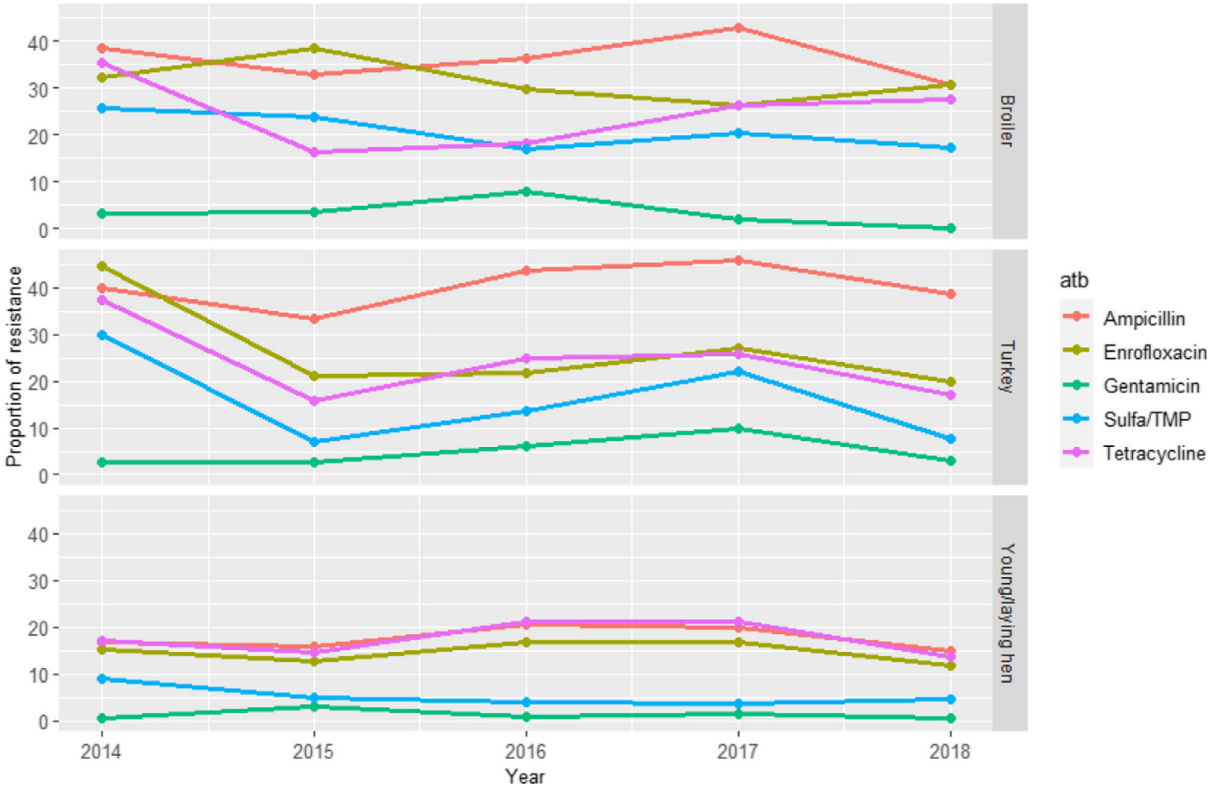


Figure 8: Proportion (%) of clinical poultry *E. coli* isolates resistant/intermediate resistant to seven antimicrobials of interest reported by the GERM-Vet monitoring programme

The **RESAPATH** reports include information on AMR from clinical isolates from all pathologies reported together from broilers (519–4,262 isolates/antibiotic-year), laying hens (121–2,500 isolates/antibiotic-year), ducks (108–1,179 isolates/antibiotic-year) and turkeys (145–1,863 isolates/antibiotic-year). Although there are differences depending on the host, resistance levels to tetracycline, amoxicillin, sulfa/TMP and spectinomycin were usually higher across species (Figure 9).

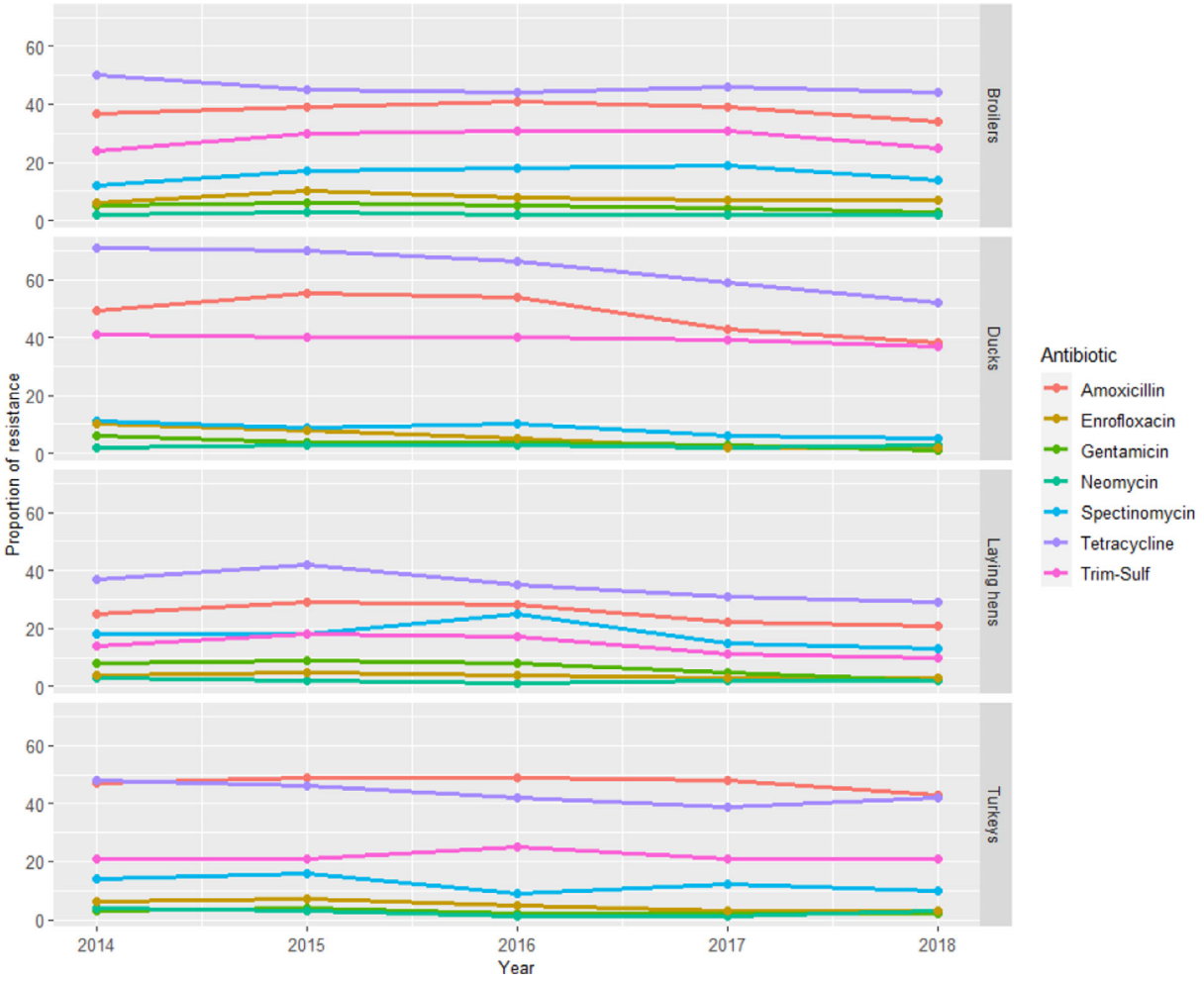


Figure 9: Proportion (%) of clinical poultry *E. coli* isolates retrieved from different hosts resistant to seven antimicrobials of interest reported by the RESAPATH monitoring programme

Finally, the **SWEDRES-Svarm** reports provide information on resistance on *E. coli* isolates retrieved from post-mortem analyses from laying hens (23–81 weeks of age) during the 2017–2018 period and reported together (n = 100). The highest levels of resistance were observed for enrofloxacin (even though quinolone use in egg production in Sweden is considered rare) and, to a lesser extent, to ampicillin and tetracycline (Figure 10).

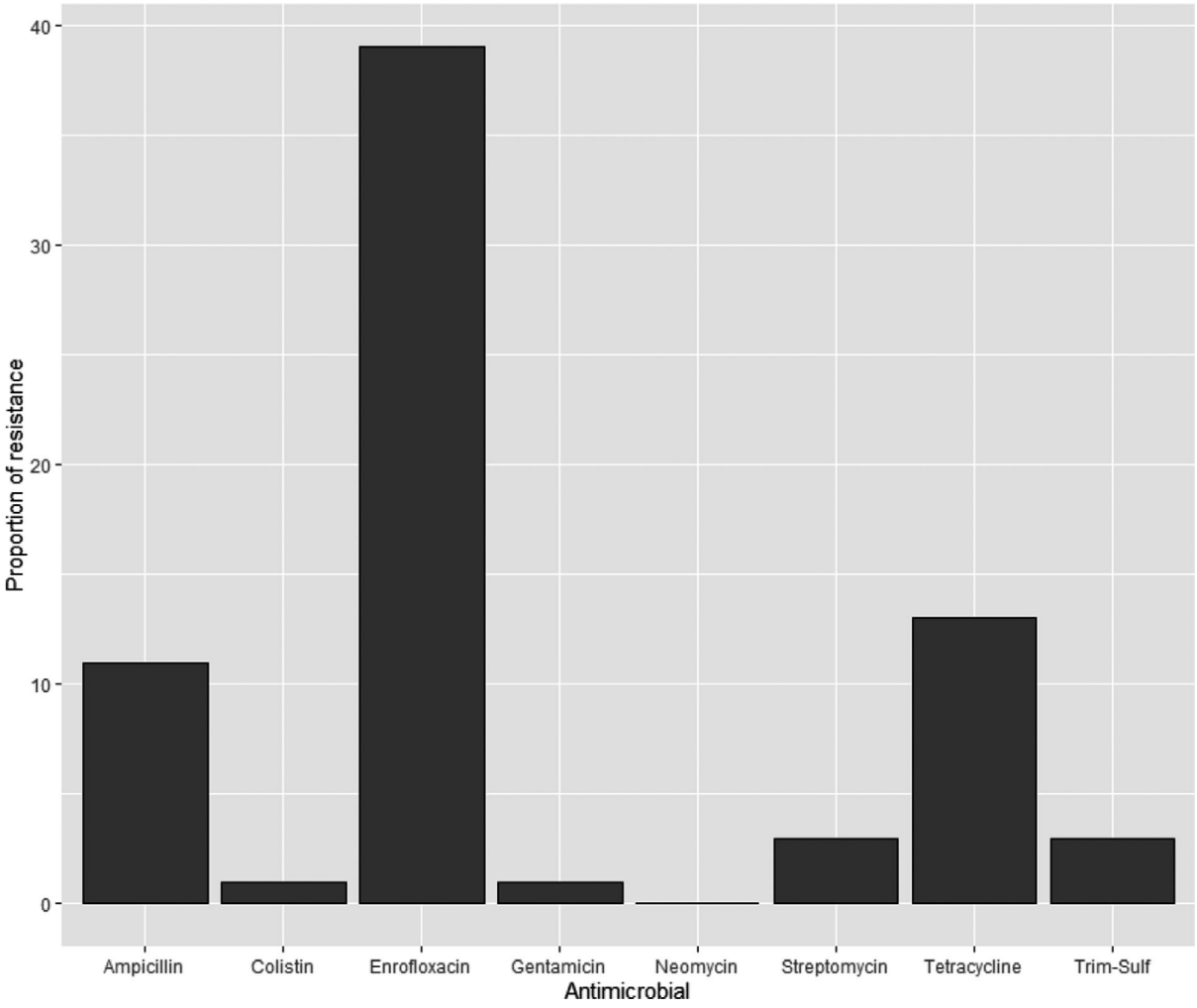


Figure 10: Proportion (%) of clinical poultry *E. coli* isolates retrieved from laying hens resistant to eight antimicrobials of interest reported by the SWEDRES-Svarm monitoring programme

3.1.4. *Enterococcus faecalis* and *E. cecorum*

3.1.4.1. Results of the extensive literature review

Enterococci are commensals of the intestinal tract. In chickens, enterococcal species like *E. faecalis* and *E. cecorum* can be involved in various infections such as arthritis and osteomyelitis.

In total, six studies with ≥ 10 *E. cecorum* or *E. faecalis* isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, amoxicillin-clavulanic acid, penicillin, enrofloxacin/ ciprofloxacin, erythromycin, spiramycin, tylosin, lincomycin, gentamicin, neomycin, streptomycin, bacitracin and tetracycline/oxytetracycline/doxycycline/chlortetracycline) were included. Those studies were distributed as follows: Africa (0), Asia (0), Europe (2), Oceania (0), North America (3) and South America (1).

The distribution of *Enterococcus* spp. isolates per site of infection is shown in Figure 11.

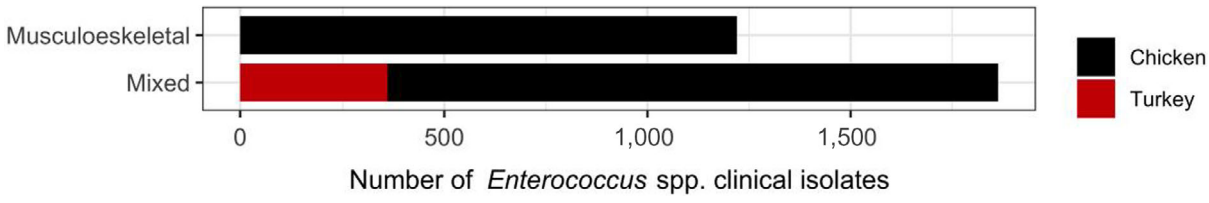
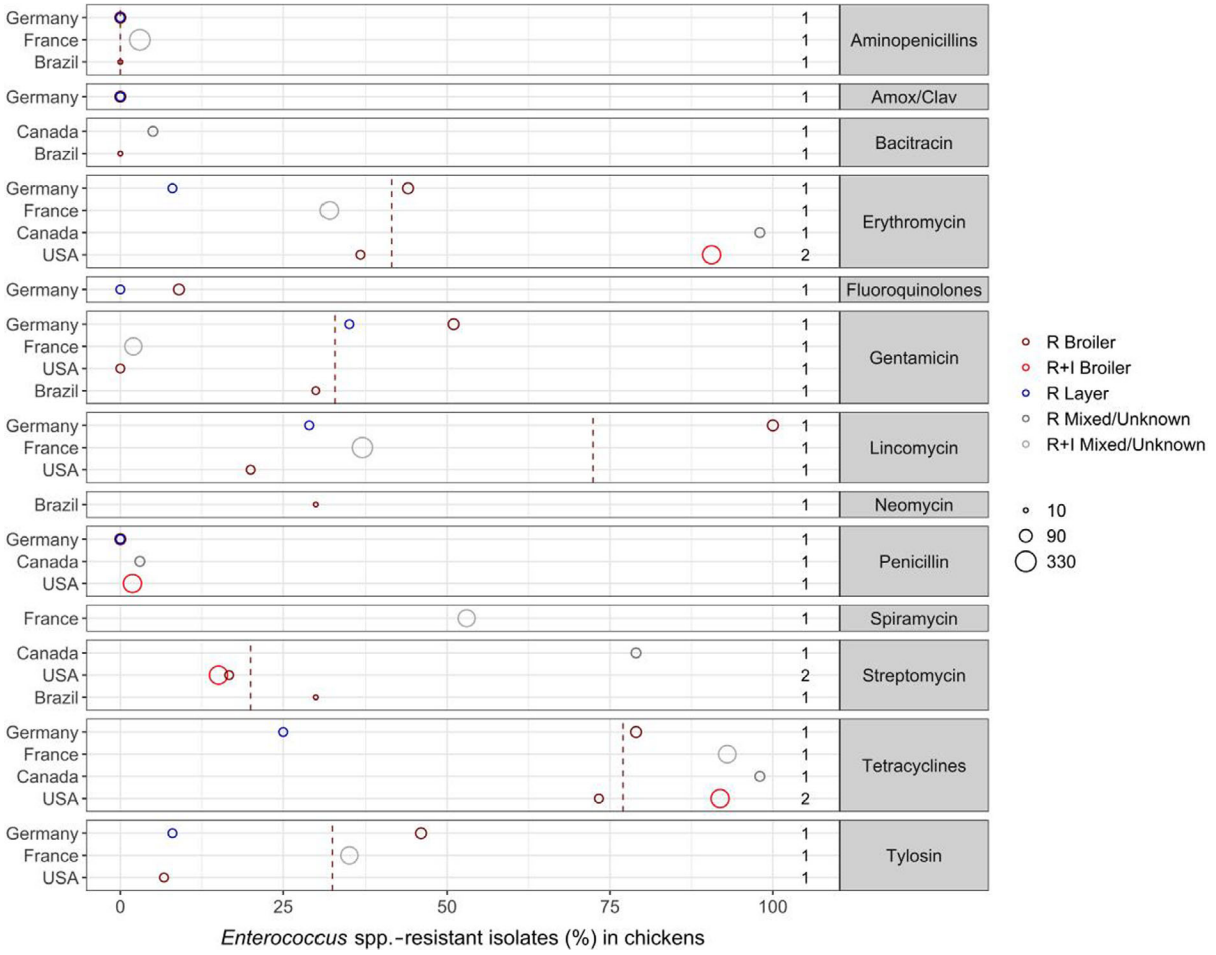


Figure 11: Distribution of *Enterococcus* spp. isolates per site of infection

No studies reported susceptibility data separately for both *E. faecalis* and *E. cecorum;* therefore, it is difficult to compare resistance levels in the two species when other study-related factors may have affected results. From the limited data available, it does however appear as if *E. cecorum* is more often susceptible to gentamicin with two chicken studies reporting 0% and 2% resistance in this species, respectively. By contrast, 20–51% of chicken *E. faecalis* isolates in three studies were resistant to gentamicin. In the following text, figure and table, susceptibility data for the two enterococcal species are presented together as *Enterococcus* spp.

Figure 12 shows for each country, and in chicken only, the proportion of resistance reported in individual studies with at least 10 *Enterococcus* isolates. Table 6 shows weighted arithmetic means, min/max proportions of resistance and SD for each antibiotic in chicken sorted by production type and continent.



Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates the chicken production type and whether a study reports resistance only (R) or resistance merged with intermediate (R + I). The dashed lines indicate weighted arithmetic mean with the same colour code as the circles. The exact percentages these lines represent are listed in Appendix E. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 12: *Enterococcus* spp. resistance data for each included study in chickens (broilers, layers, mixed and unknown chicken category), sorted by country

Chickens

The lowest levels of resistance in enterococci were observed for penicillins, including penicillin, aminopenicillins and amoxicillin-clavulanic acid. Irrespective of geographical origin and production type, studies reported either full susceptibility or a maximum of 3% resistance for these drugs. Resistance to other drugs varied a lot between studies, but with no particular geographical trends. The overall highest levels of resistance were seen for tetracyclines with five of six studies reporting ≥ 73% resistance.

In terms of production type, one German study (Maasjost et al., 2015) included *E. faecalis* isolates from both broilers and layers. For all antibiotics tested (except penicillins with 0% resistance), resistance levels were substantially higher in isolates from broilers compared with layers. This is visible from Appendix B and from the red (broiler) and blue (layer) circles representing Germany in Figure 12.

Turkeys

The study by Maasjost et al. (2015) reported susceptibility data for *E. faecalis* in turkeys (as well as chickens). Similar levels of resistance were detected in turkeys as in broilers, e.g. a high proportion (85%) of isolates was resistant to tetracycline (see Appendix B, also for other antibiotics).

Table 7: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation in *Enterococcus* spp. for the target antimicrobials in chickens in each continent. NA means that the standard deviation cannot be calculated as only one study is included

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Aminopenicillins	Europe	Broiler	1	57	0	0	0	NA
Aminopenicillins	Europe	Layer	1	30	0	0	0	NA
Aminopenicillins	Europe	Mixed/ Unknown	1	330	3	3	3	NA
Aminopenicillins	South America	Broiler	1	10	0	0	0	NA
Amox/Clav	Europe	Broiler	1	57	0	0	0	NA
Amox/Clav	Europe	Layer	1	30	0	0	0	NA
Bacitracin	North America	Mixed/ Unknown	1	42	5	5	5	NA
Bacitracin	South America	Broiler	1	10	0	0	0	NA
Erythromycin	Europe	Broiler	1	57	44	44	44	NA
Erythromycin	Europe	Layer	1	30	8	8	8	NA
Erythromycin	Europe	Mixed/ Unknown	1	220	32	32	32	NA
Erythromycin	North America	Broiler	2	270	84.6	36.7	90.6	17
Erythromycin	North America	Mixed/ Unknown	1	42	98	98	98	NA
Fluoroquinolones	Europe	Broiler	1	57	9	9	9	NA
Fluoroquinolones	Europe	Layer	1	30	0	0	0	NA
Gentamicin	Europe	Broiler	1	57	51	51	51	NA
Gentamicin	Europe	Layer	1	30	35	35	35	NA
Gentamicin	Europe	Mixed/ Unknown	1	208	2	2	2	NA
Gentamicin	North America	Broiler	1	30	0	0	0	NA
Gentamicin	South America	Broiler	1	20	30	30	30	NA
Lincomycin	Europe	Broiler	1	57	100	100	100	NA
Lincomycin	Europe	Layer	1	30	29	29	29	NA
Lincomycin	Europe	Mixed/ Unknown	1	319	37	37	37	NA

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Lincomycin	North America	Broiler	1	30	20	20	20	NA
Neomycin	South America	Broiler	1	10	30	30	30	NA
Penicillin	Europe	Broiler	1	57	0	0	0	NA
Penicillin	Europe	Layer	1	30	0	0	0	NA
Penicillin	North America	Broiler	1	240	1.9	1.9	1.9	NA
Penicillin	North America	Mixed/ Unknown	1	42	3	3	3	NA
Spiramycin	Europe	Mixed/ Unknown	1	204	53	53	53	NA
Streptomycin	North America	Broiler	2	270	15.2	15.1	16.7	0.5
Streptomycin	North America	Mixed/ Unknown	1	42	79	79	79	NA
Streptomycin	South America	Broiler	1	10	30	30	30	NA
Tetracyclines	Europe	Broiler	1	57	79	79	79	NA
Tetracyclines	Europe	Layer	1	30	25	25	25	NA
Tetracyclines	Europe	Mixed/ Unknown	1	220	93	93	93	NA
Tetracyclines	North America	Broiler	2	270	89.8	73.3	91.9	5.9
Tetracyclines	North America	Mixed/ Unknown	1	42	98	98	98	NA
Tylosin	Europe	Broiler	1	57	46	46	46	NA
Tylosin	Europe	Layer	1	30	8	8	8	NA
Tylosin	Europe	Mixed/ Unknown	1	209	35	35	35	NA
Tylosin	North America	Broiler	1	30	6.7	6.7	6.7	NA

3.1.4.2. Results from the national AMR monitoring reports

Information on AMR on clinical *E. cecorum* isolates is also included in the **RESAPATH** reports, with between 124 and 445 isolates retrieved from laying hens and broilers (all pathologies reported together) being tested each year between 2014 and 2018 with up to seven antimicrobials. Very high levels of resistance were observed for tetracycline, while values for erythromycin, lincomycin, spiramycin and tylosin ranged between 30% and 75% (with large variations depending on the year), and resistance to amoxicillin and gentamicin was always $\leq$ 5% (Figure 13).

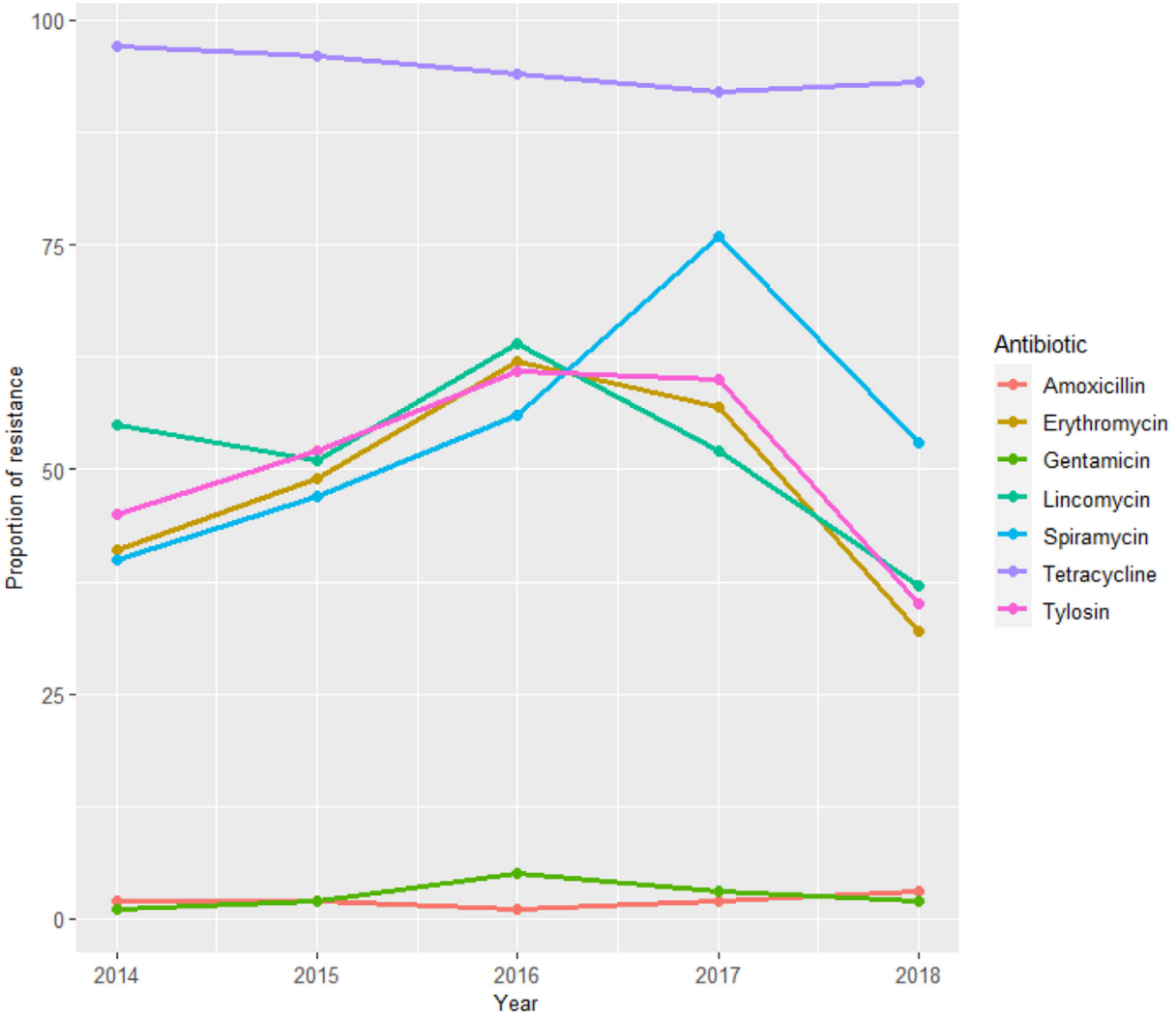


Figure 13: Proportion (%) of clinical *E. cecorum* isolates retrieved from hens and broiler resistant to seven antimicrobials of interest reported by the RESAPATH monitoring programme

The **GERM-Vet** reported years 2014–2018 resistance data for poultry clinical isolates from different clinical disease from the following bacterial species of interest *Enterococcus faecalis* (from 2016 onwards). Isolates were sampled in different laboratories according to a national sampling plan on diseased animals. Resistance was determined according to the CLSI standards using the broth micro dilution method. *E. faecalis* was sampled from septicaemic poultry. Even though AMR testing included a variety of different antimicrobial substances only those stated as resistant/intermediate resistant in the report are mentioned here. *E. faecalis* isolates were reported for all sampled groups/species cumulated. Isolate numbers in different years were 26 for 2016, 22 for 2017 and 28 for 2018. No resistant isolates were identified in 2016–2018 for being resistant against ampicillin, penicillin and vancomycin. High levels for erythromycin resistance remain high over the years with 76.9% in the year 2016 and 81.8% and 82.1% in the years 2017 and 2018.

3.1.5. *Staphylococcus aureus*

3.1.5.1. Results of the extensive literature review

As in many other animals, *S. aureus* is part of the commensal skin flora in poultry. As an opportunistic pathogen, it may cause various infections such as arthritis, ulcerative pododermatitis ('bumblefoot'), osteomyelitis and tenosynovitis.

In total, five studies with ≥ 10 *S. aureus* isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, enrofloxacin/ciprofloxacin, erythromycin, tylosin, tilmicosin, tylvalosin, gentamicin, neomycin, spectinomycin, streptomycin, sulfonamide-trimethoprim and tetracycline/

oxytetracycline/doxycycline/chlortetracycline) were included. Those studies were distributed as follows: Africa (0), Asia (1), Europe (4), Oceania (0), North America (0) and South America (0). The distribution of *S. aureus* isolates per site of infection is shown in Figure 14.

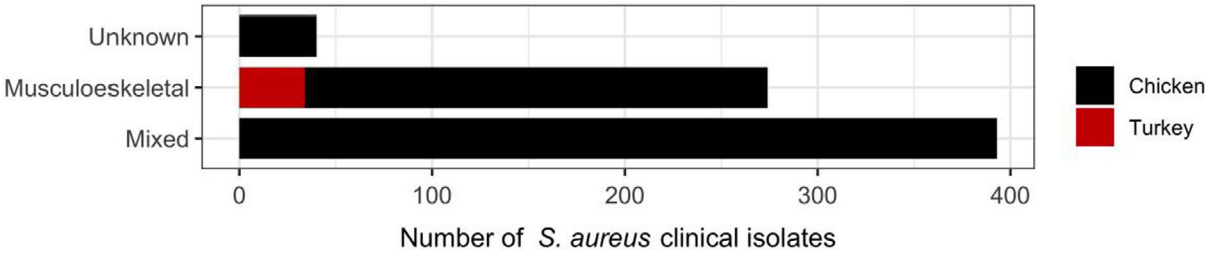
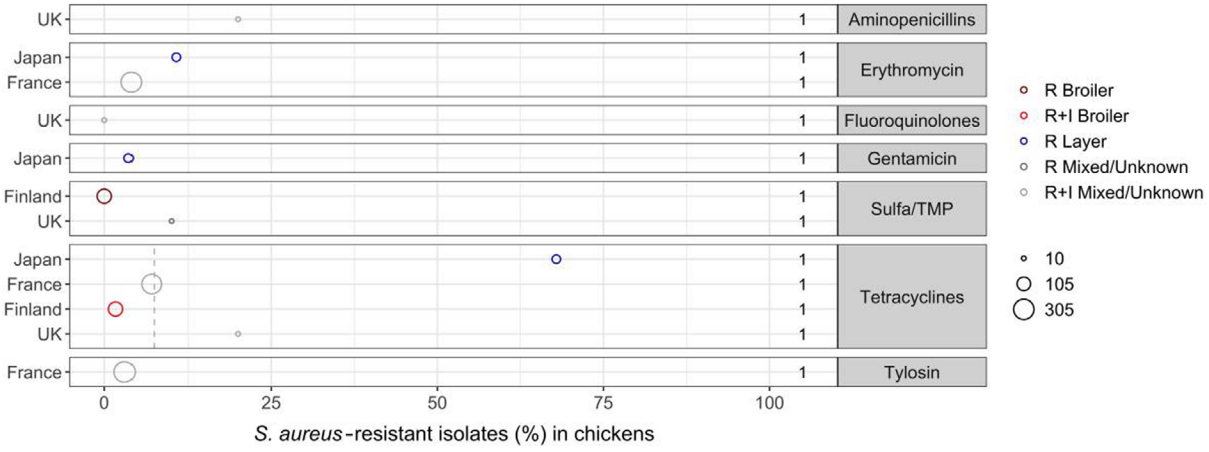


Figure 14: Distribution of *S. aureus* isolates per site of infection

Figure 15 shows for each country, and in chickens only, the proportion of resistance reported in individual studies with at least 10 *S. aureus* isolates. Table 7 shows weighted arithmetic means, min/max proportions of resistance and SD for each antibiotic in chicken sorted by production type and continent.



Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates the chicken production type and whether a study reports resistance only (R) or resistance merged with intermediate (R + I). The dashed lines indicate weighted arithmetic mean with the same colour code as the circles. The exact percentages these lines represent are listed in Appendix E. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 15: *Staphylococcus aureus* resistance data for each included study on chickens (broiler, layer, mixed and unknown chicken category), sorted by country

Chickens

The production type was distinct in the four studies reporting susceptibility data for chickens: broilers, layers, hens and broilers, unknown. Therefore, results are not easy to compare. Overall, fairly low levels of resistance (≤ 20%) were observed across antimicrobials in chicken, except for a Japanese study (Baba et al., 2012) reporting 67.9% of 28 isolates resistant to oxytetracycline.

Turkeys

A single French study on turkeys (Argudin et al., 2013) reported that 97% of 34 isolates were resistant to tetracycline. Data for other relevant drugs were not available.

Table 8: Proportion of resistance (%R or %R + I) in *S. aureus* for the target antimicrobials in chickens in each continent included in the studies

Antibiotic	Continent	Production type	No. of papers	N (number of isolates)	Proportion of resistance (%)
Aminopenicillins	Europe	Mixed/Unknown	1	10	20
Erythromycin	Asia	Layer	1	28	10.7
Erythromycin	Europe	Mixed/Unknown	1	280	4
Fluoroquinolones	Europe	Mixed/Unknown	1	10	0
Gentamicin	Asia	Layer	1	28	3.6
Sulfa/TMP	Europe	Broiler	1	120	0
Sulfa/TMP	Europe	Mixed/Unknown	1	10	10
Tetracyclines	Asia	Layer	1	28	67.9
Tetracyclines	Europe	Broiler	1	120	1.7
Tetracyclines	Europe	Mixed/Unknown	2	289	7.4
Tylosin	Europe	Mixed/Unknown	1	309	3
Aminopenicillins	Europe	Mixed/Unknown	1	10	20

3.1.5.2. Results from the national AMR monitoring reports

Information on AMR in clinical *S. aureus* isolates was included in the FINRES-Vet, RESAPATH, UK-VARSS and GERM-Vet reports.

FINRES-Vet isolates (8–26 tested each year with up to five antimicrobials of interest) were retrieved from tenosynovitis cases in broilers, and no resistant isolates to cefoxitin, oxacillin, oxytetracycline, tetracycline or sulfa/TMP period were found during the 2016–2019 (of note, tenosynovitis is only occasionally treated with antimicrobials in broiler parent flocks and production flocks have not been treated since 2010).

In the **RESAPATH** reports information on between 144 and 457 isolates tested each year with up to 11 antimicrobials of interest and retrieved from hens and broilers (all pathologies reported together) are provided for the 2014–2018 period. Resistance levels were < 15% for all antimicrobials except tetracycline (and doxycycline, included only in 2017–2018 with resistance levels of 15 and 14%, respectively, not shown in graph), for which a clear decreasing trend over this period is observed (from ~ 25% in 2014 to 7% in 2018) (Figure 16).

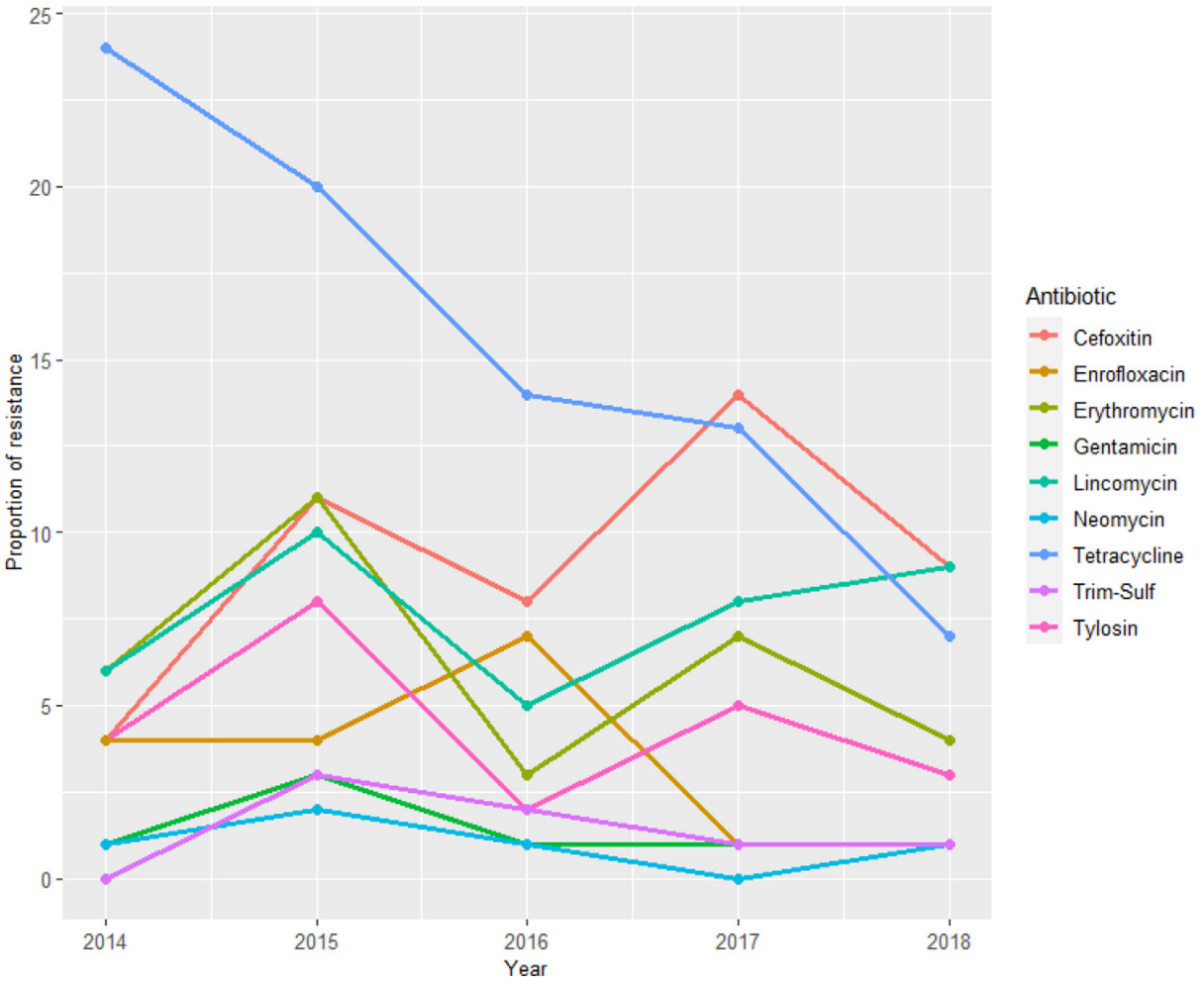


Figure 16: Proportion (%) of clinical *S. aureus* isolates retrieved from hens and broiler resistant to nine antimicrobials of interest reported by the RESAPATH monitoring programme

The **UK-VARSS** reports included information on very limited numbers of isolates during the 2015–2019 period (1–15 each year, for a total of 26–33 isolates tested with up to nine antimicrobials – in addition two isolates were tested with penicillin and one was resistant, data not shown). When resistance levels of all isolates considered together are considered, the highest levels of resistance were found for tetracycline (6/33 isolates resistant) and doxycycline (4/33) (Figure 17).

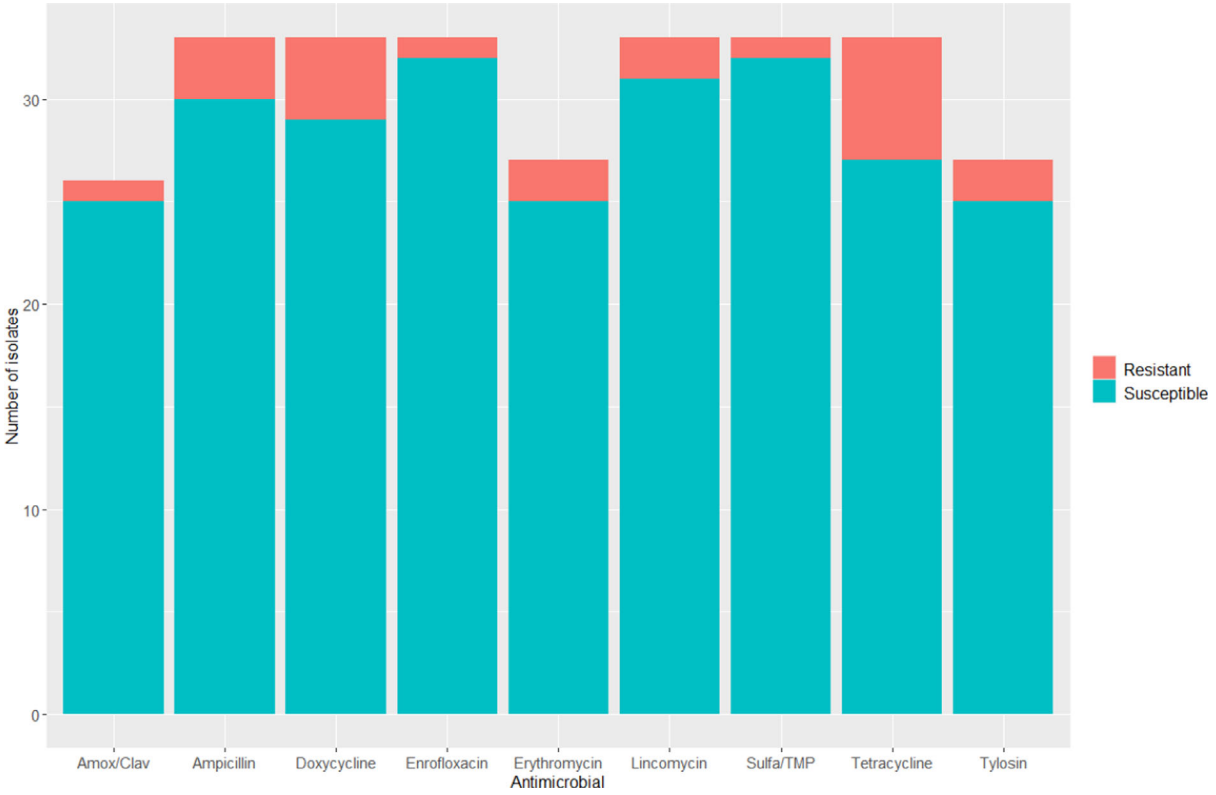


Figure 17: Number of clinical *S. aureus* isolates retrieved from chickens in England and Wales between 2015 and 2019 that were susceptible and resistant to nine antimicrobials of interest reported by the UK-VARSS monitoring programme

Finally, the **GERM-Vet** reported between 2014 and 2018 resistance data for poultry clinical isolates from different clinical disease for *S. aureus* (all years). Isolates were sampled in different laboratories according to a national sampling plan on diseased animals. Resistance was determined according to the CLSI standards using the broth micro dilution method.

S. aureus isolates were reported in cumulation for all groups/species sampled with numbers of 35 in 2014, 56 in 2015, 41 in 2016, 35 in 2017 and 32 in 2018. No resistance was detected against vancomycin and trimethoprim/sulfamethoxazole but high levels of resistance were detected for erythromycin, penicillin and tetracycline; resistance against gentamicin was low in all years (under 5%) out of 2017 when 11.5% of the isolates tested resistant or intermediate resistant.

3.1.6. *Riemerella anatipestifer*

3.1.6.1. Results of the extensive literature review

Riemerella anatipestifer is primarily an infectious agent of ducklings up to 6 weeks of age. It causes infectious serositis and septicaemia and is associated with high morbidity and mortality. Fibrinous pericarditis and peritonitis are common post-mortem findings.

Four eligible studies from China reported susceptibility data for *R. anatipestifer*. Due to the lack of breakpoints for this Gram-negative bacterium, three studies had used human CLSI *Streptococcus* breakpoints to interpret data for this pathogen. One of the studies reported 54% of 79 isolates resistant to erythromycin (Zheng et al., 2012), and the other found 91% of 212 isolates resistant to tetracycline (Zhu et al., 2018). The third study found 99.3% of 137 isolates resistant to enrofloxacin (Zhu et al., 2019), although it is unclear how enrofloxacin MICs were interpreted, as this drug is not part of breakpoint tables for human pathogens. The fourth study also referred to human CLSI breakpoints, but without further specification (Xing et al., 2015). That study reported data for six drugs with the lowest and highest proportions of resistance reported for ampicillin (25%) and gentamicin (56%), respectively. This study also reported resistance data for enrofloxacin, although the origin of the breakpoint from human CLSI guidelines is questionable.

3.1.7. *Clostridium perfringens*

3.1.7.1. Results of the extensive literature review

Clostridium perfringens (mostly type A) causes necrotic enteritis in poultry. The disease is an acute enterotoxaemia characterised by sudden onset and high mortality. Characteristic necrotic lesions can be seen in the intestine post-mortem.

Three eligible studies from Canada (Slavic et al., 2011), South Korea (Wei et al., 2020) and the USA (Mwangi et al., 2019) reported susceptibility data for *C. perfringens*. The former two studies used the same visually determined ECOFFs for interpretation of susceptibility, whereas the latter used CLSI human clinical breakpoints. Only Mwangi et al. (2019) specified the production type (broilers).

Chickens

All three studies found high levels (50.8–62%) of resistance to tetracycline. Moderate (18.5%) to high (65%) resistance levels were observed for bacitracin, whereas penicillin and amoxicillin resistance was rare with proportions of only 0% and 9% being reported by Wei et al. (2020) and Mwangi et al. (2019). The proportion of resistance to erythromycin was either very low (2%; Slavic et al. (2011)) or moderate (29.2%; Wei et al. (2020)).

Turkeys

Slavic et al. (2011) also reported data for turkey and found almost the same levels of resistance as in chicken isolates. The only exception was for tetracycline with a higher proportion of turkey isolates (88%) being resistant.

3.1.8. *Avibacterium (Haemophilus) paragallinarum*

3.1.8.1. Results of the extensive literature review

A. paragallinarum is the cause of infectious coryza in chickens. Coryza is a contagious disease of the upper respiratory tract causing various clinical signs depending on the severity of disease. Some of the typical clinical signs include nasal discharge, swollen head, depression and reduced egg production. Post-mortem lesions involve mainly the airways, e.g. bronchitis, airsacculitis and pneumonia.

Two eligible studies from Thailand (Chukiatsiri et al., 2012) and South Korea (Jeong et al., 2017) reported susceptibility data for *A. paragallinarum*, but notably only in 18 and 20 chicken isolates from unknown production type and layers, respectively. The two studies used the same breakpoints (Jeong referred to Chukiatsiri), which included various veterinary CLSI breakpoints and interpretive criteria provided by the disk manufacturer. In the absence of *A. paragallinarum*-specific breakpoints, it was not clear how breakpoints were adapted from other species, therefore results are extremely questionable in terms of clinical relevance. Nevertheless, for all drugs tested (except tylosin) resistance levels were higher in isolates from Thailand compared with South Korea (for further details, see Appendix B).

3.1.9. *Pasteurella multocida*

3.1.9.1. Results of the extensive literature review

Pasteurella multocida is the cause of fowl cholera, a highly contagious infection affecting both domestic and wild birds. The disease typically presents as a severe or fatal acute septicaemia with haemorrhages and accumulation of fluid in body cavities seen at post-mortem examination. Other lesions, and sometimes more local lesions, can be seen in chronic cases.

One eligible study from the USA reported susceptibility data for *P. multocida* (Jones et al., 2013). The study comprised 207 chicken isolates from non-specified clinical origin in broiler flocks and breeders. The highest levels of resistance were observed for tylosin (97%) and streptomycin (60%), whereas for all other drugs proportions of resistance were $\leq$ 21%. Although the study specified the exact MIC breakpoints, the source of these breakpoints was unclear. Notably, the authors referred to the CLSI M31-A2 veterinary guideline, but this document has no breakpoint for drugs such as amoxicillin (which was tested) and, even if the amoxicillin breakpoint was adapted from ampicillin, the odd breakpoint for susceptibility ($\leq$ 3 mg/L) does not exist in that document.

3.1.10. *Gallibacterium anatis*

3.1.10.1. Results of the extensive literature review

Gallibacterium anatis is a commensal bacterium of the upper respiratory tract and lower reproductive tract of chickens. It is also an opportunistic pathogen capable of causing both localised and systemic infections. Therefore, many different pathological lesions may appear at post-mortem.

One eligible study from the USA reported susceptibility data for *G. anatis* (Jones et al., 2013). The study comprised 84 chicken isolates from non-specified clinical origin in broiler flocks and breeders. Isolates were tested and results interpreted as for *P. multocida* reported by the same study (see previous section), therefore the same reservations should be made for use of results. For some antibiotics tested in both species (amoxicillin, neomycin, sulfonamide-trimethoprim), resistance levels were higher in *G. anatis* than in *P. multocida*. For other antibiotics (streptomycin, gentamicin) it was the other way round, with higher levels detected in *P. multocida* (for details, see Appendix B).

3.1.11. *Bordetella avium*

3.1.11.1. Results of the extensive literature review

Bordetella avium is the cause of turkey coryza, a contagious upper respiratory tract infection in many ways similar to the coryza seen in chicken (see under *A. paragallinarum*).

One eligible study from Egypt reported susceptibility data for *B. avium* (Eldin et al., 2020). The study comprised only 14 turkey isolates, and results were interpreted using human CLSI guidelines without further specification. So, the clinical relevance of results is questionable. The lowest level of resistance (14%) was observed for the aminoglycosides neomycin and gentamicin, whereas the highest level of resistance (93%) was observed for penicillin.

3.1.12. *Mycoplasma gallisepticum*

3.1.12.1. Results of the extensive literature review

Mycoplasma gallisepticum is capable of causing chronic respiratory disease in chickens and sinusitis in turkeys. Clinical signs are associated with upper respiratory infections, and reduced egg production may also be seen.

One eligible study from Egypt reported susceptibility data for *M. gallisepticum* (Ammar et al., 2016). The study comprised 14 turkey isolates, and results were interpreted according to previously established criteria for MIC testing in veterinary *Mycoplasma* species(Hannan, 2000). All isolates were susceptible to tiamulin and tylosin, whereas 35.7% of isolates were resistant to erythromycin.

3.2. ToR 2: identifying the most relevant bacteria in the EU

Following the methodology presented in the scientific opinion on the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021), the evidence available was assessed individually by all working group members who provided individual judgements on the perceived relevance to poultry health of the antimicrobial-resistant bacteria included in the list.

After discussion of the individual judgements for each bacterium (relevant/non-relevant/cannot be assessed based on available evidence), it was agreed with $\geq$ 66% certainty that the most relevant antimicrobial-resistant bacteria in poultry in the EU were *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus cecorum* (Figure 18). For *E. coli*, the main reasons for its selection were its clinical importance as one of the main disease-related causes of economic losses for the poultry industry worldwide (Barnes et al., 2008), and the very large number of AST results (representing the vast majority of all results retrieved through the ELR) indicating high levels of resistance against several of the antimicrobial classes used to treat the infection in poultry (e.g. tetracyclines, sulfonamides). Although the limited number of studies on laying hens suggested that resistance levels were lower in this population, most results available came from studies in broiler flocks, flocks with mixed production types or chickens for which the production type was not available, and resistance levels were consistently higher for all those (Table 3; Figures 4 and 5). Although high resistance levels to fluoroquinolones were also reported in several studies from different continents, values were generally lower for Europe in agreement with results from national monitoring programmes that indicated that, in fact, resistance to this antimicrobial class is not common (Figures 7 and 8). For the other poultry

species included in the literature review a much lower number of studies was found, but the general trend was similar (with high resistance levels to tetracyclines and potentiated sulfonamides).

For *E. faecalis* and *E. cecorum* the amount of evidence retrieved was much lower, and results from both the ELR and the national control programmes indicated a high degree of susceptibility to penicillins/aminopenicillins. Still, they were also included among the most relevant antimicrobial resistant bacteria due to their increasing clinical importance in the last decades, problems associated with their treatment (often due to a late etiological diagnosis) and their wide distribution, along with the high levels of resistance found for certain antimicrobials, which are also widely used for their treatment (lincosamides, spectinomycin), although overall this resulted in a wider degree of uncertainty.

None of the remaining bacterial pathogens assessed in this opinion were judged to be among the most relevant antimicrobial-resistant bacteria given: (i) the lower clinical relevance for several of them, (ii) the limited availability of antimicrobials in some cases (i.e. due to lack of drugs with withdrawal times compatible with production cycles) therefore creating therapeutic challenges not related with AMR and (iii) the very limited evidence available on treatment failures or frequency of AMR. Furthermore, in the low number of studies found often the use of non-clinical breakpoints (or CBPs borrowed from other species) makes interpretation of results very difficult, therefore leading to very broad uncertainty ranges for most of the assessed pathogens (Figure 18).

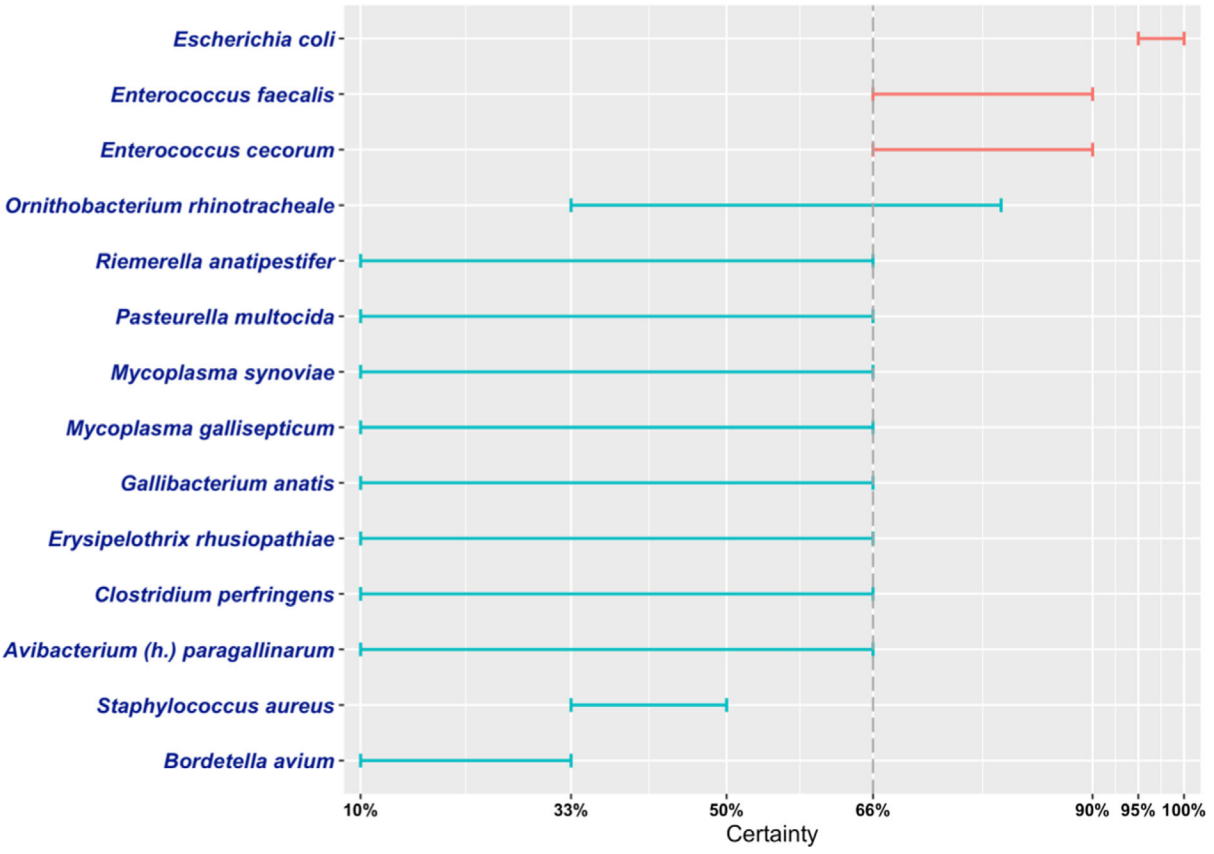


Figure 18: Level of certainty for the inclusion of the selected antimicrobial resistant pathogens of poultry species among the most relevant in the EU

In red are the most relevant bacteria based on the threshold of 66% of the lower certainty bound (dashed line).

4. Conclusions

In this opinion, EFSA presents the results of the assessment conducted to answer ToR 1 (global situation of antimicrobial-resistant animal bacteria) and first part of ToR 2 (identifying the most relevant resistant bacteria in the EU) as they are described and interpreted in the ad hoc methodology

(EFSA AHAW Panel, 2021). The second parts of ToR 2 and ToR 3, namely the animal health impact of the selected species on poultry in the EU, and their eligibility for being listed and categorised as part of the AHL, will be assessed in the next step of this EFSA project.

The scientific assessment of the global situation of the resistant bacterial poultry pathogens included in this opinion and of their EU relevance is hampered by several important sources of uncertainty derived from the available data and the methodology followed in this assessment, as mentioned in section 2.4 of EFSA AHAW Panel (2021) and in the preceding sections of this opinion:

- Due to the scope of the ELR, only studies published in the last 10 years and in English were considered eligible (except for the GERM-Vet report, originally in German), therefore introducing a possible selection bias.
- Information on the rationale and study design for the references retrieved in the ELR was limited and very heterogeneous, making the detailed assessment of the representativeness of the isolates included in each study very difficult. For example, one-fifth of the references (13/66) included isolates collected through the regular testing of veterinary diagnostic laboratories or from samples collected at the slaughterhouse, for which typically very limited information is available. Moreover, isolates included in the studies may originate from animals subjected to previous antimicrobial treatments, which may be associated with higher levels of AMR in tested isolates. However, this information was typically not available (with only one study mentioning routine use of several compounds in the sampled flocks). Furthermore, several of the bacterial species included here can also be found in healthy animals (e.g. *E. coli, E. faecalis*), and thus, their isolation in diseased animals does not imply they were always the causative agent. However, the proportion of cases in which this happened cannot be quantified.
- Even though only studies exceeding a minimum quality threshold were included (e.g. use of internationally accepted standards) the laboratory methodology used was also diverse (e.g. use of disk diffusion or microdilution methods, clinical breakpoints or ECOFFs, consideration or not of the intermediate category, etc.). Therefore, descriptive statistics provided here (average proportion of resistant isolates for bacterium, country and antimicrobial) should be interpreted carefully, as they may not be representative of the true underlying situation. In addition, in cases in which the sample size was small the confidence on the estimates would also be affected.
- Furthermore, interpretation of the clinical significance of the frequencies of resistance provided in most studies included is particularly difficult due to the absence of adapted clinical breakpoints for the poultry species assessed here, therefore leading to the use of breakpoints from other species (human or animal) that may not necessarily correlate with the clinical outcome on treated animals.
- AMR data referring to one or more of the bacterial pathogens of interest were retrieved from five national AMR monitoring reports. However, comparison of data reported in the different countries is difficult due to differences in: (i) the bacterial species considered, (ii) the geographical and temporal coverage of each report, (iii) the choice of antimicrobials included in the panel for AST and (iv) the methods for antimicrobial susceptibility determination (disk diffusion vs. broth microdilution, clinical breakpoints vs. ECOFFs).
- Finally, and specifically for this opinion, EFSA was tasked to address the global state of play considering several poultry species/categories (chickens - laying hen and broiler -, turkey, duck, goose, gamebirds and ratites). However, most of the data retrieved referred to chickens and more specifically to broiler. Therefore limited conclusions can be extracted in terms of differences between categories/species.

National monitoring systems for AMR in diseased poultry are only available in certain countries and there are limitations that hamper the comparability of data reported by different countries. Furthermore, most of these reports included very limited sample sizes, and therefore, no definitive conclusions in terms of AMR levels in poultry populations based on the EU national reports assessed in this opinion can be made, although stable AMR trends were found for most pathogen–drug combinations and levels of resistance were in general low for most pathogen–antimicrobial combinations. Although the significance of these observations should not be overinterpreted due to the above-mentioned limitations, assuming that sampling and methodological biases are relatively constant over time for a given monitoring programme, these longitudinal data could be helpful to detect the potential emergence of new AMR phenotypes of clinical importance or changes in resistance

proportions in poultry pathogens, and therefore help to guide antimicrobial stewardship. This could be particularly important for certain pathogens that have acquired increased relevance due to changes in management (e.g. cessation of growth-promotion uses and decrease in prophylactic use of antimicrobials for *Enterococcus* (Smyth and McNamee, 2008), increase in free-range production of laying hens for *P. multocida* (Dahl et al., 2002).

EFSA provided a global state of play for the following bacteria: *Escherichia coli*, *Enterococcus faecalis, Enterococcus cecorum, Staphylococcus aureus*, *Riemerella antipestifer, Clostridium perfringens*, *Avibacterium paragallinarum, Bordetella avium, Mycoplasma gallisepticum, Pasteurella multocida, Gallibacterium anatis, Mycoplasma synoviae, Ornithobacterium rhinotracheale* and *Erysipelothrix rhusiopathiae*.

Among those bacteria, based on the evidence available and expert opinion, EFSA identified *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus cecorum* as the most relevant antimicrobial-resistant poultry pathogens in the EU with $\geq$ 66% certainty.

Several major data gaps were identified, derived mainly from the lack of information from many countries in the world (and to a lesser extent from some regions in Europe), the insufficient information on the origins of the bacterial isolates tested (which could result in unknown selection biases) and the variety of antimicrobials, methodologies and breakpoints used to generate the data considered in this assessment.

The impact of the uncertainties deriving from these data gaps on the scientific assessment was incorporated into the results through expert opinion.

5. Recommendations

Data on AMR in bacterial pathogens are necessary to enhance animal health, promote the rational use of antimicrobials and identify specific therapeutic challenges attributable to AMR. The very limited information on AMR levels found for most pathogens included in this assessment, coupled with the lack of clinical breakpoints for the vast majority of drug–pathogen combinations, highlight the need for generating information on frequency of clinically relevant resistant phenotypes in poultry pathogens. This lack of information was particularly evident for poultry species other than chickens (and in chickens, for laying hens, probably related to the more limited use of antimicrobials in this production category).

In the future, harmonisation of the methodology used by national surveillance programmes, including sampling procedures and AST standards, as well as the development of supra-national monitoring systems, could allow more meaningful comparisons between countries (Mader et al., 2021). In addition, access to raw AST data generated by such programmes would facilitate comparisons, by enabling data interpretation with the same criteria (CBPs or ECOFFs), provided that programmes produce AST data with the same laboratory method.

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Abbreviations

AHAW	Animal Health and Welfare
AHL	Animal Health Law
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
CLSI	Clinical and Laboratory Standards Institute
ECOFF	epidemiological cut-off
ELR	extensive literature review
ESC	extended-spectrum cephalosporinase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
I	intermediate
MIC	minimum inhibitory concentration
MR	methicillin resistance
R	resistant
S	susceptible
SD	standard deviation
SSTI	skin and soft tissue infections
ToR	Term of Reference

Appendix A – Search strings applied

1) PubMed:

Common search string "Antimicrobials"

((“antibiotic”[Title/Abstract] OR “antibiotics”[Title/Abstract] OR “antimicrobial”[Title/Abstract] OR “antimicrobials”[Title/Abstract] OR “Anti-Bacterial Agents”[MeSH Terms:noexp]) AND (“resistan*”[Title/Abstract] OR “susceptib*”[Title/Abstract])) OR (“Microbial Sensitivity Tests”[MeSH Terms] OR “drug resistance, microbial”[MeSH Terms])

Host-based strings:

“Poultry”[MeSH Terms] OR “Chickens”[MeSH Terms] OR “Ducks”[MeSH Terms] OR “Geese”[MeSH Terms] OR “Quail”[MeSH Terms] OR “Struthioniformes”[MeSH Terms] OR “chicken”[Title/Abstract] OR “Chickens”[Title/Abstract] OR “broiler”[Title/Abstract] OR “broilers”[Title/Abstract] OR “layers”[Title/Abstract] OR “Poultry”[Title/Abstract] OR “turkeys”[Title/Abstract] OR “goose”[Title/Abstract] OR “Geese”[Title/Abstract] OR “duck”[Title/Abstract] OR “Ducks”[Title/Abstract] OR “pheasant”[Title/Abstract] OR “pheasants”[Title/Abstract] OR “ostrich”[Title/Abstract] OR “ostriches”[Title/Abstract] OR “grey partridge”[Title/Abstract] OR “grey partridges”[Title/Abstract] OR “Quail”[Title/Abstract] OR “quails”[Title/Abstract]

‘Bacterial species’

((((((((((((((“Haemophilus paragallinarum”[Mesh]) OR “Bordetella avium”[Mesh]) OR “Enterococcus cecorum” [Supplementary Concept]) OR “Gallibacterium anatis” [Supplementary Concept]) OR “Gallibacterium melopsittaci” [Supplementary Concept]) OR “Gallibacterium salpingitidis” [Supplementary Concept]) OR “Gallibacterium trehalosifermentans” [Supplementary Concept]) OR “Mycoplasma gallisepticum”[Mesh]) OR “Mycoplasma synoviae”[Mesh]) OR “Ornithobacterium rhinotracheale” [Supplementary Concept]) OR “Riemerella anatipestifer” [Supplementary Concept]) OR “Enterococcus faecalis”[Mesh]) OR “Escherichia coli”[Mesh]) OR “Staphylococcus aureus”[Mesh]) OR “Clostridium perfringens”[Mesh]) OR “Erysipelothrix”[Mesh]) OR “Pasteurella multocida”[Mesh]) OR (“Avibacterium paragallinarum”[Title/Abstract] OR “Haemophylus paragallinarum”[Title/Abstract] OR “Bordetella avium”[Title/Abstract] OR “Enterococcus cecorum”[Title/Abstract] OR “Gallibacterium”[Title/Abstract] OR “Mycoplasma gallisepticum”[Title/Abstract] OR “Mycoplasma synoviae”[Title/Abstract] OR “Ornithobacterium rhinotracheale”[Title/Abstract] OR “Riemerella anatipestifer”[Title/Abstract] OR “Enterococcus faecalis”[Title/Abstract] OR “Escherichia coli”[Title/Abstract] OR “Staphylococcus aureus”[Title/Abstract] OR “Clostridium perfringens”[Title/Abstract] OR “Erysipelothrix rhusiopathiae”[Title/Abstract] OR “Pasteurella multocida”[Title/Abstract])

2) Embase:

Common search string "Antimicrobials"

1. antibiotic resistance/or exp antibiotic sensitivity/or exp drug resistance/
2. susceptib*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. resistan*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. 2 or 3
5. antibiotic.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6. antibiotics.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. antimicrobial.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

8. antimicrobials.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9. 5 or 6 or 7 or 8
10. antibiotic agent/
11. 10 or 9
12. 11 and 4
13. 12 or 1

Host-based strings:

1. chicken/
2. poultry/
3. "turkey (bird)"/
4. goose/
5. duck/
6. phasianinae/
7. perdix perdix/
8. quail/
9. ostrich/
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (chicken or chickens or broiler or broilers or turkeys or goose or geese or duck or ducks or poultry or pheasant or pheasants or "grey partridge" or "grey partridges" or quail or quails or ostrich or ostriches).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
12. 10 or 11

'Bacterial species'

1. infectious coryza/
2. Haemophilus paragallinarum/
3. Bordetella avium/
4. Enterococcus faecalis/
5. Mycoplasma gallisepticum/
6. Mycoplasma synoviae/
7. ornithobacterium/
8. riemerella anatipestifer/
9. Escherichia coli/
10. Staphylococcus aureus/
11. Clostridium perfringens/
12. Erysipelothrix rhusiopathiae/
13. Pasteurella multocida/
14. ("Avibacterium paragallinarum" or "Bordetella avium" or "Enterococcus cecorum" or "Gallibacterium" or "Mycoplasma gallisepticum" or "Mycoplasma synoviae" or "Ornithobacterium rhinotracheale" or "Riemerella anatipestifer" or "Enterococcus faecalis" or "Escherichia coli" or "Staphylococcus aureus" or "Clostridium perfringens" or "Erysipelothrix rhusiopathiae" or "Pasteurella multocida").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

Appendix B – Excel file with all the data extracted

Information on all the full-text studies that were assessed, including the reason for exclusion for those that were excluded at the full-text screening and the data extracted from the included studies, can be consulted at https://doi.org/10.5281/zenodo.5106261.

Appendix C – Clinically relevant antibiotics for which data were extracted

Main infection types (not exclusive list)	Bacterial species	Text book 'Antimicrobial Therapy in Veterinary Medicine, 5th edn' by Giguère, Prescott and Dowling	Canadian guidelines	Dutch guidelines (numbers in brackets refer to 1st, 2nd or 3rd choice)	French guidelines	Antibiotics to extract data from divided by bacterial species (NB: Although each pathogen is listed next to a disease, the selected antibiotics should cover all diseases each pathogen causes)
Colibacillosis Airsacculitis	Escherichia coli	Enrofloxacin Oxytetracycline Chlortetracycline Penicillins Spectinomycin Streptomycin Sulfa/TMP	Amoxicillin Sulfa/TMP Sulfa/OMP Tetracycline Sulfonamides	Doxycycline (1) Oxytetracycline (1) Sulfaquinoxaline (1) Sulfa/TMP (1) Amoxicillin (2) Ampicillin (2) Flumequine (2) Lincomycin (2) Spectinomycin (2) Difloxacin (3) Enrofloxacin (3)	Colistin Amoxicillin Ampicillin Sulfa/TMP Oxytetracyclines Quinolones	**Aminopenicillins (ampicillin, amoxicillin)** **Colistin, polymyxin** **Enrofloxacin, ciprofloxacin** **Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)** **Sulfa/TMP** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)**
Omphalitis	Escherichia coli	Enrofloxacin Gentamicin Oxytetracycline Chlortetracycline Aminopenicillins Spectinomycin Streptomycin Sulfonamide	Amoxicillin Sulfamethazine Gentamicin Spectinomycin/ lincomycin	N/A	N/A	
Chronic respiratory disease	Mycoplasma spp.	Enrofloxacin* Oxytetracycline Chlortetracycline Spectinomycin Tylosin	Chlortetracycline Tetracycline	Doxycycline (1) Oxytetracycline (1) Lincomycin (1) Tiamulin (1) Tylosin (1) Lincomycin/ spectinomycin (2) Tilmicosin (2) Tylvalosin (2) Difloxacin (3) Enrofloxacin (3)	N/A	**Lincomycin** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** **Tiamulin** **Enrofloxacin, ciprofloxacin** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)** **Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)**
Erysipelas	Erysipelothrix rhusiopathiae	Penicillin	Penicillin Erythromycin Lincomycin	Oxytetracycline (1) Sulfa/TMP (1) Amoxicillin (2) Ampicillin (2) Tylosin (2)	Penicillin Macrolides	**Penicillin** **Aminopenicillin (ampicillin, amoxicillin)** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** **Lincomycin** **Sulfa/TMP** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)**

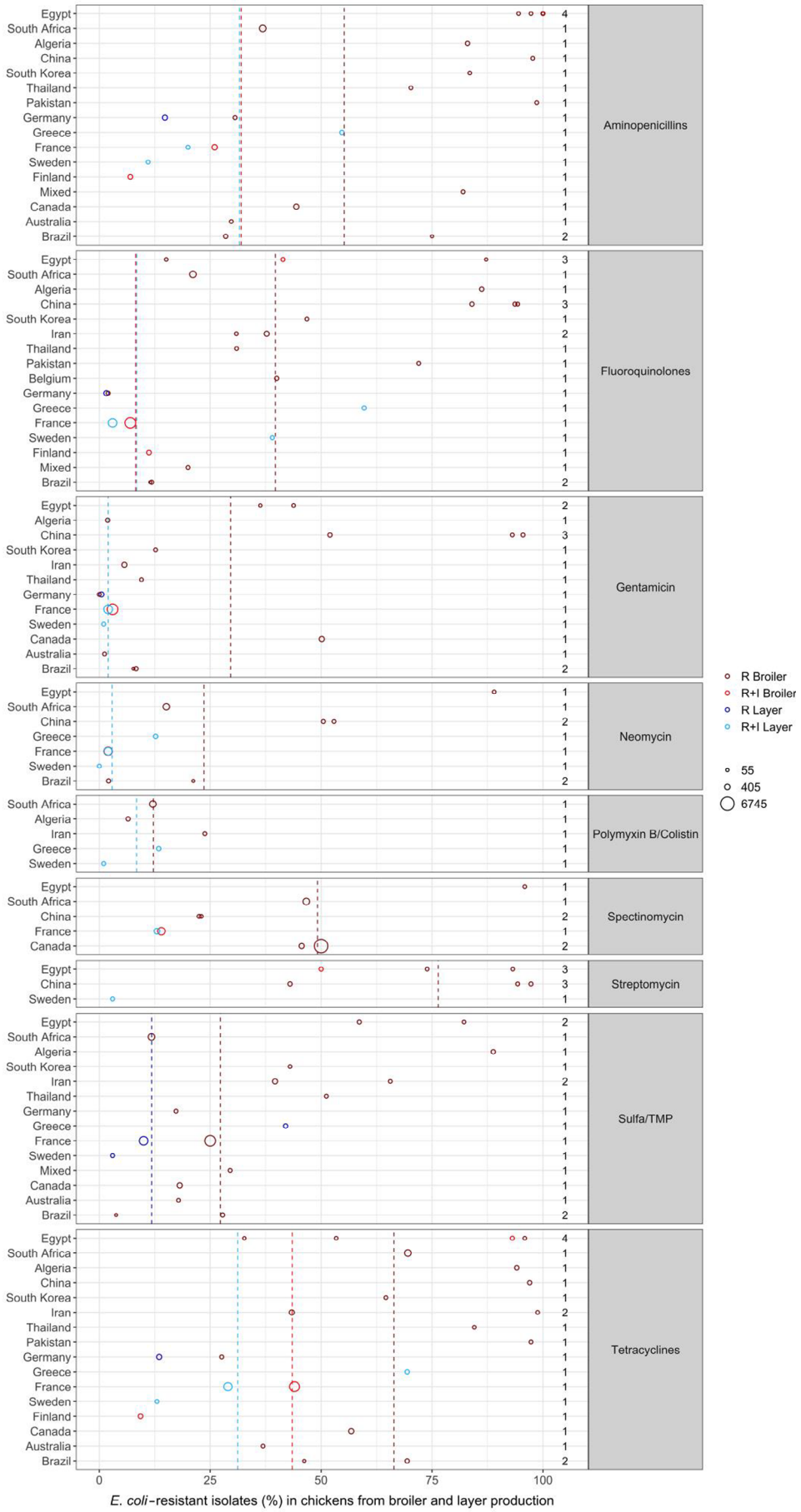
Main infection types (not exclusive list)	Bacterial species	Text book 'Antimicrobial Therapy in Veterinary Medicine, 5th edn' by Giguère, Prescott and Dowling	Canadian guidelines	Dutch guidelines (numbers in brackets refer to 1st, 2nd or 3rd choice)	French guidelines	Antibiotics to extract data from divided by bacterial species (NB: Although each pathogen is listed next to a disease, the selected antibiotics should cover all diseases each pathogen causes)
Fowl cholera	Pasteurella multocida	Enrofloxacin* Oxytetracycline Chlortetracycline Penicillins Spectinomycin Streptomycin Sulfonamide	Tetracycline Oxytetracycline Chlortetracycline Sulfa/TMP Sulfa/OMP Tilmicosin Penicillin Florfenicol	Doxycycline (1) Oxytetracycline (1) Sulfadimidine (1) Sulfa/TMP (1) Flumequine (2) Enrofloxacin (3)	Penicillins Aminopenicillins Fluoroquinolones Sulfa/TMP Tetracyclines	**Penicillin** **Aminopenicillins (ampicillin > amoxicillin)** **Enrofloxacin > ciprofloxacin** **Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)** **Sulfa/TMP** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)**
Infectious serositis or new duck disease	Riemerella anatipestifer	N/A	N/A	N/A	Sulfa/TMP Quinolones Ampicillin Amoxicillin Tetracyclines Colistin Macrolides Aminoglycosides	**Aminopenicillins (ampicillin > amoxicillin)** **Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)** **Colistin, polymyxin** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** **Sulfa/TMP** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)**
Necrotic enteritis	Clostridium perfringens	Bacitracin Bambermycins Lincomycin Neomycin Penicillins Spectinomycin Streptomycin Tylosin Virginiamycin	Bacitracin Lincomycin Neomycin Penicillin Sulfa/TMP Tetracycline Tylosin	Penicillin (1) Doxycycline (1) Oxytetracycline (1) Amoxicillin (2) Ampicillin (2) Tylosin (2)	N/A	Penicillin Aminopenicillins **(ampicillin > amoxicillin)** Lincomycin **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** Tetracyclines **(tetracycline, oxytetracycline, chlortetracycline, doxycycline)** **Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)** Bacitracin

Main infection types (not exclusive list)	Bacterial species	Text book 'Antimicrobial Therapy in Veterinary Medicine, 5th edn' by Giguère, Prescott and Dowling	Canadian guidelines	Dutch guidelines (numbers in brackets refer to 1st, 2nd or 3rd choice)	French guidelines	Antibiotics to extract data from divided by bacterial species (NB: Although each pathogen is listed next to a disease, the selected antibiotics should cover all diseases each pathogen causes)
Fowl coryza	Avibacterium (Haemophilus) paragallinarum	Erythromycin Oxytetracycline Chlortetracycline Streptomycin Sulfonamide Tylosin	Tetracycline Bacitracin Tylosin Sulfa/TMP	Doxycycline (1) Oxytetracycline (1) Sulfa/TMP (1) Amoxicillin (2)	N/A	**Aminopenicillins (ampicillin, amoxicillin) Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin) Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline) Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin) Sulfa/TMP Bacitracin**
	Bordetella avium	N/A	Chlortetracycline Sulfa/TMP Sulfa/OMP	N/A	N/A	**Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline) Sulfa/TMP + Antibiotics included ad hoc depending on what was reported and by taking into account intrinsic resistance**
	Gallibacterium spp. (anatis)	N/A	N/A	N/A	N/A	**Penicillin Aminopenicillins (ampicillin > amoxicillin) Enrofloxacin > ciprofloxacin Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin) Sulfa/TMP Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline) Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)**

Main infection types (not exclusive list)	Bacterial species	Text book 'Antimicrobial Therapy in Veterinary Medicine, 5th edn' by Giguère, Prescott and Dowling	Canadian guidelines	Dutch guidelines (numbers in brackets refer to 1st, 2nd or 3rd choice)	French guidelines	Antibiotics to extract data from divided by bacterial species (NB: Although each pathogen is listed next to a disease, the selected antibiotics should cover all diseases each pathogen causes)
Arthritis	Mycoplasma hyosynoviae	Enrofloxacin Oxytetracycline Chlortetracycline Spectinomycin Tylosin	Oxytetracycline Chlortetracycline Tylosin	Doxycycline (1) Oxytetracycline (1) Lincomycin (1) Tiamulin (1) Lincomycin/ spectinomycin (2) Tilmicosin (2) Tylosin (2) Enrofloxacin (3)	Tetracyclines Macrolides Lincosamides Pleuromutilins	**Lincomycin** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** **Tiamulin** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)** **Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)** **Enrofloxacin, ciprofloxacin**
	Enterococcus faecalis/caecorum	N/A	N/A	N/A	N/A	**Antibiotics included ad hoc depending on what was reported and by taking into account intrinsic resistance**
	Ornithobacterium rhinotracheale	N/A	N/A	Doxycycline (1) Oxytetracycline (1) Amoxicillin (2)	Amoxicillin Tetracycline Doxycycline Pleuromutilins Macrolides	**Aminopenicillins (ampicillin, amoxicillin)** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** **Tiamulin**
	Staphylococcus aureus	Erythromycin Novobiocin Oxytetracycline Chlortetracycline Penicillins Spectinomycin Streptomycin	Erythromycin Sulfa/TMP Sulfa/OMP Tetracycline Gallimycin Penicillin	Doxycycline (1) Oxytetracycline (1) Sulfa/TMP (1) Amoxicillin (2) Ampicillin (2)	Aminoglycosides Amoxicillin Ampicillin Enrofloxacin Macrolides Sulfa/TMP Tetracyclines	**Aminoglycosides (spectinomycin, streptomycin, gentamicin, neomycin)** **Aminopenicillins (ampicillin > amoxicillin)** **Enrofloxacin, ciprofloxacin** **Macrolides (erythromycin, tylosin, tilmicosin, tylvalosin)** **Sulfa/TMP** **Tetracyclines (tetracycline, oxytetracycline, chlortetracycline, doxycycline)**

Appendix D – Data on proportion of resistance, sorted by country

The figure below shows, for *E. coli* in chicken, resistance proportion data sorted by country. Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates the chicken production type and whether a study reports resistance only (R) or resistance merged with intermediate (R + I). The dashed lines indicate weighted arithmetic mean with the same colour code as the circles. The exact percentages these lines represent are listed in Appendix E. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.


Aminopenicillins
Egypt 4
South Africa 1
Algeria 1
China 1
South Korea 1
Thailand 1
Pakistan 1
Germany 1
Greece 1
France 1
Sweden 1
Finland 1
Mixed 1
Canada 1
Australia 1
Brazil 2
Fluoroquinolones
Egypt 3
South Africa 1
Algeria 1
China 3
South Korea 1
Iran 2
Thailand 1
Pakistan 1
Belgium 1
Germany 1
Greece 1
France 1
Sweden 1
Finland 1
Mixed 1
Brazil 2
Gentamicin
Egypt 2
Algeria 1
China 3
South Korea 1
Iran 1
Thailand 1
Germany 1
France 1
Sweden 1
Canada 1
Australia 1
Brazil 2
Neomycin
Egypt 1
South Africa 1
China 2
Greece 1
France 1
Sweden 1
Brazil 2
Polymyxin B/Colistin
South Africa 1
Algeria 1
Iran 1
Greece 1
Sweden 1
Spectinomycin
Egypt 1
South Africa 1
China 2
France 1
Canada 2
Streptomycin
Egypt 3
China 3
Sweden 1
Sulfa/TMP
Egypt 2
South Africa 1
Algeria 1
South Korea 1
Iran 2
Thailand 1
Germany 1
Greece 1
France 1
Sweden 1
Mixed 1
Canada 1
Australia 1
Brazil 2
Tetracyclines
Egypt 4
South Africa 1
Algeria 1
China 1
South Korea 1
Iran 2
Thailand 1
Pakistan 1
Germany 1
Greece 1
France 1
Sweden 1
Finland 1
Canada 1
Australia 1
Brazil 2
0
25
50
75
100
E. coli-resistant isolates (%) in chickens from broiler and layer production
R Broiler
R+I Broiler
R Layer
R+I Layer
55
405
6745

Appendix E – Exact percentages of weighted arithmetic means of %R and %R + I, respectively, displayed as dashed lines in figures

Chicken

Antibiotic	How resistance is reported (%R or %R + I) and production type	Weighted arithmetic mean proportion of resistance (%)	Maximum resistance % observed	Minimum resistance % observed	Standard deviation	Bacterial species/genus
Aminopenicillins	R_Broiler	55.2	100	28.5	25.4	*E. coli*
Aminopenicillins	R_Mixed	61.4	89.2	25.7	31.6	*E. coli*
Aminopenicillins	R_Unknown	79.1	100	71.7	9.2	*E. coli*
Aminopenicillins	R+I_Broiler	32	100	7	30.4	*E. coli*
Aminopenicillins	R+I_Layer	31.6	54.7	11	19.4	*E. coli*
Fluoroquinolones	R_Broiler	39.7	94.3	2	28.3	*E. coli*
Fluoroquinolones	R_Mixed	32.5	47.7	12.9	17.3	*E. coli*
Fluoroquinolones	R_Unknown	51.9	60.1	0	14	*E. coli*
Fluoroquinolones	R+I_Broiler	8.2	41.4	7	5.8	*E. coli*
Fluoroquinolones	R+I_Layer	8.4	59.7	3	15.6	*E. coli*
Gentamicin	R_Broiler	29.6	95.5	0	30.3	*E. coli*
Gentamicin	R_Mixed	19	36.9	2	14.1	*E. coli*
Gentamicin	R_Unknown	37.3	70.5	1	20.5	*E. coli*
Gentamicin	R+I_Layer	2	2	1	0.2	*E. coli*
Neomycin	R_Broiler	23.6	89	2.1	21.4	*E. coli*
Neomycin	R_Unknown	30.5	54.4	21.9	13.3	*E. coli*
Neomycin	R+I_Layer	2.9	12.7	0	3.2	*E. coli*
Polymyxin B/Colistin	R_Broiler	12.2	23.8	6.5	3.9	*E. coli*
Polymyxin B/Colistin	R+I_Layer	8.4	13.4	1	6.1	*E. coli*
Spectinomycin	R_Broiler	49.2	95.9	22.5	6.2	*E. coli*
Spectinomycin	R_Unknown	15.4	16.7	14.6	1	*E. coli*
Streptomycin	R_Broiler	76.4	97.3	43	23.1	*E. coli*
Streptomycin	R_Mixed	52.7	71.5	20.8	20.3	*E. coli*
Streptomycin	R_Unknown	63.6	68.3	48.8	7.4	*E. coli*
Sulfa/TMP	R_Broiler	27.3	88.8	3.8	15.2	*E. coli*
Sulfa/TMP	R_Layer	11.8	42	3	8.2	*E. coli*
Sulfa/TMP	R_Mixed	60.3	81.5	26.7	18.9	*E. coli*
Sulfa/TMP	R_Unknown	74.2	82.8	58.5	6.5	*E. coli*
Tetracyclines	R_Broiler	66.4	98.8	27.6	19.7	*E. coli*
Tetracyclines	R_Mixed	71	90.8	45.5	22.5	*E. coli*
Tetracyclines	R_Unknown	87	100	69.9	10.8	*E. coli*
Tetracyclines	R+I_Broiler	43.5	93.1	9.3	12.8	*E. coli*
Tetracyclines	R+I_Layer	31.2	69.4	13	11.4	*E. coli*
Aminopenicillins	R_Broiler	0	0	0	0	*Enterococcus* spp.
Erythromycin	R_Broiler	41.5	44	36.7	3.5	*Enterococcus* spp.
Gentamicin	R_Broiler	32.8	51	0	22	*Enterococcus* spp.
Lincomycin	R_Broiler	72.4	100	20	38.2	*Enterococcus* spp.
Streptomycin	R_Broiler	20	30	16.7	5.8	*Enterococcus* spp.
Tetracyclines	R_Broiler	77	79	73.3	2.7	*Enterococcus* spp.
Tylosin	R_Broiler	32.4	46	6.7	18.8	*Enterococcus* spp.
Bacitracin	R_Unknown	46.1	64	18.5	22.3	*C. perfringens*
Erythromycin	R_Unknown	12.7	29.2	2	13.3	*C. perfringens*
Tetracyclines	R_Unknown	57.6	62	50.8	5.5	*C. perfringens*

Poultry species other than chicken

Antibiotic	How resistance is reported (%R or %R + I) and poultry species	Weighted arithmetic mean proportion of resistance (%)	Maximum resistance % observed	Minimum resistance % observed	Standard deviation	Bacterial species/genus
Aminopenicillins	R_Turkey	61.1	76	38.8	14.8	*E. coli*
Fluoroquinolones	R_Turkey	26.7	36	9.2	10	*E. coli*
Gentamicin	R_Turkey	16.7	19.5	3.1	5.6	*E. coli*
Streptomycin	R_Turkey	66.5	75.3	60.4	7.3	*E. coli*
Sulfa/TMP	R_Turkey	26.5	67.1	5.7	16.5	*E. coli*
Tetracyclines	R_Duck	58.3	100	52	16.2	*E. coli*
Tetracyclines	R_Turkey	51	83.1	16.9	14.8	*E. coli*
Erythromycin	R_Duck	46.8	53.8	35.4	9	*R. anatipestifer*
Tetracyclines	R_Duck	82	90.6	43.8	18.2	*R. anatipestifer*