SCIENTIFIC OPINION

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

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Abstract

In this opinion, the antimicrobial-resistant bacteria responsible for transmissible diseases that constitute a threat to the health of horses have been assessed. The assessment has been performed following a methodology composed of information collected via an extensive literature review and expert judgement. Details on the methodology used for this assessment are explained in a separate opinion. A global state of play of antimicrobial-resistant *Actinobacillus equuli, Dermatophilus congolensis, Enterococcus* spp.*, Escherichia coli, Klebsiella pneumoniae, Pasteurella* spp.*, Pseudomonas aeruginosa, Rhodococcus equi, Staphylococcus aureus* and *Streptococcus dysgalactiae* subsp*. dysgalactiae/equisimilis* and *Streptococcus equi* subsp. *equi* and subsp. *zooepidemicus* has been provided. Among those bacteria, EFSA identified *E. coli*, *Staphylococcus aureus* and *R. equi* with more than 66% certainty as the most relevant antimicrobial-resistant bacteria in the EU, given their importance as causative agents of clinical disease in horses and the significant levels of resistance to clinically relevant antimicrobials. The animal health impact of these 'most relevant' bacteria as well as their eligibility of being listed and categorised within the animal health law framework will be assessed in separate scientific opinions.

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1. Introduction

The European Food Safety Authority (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 for 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 dogs and cats 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 dogs and cats.

2. Data and methodologies

The methodology applied for this opinion is described in a dedicated document that 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 horses had been agreed upon by the EFSA working group: *Actinobacillus equuli, Dermatophilus congolensis, Enterococcus* spp.*, Escherichia coli, Klebsiella pneumonia, Pasteurella* spp.*, Pseudomonas aeruginosa, Rhodococcus equi, Staphylococcus aureus, Streptococcus dysgalactiae* subsp. *dysgalactiae/equisimilis, Streptococcus equi* subsp. *equi* and subsp. *zooepidemicus*. The extensive literature review was carried out by the University of Copenhagen under the contract OC/EFSA/ALPHA/2020/02 – LOT 1.[2] On 30 November 2020, two different search strings (Appendix A) were applied in PubMed and Embase resulting in a search result of 548 unique abstracts published since 2010. Initial search strings did not include *Streptococcus equi* subsp. *equi* or *S. equi* subsp. *zooepidemicus*, which were the subject of a separate search made on 8 April 2021. This additional search resulted in 52 abstracts published since 2010. Forty of the abstracts were not detected in the first search, hence a total of 588 unique abstracts were identified from both searches. 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 inclusion and exclusion of studies. When available, the full text of articles was downloaded into EndNote software. In addition, an explorative search for the most recent national AMR surveillance reports reporting AMR 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 ELR as isolates

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[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

included in these reports can be assumed to originate from the same sampled populations and the most recent versions would therefore include the most updated AMR data. AMR data in the full texts and national reports were evaluated for eligibility by applying the exclusion criteria as described in the ad hoc method followed for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021), with the following changes of the standard methodology:

- Exclusion criterion 3: studies reporting AMR data at the genus level were accepted for *Klebsiella* spp. and *Pseudomonas* spp. since species within the genus usually have the same breakpoints and data were often reported this way. In addition, *Enterococcus* spp., *Klebsiella* spp., *Pasteurella* spp. and *Pseudomonas* spp. were already included in the literature search at the genus level.
- Exclusion criterion 8: minimum number of isolates in a study to be considered acceptable was set at 50 for *Staphylococcus aureus* and *E. coli* and at the default of 10 or more for the other bacterial species (the minimum number is for the whole study, meaning that in one study there could be less than 50 *E. coli* from one country, but when isolates from different countries are added, the limit of 50 is applied; also, one study could have 25 *E. coli* isolates from one study period and 25 from another, and by merging those time periods, the limit of 50 isolates would be reached.
- Exclusion criterion 16: studies where AMR was only assessed genotypically (except for studies where *mecA* was used to infer the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA), which were considered eligible).

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 from all the full-text studies assessed, including the reason for exclusion for those that were excluded at the full-text screening, is presented in Appendix B.

AMR was assessed for clinically relevant antimicrobials within the European Medicines Agency's Antimicrobial Advice Ad Hoc Expert Group (AMEG) categories B–D 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). An exception was made for *Rhodococcus equi* since rifampicin, classified in category A, was included in the scope of the review since the very limited availability of therapeutic options for its treatment has led to its use in the field. The list of clinically relevant antibiotics for each target bacterial species in horses is shown in Appendix C. 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 methicillin in *Staphylococcus aureus*, data for oxacillin, cefoxitin and the presence of the *mecA* gene were accepted. If data for more than one of these antimicrobials were available in the same study, we included the one for which more isolates were tested. If the same number of isolates was tested for the different antimicrobials, the order of preference for selection was *mecA* > cefoxitin > oxacillin.
- For third-generation cephalosporins (3GCs) in Enterobacterales (as an indicator of extended-spectrum beta-lactamase/AmpC), the order of preference was cefpodoxime > cefotaxime > ceftazidime > ceftriaxone > ceftiofur. If data for more than one of these antimicrobials were available in the same study, we included the one for which more isolates were tested. If resistance to at least one of these five 3GCs was not reported, we included instead – when available – other phenotypic data indicating presence of ESBL/AmpC, typically data from a double disk synergy test) (EUCAST, 2017).
- For fluoroquinolones, the order of preference was enrofloxacin > ciprofloxacin.
- For tetracycline resistance in staphylococci and streptococci, the order of preference was doxycycline > tetracycline > oxytetracycline.
- For polymyxin in *Pseudomonas* spp., the order of preference was polymyxin B > colistin.
- For penicillin resistance in enterococci, the order of preference was ampicillin > amoxicillin > penicillin.

For each study, when clinical breakpoints (CBPs) were used, AMR data were extracted as proportions of resistant isolates (%R) and/or as proportions 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

for the target pathogens, therefore only %R was reported. Similarly, when the presence of genes (e.g. *mecA*) was used as an indication of resistance, the proportion of isolates carrying the gene was reported as the %R. Moreover, the following decisions were made when evaluating datasets:

- When no information on the I category was provided in a study, we considered that the reported %R only comprised resistant isolates (i.e. I isolates had not been included in the same category).
- When the proportion 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 (see Appendix B) but used only %R for the analysis of this opinion.
- When epidemiological cut-off values (ECOFFs) were used, the proportions of non-wild-type isolates were reported in the same column 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

Out of the 588 abstracts retrieved in the literature search, 113 studies and three national AMR monitoring reports (116/592, 20%) were considered initially eligible. The assessment of the full text of these 116 references selected resulted in the exclusion of 88 (76%) of them based on the criteria described in the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021), leading to a total of 28 selected studies for which the full text was available. The main reasons for exclusion were an insufficient number of isolates in the study below the pre-established thresholds (20 studies), unclear criteria for selection of isolates leading to a high risk of data duplication between studies (14 studies) and no availability of the full text (9 studies) (Table 1).

Table 1: 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 for exclusion	Code in Appendix B	Number of studies
Less than a minimum number of isolates are included in the study	8	20
Full text not available	10	16
MIC data reported without interpretation	12	5
Unclear criteria for selection of isolates, risk of duplication	14	4
Experimental pharmacokinetic study	17[(b)]	4
Study investigating AMR in a subset of resistant clinical isolates	17[(b)]	4
Study on clinical outcome related to AMR	17[(b)]	4
AMR data from multiple host species reported together	2	3
Same animals sampled repeatedly	6	3
Zoonotic transmission study	17[(b)]	3
AMR data reported at bacterial genus level or above (except for *Klebsiella*, *Enterococcus*, *Pasteurella* and *Pseudomonas*)	3	2
Study does not follow a standard for antimicrobial susceptible testing or a standard is not reported	4	2
Percentage of resistant isolates not reported	7	3
AMR data included in another included study	9	2
Clinical investigation but with no AMR data	17[(b)]	2
Experimental laboratory investigation with no AMR data	17[(b)]	2

(a): Other 18 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.

When considering the 28 studies included in the literature review, no studies on AMR in *A. equuli*, *D. congolensis* or *Streptococcus dysgalactiae* isolates from diseased horses were found. *Escherichia coli* (n = 14), *Staphylococcus aureus* (n = 10) and *Streptococcus equi* subsp. *zooepidemicus* (n = 9) were the three most common bacterial species for which AMR data were reported, with between two and six studies available for the remaining bacterial species (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 = 28)*
Escherichia coli	14
Staphylococcus aureus	10
Streptococcus equi subsp. *zooepidemicus*	9
Klebsiella spp.	6
Pseudomonas spp.	6
Rhodococcus equi	5
Streptococcus equi subsp. *equi*	3
Streptococcus dysgalactiae subsp. *dysgalactiae/equisimilis*	2
Pasteurella spp.	2
Enterococcus spp.	1
Actinobacillus equuli	0
Dermatophilus congolensis	0

*: One study could provide information on one or more bacterial species.

Nine of the 28 selected studies were published in 2019 and no studies for 2011 were available (Figure 1).
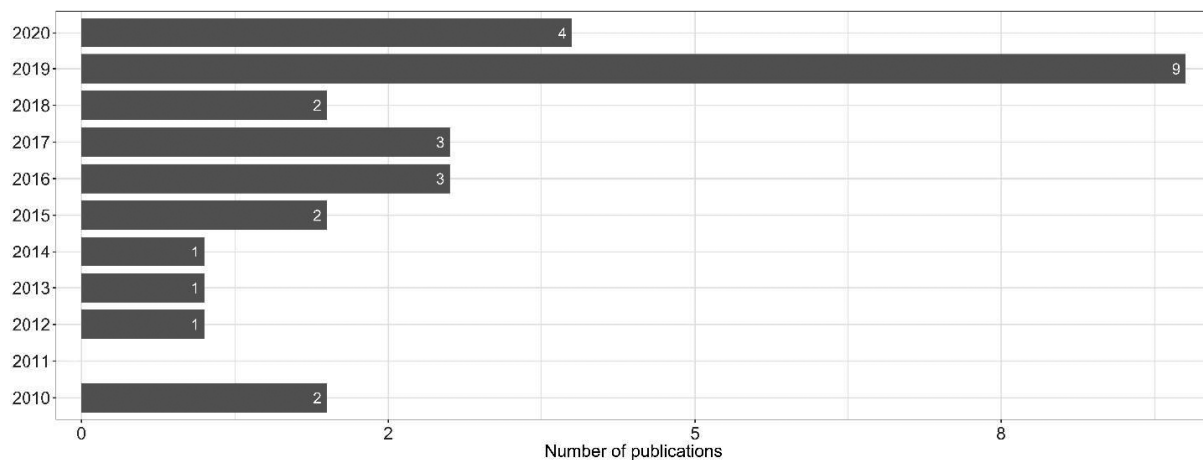
Figure 1: Year of publication of the 28 studies included in the extensive literature review

The data from the included studies originated from 11 countries on three continents (Europe, America and Oceania), with one study providing data from two countries. The vast majority of the studies reporting AMR data in horses originated from Europe (16 studies, of which seven came from France) and North America (nine from the USA and two from Canada) (Figure 2).
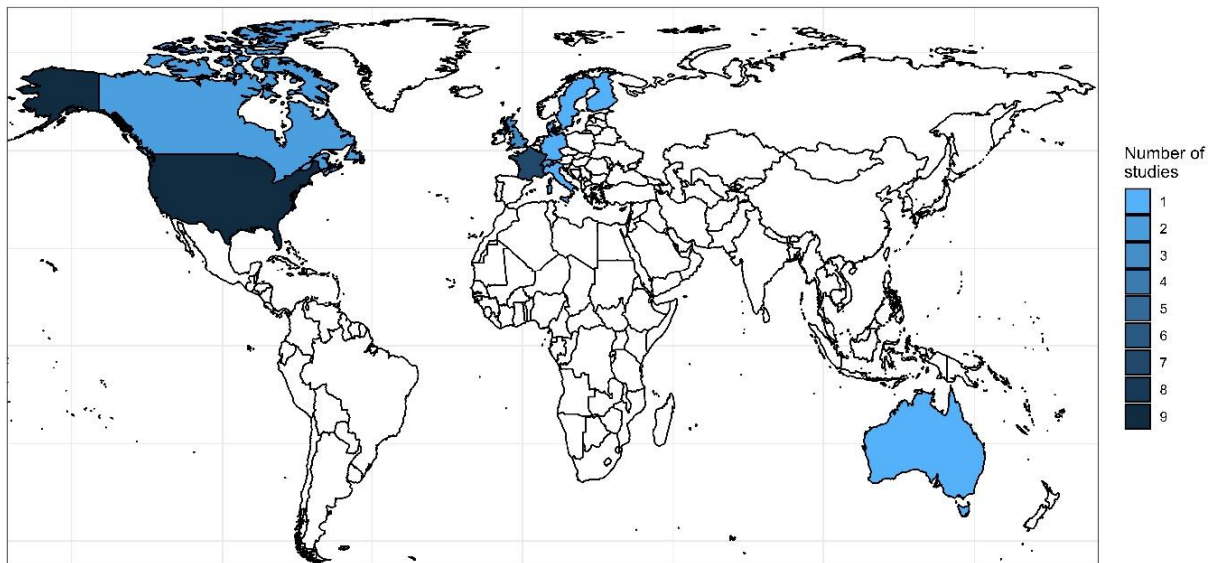
Figure 2: Geographical distribution of the 28 studies included reporting AMR data in horses

In terms of the type of isolates included in the study, studies were divided into: (i) those with isolates deriving from a clearly defined population of horses in a clinic, hospital, farm or similar; and (ii) those with isolates from a diagnostic laboratory without any background or information provided from the patients. Eighteen studies had isolates from a clearly defined animal population, whereas nine studies had isolates from diagnostic laboratories without further specification. For the last study, isolate origin was very poorly defined, hence the only information available was that isolates were of clinical origin and from horses.

3.1.2. AMR frequency data

The following pathogen-specific sections summarise the AMR data obtained for bacterial pathogens in horses.

The AMR data from different studies are extremely difficult to compare due to differences in study design, population, methods, interpretive criteria, etc. The number of antimicrobial susceptibility testing (AST) results for any given antimicrobial extracted from the selected references (total of 51,684; Appendix B) varied widely between bacterial species, with the first four pathogens accounting for 81.7% of all results (*S. equi* subsp. *zooepidemicus*: 17,954; *E. coli*: 13,261; *S. aureus*: 6,686 and *R. equi*: 4,326). Among the remaining pathogens, over 1,000 AST results for any given antimicrobial were also available for *Pseudomonas* spp. (2,983), *S. dysgalactiae* subsp. *equisimilis* (2,633), *Klebsiella* spp. (1,769) and *S. equi* subsp. *equi* (1,478), while fewer than 500 results were found for *Pasteurella* spp. (480) and *Enterococcus* spp. (114). Laboratory methods used to determine the resistance phenotype of the bacterial strains were based primarily on disk diffusion techniques (41,912, 81.1%) followed by broth microdilution (5,289) and PCR for detection of resistance genes (2,964). For one study, yielding 1,519 test results on five pathogens retrieved from urinary tract infection samples, the method was not stated but it was said to be according to CLSI guidelines and was finally included (Davis et al., 2013). The main approach for interpreting the AST results was based on CBPs (mentioned as the standard for interpretation for 46,226 tests, 89.4%) followed by ECOFFs (2,447). In the remaining cases, either both options (CBPs and ECOFFs) are mentioned in the reference, or the actual breakpoint is not clearly stated.

Furthermore, the definition of AMR differed across studies, as the intermediate category defined by CBPs was included in the calculation of AMR frequencies in some studies, whereas it was omitted in others. Figures displaying the proportion of resistance for each bacterial pathogen indicate whether % R or %R + I was reported; hence this should be taken into account when comparing studies. It is also important to mention that, compared with some other animal species, relatively few host-specific CBPs exist for horse pathogens. This complicates the interpretation of data, as in most studies it was unclear whether the CBPs used were adapted from other animal species or from humans, and whether the CBPs were specific to one or another organ or body site. Therefore, the outcomes of the present

review should be interpreted and cited with caution, as all specificities of individual studies cannot be taken into consideration. In order to support conclusions made from the figures or tables (e.g. a high proportion of resistance in a certain country or continent), it is strongly recommended to consult the relevant papers and check whether the results may be biased by previous antimicrobial treatment, sampling of animals in a certain environment, the use of certain diagnostic methods or breakpoints, or other factors.

3.1.3. Results of the ELR by bacterium

3.1.3.1. *Escherichia coli*

Escherichia coli are a group of opportunistic bacteria and a common component of the intestinal microbiota. Most of them are harmless but some strains are highly pathogenic and can cause severe infections with different clinical forms, such as mare endometritis. For the past two decades, extended-spectrum cephalosporinase (ESC)-producing Enterobacterales have emerged in animals. The most common type occurring in horses is the extended-spectrum beta-lactamase (ESBL) variant $bla_{CTX-M-1}$, which has been found on multiple occasions in the faeces of horses. Despite the *in vitro* sensitivity of ESBL-producers to beta-lactamase inhibitors, beta-lactams are generally not recommended for treatment of infections caused by any ESC-producing isolates. Furthermore, ESC-producing isolates are often co-resistant to other drugs, thus limiting treatment options when these multidrug-resistant (MDR) isolates are discovered. In total, 14 eligible studies with $\geq$ 50 *E. coli* isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, amoxicillin-clavulanic acid, enrofloxacin/ciprofloxacin, gentamicin, 3GCs, sulfonamide-trimethoprim) were included. Among these, nine and five studies included isolates from Europe and North America, respectively. Other continents were not represented.

The distribution of *E. coli* isolates for which AST data were available per site of infection is shown in Figure 3. Mostly, AMR was reported separately for isolates from the reproductive tract or together for isolates deriving from different organs.
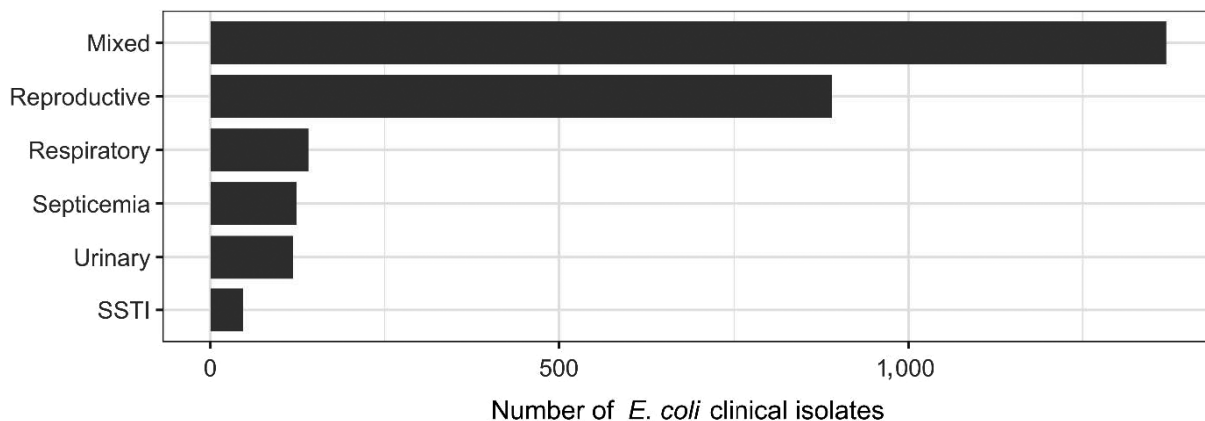
Mixed: isolates recovered from multiple sites reported together; SSTI: skin and soft tissue infections.

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

AMR data for *E. coli* were only available from studies representing Europe and North America. For countries on these continents, Figure 4 shows the proportion of resistance reported in individual studies with at least 50 *E. coli* isolates.

Overall, resistance to all drugs varied between studies and countries and even within the countries represented by multiple studies (USA, Canada, France and the UK), with no clear time trend present in the data. Such variation makes it difficult to emphasise one region/continent with particularly high or low resistance levels. The majority of studies with *E. coli* AMR data reported %R + I rather than %R alone (Figure 4), hence at least in that regard data from most studies were comparable.
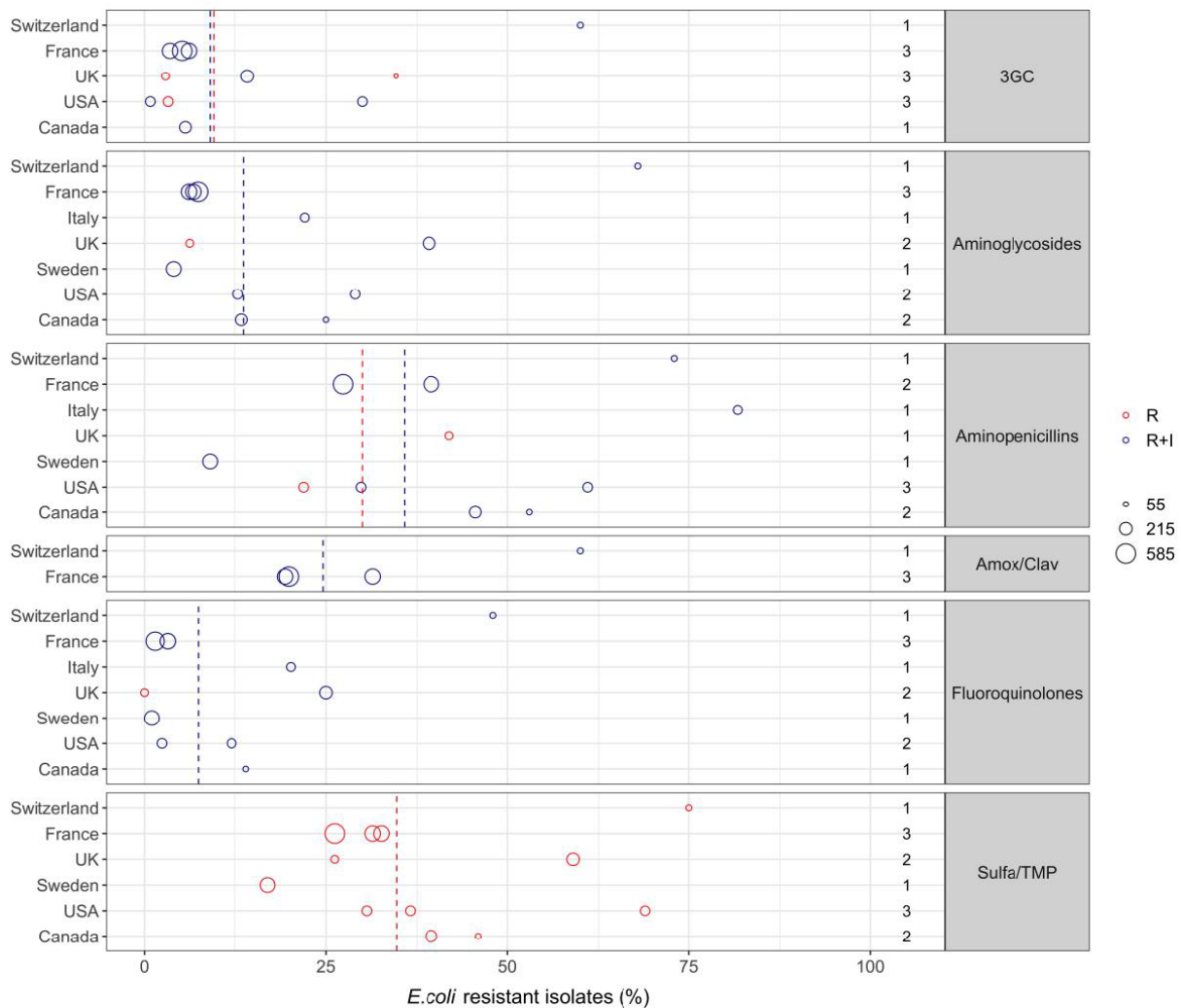
Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of the circle illustrates resistance only (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R (red dashed line) or %R + I (blue dashed line). The exact percentages these lines represent are listed in Appendix D. Numbers written to the left of the antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 4: *Escherichia coli* resistance data for each included study sorted by country

Eight of the 11 studies with data on **3GC**s had tested isolates for susceptibility to ceftiofur. Unlike cefpodoxime and cefotaxime, this drug is a less optimal indicator for ESBL/AmpC-producing Enterobacterales (see Methods section above), but it is more commonly used for treatment of horses than other 3GCs. Most studies had 3GC resistance levels below 10%, but two studies from the UK (Johns and Adams, 2015; Bortolami et al., 2019) and two studies from the USA (Davis et al., 2013; Elias et al., 2020) had higher levels ranging from 14.2% to 34.6% of isolates. A third study from the USA reported only 0.8% of isolates resistant to 3GC. Interestingly, this percentage was from foals sampled at hospital admission, whereas the same study reported a proportion of resistant isolates of 20.7% among *E. coli* obtained > 48 h after admission (latter data not included). This example illustrates how isolates from hospitalised patients are more commonly resistant than isolates from the community, probably due to the selective pressure and spread in hospital environments. The highest proportion of resistance to 3GCs (60%) was reported in a study from Switzerland (van Spijk et al., 2016). That study also comprised hospitalised patients and the authors concluded that two likely reasons for high resistance levels (also to other drugs; see the statistics for Switzerland in Appendix D) were an overrepresentation of complicated cases and many referral patients that had been treated with antibiotics prior to referral. One of the included studies reported ceftiofur resistance interpreted

'according to EUCAST clinical breakpoints' (Duchesne et al., 2019), and Davis et al. (2013) conducted susceptibility testing according to CLSI human CBPs. The problem with those studies is that neither human CLSI documents nor EUCAST tables have CBPs for ceftiofur, which is a veterinary-specific drug. Hence, the actual interpretation and thereby usefulness of such data is questionable.

Sulfonamide-trimethoprim combinations comprise in some countries the only registered antibiotic for oral use in horses. Resistance to that combination was common with an average proportion of resistance of 32.0% and 43.5% in Europe and North America, respectively (Table 2).

Average resistance levels for **aminopenicillins** were approximately the same as for sulfonamide-trimethoprim, with 32.5% and 41.3% of isolates in Europe and the USA being resistant to these drugs. Amoxicillin-clavulanic acid was only tested in four studies, but in all of them the levels of resistance were somewhat lower than for aminopenicillins without beta-lactamase inhibitor.

Overall, the lowest levels of resistance were observed for **gentamicin** and especially **fluoroquinolones**, and there was a lower level of resistance in Europe than in North America (Figure 4, Table 3).

Table 3: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *E. coli* for the target antimicrobials on each continent included in the studies

Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic average proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC	Europe	7	1,677	8.9	2.9	60	21.6
	N. America	4	546	9.3	0.8	30	13.5
Aminoglycosides (gentamicin)	Europe	8	2,037	12.3	4	68	22.8
Aminoglycosides	N. America	4	479	18.5	12.9	29	8.2
Aminopenicillins	Europe	6	1,481	32.7	9	81.7	27.5
Aminopenicillins	N. America	5	603	41.3	21.9	61	16.2
Amox/Clav	Europe	4	1,332	24.6	19.4	60	19
Fluoroquinolones	Europe	8	1,957	6.9	0	48	17.1
Fluoroquinolones	N. America	3	300	8.4	2.4	14	6.2
Sulfa/TMP	Europe	7	1935	31.9	17	75	20.8
Sulfa/TMP	N. America	5	603	43.5	30.6	69	14.9

3.1.3.2. *Staphylococcus aureus*

Staphylococcus aureus can reside in the skin and mucous membranes of horses, and it may cause various infections, including post-surgical infections. As in other animals, MRSA has emerged in horses. The recent decade has seen a shift in clonal lineages affecting horses, and nowadays clonal complex (CC) 398 appears to be by far the most common MRSA lineage in this species. Typing studies have shown that horses appear to have a specific host-adapted CC398 lineage differing from the variants spreading, for example, in pig production. In total, 10 eligible studies with ≥ 50 *S. aureus* isolates and results for one or more of the relevant antibiotics (enrofloxacin/ciprofloxacin, fusidic acid, gentamicin, methicillin, sulfonamide-trimethoprim, tetracyclines) were included. Among these, eight, one and one studies included isolates from Europe, North America and Oceania, respectively. Other continents were not represented.

The distribution of *S. aureus* isolates with AST data available per site of infection is shown in Figure 5. The majority of isolates were from unspecified infections.
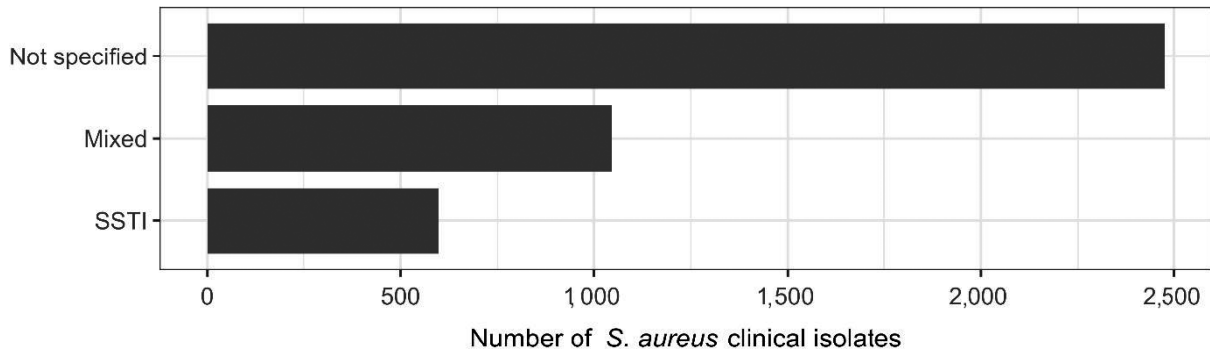
Mixed: isolates recovered from multiple sites reported together; SSTI: skin and soft tissue infections.

Figure 5: Distribution of *S. aureus* isolates per site of infection

A total of 10 studies reported susceptibility data for *S. aureus*, including six from France and one each from Australia, Sweden, Switzerland and the USA (Figure 6, Table 4).

Despite the inclusion of six French studies, there was no obvious evidence of data duplication, although – as an exception – *S. aureus* from the RESAPATH surveillance network was included from two time periods, namely from 2010 to 2015 (Haenni et al., 2017) and from 2018 (Resapath, 2020).
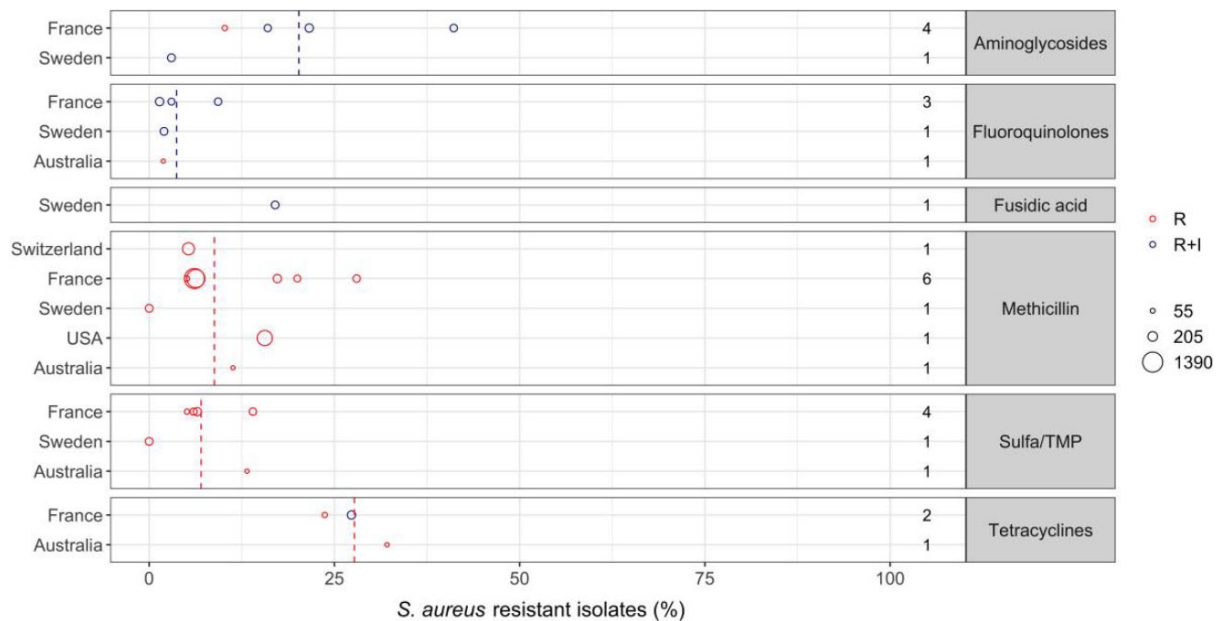
Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance only (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R (red dashed line) or %R + I (blue dashed line). The exact percentages these lines represent are listed in Annex D. Numbers written to the left of the antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 6: *Staphylococcus aureus* resistance data for the 10 included studies sorted by country

With regards to **methicillin resistance** (MR), there was a clear tendency for increasing resistance over time in France, as the three earliest studies with isolates from the years just before and after 2010 (Haenni et al., 2010, 2017; Guerin et al., 2017) reported 5.1–6.3% MR, whereas the three latest studies with isolates collected after 2015 reported 17.3–28.0% MR (Duchesne et al., 2019; Leon et al., 2020; Resapath, 2020). It should be noted that MR from the earlier studies was based on *mecA* PCR, whereas cefoxitin resistance was the MRSA indicator in the three later studies. Further, the most recent French study (Leon et al., 2020) included only samples from horses with prior antimicrobial treatment,

hence this bias should be taken into account. MR in the other countries ranged from 0% in Sweden (Swedres-Svarm, 2019) to 15.6% in the USA (Adams et al., 2018).

Resistance to **fluoroquinolones** was generally low (< 3%), except for the latest French study, which reported 9.3% resistance in isolates from 2019 (Leon et al., 2020).

Resistance to **gentamicin** was low in Sweden (3%), but ranged from 10.6% to 41.1% in France, again with the most recent – and biased – study from Leon et al. (2020) reporting the highest proportion.

Resistance to **sulfonamide-trimethoprim** varied from 0% in Sweden to 14.0% in France (Leon et al., 2020). A proportion of resistance nearly as high was observed in Australia with Saputra et al. (2017) reporting 13.2%.

The only three studies that included information on resistance to tetracyclines (two French and the single Australian study (Haenni et al., 2010; Saputra et al., 2017; Duchesne et al., 2019) reported consistent and fairly high levels of resistance (23.7–32.1%).

Susceptibility to **fusidic acid** was only tested in the Swedish study, which reported 17% of isolates resistant to that drug (Swedres-Svarm, 2019). The clinical relevance of this finding is probably low, as fusidic acid is used as a topical agent in veterinary medicine.

Table 4: Weighted arithmetic average, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *S. aureus* for the target antimicrobials on each continent included in the studies. NA means that SD cannot be calculated as only one study is included

Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic average proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Aminoglycosides (gentamicin)	Europe	5	524	19	3	41.1	14.5
Fluoroquinolones	Europe	4	453	3.7	1.4	9.3	3.6
Fluoroquinolones	Oceania	1	53	1.9	1.9	1.9	NA
Fusidic acid	Europe	1	118	17	17	17	NA
Methicillin	Europe	8	3,365	7.3	0	27.1	9.2
Methicillin	N. America	1	689	15.6	15.6	15.6	NA
Methicillin	Oceania	1	53	11.3	11.3	11.3	NA
Sulfa/TMP	Europe	5	520	6.3	0	14	5
Sulfa/TMP	Oceania	1	53	13.2	13.2	13.2	NA
Tetracyclines	Europe	2	198	26.2	23.7	27.3	2.5
Tetracyclines	Oceania	1	53	32.1	32.1	32.1	NA

3.1.3.3. *Streptococcus equi* and *S. dysgalactiae* subsp. *equisimilis*

Streptococcus equi is a major equine pathogen comprising two important subspecies. *Streptococcus equi* subsp. *equi* (*S. equi*) is the cause of strangles, a very contagious infection of the upper airways with abscessation of regional lymph nodes. *Streptococcus equi* subsp. *zooepidemicus* (*S. zooepidemicus*) is a commensal residing in the skin and mucous membranes of horses. It is an opportunistic pathogen capable of causing various infections, including airway infections and infections of the genital and urinary tracts. *Streptococcus dysgalactiae* subsp. *equisimilis* (*S. equisimilis*) predominantly resides in the skin and vagina of horses and is – similar to *S. zooepidemicus* – capable of causing a variety of different opportunistic infections in horses. In total, nine eligible studies with ≥ 10 *Streptococcus* isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, ceftiofur, enrofloxacin/ciprofloxacin, gentamicin, penicillin, sulfonamide-trimethoprim, tetracyclines) were included. Among these, five and four studies included isolates from Europe and North America, respectively. Other continents were not represented.

The distribution of *Streptococcus* isolates for which AST data were available per site of infection is shown in Figure 7. The majority of isolates was from mixed sites of infection.
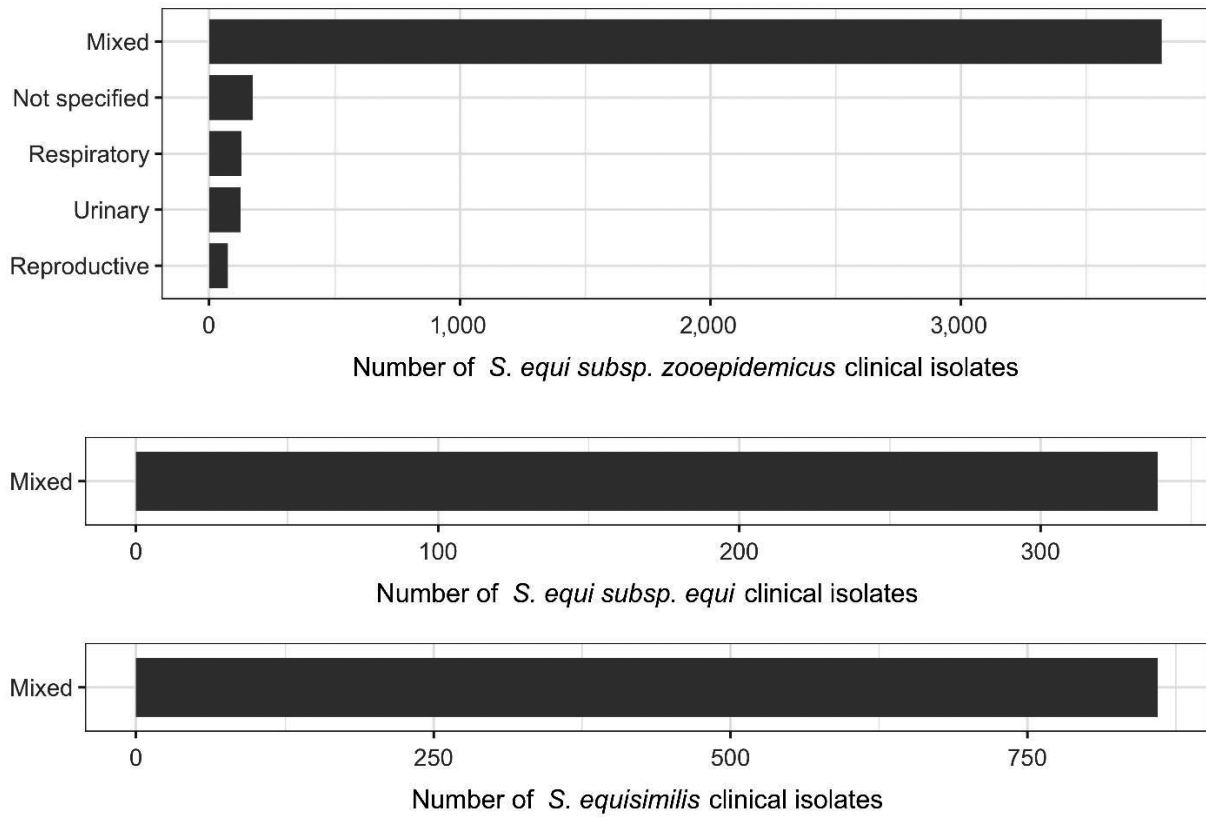
Mixed: isolates recovered from multiple sites reported together.

Figure 7: Distribution of *S. equisimilis*, *S. equi* and *S. zooepidemicus* isolates per site of infection

A total of nine, three and two studies reported resistance data for *S. zooepidemicus*, *S. equi* and *S. equisimilis*, respectively (Figure 8, Table 5).
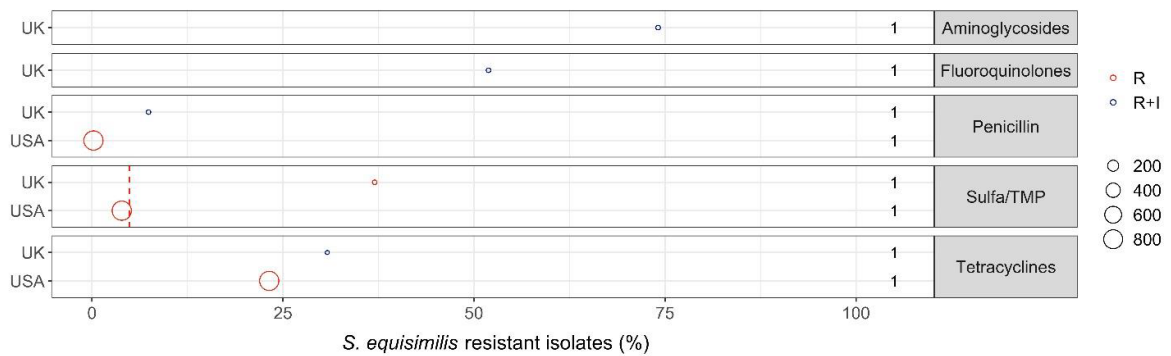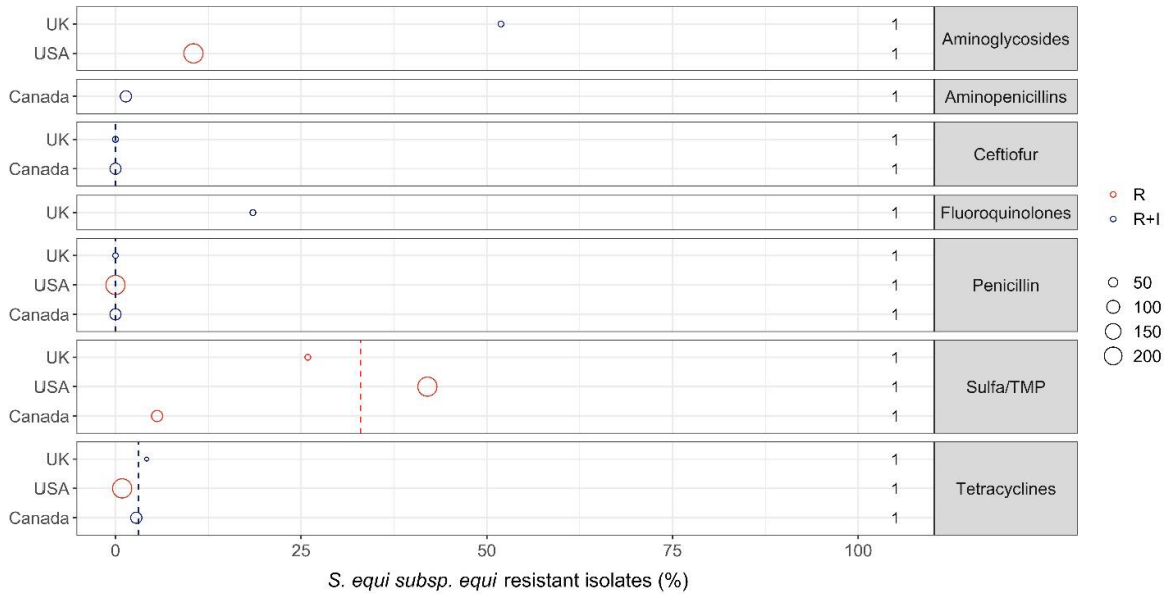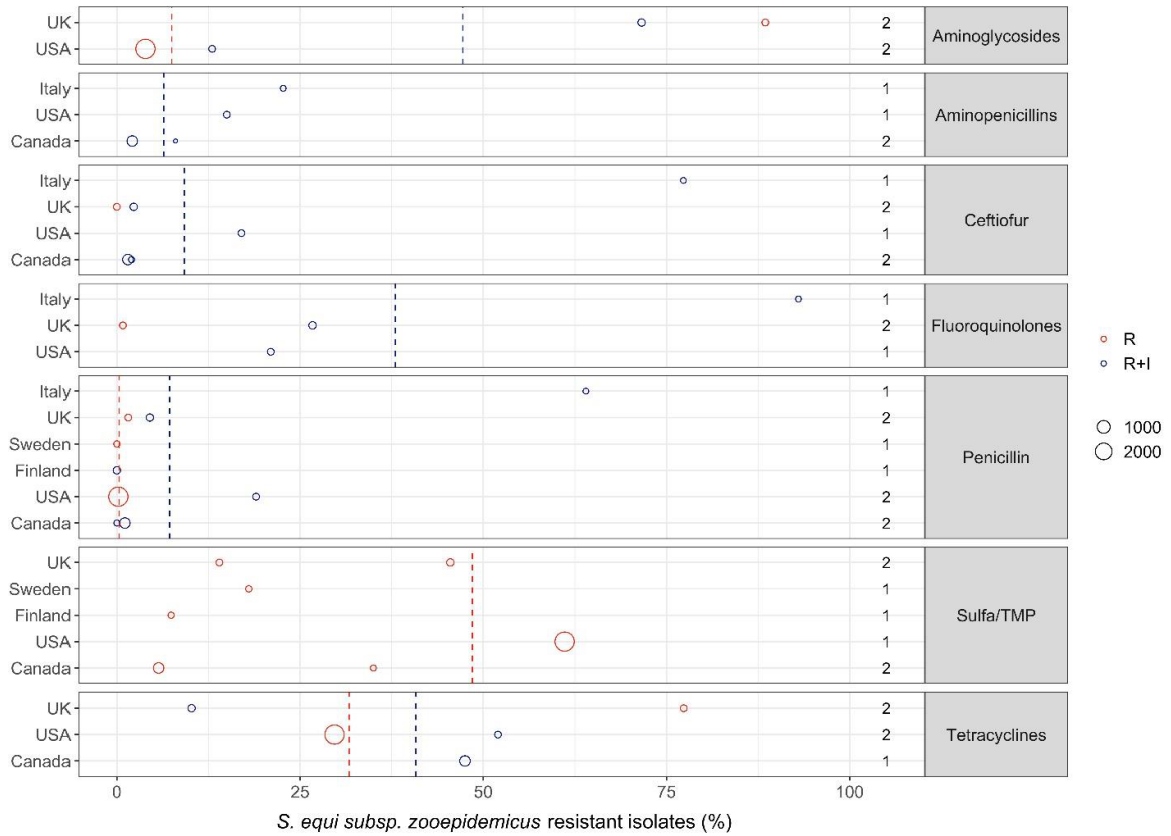
S. equi subsp. zooepidemicus resistant isolates (%)

S. equi subsp. equi resistant isolates (%)

S. equisimilis resistant isolates (%)

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 whether the percentage represents resistance only (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R (red dashed line) or %R + I (blue dashed line). The exact percentages these lines represent are listed in Appendix D. Numbers written to the left of the antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 8: *Streptococcus equi, S. equisimilis* and *S. zooepidemicus* resistance data for the included studies sorted by country

Penicillin is considered the drug of choice for treatment of streptococcal infections in horses, and this is supported by most studies reporting very little (< 10%) or even no resistance to this drug among the three streptococcal (sub)species. The most noteworthy exception was an Italian study reporting penicillin resistance in 64% of 75 *S. zooepidemicus* isolates from mare endometritis (Pisello et al., 2019). The authors had no explanation for that, but speculated that frequent empiric antimicrobial treatment could be a plausible cause. Interestingly, the same study reported somewhat lower resistance (22.7%) to ampicillin. A moderate to high level of penicillin resistance (19%) was observed by Davis et al. (2013), and no obvious explanation was evident for that study either. Except for the study by Pisello et al. (2019), levels of resistance for the beta-lactam alternatives ampicillin and ceftiofur followed more or less the levels reported for penicillin.

Resistance in streptococci was more pronounced to non-betalactams with the highest mean proportion of resistance (48.5%) being observed for **sulfonamide-trimethoprim** in *S. zooepidemicus*. This high level was particularly influenced by a large American study reporting 61.1% of 2,893 isolates resistant to this combination (Erol et al., 2012). It should be noted that this study did not specify from which CLSI guideline the breakpoint was derived, hence it is unknown how comparable the data are to other studies.

Fairly high mean proportions of resistant isolates were also observed for **tetracyclines**, but for this drug class there was a large difference between the two *S. equi* subspecies. This was particularly noticeable in two studies reporting only 2.8 and 0.9% tetracycline resistance in *S. equi*, whereas the same studies reported 47.5 and 29.3% resistance in *S. zooepidemicus* (Erol et al., 2012; Awosile et al., 2018).

Resistance to **aminoglycosides** and **fluoroquinolones** varied substantially between studies, e.g. Fonseca et al. (2020) reported 88.5% of 130 *S. zooepidemicus* isolates resistant to gentamicin, whereas Erol et al. (2012) found only 3.9% of 2,893 isolates to be resistant.

Table 5: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *S. equi, S. equisimilis* and *S. zooepidemicus* for the target antimicrobials on each continent included in the studies. NA means that SD cannot be calculated as only one study is included

| Bacterium	Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
S. zooepidemicus	Aminoglycosides (gentamicin)	Europe	2	306	78.8	71.6	88.5	11.9
	Aminoglycosides (gentamicin)	N. America	2	3,019	4.3	3.9	13	6.4
	Aminopenicillins	Europe	1	75	22.7	22.7	22.7	NA
	Aminopenicillins	N. America	3	712	4.7	2.1	15	6.5
	Ceftiofur	Europe	3	381	16.3	0	77.3	44
	Ceftiofur	N. America	3	761	4.1	1.5	17	8.8
	Fluoroquinolones	Europe	3	381	30.9	0.8	93	47.5
	Fluoroquinolones	N. America	1	126	21	21	21	NA

Bacterium	Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
	Penicillin	Europe	5	652	8.9	0	64	28
	Penicillin	N. America	4	3,654	1	0	19	9.3
	Sulfa/TMP	Europe	4	497	24.7	7.4	45.5	16.8
	Sulfa/TMP	N. America	3	3,526	51.9	5.7	61.1	27.7
	Tetracyclines	Europe	2	296	39.7	10.2	77.3	47.5
	Tetracyclines	N. America	3	3,568	33.2	29.7	52	11.8
S. equi	Aminoglycosides (gentamicin)	Europe	1	27	51.9	51.9	51.9	NA
	Aminoglycosides (gentamicin)	N. America	1	240	10.5	10.5	10.5	NA
	Aminopenicillins	N. America	1	72	1.4	1.4	1.4	NA
	Ceftiofur	Europe	1	27	0	0	0	NA
	Ceftiofur	N. America	1	72	0	0	0	NA
	Fluoroquinolones	Europe	1	27	18.5	18.5	18.5	NA
	Penicillin	Europe	1	26	0	0	0	NA
	Penicillin	N. America	2	312	0	0	0	0
	Sulfa/TMP	Europe	1	27	25.9	25.9	25.9	NA
	Sulfa/TMP	N. America	2	312	33.6	5.6	42	25.7
	Tetracyclines	Europe	1	24	4.2	4.2	4.2	NA
	Tetracyclines	N. America	2	312	1.3	0.9	2.8	1.3
S. equisimilis	Aminoglycosides (gentamicin)	Europe	1	27	74.1	74.1	74.1	NA
	Fluoroquinolones	Europe	1	27	51.9	51.9	51.9	NA
	Penicillin	Europe	1	27	7.4	7.4	7.4	NA
	Penicillin	N. America	1	833	0.2	0.2	0.2	NA
	Sulfa/TMP	Europe	1	27	37	37	37	NA
	Sulfa/TMP	N. America	1	833	3.9	3.9	3.9	NA
	Tetracyclines	Europe	1	26	30.8	30.8	30.8	NA
	Tetracyclines	N. America	1	833	23.2	23.2	23.2	NA

3.1.3.4. *Klebsiella* spp.

Klebsiella spp. are opportunistic pathogens residing in the intestinal tract. Although they occur with lower frequency than *E. coli*, they are generally capable of causing the same type of infections in horses. *Klebsiella pneumoniae* is special in the sense that it is one of the most common causes of mare endometritis with certain strains (of particular capsule types) being transmitted venereally. In total, six eligible studies with ≥ 10 *Klebsiella* spp. isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, amoxicillin-clavulanic acid, enrofloxacin/ciprofloxacin, gentamicin, 3GCs, sulfonamide-trimethoprim) were included. Among these, four and two studies included isolates from Europe and North America, respectively. Other continents were not represented.

The distribution of *Klebsiella* spp. isolates per site of infection is shown in Figure 9. For most isolates, resistance was reported together for isolates deriving from different organs.
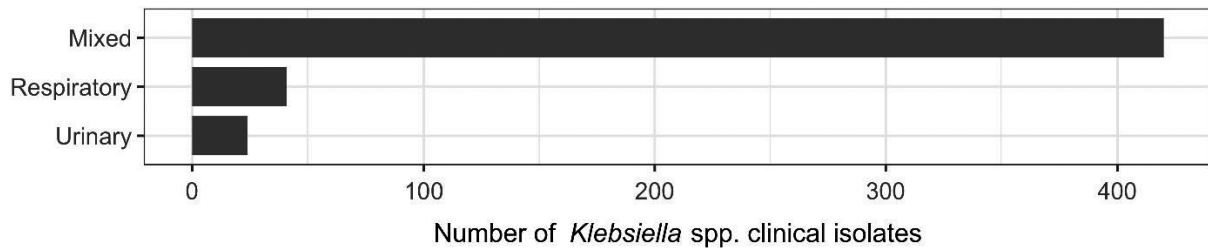
Mixed: isolates recovered from multiple sites reported together.

Figure 9: Distribution of *Klebsiella* spp. isolates per site of infection

AMR data for *Klebsiella* spp. were only available from six studies representing Europe (n = 4) and North America (n = 2). Figure 10 shows the proportion of resistance reported in individual studies with at least 10 *Klebsiella* spp. isolates.
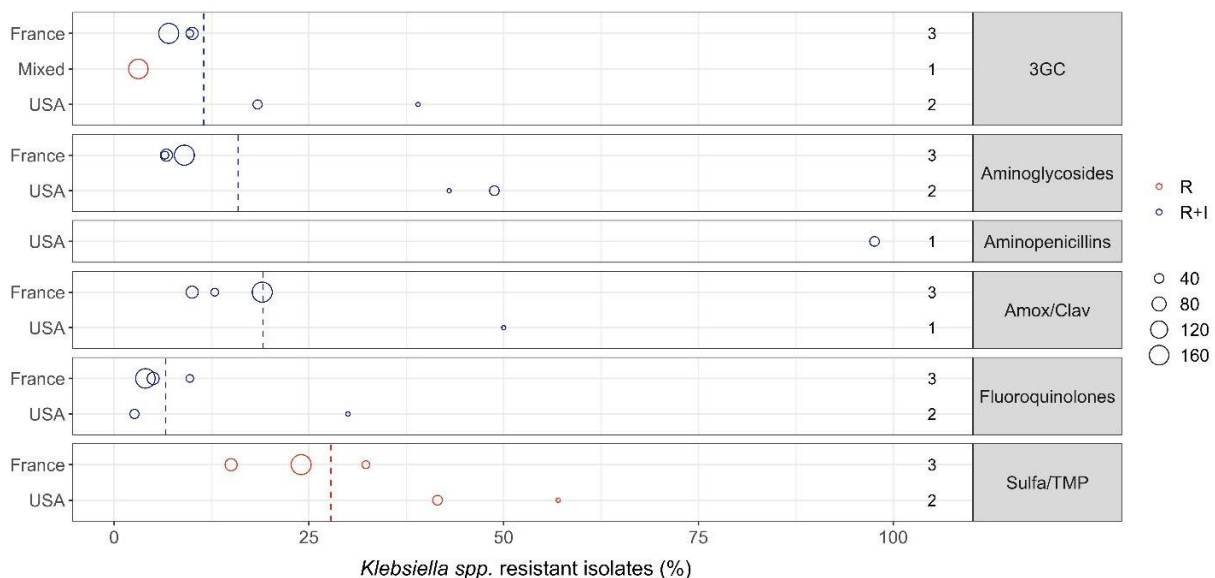
Each circle represents one study and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance only (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R (red dashed line) or %R + I (blue dashed line). The exact percentages these lines represent are listed in Appendix D. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 10: *Klebsiella* spp. resistance data for each included study sorted by country where 'mixed' refers to Ewers et al. (2014) reporting data from horses in Denmark and Germany

Overall, resistance in *Klebsiella* spp. was higher in isolates from North America, more specifically the USA, than Europe (Figure 10), but the limited number of studies on this bacterial species hamper generalisation of continent-specific patterns.

As for *E. coli*, resistance to **3GCs** was mostly tested using ceftiofur. The only exception was a study on horses in Germany and Denmark, which used a double disc synergy test to verify ESBL-production (Ewers et al., 2014). That study reported the lowest level of 3GC resistance (3%) in a collection of 160 isolates representing different *Klebsiella* species, whereas the three other European studies reported slightly higher levels but always below 10%. The two American studies reported 18% and 39% 3GC resistance, but these proportions were based on only 38 and 24 isolates, respectively. Furthermore, one of these studies (Davis et al., 2013) used human breakpoints for interpretation of ceftiofur susceptibility – a limitation elaborated in the section above on *E. coli*.

The lowest levels of resistance were seen for **fluoroquinolones** with less than 10% reported in five of six studies.

Similarly low levels of resistance were observed for **gentamicin** in *Klebsiella* isolates of European origin (range: 6.5–9%), whereas both American studies reported much higher levels of resistance to this drug, namely 43% (Davis et al., 2013) and 49% (Estell et al., 2016). Apart from the uncertainty related to there being relatively few isolates, such a high level of resistance could perhaps be explained by the fact that horses in Estell et al. (2016) were patients in a specialised veterinary teaching hospital. For Davis et al. (2013), there was no clear explanation of the observed widespread resistance to both gentamicin and other drugs, as the isolates had a more heterogeneous origin with some being from patients in an equine referral centre and others from patients in general practice.

As in *E. coli*, resistance to **sulfonamide-trimethoprim** and **amoxicillin-clavulanic acid** was more common than for most other drugs, and again the tendency was a higher proportion of resistance in North America (Figure 6 and Table 6). It should be noted that resistance to amoxicillin-clavulanic acid may not be fully comparable between studies, since some studies reported *K. pneumoniae*, and others (e.g. Resapath (2020)) *Klebsiella* without further specification of the actual species. In that regard, *K. aerogenes* is known to be intrinsically resistant to this drug, whereas other *Klebsiella* species are not.

Resistance to **aminopenicillins** without beta-lactamase inhibitor was only reported in one study (Estell et al., 2016). The finding of 97.6% resistant isolates was expected, since aminopenicillins have limited or no activity against gram-negative bacteria such as *K. pneumoniae*.

Table 6: Weighted arithmetic average, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *Klebsiella* spp. for the target antimicrobials on each continent included in the studies. NA means that SD cannot be calculated as only one study is included

Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic average proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC	Europe	4	420	6.1	3.1	10	3.2
3GC	N. America	2	62	26.4	18.4	39	14.6
Aminoglycosides (gentamicin)	Europe	3	260	8.2	6.5	9	1.4
Aminoglycosides (gentamicin)	N. America	2	65	46.7	43	48.8	4.1
Aminopenicillins	N. America	1	41	97.6	97.6	97.6	NA
Amox/Clav	Europe	3	260	16.2	10	19	4.6
Amox/Clav	N. America	1	24	50	50	50	NA
Fluoroquinolones	Europe	3	251	4.9	4	9.7	3
Fluoroquinolones	N. America	2	62	13.2	2.6	30	19.4
Sulfa/TMP	Europe	3	259	22.9	15	32.3	8.7
Sulfa/TMP	N. America	2	65	47.2	41.5	57	11

3.1.3.5. *Pseudomonas* spp.

Pseudomonas spp. are environmental organisms that also act as opportunistic pathogens capable of causing a wide range of infections in animals. In horses, *P. aeruginosa* is one of the venereally transmitted agents involved in mare endometritis.

The distribution of *Pseudomonas* spp. isolates per site of infection is shown in Figure 11.
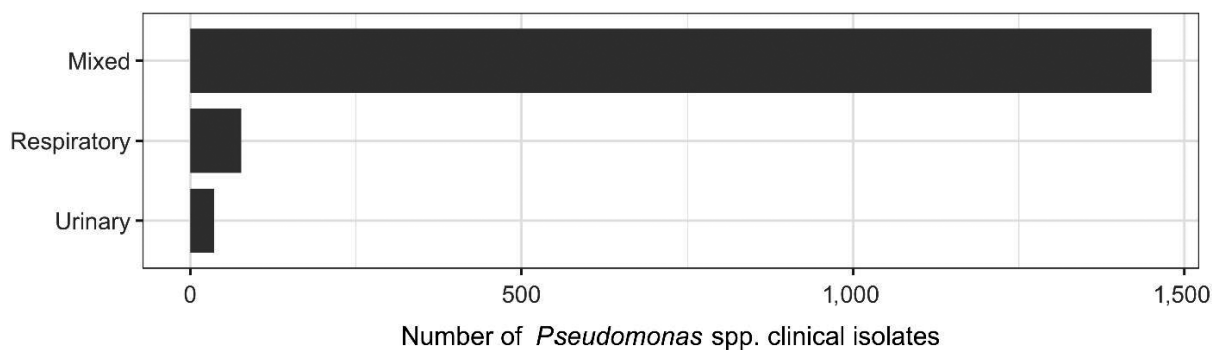
Mixed: isolates recovered from multiple sites reported together.

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

A total of six eligible studies, comprising three from France, one from Switzerland, one from Sweden and one from the USA, reported AMR data for one or more relevant antibiotics (enrofloxacin/ ciprofloxacin, gentamicin, polymyxin/colistin) in ≥ 10 *Pseudomonas* spp. isolates of clinical equine origin (Figure 12, Table 7).
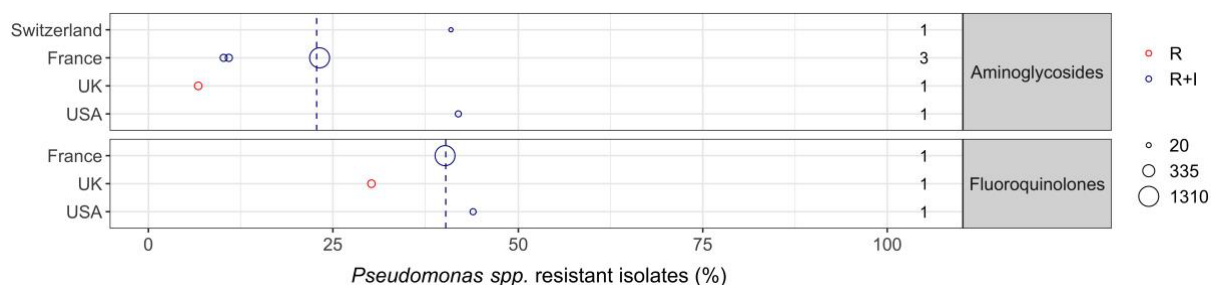
Each circle represents one study and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance only (red circle) or resistance merged with intermediate (blue circle). The blue dashed line indicates, for each antibiotic, the weighted arithmetic mean of %R + I. The exact percentages these lines represent are listed in Appendix D. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 12: *Pseudomonas* spp. resistance data for the six included studies sorted by country

Notably, fairly high levels of resistance to **fluoroquinolones** (25.0–46.2%) were observed in the three studies reporting data for this drug class. The highest proportion of resistance was detected in France by Bourely et al. (2020) based on a large collection of 1,307 isolates from various infection sites. From experience with analysis of data from dogs and cats, data for *Pseudomonas* spp. should be interpreted with care, since (i) AMR data for the two fluoroquinolones, ciprofloxacin and enrofloxacin, are not readily comparable, and (ii) %R cannot be compared with %R + I for enrofloxacin. With regard to the first point, all data for equine *Pseudomonas* isolates were based on testing enrofloxacin. For the second point, one study reported %R and two others %R + I (Figure 10).

The average proportion of resistance to **gentamicin** was lower than for fluoroquinolones (Figure 12). The highest and lowest proportions were detected in studies from the USA (42.0%, Davis et al. (2013) and the UK (6.5%, Fonseca et al. (2020), respectively, but also for this drug there are difficulties in comparing %R with %R + I based on the experience from the analysis of dog and cat AMR data. Both for fluoroquinolones and gentamicin, this issue could have been explored further if %I had been reported separately, but unfortunately this was not the case for any of the studies. Adding to the difficulties of comparison is the use of different breakpoints and that four of the studies reported data for *P. aeruginosa* and two for *Pseudomonas* spp., respectively.

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

Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic average proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Aminoglycosides (gentamicin)	Europe	5	1,527	21.6	6.8	41	14.1
Aminoglycosides (gentamicin)	N. America	1	36	42	42	42	NA
Fluoroquinolones	Europe	2	1,384	39.6	30.2	40.2	7
Fluoroquinolones	N. America	1	36	44	44	44	NA

3.1.3.6. *Rhodococcus equi*

Rhodococcus equi is present in soil and often in the gastrointestinal tract of animals. It can cause infection in humans and various animal species, but is best known for its ability to cause severe bronchopneumonia in foals.

The distribution of *R. equi* isolates per site of infection is shown in Figure 13. As expected, the vast majority of isolates were from respiratory infections.
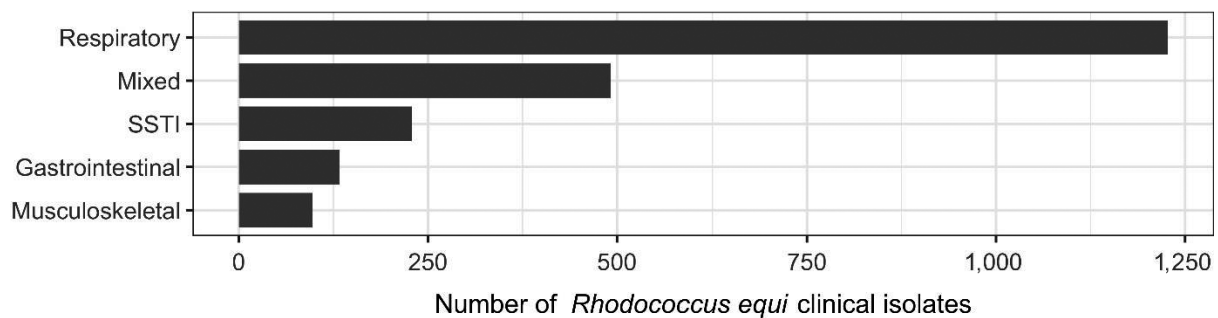
Mixed: isolates recovered from multiple sites reported together; SSTI: skin and soft tissue infections.

Figure 13: Distribution of *R. equi* isolates per site of infection

A total of five eligible studies, including three from the USA, one from Canada and one from France, reported AMR data for one or both relevant antibiotics (erythromycin and rifampicin, included in the scope of the ELR despite being included in Category A of the AMEG list due to the limited therapeutic options for this pathogen) in ≥ 10 *R. equi* isolates (Figure 14, Table 8).
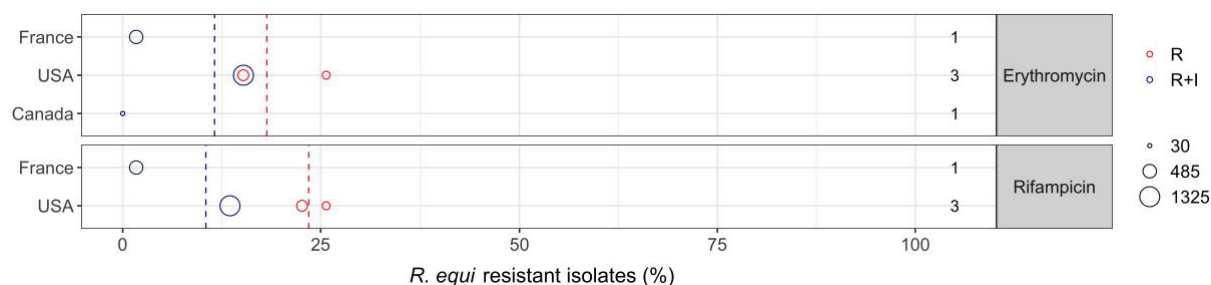
Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance only (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R (red dashed line) or %R + I (blue dashed line). The exact percentages these lines represent are listed in Appendix D. Numbers written to the left of antibiotic names reflect the number of studies for a certain drug/country combination.

Figure 14: *Rhodococcus equi* resistance data for the five included studies sorted by country

Overall, the lowest levels of resistance were detected in France with a proportion of only 1.7% for both erythromycin and rifampicin. Somewhat higher levels of resistance were reported for both drugs in the American studies, although one study found all 30 isolates investigated to be susceptible to erythromycin (Erol et al., 2020). It is worth noting that one study (Berghaus et al., 2015) reported data separately for the I category, but found only 0% and 2% of isolates intermediate for erythromycin and rifampicin, respectively. This could indicate that %R and %R + I data are somewhat comparable, unlike for *Pseudomonas* as explained above. All studies used human breakpoints from either EUCAST or CLSI, as there are no veterinary CBPs available for *R. equi*. Accordingly, the clinical relevance of the findings is unknown.

Table 8: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted SD in *R. equi* for the target antimicrobials on each continent included in the studies. NA means that SD cannot be calculated as only one study is included

Antibiotic	Continent	No. of papers	Number of isolates	Weighted arithmetic average proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Erythromycin	Europe	1	462	1.7	1.7	1.7	NA
Erythromycin	N. America	4	1,716	15.6	0	25.7	10.6
Rifampicin	Europe	1	462	1.7	1.7	1.7	NA
Rifampicin	N. America	3	1,686	15.7	13.6	25.7	6.3

3.1.3.7. *Pasteurella* spp.

Pasteurella spp. are commensals of the upper respiratory tract and occasionally opportunistic pathogens involved in respiratory infections. Unlike some other animal species, horses are not particularly prone to infection caused by bacteria representing this genus. *Pasteurella caballi* is a host-specific species adapted to the upper respiratory tract of horses.

The distribution of the *Pasteurella* spp. isolates per site of infection is shown in Figure 15. As expected, the vast majority of isolates were from respiratory infections.
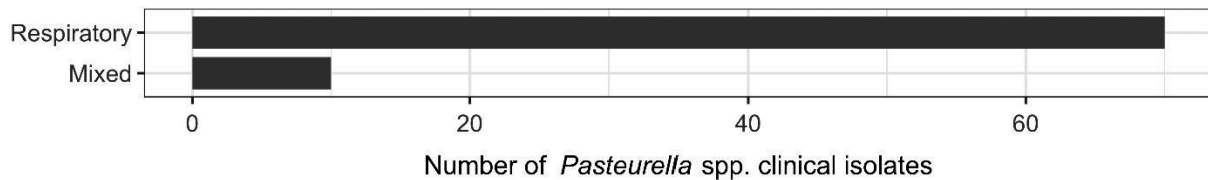
Mixed: isolates recovered from multiple sites reported together.

Figure 15: Distribution of *Pasteurella* spp. isolates per site of infection

AMR data for one or more of the relevant drugs (ampicillin/amoxicillin, enrofloxacin/ciprofloxacin, gentamicin, penicillin, sulfonamide-trimethoprim, tetracyclines, 3GCs) in ≥ 10 *Pasteurella* spp. isolates were only available from one Canadian and one British study. The Canadian study (Awosile et al., 2018) reported resistance in only 10 *P. caballi* isolates of mixed origin, hence interpretation from this small data set is near impossible. The British study (Fonseca et al., 2020) included 70 *Pasteurella* isolates from respiratory infections and reported moderate to low levels of resistance to most drugs, especially tetracyclines (Figure 16). Perhaps the most surprising finding was that just under 10% of isolates were resistant to ampicillin, since *Pasteurella* is very rarely resistant to beta-lactams.
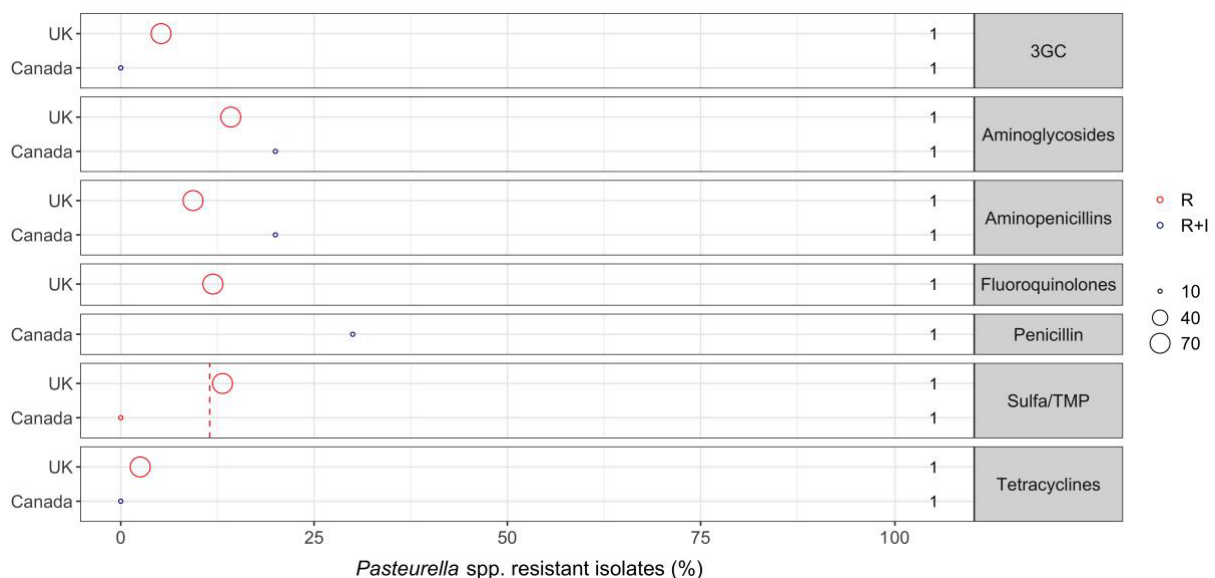

Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance only (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic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

Figure 16: *Pasteurella* spp. resistance data for the two included studies

3.1.3.8. *Enterococcus* spp.

Enterococci are found in the intestinal tract of animals and humans and regarded as opportunistic pathogens. Unlike for some other animals, enterococci have not been associated with any specific infection site in horses. Care should be taken when assessing growth of enterococci, as they often occur as contaminants in mixed cultures.

Only one eligible study reported resistance data for ≥ 10 enterococcal isolates in horses (van Spijk et al., 2016). The 38 isolates in that study were from various infection sites including urine, skin, soft tissue and the reproductive system. Enterococci are known to be intrinsically resistant to sulfa-TMP and this was illustrated in the study with 100% of isolates being resistant to that drug combination. Furthermore, a large proportion of isolates (68%) was resistant to enrofloxacin, whereas 21% were

resistant to ampicillin. The representativeness of the study is limited, as all isolates originated from horses in one hospital in Switzerland.

3.1.4. Assessment of data from national AMR surveillance reports

Relevant AMR data in one or more of the pathogens of interest in this opinion were extracted from the last published version of three national AMR reports (FINRES – Finland, SWEDRES-Svarm – Sweden and RESAPATH – France) and included in the outcome of the ELR presented above. Additional details/data provided in previous versions of the reports from these monitoring programmes (up to the previous five years) were extracted and are presented in the following section, along with differences/similarities with results presented in Section 3.1.3. Data included in the FINRES and SWEDRES-Svarm reports originated from isolates cultured from clinical submissions primarily at a central laboratory where the AST was also conducted. In contrast, in the RESAPATH reports AST results from isolates submitted to one of 71 laboratories (in 2018) are presented together. Assessment of changes in AMR 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) or because data on isolates retrieved over several years were presented together. Furthermore, between-country comparisons must be performed carefully since different methodologies are applied to obtain the results presented in each report, and results provided here are those provided in the reports (e.g. without accounting for the use of different breakpoints. A comparison of the methodology, bacterial pathogens, number of isolates and temporal coverage of the information provided in the last five reports of each monitoring programme is provided below (Table 9), and additional details on each programme follow.

Table 9: AMR methodology, bacterial species, host species, number of isolates and temporal coverage of the information on pathogens of interest from horses provided in the three national AMR surveillance reports (up to the last 5 years) reviewed in this opinion

Programme	FINRES	SWEDRES-Svarm	RESAPATH
Country	Finland	Sweden	France
Laboratory method	Disk diffusion	Broth microdilution	Disk diffusion
AST interpretation	Clinical breakpoints	ECOFFs	ECOFFs
S. equi subsp. *zooepidemicus*	Yes	Yes	Yes
Origin (number of isolates)	Not specified (29–56/year)	Mainly respiratory (81–129/year)	Reproductive (391–617/year)
Years covered	2014–2019	2014–2018	2014–2018
S. aureus	Yes	Yes	Yes
Origin (number of isolates)	No info	Skin (75–132/year)	Skin and soft tissue (72–107/year)
Years covered	No info	2014–2018	2014–2018
E. coli	No	Yes	Yes
Origin (number of isolates)		Genital tract (186–324/year)	Different locations (31–522/year)
Years covered		2014–2018	2014–2018
Klebsiella spp.	No	No	Yes
Origin (number of isolates)			All pathologies (103–169/year)
Years covered			2014–2018

3.1.4.1. FINRES (Finland)

The FINRES report includes information on antimicrobial resistance of *S. aureus* and *S. equi* subsp. *zooepidemicus* (*S. zooepidemicus*) clinical isolates provided by the Clinical Microbiology Laboratory of the Faculty of Veterinary Medicine of the University of Helsinki, with specimens coming from the Veterinary Teaching Hospital of the University (~ 36% of specimens) and from private veterinary clinics (~ 64%). Resistance was tested using the disk diffusion technique and results were interpreted using (when available, veterinary) CLSI CBPs. Information on resistance in equine *S. aureus* is provided

jointly with data coming from other companion animals (cats and dogs), and thus cannot be assessed separately, and therefore detailed information on resistance is only provided for *S. zooepidemicus*. The proportion of resistance to three antimicrobials of interest for this opinion (penicillin, tetracycline and sulfonamide-trimethoprim) in this bacterial species is reported for the whole 2014–2018 period, but yearly data were kindly provided by Thomas Grönthal (University of Helsinki, Faculty of Veterinary Medicine) for this scientific opinion.

The proportion of resistance to sulfonamide-trimethoprim and tetracycline (provided only for 2015–2019), tested in a limited number of isolates each year (ranging from 20 to 56) varied over time, with higher values recorded in 2016–2017 (and also in 2019 for sulfonamide-trimethoprim) (Figure 17). In general, resistance to tetracycline appears to be much higher (55–76%) than for sulfonamide-trimethoprim (3–12%), whereas no penicillin-resistant isolates were found throughout the 5 years. Resistance levels to penicillin and sulfonamide-trimethoprim are lower than the weighted average means reported in Table 5 for the collective assessment of European study results, while values are higher for tetracyclines, although a very large variation across studies was reported even when considering only Europe, particularly for sulfonamide-trimethoprim.
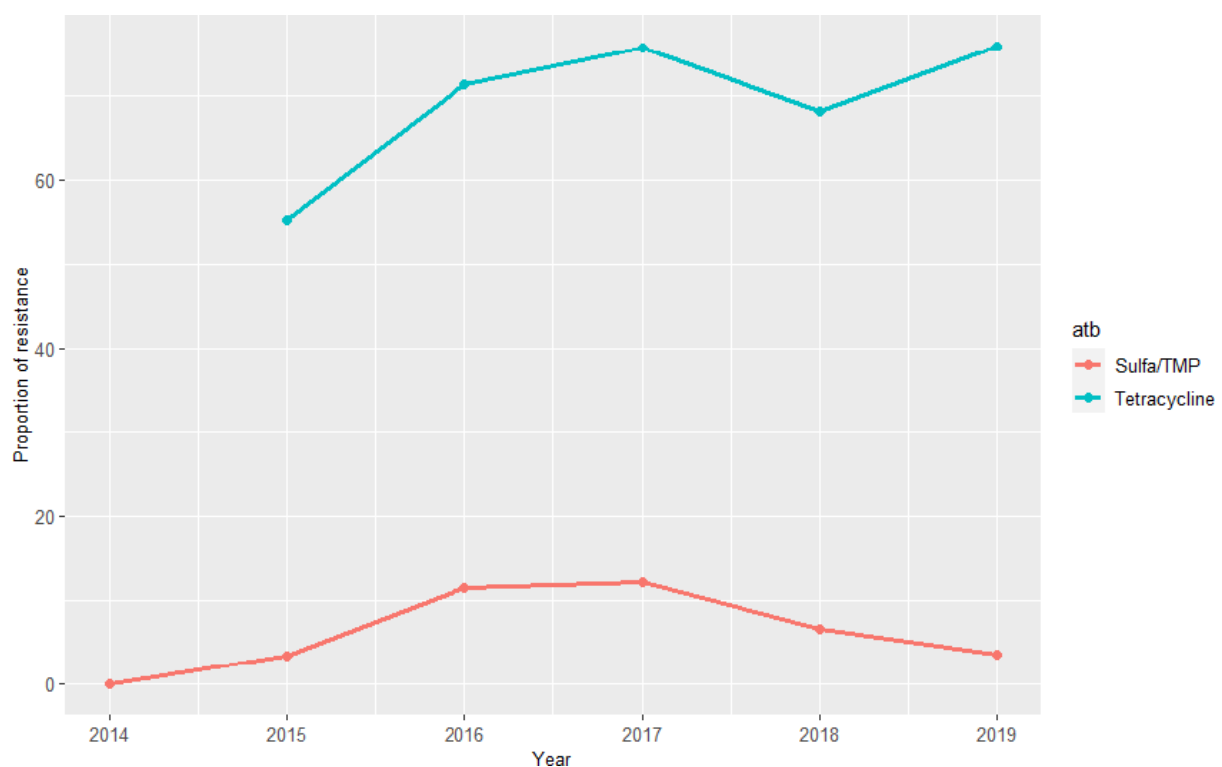
Figure 17: Proportion (%) of equine *S. zooepidemicus* isolates resistant to the following antimicrobials (atb): tetracyclines and sulfonamide-trimethoprim (Sulfa/TMP) retrieved from clinical samples included in the FINRES monitoring programme

3.1.4.2. SWEDRES-Svarm (Sweden)

AMR data from equine clinical isolates have been routinely included in the SWEDRES-Svarm report for over 15 years. The last five SWEDRES-Svarm published reports (including data generated between 2014 and 2018) provide data on resistance to several antimicrobials included in this scientific opinion for *E. coli*, *S. aureus* and *S. zooepidemicus*. Clinical isolates were tested primarily at the Swedish National Veterinary Institute using the broth microdilution method and results were interpreted according to the ECOFFs recommended by EUCAST.

For *E. coli*, data on 3GCs (cefotaxime), aminoglycosides (gentamicin), aminopenicillins (ampicillin), fluoroquinolones (enrofloxacin) and sulfonamide-trimethoprim are available for between 186 and 324 isolates retrieved from the genital tract of mares and tested yearly between 2014 and 2018. Resistance levels were low (< 5%) for all antimicrobials except ampicillin (7–11%) and sulfonamide-trimethoprim (12–17%), for which a sustained increase in the proportion of resistant isolates was

observed over the 5-year period (Figure 18) after a decrease experienced over the period 2009–2013 (Swedres-Svarm, 2018). Apparent trends in the change of proportion of resistant isolates were not evident for any other antimicrobial (Figure 18). Resistance levels in this collection of clinical isolates are consistently lower than the weighted arithmetic means provided in Table 3 for European studies, and in fact represent the minimum values observed in Europe for several antimicrobials. This is despite ECOFFs being lower than CBPs for several drugs, hence percentages of non-susceptibility are not directly comparable to other data.
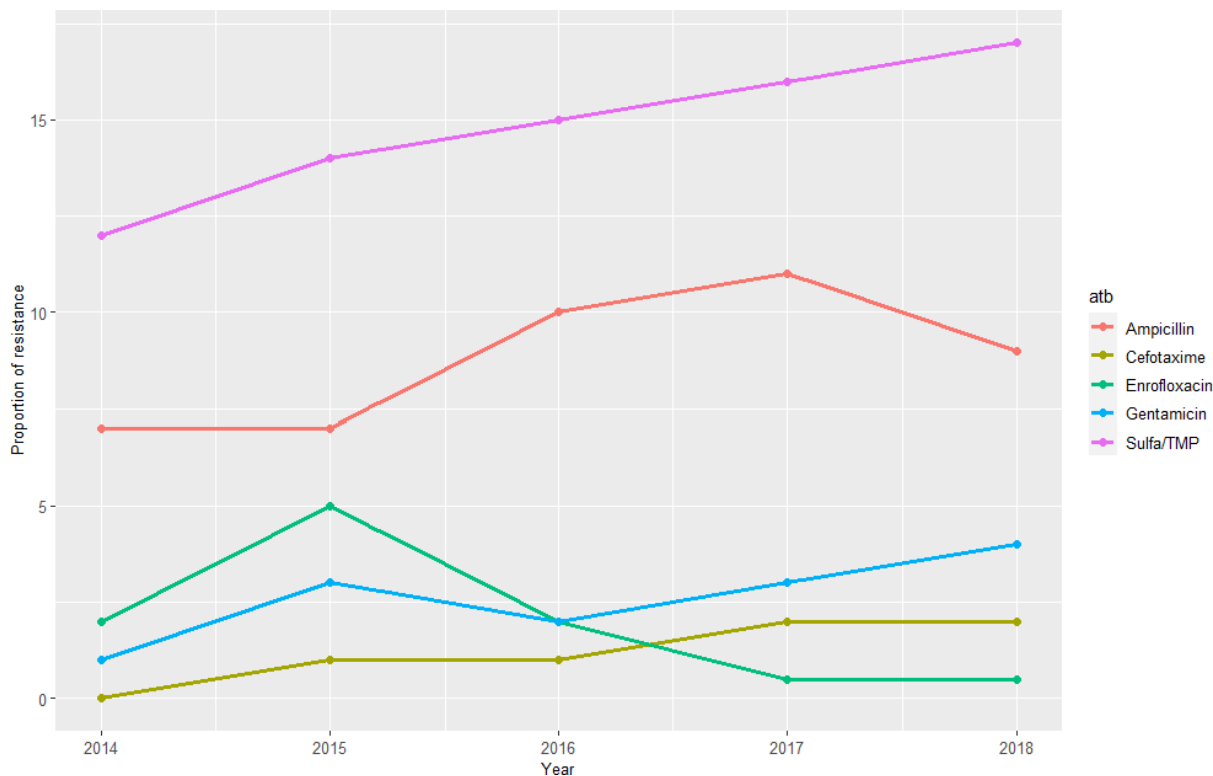
Figure 18: Proportion (%) of clinical equine *E. coli* isolates retrieved from the genital tract of mares resistant to the five antimicrobials (atb) of interest reported by the SWEDRES-Svarm monitoring programme

The 2015–2019 SWEDRES-Svarm reports also include resistance data on *S. aureus* retrieved from clinical skin samples (between 75 and 132 isolates tested yearly with lower numbers for specific antimicrobials in 2016). Antimicrobials considered in the panel included aminoglycosides (gentamicin), fluoroquinolones (enrofloxacin), fusidic acid (tested in 2015–2018), cefoxitin and oxacillin (tested in 2015–2018 and 2014–2017, respectively), sulfonamide-trimethoprim and tetracycline. Resistance levels were generally low (< 5%) for all antimicrobials except fusidic acid, with resistance levels that varied largely depending on the year, and the last data point for oxacillin (Figure 19). Somewhat different levels of resistance to oxacillin and cefoxitin were found in certain years, both below the levels of weighted arithmetic means reported for MR for European *S. aureus* isolates (Table 4). Resistance levels for the remaining antimicrobials were either lower (gentamicin, sulfonamide-trimethoprim and especially tetracycline) or similar (enrofloxacin, fusidic acid – only study in Europe) to the weighted means for other antimicrobials reported in Table 4.
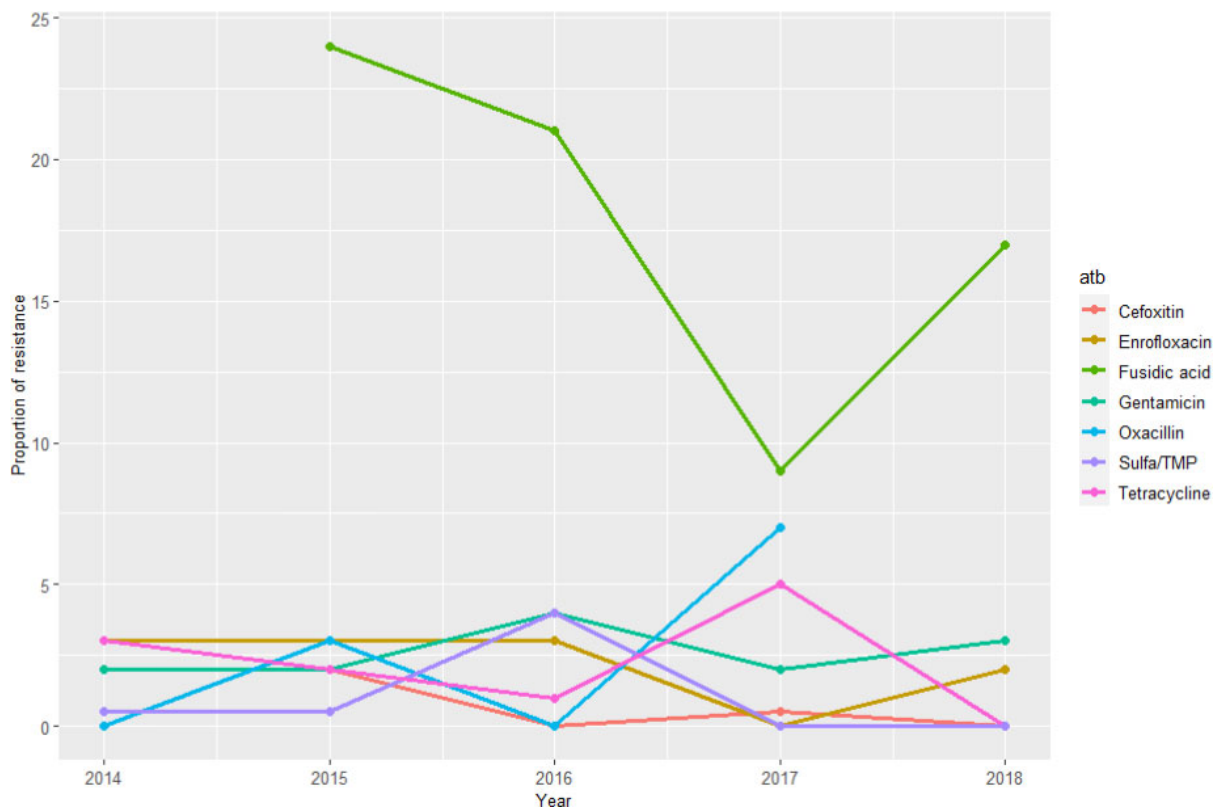
Figure 19: Proportion (%) of clinical equine *S. aureus* isolates retrieved from skin samples resistant to six antimicrobials (atb) of interest reported by the SWEDRES-Svarm monitoring programme

Finally, for *S. zooepidemicus*, between 81 and 129 clinical isolates, retrieved from different locations but mainly from respiratory samples, were tested for resistance to penicillin and sulfonamide-trimethoprim in 2014–2018 (isolates were also tested for resistance to ampicillin and tetracycline in 2014, yielding resistance levels of 0 and 2%, respectively). While no penicillin-resistant isolate was found throughout the study period, resistance to sulfonamide-trimethoprim increased from levels around 5–7% before 2017 to 18% in isolates collected in 2018 (Figure 20). Although sulfonamide/trimethoprim resistance levels in Swedish clinical *S. zooepidemicus* are still below the weighted arithmetic mean reported for all European isolates (Table 4, ∼ 25%), values recorded at the end of the study period are closer to it. The lack of penicillin resistance reported for equine *S. zooepidemicus* clinical isolates are, however, in the lower range of values reported in the European studies (Table 4).
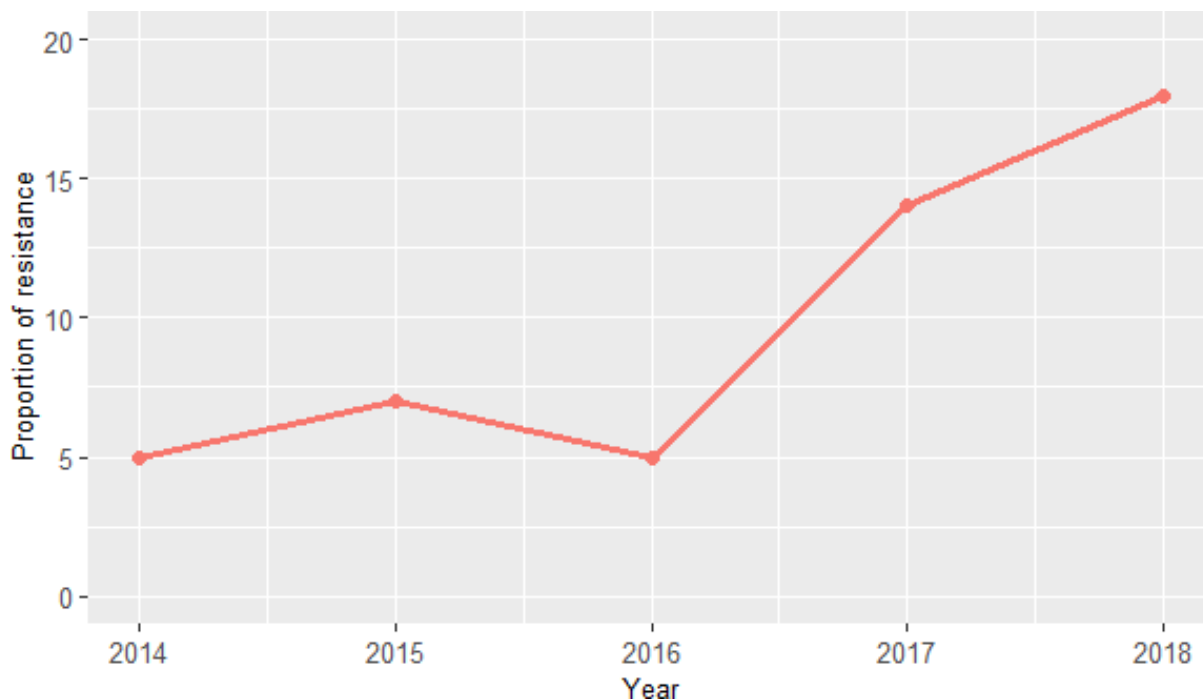
Figure 20: Proportion (%) of clinical equine *S. zooepidemicus* isolates retrieved mainly from respiratory samples resistant to sulfonamide-trimethoprim reported by the SWEDRES-Svarm monitoring programme

3.1.4.3. RESAPATH (France)

The RESAPATH reports published in 2015–2019 reported resistance data for equine clinical *E. coli* (from reproductive, respiratory and skin and soft tissue infections), *S. aureus* (from skin and soft tissue infections), *S. zooepidemicus* (from reproductive samples) and *Klebsiella* spp. (from all pathologies). *Streptococcus zooepidemicus* AMR data are provided grouped with data from other Group C streptococci and while these data were not included in the ELR (since isolates were not identified at the required taxonomic level), they are described here given that equine clinical isolates from Group C streptococci would typically belong to a bacterial species of interest in the opinion (*S. equi* subsp. *equi* or *zooepidemicus* and *S. dysgalactiae* subsp. *dysgalactiae* or *equisimilis*). Resistance data are generated at laboratories that are part of the French surveillance network for AMR in bacteria from diseased animals, and because multiple laboratories may contribute data, the number of isolates tested for different antimicrobials may differ. Resistance is determined according to the disk diffusion method (AFNOR NF U47-107 standard), and results are interpreted according to the veterinary guidelines of the Antibiogram Committee of the French Society of Microbiology (CA-SFM), which are closer to the EUCAST ECOFFs than to CLSI CBPs.

For *E. coli*, data on resistance to all antimicrobials/antimicrobial classes of interest were provided for clinical isolates mainly from reproductive samples (445–522 isolates/year), although data from isolates retrieved from respiratory samples (31–86 samples/year) and skin and soft tissue infections (41–72 isolates/year) are also provided. Resistance levels were higher ($\geq$ 20% for most years) for amoxicillin, amoxicillin-clavulanic acid and sulfonamide-trimethoprim than for ceftiofur, enrofloxacin and gentamicin, although differences were clearer in reproductive isolates (with resistance levels < 10% for the latter three antimicrobials) than in isolates from other locations, in which a lower sample size was achieved (Figure 21). In fact, resistance to 3GCs, fluoroquinolones and aminoglycosides was 2–3 times higher in respiratory and SSTI isolates than those from reproductive samples, although given the limited number of isolates tested for the former categories, results should be interpreted with care. Overall, no clear trends in the proportion of resistant isolates were observed over the five years considered, particularly for reproductive tract isolates, where the *E. coli* population was better represented.
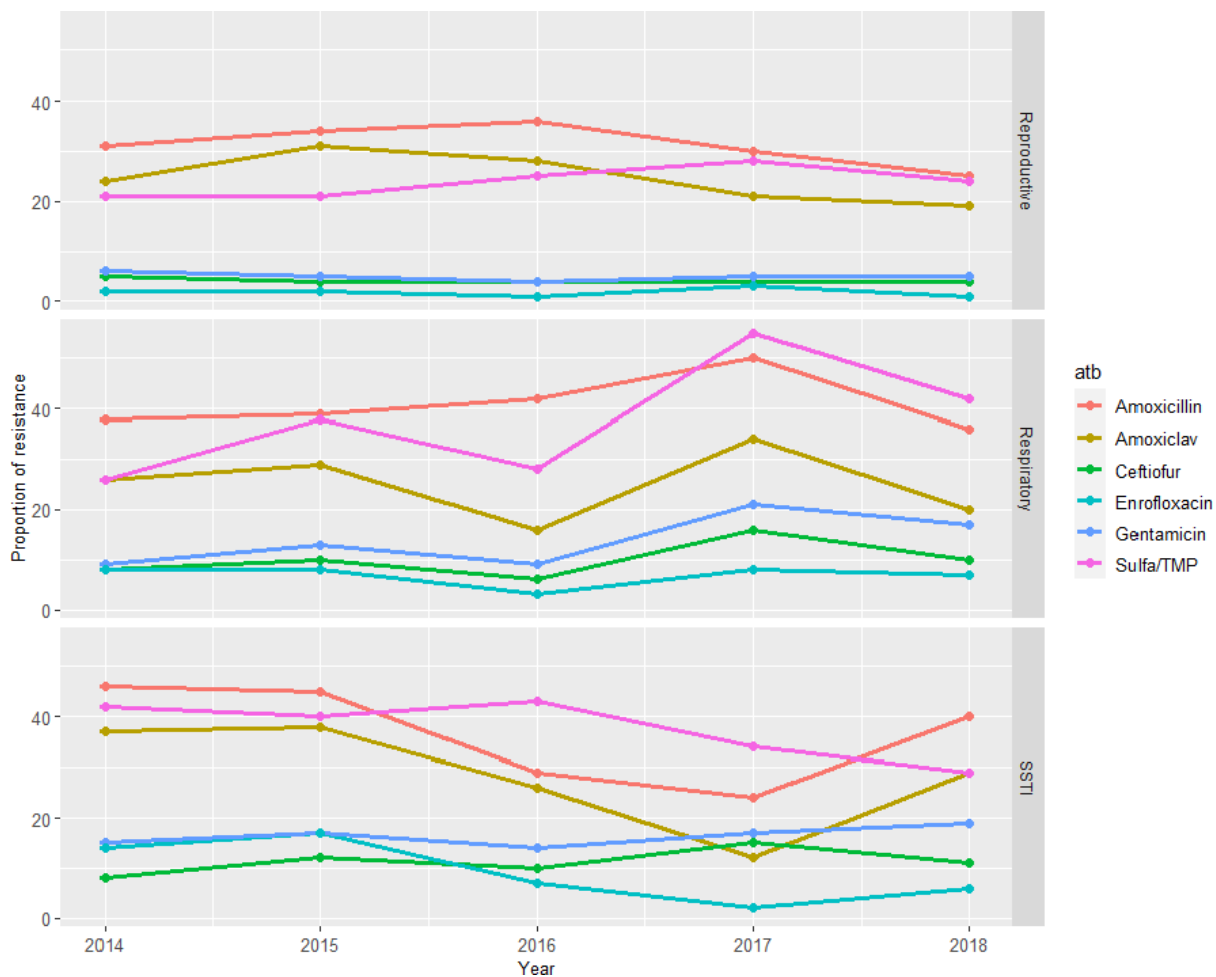
Figure 21: Proportion (%) of clinical equine *E. coli* isolates retrieved from reproductive, respiratory and skin and soft tissue infection (SSTI) samples resistant to six antimicrobials (atb) of interest reported by the RESAPATH monitoring programme

If the results from only reproductive isolates are considered, the levels of resistance to all tested antimicrobials were similar to (aminopenicillins, amoxicillin-clavulanic acid) or lower than (3GCs, aminoglycosides, fluoroquinolones, sulfonamide-trimethoprim) the weighted arithmetic means estimated based on all *E. coli* European studies (Table 3), although resistance levels from *E. coli* cultured from other samples were in the higher ranges, highlighting the variation found even within this specific dataset.

Regarding *S. aureus* AMR data, the number of isolates tested for resistance to one of the antimicrobials of interest in this opinion included in the report (gentamicin, enrofloxacin, oxacillin-cefoxitin, sulfonamide-trimethoprim and tetracycline) ranged between 72 and 107. Levels of resistance were higher (> 10%) for cefoxitin, gentamicin and tetracycline than for enrofloxacin and sulfonamide-trimethoprim (< 7%), with oxacillin resistance ranging between the two groups (Figure 22). Although the proportion of resistant isolates varied depending on the year (particularly for oxacillin), no clear trend was observed, particularly when considering the last 3–4 years.
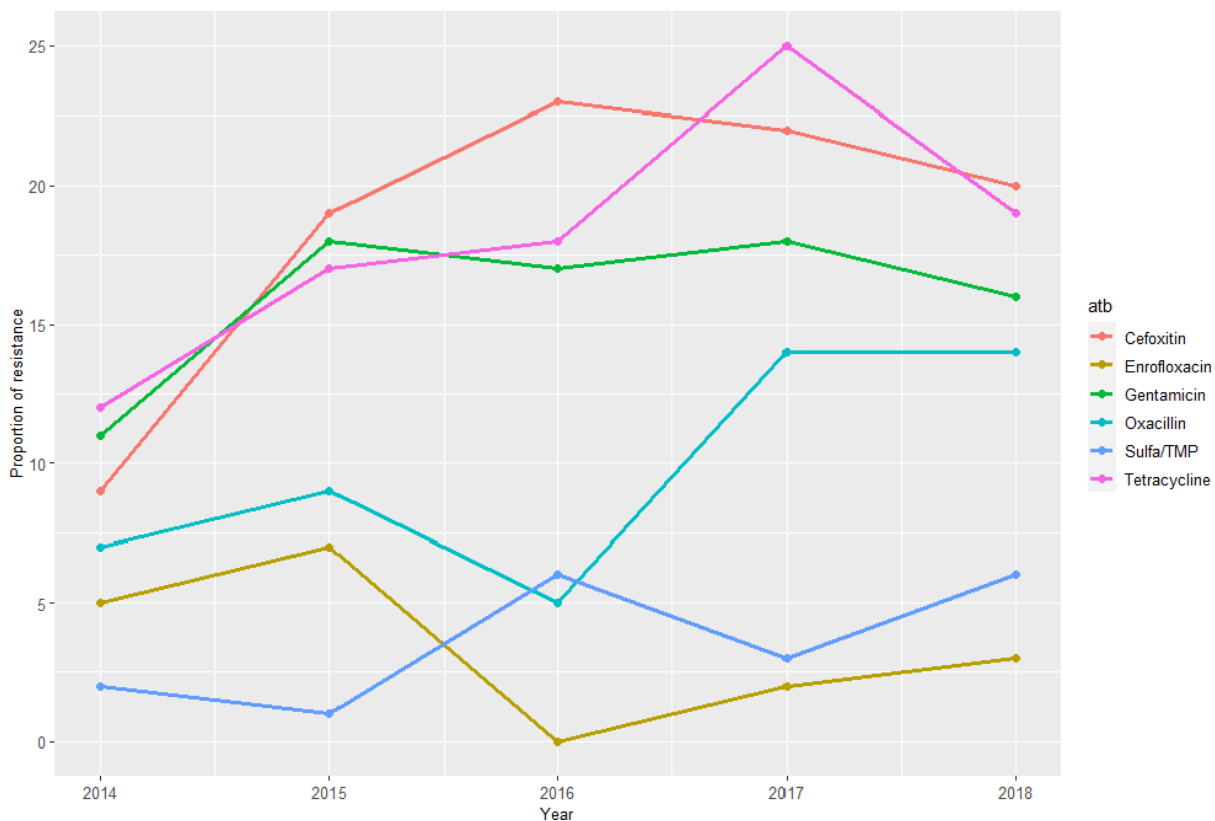
Figure 22: Proportion (%) of clinical equine *S. aureus* isolates retrieved from skin and soft tissue infections resistant to six antimicrobials (atb) of interest reported by the RESAPATH monitoring programme

The resistance levels found in the French *S. aureus* collection were similar to the weighted arithmetic means calculated considering all European *S. aureus* isolates, except for cefoxitin (and to a lesser extent oxacillin) when used as a surrogate for MR, which was closer to the maximum value (27.1%) found for any study than to the mean (7.3%), although a modest decrease in resistance levels was seen for the last two years (Table 4).

AMR data on between 391 and 617 *S. zooepidemicus* and other Group C streptococci retrieved from reproductive samples and tested for resistance to gentamicin, enrofloxacin, sulfonamide-trimethoprim and tetracycline were included in the 2015–2019 reports. In addition, 77 and 72 isolates were also tested for resistance to ampicillin in 2014 and 2015, respectively (no resistance detected). Resistance levels to enrofloxacin and tetracyclines were remarkably high (> 60%), particularly in the case of the fluoroquinolone (Figure 23). In contrast, resistance to gentamicin remained at around 1% throughout the five years considered, while sulfonamide/trimethoprim resistance was much higher in the two most recent years (> 30%) compared with the previous three (≤ 10%). When results from RESAPATH are compared with data presented in Table 4 for the streptococci species of interest in this opinion, resistance levels reported by RESAPATH are consistently higher for fluoroquinolones (when considering the weighted arithmetic means from European studies or those from other regions of the world) and to a lower extent for tetracycline, while resistance was below values reported for aminoglycosides in any study (but closer to the lower values reported for studies on *Streptococcus* resistance in North America, which ranged between 3.9% and 14%) (Table 4). Levels of resistance to sulfonamide-trimethoprim reported in the later years were also closer to the weighted arithmetic mean obtained for this antimicrobial in other European studies (Table 4).
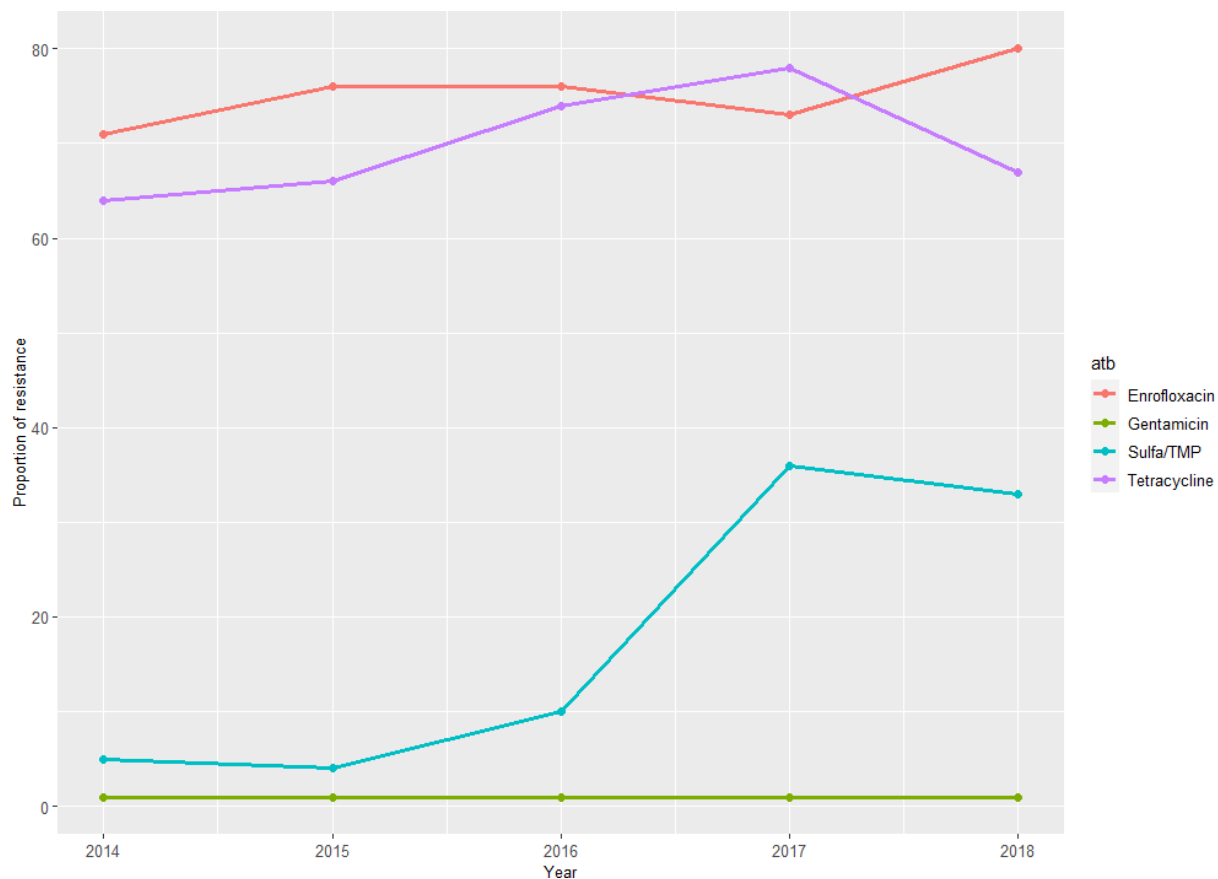
Figure 23: Proportion (%) of clinical equine *S. zooepidemicus* isolates retrieved from reproductive samples resistant to four antimicrobials (atb) of interest reported by the RESAPATH monitoring programme

Finally, the RESAPATH reports also include resistance data from *Klebsiella* spp. isolates retrieved from different pathologies which were tested for resistance using antimicrobials of interest for this opinion. Between 103 and 169 isolates were tested each year with ceftiofur (in 2014 cefotaxime and ceftazidime was also used for 41 isolates, yielding 0% and 2% of resistant isolates, respectively), gentamicin, amoxicillin-clavulanic acid, enrofloxacin and sulfonamide-trimethoprim. Although levels of resistance varied depending on the antimicrobial (sulfonamide-trimethoprim > amoxicillin-clavulanic > gentamicin > ceftiofur > enrofloxacin), a very similar pattern was found for all antimicrobials, with an increase in the proportion of resistant isolates (with a very similar slope) in 2014–2017 that was followed by a decrease in 2018 (Figure 24). The proportion of resistant isolates in 2018 was similar to (or only slightly above) the weighted arithmetic means for European studies presented in Table 6 for all antimicrobials, but values recorded in 2017 were considerably higher (being close to or above the maximum levels of resistance reported in Table 6). This variability over time in the resistance levels for this bacteria highlights the difficulties of assessing the representativeness of the results in the absence of additional information on the tested strains, since these changes could reflect variation in the bacterial population being tested (e.g. different relative proportions of isolates from different sites). Nevertheless, the proportion of *Klebsiella* strains originating from different pathologies included in the test experienced only relatively minor changes (e.g. from 46% of reproductive isolates among all *Klebsiella* strains tested in 2017 to 56% in 2018) and the main origins remained similar (reproductive > respiratory > SSTI ~unspecified), and thus the source and representativeness of these variations in resistance levels cannot be fully assessed in the absence of additional information.
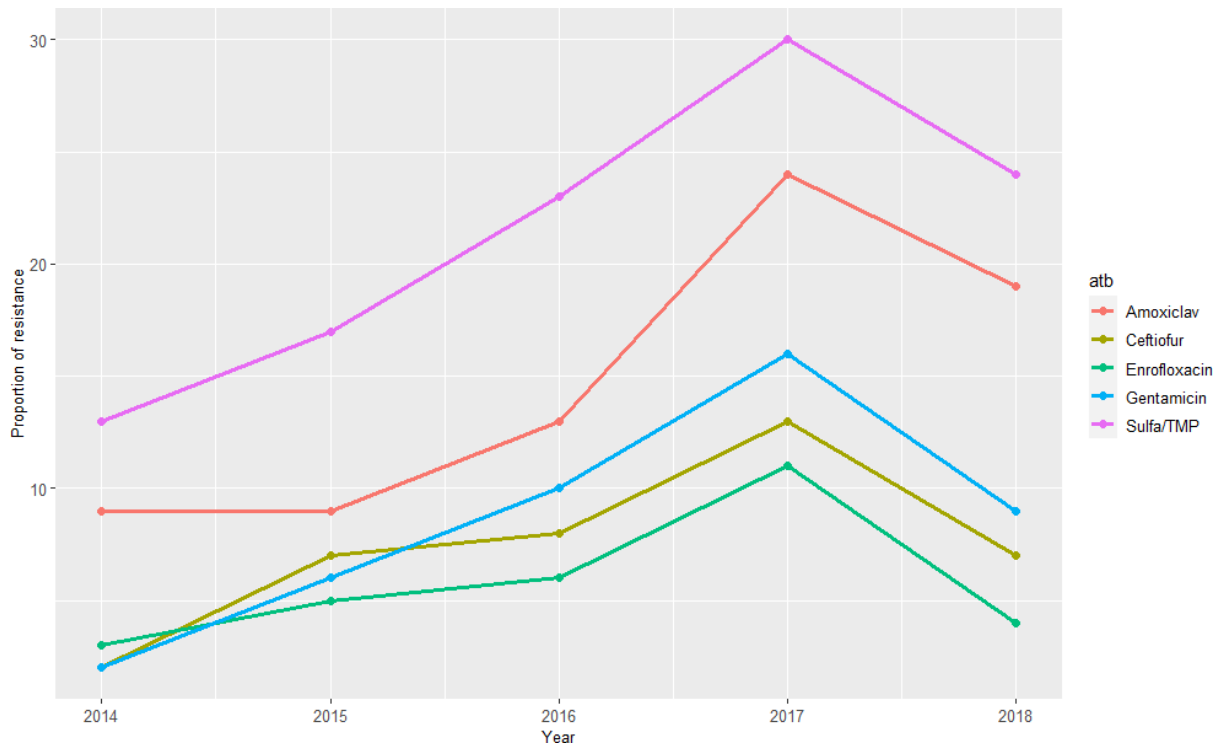
Figure 24: Proportion (%) of clinical equine *Klebsiella* spp. isolates retrieved from all pathologies resistant to five antimicrobials (atb) of interest reported by the RESAPATH monitoring programme

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 followed 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 in order to provide an individual judgement on the perceived relevance of each of the bacteria included in the list for horses.

After discussion of individual judgements on whether each bacterial species was among the most relevant antimicrobial-resistant bacteria in the EU for horses (and the certainty of the judgement), it was agreed with > 66% certainty that the most relevant resistant bacteria for the EU were *E. coli*, *S. aureus* and *R. equi* (Figure 25). This is due to their frequent implication in clinical disease in horses and the emergence of resistance to all clinically relevant antimicrobials both globally and in the EU. For the first two species, multidrug-resistant strains displaying resistance to beta-lactam antibiotics (i.e. MRSA and ESBL-producing *E. coli*) and often co-resistance to alternative antimicrobial classes have globally emerged in the horse population over the last decade. The importance of these two bacterial species as horse pathogens is further emphasised by the high number of studies (Table 2) and AST results for the antimicrobials of interest retrieved through this ELR (~ 13,000 for *E. coli*, ~ 6,500 for *S. aureus*) and, and by their inclusion in all (*E. coli*) and two (*S. aureus*) of the three national monitoring programmes reporting data on AMR from equine clinical isolates (Table 9). *Rhodococcus equi* was also included among the most relevant resistant bacteria for the EU due to the ubiquitous occurrence of this horse pathogen in Europe, the severity of infections, and the alarming levels of resistance to the only therapeutic option available for treatment of the disease caused by this pathogen (which includes an antimicrobial in the A category of the AMEG classification, rifampicin, combined with a macrolide) found in the ELR for North America. Previous studies have suggested an increase in the frequency of this resistance in the last 20 years at least in the USA (probably due to the extended treatment of subclinical infections) (Giguere et al., 2017), including the emergence of horizontally transferrable resistance to macrolides and the increasing isolation of strains resistant to both macrolides and rifampicin. The low number of studies retrieved by the ELR for this pathogen is probably attributable to the difficulty of collecting clinical specimens due to the acute progression of

the disease and the invasiveness of the procedure required for the collection of specimens from the lower respiratory tract and the abdominal cavity of infected foals. This has resulted in very limited information on the frequency of AMR in this important equine pathogen.

Even though high levels of resistance were also described in some studies for *Pseudomonas* spp. and *Klebsiella* spp., the more limited evidence, in terms of number of studies and amount of AST data, resulted in a lower certainty regarding their inclusion among the most EU-relevant AMR pathogens. Moreover, these bacterial species are often associated with endometritis in mares, which is typically managed by intrauterine infusion of antibiotic or antiseptic products that result in drug concentrations that are significantly higher than those achieved by systemic treatment and used for setting CBPs for susceptibility testing. Thus, the clinical predictive value of susceptibility testing is lower for these infections managed by local treatment. In the case of *S. zooepidemicus*, it was one of the bacterial species for which more data on frequency of AMR was retrieved and it is undoubtedly one of the most important horse pathogens. Even though some data indicated the existence of a certain degree of resistance to antimicrobials relevant for its treatment, most studies and all national monitoring programmes indicate that resistance to the first therapeutic option (penicillins) is uncommon in spite of its common use in horses, which also resulted in lower certainty regarding its EU relevance.

Fewer data were available for the other streptococci considered in the opinion but similar trends regarding high susceptibility to penicillins was also found in the ELR, and thus they were judged less clinically important than *S. zooepidemicus*. Similarly, few or no data on AMR were retrieved for *Enterococcus* spp., *Pasteurella* spp., *D. congolensis* and *A. equuli*, which, coupled with their more limited impact as horse pathogens, suggests that in fact they are not among the EU's most relevant antimicrobial-resistant pathogens, as reflected by the low certainty in the consensus judgement for these species (Figure 19).
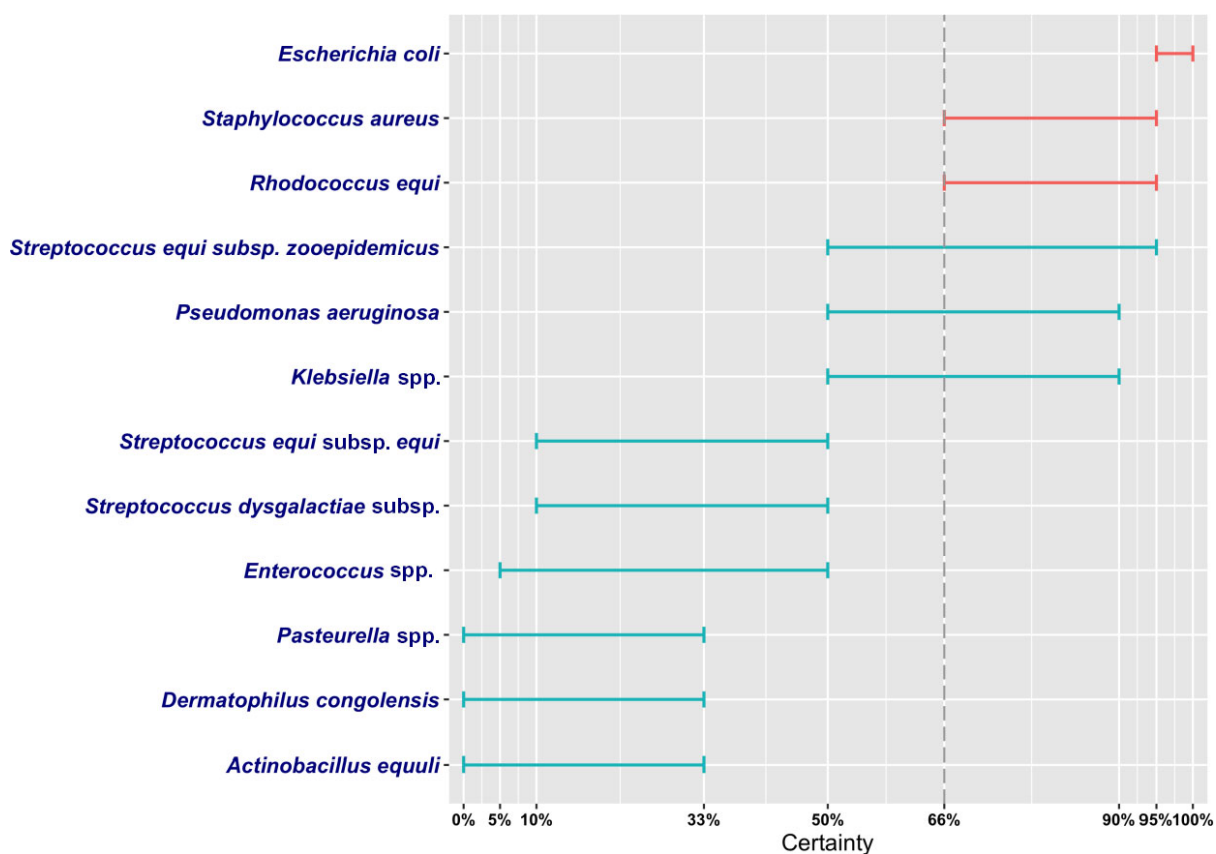

Figure 25: Level of certainty for the inclusion of the selected antimicrobial-resistant pathogens of horses among the most relevant in the EU

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 part of ToR 2 and ToR 3, namely the animal health impact of the selected species on horses in the EU, and their eligibility of being listed and categorised in the framework of the AHL, will be assessed in another EFSA report.

The scientific assessment of the global situation of the resistant bacterial pathogens of horses 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 et al. (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 (with the only exception of the GERMVET report), therefore introducing a selection bias that could lead to the absence of data from several areas of the world where these resistant pathogens may still be highly relevant.
- 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, approximately one-third of the references (9/28) included isolates collected through the regular testing of veterinary diagnostic laboratories for which typically very limited information is available. Moreover, they often originate from animals subjected to previous antimicrobial treatments, which has been demonstrated to be associated with higher levels of resistance in tested isolates, but this information is often not provided in the studies. Furthermore, several of the bacterial species included here can also be found in healthy animals (e.g. *E. coli*, *S. aureus*). Therefore, even if they originated from diseased animals, they may not have been the causative agent in a proportion of cases that cannot be quantified.
- Although only studies exceeding a minimum quality threshold were included (e.g. use of internationally accepted standards), the methodology used was also diverse (e.g. use of disk diffusion or microdilution methods, CBPs or ECOFFs, consideration or not of the intermediate category, etc.). Therefore, the descriptive statistics that are provided here (average proportion of resistant isolates for bacterium, country and antimicrobial) should be considered carefully, as they may not be representative of the true underlying situation, particularly in cases where the sample size was small.
- AMR data referring to one or more of the bacterial pathogens of interest were retrieved from three national AMR monitoring reports. However, comparison of data reported in the different countries is difficult due to differences in: (a) the bacterial species considered; (b) the geographical and temporal coverage of each report; (c) the choice of antimicrobials included in the panel for AST; (d) the methods for antimicrobial susceptibility determination (disk diffusion vs. broth microdilution, CBPs vs. ECOFFs); and (e) the limited sample sizes achieved and the potential biases associated with the process by which the panels of isolates were built.

EFSA has summarised the global state of play on antimicrobial resistance for the following bacteria: *A. equuli*, *D. congolensis*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella* spp., *Pasteurella* spp., *Pseudomonas* spp., *Rhodococcus equi*, *Staphylococcus aureus*, *Streptococcus dysgalactiae* subsp. *dysgalactiae/equisimilis*, *Streptococcus equi* subsp. *equi* and *S. equi* subsp. *zooepidemicus*.

Among those bacteria, based on the evidence available and expert opinion, EFSA identified *E. coli*, *S. aureus* and *R. equi* as the most relevant antimicrobial-resistant horse pathogens in the EU with > 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.   Recommendation

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 wide ranges of AMR levels observed in pathogenic bacteria isolated from horses in the same region or country highlight the difficulties in obtaining reliable estimates from scientific publications, which are often based on susceptibility testing of specific (and often biased) strain collections. National monitoring systems for AMR in diseased horses are only available in a few countries and there are limitations that hamper the comparability of data reported by different countries (Mader et al., 2021). Moreover, the few available national reports have limited geographical scope when considering the global situation, particularly outside Europe. Because of the very limited sample sizes it is difficult to extract definitive conclusions in terms of AMR levels in horse populations based on the EU national reports assessed in this opinion, although stable AMR trends were found for most pathogen–drug 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 can be helpful to detect the emergence of new antimicrobial-resistant phenotypes of clinical importance in pathogens of horses, and thus help to guide antimicrobial stewardship. This may be particularly relevant for the case of *R. equi*, for which high levels of resistance have been described to the only therapeutic options available in the USA, and *S. zooepidemicus*, to ensure that clinical isolates remain susceptible to penicillins.

In the future, standardisation and harmonisation of the methodology used by national surveillance programmes, including selection criteria for collecting bacterial isolates and performance of AST would allow more meaningful comparisons between countries. Alternatively, access to raw AST data generated by such programmes could enable analysis of data from different countries using the same interpretive criteria (CBPs or ECOFFs) and facilitating identification of geographical differences in the distribution of specific antimicrobial-resistant phenotypes of clinical relevance.

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Abbreviations

3GC	third-generation cephalosporin
AHL	animal health law
AST	antimicrobial susceptibility testing
CLSI	Clinical and Laboratory Standards Institute
ECOFF	epidemiological cut-off
ELR	extensive literature review
ESBL	extended-spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
I	intermediate
MIC	minimum inhibitory concentration

MR	methicillin resistance
MRSA	methicillin-resistant *Staphylococcus aureus*
PCR	polymerase chain reaction
R	resistant
S	susceptible

Appendix A – Search strings applied

A.1. Pubmed

a) 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])

A.1.1. Host-based strings

"Horse"[Title/Abstract] OR "Horses"[Title/Abstract] OR "Equine"[Title/Abstract] OR "Horses"[MeSH Terms]

A.1.2. "Bacterial species"

"Actinobacillus equuli"[MeSH Terms] OR "Actinomyces"[MeSH Terms] OR "Bacteroides"[MeSH Terms] OR "Clostridium septicum"[MeSH Terms] OR "Clostridium chauvoei"[MeSH Terms] OR "Clostridium novyi"[Supplementary Concept] OR "Erysipelatoclostridium ramosum"[Supplementary Concept] OR "Clostridium sporogenes"[Supplementary Concept] OR "Enterococcus"[MeSH Terms] OR "Fusobacterium necrophorum"[MeSH Terms] OR "Neorickettsia risticii"[MeSH Terms] OR "Pasteurella"[MeSH Terms] OR "Staphylococcus intermedius"[MeSH Terms] OR "Staphylococcus pseudintermedius"[Supplementary Concept] OR "Staphylococcus delphini"[Supplementary Concept] OR "Streptococcus dysgalactiae subsp dysgalactiae"[Supplementary Concept] OR "Streptococcus dysgalactiae subsp equisimilis"[Supplementary Concept] OR "Taylorella equigenitalis"[MeSH Terms] OR "Clostridium piliforme"[Supplementary Concept] OR "Dermatophilus congolensis"[Supplementary Concept] OR "Escherichia coli"[MeSH Terms] OR "Klebsiella pneumoniae"[MeSH Terms] OR "Staphylococcus aureus"[MeSH Terms] OR "Anaplasma phagocytophilum"[MeSH Terms] OR "Bartonella henselae"[MeSH Terms] OR "Borrelia burgdorferi"[MeSH Terms] OR "Clostridium perfringens"[MeSH Terms] OR "Clostridium tetani"[MeSH Terms] OR "Lawsonia Bacteria"[MeSH Terms] OR "Pseudomonas aeruginosa"[MeSH Terms] OR "Rhodococcus equi"[MeSH Terms] OR "Burkholderia pseudomallei"[MeSH Terms] OR "Actinobacillus equuli"[Title/Abstract] OR "Actinomyces"[Title/Abstract] OR "Bacteroides"[Title/Abstract] OR "Clostridium septicum"[Title/Abstract] OR "Clostridium chauvoei"[Title/Abstract] OR "Clostridium novyi"[Title/Abstract] OR "clostridium ramosum"[Title/Abstract] OR "Clostridium sporogenes"[Title/Abstract] OR "Clostridium fallax"[Title/Abstract] OR "Enterococcus"[Title/Abstract] OR "Fusobacterium necrophorum"[Title/Abstract] OR "Neorickettsia risticii"[Title/Abstract] OR "Pasteurella"[Title/Abstract] OR "Staphylococcus intermedius"[Title/Abstract] OR "Staphylococcus pseudintermedius"[Title/Abstract] OR "Staphylococcus delphini"[Title/Abstract] OR "Streptococcus dysgalactiae subsp dysgalactiae"[Title/Abstract] OR "Streptococcus dysgalactiae subsp equisimilis"[Title/Abstract] OR "Taylorella equigenitalis"[Title/Abstract] OR "Actinobacillus lignieresii"[Title/Abstract] OR "Clostridium piliforme"[Title/Abstract] OR "Dermatophilus congolensis"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR "Klebsiella pneumoniae"[Title/Abstract] OR "Staphylococcus aureus"[Title/Abstract] OR "Anaplasma phagocytophilum"[Title/Abstract] OR "Bartonella henselae"[Title/Abstract] OR "Borrelia burgdorferi"[Title/Abstract] OR "Clostridium difficile"[Title/Abstract] OR "Clostridium perfringens"[Title/Abstract] OR "Clostridium tetani"[Title/Abstract] OR "Lawsonia intracellularis"[Title/Abstract] OR "Pseudomonas aeruginosa"[Title/Abstract] OR "Rhodococcus equi"[Title/Abstract] OR "Burkholderia pseudomallei"[Title/Abstract]

"Enterobacter"[MeSH Terms] OR "Staphylococcus aureus"[MeSH Terms] OR "Staphylococcus intermedius"[MeSH Terms] OR "Enterococcus faecalis"[MeSH Terms] OR "Enterococcus faecium"[MeSH Terms] OR "Escherichia coli"[MeSH Terms] OR "Klebsiella pneumoniae"[MeSH Terms] OR "Proteus mirabilis"[MeSH Terms] OR "Bordetella bronchiseptica"[MeSH Terms] OR "Borrelia burgdorferi"[MeSH Terms] OR "Clostridium perfringens"[MeSH Terms] OR "Pseudomonas aeruginosa"[MeSH Terms] OR "Enterobacter"[Title/Abstract] OR "Staphylococcus pseudintermedius"[Title/Abstract] OR "Staphylococcus schleiferi"[Title/Abstract] OR "Enterococcus faecalis"[Title/Abstract] OR "Enterococcus faecium"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR "Klebsiella pneumoniae"[Title/Abstract] OR "Proteus mirabilis"[Title/Abstract] OR "Staphylococcus aureus"[Title/Abstract] OR "Bordetella

bronchiseptica"[Title/Abstract] OR "Borrelia burgdorferi"[Title/Abstract] OR "Clostridium difficile"[Title/Abstract] OR "Clostridium perfringens"[Title/Abstract] OR "Pseudomonas aeruginosa"[Title/Abstract]

A.2. Embase

b) 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

A.2.1. Host-based strings

1) equus/
2) horse/or exp colt/or exp foal/or exp mare/or exp stallion/
3) stud/
4) (Horse or horses or equine).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]
5) 1 or 2 or 3 or 4

A.2.1.1. "Bacterial species"

1) ("Actinobacillus equuli" or "Actinomyces" or "Bacteroides" or "Clostridium septicum" or "clostridium chauvoei" or "clostridium novyi" or "clostridium ramosum" or "Clostridium sporogenes" or "Clostridium fallax" or Enterococcus or "Fusobacterium necrophorum" or "Neorickettsia risticii" or Pasteurella or "Staphylococcus intermedius" or "Staphylococcus pseudintermedius" or "Staphylococcus delphini" or "Streptococcus dysgalactiae subsp dysgalactiae" or "Streptococcus dysgalactiae subsp equisimilis" or "Taylorella equigenitalis" or "Actinobacillus lignieresii" or "Clostridium piliforme" or "Dermatophilus congolensis" or "Escherichia coli" or "Klebsiella pneumoniae" or "Staphylococcus aureus" or "Anaplasma phagocytophilum" or "Bartonella henselae" or "Borrelia burgdorferi" or "Clostridium difficile" or "Clostridium perfringens" or "Clostridium tetani" or "Lawsonia intracellularis" or "Pseudomonas aeruginosa" or "Rhodococcus equi" or "Burkholderia pseudomallei").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]
2) Actinobacillus equuli/
3) Clostridium septicum/

4) Clostridium chauvoei/
5) Clostridium novyi/
6) Erysipelatoclostridium ramosum/
7) Clostridium sporogenes/
8) Fusobacterium necrophorum/
9) exp enterococcus/
10) exp Neorickettsia risticii/
11) exp Actinomyces/
12) exp Bacteroides/
13) exp Pasteurella/
14) Staphylococcus intermedius/
15) Staphylococcus pseudintermedius/
16) "Streptococcus dysgalactiae subsp. equisimilis"/
17) Taylorella equigenitalis/
18) Actinobacillus lignieresii/
19) Dermatophilus congolensis/
20) Escherichia coli/
21) Klebsiella pneumoniae/
22) Staphylococcus aureus/
23) Anaplasma phagocytophilum/
24) Bartonella henselae/
25) Borrelia burgdorferi/
26) Clostridioides difficile/
27) Clostridium perfringens/
28) Clostridium tetani/
29) Desulfovibrionaceae infection/
30) Pseudomonas aeruginosa/
31) Rhodococcus hoagii/
32) Burkholderia pseudomallei/
33) 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 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34) 1 or 33

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.5055403.

Appendix C – Clinically relevant antibiotics for which data were extracted)

Bacterial species/group	Common infections	Relevant resistance tested
Staphylococcus aureus	Skin and soft tissue infections	Methicillin Sulfa/TMP Tetracyclines Enrofloxacin/ciprofloxacin Fusidic acid Gentamicin
ENTEROBACTERALES *Escherichia coli* *Klebsiella pneumoniae*	Urinary tract infections Endometritis Bacteraemia	Ampicillin/amoxicillin Amoxicillin clav Sulfa/TMP Enrofloxacin/ciprofloxacin Gentamicin 3rd gen cephalosporins (Cefpodoxime, cefotaxime, ceftazidime, ceftriaxone or ceftiofur)
Pasteurella spp.	Respiratory infections	Penicillin Aminopenicillins Gentamicin Sulfa/TMP Enrofloxacin/ciprofloxacin 3rd gen cephalosporins (Cefpodoxime, cefotaxime, ceftazidime, ceftriaxone or ceftiofur) Tetracyclines
Pseudomonas spp.	Skin and soft tissue infections Endometritis	Enrofloxacin/ciprofloxacin Gentamicin Polymyxin/colistin
ENTEROCOCCI *E. faecalis* *E. faecium*	Various	Ampicillin/amoxicillin Sulfa/TMP Enrofloxacin/ciprofloxacin Gentamicin
Rhodococcus equi	Foal pneumonia	Erythromycin Rifampicin
Streptococcus equi, *S. zooepidemicus* and *S. equisimilis*	Various, e.g. endometritis, upper airway infections, abscesses, etc.	Ampicillin/amoxicillin Ceftiofur Tetracyclines Enrofloxacin/ciprofloxacin Gentamicin Penicillin Sulfa/TMP

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

Antibiotic	How resistance is reported (%R or %R + I)	Weighted arithmetic mean prevalence of resistance (%)	Bacterial species/genus
Aminoglycosides	R + I	22.81	*Pseudomonas* spp.
Fluoroquinolones	R + I	40.30	*Pseudomonas* spp.
Aminoglycosides	R + I	20.15	*S. aureus*
Fluoroquinolones	R + I	3.74	*S. aureus*
Methicillin	R	8.73	*S. aureus*
Sulfa/TMP	R	6.95	*S. aureus*
Tetracyclines	R	27.68	*S. aureus*
3GC	R	9.48	*E. coli*
3GC	R + I	8.96	*E. coli*
Aminoglycosides	R + I	13.74	*E. coli*
Aminopenicillins	R	29.97	*E. coli*
Aminopenicillins	R + I	35.78	*E. coli*
Amox/Clav	R + I	24.56	*E. coli*
Fluoroquinolones	R + I	7.36	*E. coli*
Sulfa/TMP	R	34.66	*E. coli*
3GC	R + I	11.55	*Klebsiella* spp.
Aminoglycosides	R + I	15.87	*Klebsiella* spp.
Amox/Clav	R + I	19.05	*Klebsiella* spp.
Fluoroquinolones	R + I	6.58	*Klebsiella* spp.
Sulfa/TMP	R	27.79	*Klebsiella* spp.
Sulfa/TMP	R	11.52	*Pasteurella* spp.
Erythromycin	R	18.19	*R. equi*
Erythromycin	R + I	11.56	*R. equi*
Rifampicin	R	23.51	*R. equi*
Rifampicin	R + I	10.49	*R. equi*
Sulfa/TMP	R	4.94	*S. equisimilis*
Aminoglycosides	R	7.54	*S. equi* subsp. *zooepidemicus*
Aminoglycosides	R + I	47.15	*S. equi* subsp. *zooepidemicus*
Aminopenicillins	R + I	6.41	*S. equi* subsp. *zooepidemicus*
Ceftiofur	R + I	9.23	*S. equi* subsp. *zooepidemicus*
Fluoroquinolones	R + I	37.98	*S. equi* subsp. *zooepidemicus*
Penicillin	R	0.25	*S. equi* subsp. *zooepidemicus*
Penicillin	R + I	7.24	*S. equi* subsp. *zooepidemicus*
Sulfa/TMP	R	48.50	*S. equi* subsp. *zooepidemicus*
Tetracyclines	R	31.75	*S. equi* subsp. *zooepidemicus*
Tetracyclines	R + I	40.81	*S. equi* subsp. *zooepidemicus*
Ceftiofur	R + I	0	*S. equi* subsp. *equi*
Penicillin	R + I	0	*S. equi* subsp. *equi*
Sulfa/TMP	R	32.99	*S. equi* subsp. *equi*
Tetracyclines	R + I	3.15	*S. equi* subsp. *equi*