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Assessment of animal diseases caused by bacteria resistant to antimicrobials: sheep and goats

EFSA Panel on Animal Health and Welfare (AHAW),
Søren Saxmose Nielsen, Dominique Joseph Bicout, Paolo Calistri, Elisabetta Canali, Julian Ashley Drewe, Bruno Garin-Bastuji, Jose Luis Gonzales Rojas, Christian Gortazar Schmidt, Mette Herskin, Virginie Michel, Miguel Angel Miranda Chueca, Barbara Padalino, Paolo Pasquali, Helen Clare Roberts, Hans Spoolder, Karl Stahl, Antonio Velarde, Arvo Viltrop, Christoph Winckler, Jeroen Dewulf, Luca Guardabassi, Friederike Hilbert, Rodolphe Mader, Francesca Baldinelli and Julio Alvarez

Abstract

In this opinion, the antimicrobial-resistant bacteria responsible for transmissible diseases that constitute a threat to the health of sheep and goats have been assessed. The assessment has been performed following a methodology based on information collected by an extensive literature review and expert judgement. Details of the methodology used for this assessment are explained in a separate opinion. A global state of play on antimicrobial resistance in clinical isolates of *Staphylococcus aureus*, *Escherichia coli* (non-VTEC), *Pseudomonas aeruginosa*, *Dichelobacter nodosus*, *Moraxella ovis*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma ovipneumoniae*, *Mycoplasma agalactiae*, *Trueperella pyogenes*, *Streptococcus uberis*, *Bibersteinia trehalosi*, *Campylobacter fetus*, *Mycoplasma mycoides* subsp. *capri*, *Mycoplasma capricolum* subsp. *capricolum*, *Fusobacterium necrophorum* is provided. Among those bacteria, EFSA identified *E. coli* with $\geq$ 66% certainty as being the most relevant antimicrobial-resistant bacteria in sheep and goat in the EU based on the available evidence. The animal health impact of these most relevant bacteria, as well as their eligibility for being listed and categorised within the animal health law framework will be assessed in separate scientific opinions.

Keywords: antimicrobial resistance, animal health law, extensive literature review, small ruminants, sheep, goats

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Correspondence: alpha@efsa.europa.eu

Panel members: Søren Saxmose Nielsen, Julio Alvarez, Dominique Joseph Bicout, Paolo Calistri, Elisabetta Canali, Julian Ashley Drewe, Bruno Garin-Bastuji, Jose Luis Gonzales Rojas, Christian Gortazar Schmidt, Mette Herskin, Virginie Michel, Miguel Angel Miranda Chueca, Barbara Padalino, Paolo Pasquali, Helen Clare Roberts, Hans Spoolder, Karl Stahl, Antonio Velarde, Arvo Viltrop and Christoph Winckler.

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1. Introduction

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 existing 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, Appendix D according to Articles 8 and 9 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 sheep and goats 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 sheep and goats.

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 bacteria for sheep and goats had been agreed upon by the EFSA working group: *Staphylococcus aureus, Escherichia coli* (non-VTEC), *Pseudomonas aeruginosa*, *Dichelobacter nodosus*, *Moraxella ovis*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma ovipneumoniae*, *Mycoplasma agalactiae*, *Trueperella pyogenes*, *Streptococcus uberis*, *Bibersteinia trehalosi*, *Campylobacter fetus*, *Mycoplasma mycoides* subsp. *capri*, *Mycoplasma capricolum* subsp. *capricolum*, *Fusobacterium necrophorum*. The extensive literature review was carried out by the University of Copenhagen under the contract OC/EFSA/ALPHA/2020/02 – LOT 1.[2] On 3 May 2021, two different search strings (Appendix A) were applied in PubMed and Embase, respectively, resulting in a total of 727 unique abstracts published since 2010. Upon import into the Rayyan software, these abstracts were screened by a senior scientist, following the criteria described in the protocol for inclusion and exclusion of studies. When available, the full text of abstracts was downloaded into the Endnote software. In addition, the national antimicrobial resistance (AMR) monitoring reports from France (RESAPATH) and United Kingdom (UK-VARSS) were downloaded and used in the ELR.

Only the latest version of these monitoring reports was included in the ELR as it was assumed that isolates described in these reports originate from the same sampled populations, and therefore, only the most recent version would include the most up-to-date AMR data. The previous versions (last 5 years) of the national AMR monitoring reports were not included in the ELR and analysed separately to

[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

assess changes of AMR over time when possible. AMR data in the full texts of national reports were evaluated for eligibility 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 deviations from the standard methodology:

- Exclusion criterion 8: The minimum number of isolates in a study to be considered acceptable was set at 50 for *E. coli* and *S. aureus* 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 cut-off 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* and/or *mecC* was used to infer the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA), which were considered eligible.

Year of bacterial isolation was neither extracted nor reported from the included studies, as in most studies, isolates had been collected over multiple years with no indication on the number of isolates per year. An exception to this rule was here applied when only data from a certain time period within a study were extracted (in the case of national reports reporting multiple years, when only the last data points were considered).

Information extracted from the eligible assessed full-text reports/publications is described in the scientific opinion on the ad hoc method applied in the assessment (EFSA AHAW Panel, 2021). Information on all the full-text studies that were assessed, including the reason for exclusion for those that were excluded at the full-text screening, is presented in Appendix B. AMR was assessed for clinically relevant antibiotics according to the method detailed in Section 2.1.3 of the ad hoc method for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL (EFSA AHAW Panel, 2021). The list of clinically relevant antibiotics for each target bacterial species in sheep and goats considered in this opinion 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 staphylococci, data for oxacillin, cefoxitin and added presence of the *mecA* and *mecC* 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 was *mecA* + *mecC* > cefoxitin > oxacillin.
- For third-generation cephalosporin (3GC) in Enterobacterales (as 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 the presence of ESBL/AmpC, typically data from a double disc synergy test (EUCAST, 2017).
- For fluoroquinolone, the order of preference was enrofloxacin > ciprofloxacin, meaning we always selected enrofloxacin if resistance data for both drugs were available.
- For tetracycline, the order of preference was tetracycline > oxytetracycline > doxycycline > chlortetracycline; therefore, we always selected tetracycline if resistance data for all four drugs, or tetracycline + one of the other drugs, were present.

For each study, AMR data were extracted as percentages of resistant isolates (%R) and/or as percentages of non-susceptible isolates by combining resistant and intermediate (I) isolates (%R + I). Moreover, the following decisions were made when evaluating data sets:

- When no information on the I category was provided in a study, we considered that the reported %R only considered resistant isolates (i.e. I isolates had not been included in the R category).
- When proportion of susceptibility (%S) was reported with no information on I, it was not possible to calculate %R. Instead, we calculated (%R + I) as 100% – %S.

- When a study using ECOFFs reported %R, we considered this as %R + I, as the I category is always part of the non-wild-type population.
- When %I was reported separately, we extracted that along with %R and calculated %R + I.
- For some drugs and the presence of *mecA*/*mecC*, there is no I category for the bacterial species included; therefore for those we could only report %R, irrespective of the assumptions mentioned above.

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

3.1.1.1. Data from the extensive literature review

After screening the 727 abstracts, 50 publications were selected for evaluation according to the criteria listed under methods. Of these 50 publications, 38 were excluded with the reasons for exclusion highlighted in columns D and E of Appendix B. The reasons for exclusion of isolates are listed in Table 1. The most common reasons for exclusion were that: only MIC data were reported without interpretation on susceptibility/resistance of isolates (n = 9); fewer than the specified minimum number of isolates were included in the study (n = 8); and that data from isolates coming from species other than sheep and goats were reported together with isolates from sheep and goats (n = 6).

Table 1: Reasons for exclusion of publications after full-text evaluation affecting more than one publication (a publication could be excluded for more than one reason)[(a)]

Reason	Code in Appendix B	Number of publications
Minimum inhibitory concentration data reported without interpretation	12	9
Fewer than the minimum number of isolates are included in the study	8	8
AMR data from multiple host species (other than sheep and goat) reported together	2	6
Inclusion of non-clinical isolates that cannot be distinguished from clinical isolates	5	3
Study does not follow a standard for antimicrobial susceptibility testing or a standard is not reported	4	2
Percentage of resistant isolates not reported	7	2
Criteria for selection of isolates unclear and/or high risk of data duplication	14	2

(a): The other eight reasons for exclusion affecting one study each are not reported in this table and are listed in Appendix B.

After exclusion of these references, 12 eligible publications with information on clinical isolates were selected for data extraction. In addition, two national reports representing France and the UK were selected, as they contained eligible AMR data on clinical isolates from sheep and goats according to the same set of eligibility criteria mentioned above. This gave, in total 14 eligible publications that were taken forward to the data extraction stage.

An overview of the number of eligible publications for each target bacterium is shown in Table 2. Eligible publications were only retrieved for five of the 16 pathogens considered in the literature review.

Table 2: Number of eligible publications from which AMR data were extracted

Bacterial species	Number of eligible publications for data extraction (n = 14)[(a)]
Escherichia coli	8
Staphylococcus aureus	4
Pasteurella multocida	4

Bacterial species	Number of eligible publications for data extraction (n = 14)[(a)]
Mannheimia haemolytica	4
Bibersteinia trehalosi	2
Streptococcus uberis	0
Dichelobacter nodosus	0
Moraxella ovis	0
Mycoplasma ovipneumoniae	0
Mycoplasma agalactiae	0
Mycoplasma mycoides subsp. *capri*	0
Mycoplasma capricolum subsp. *capricolum*	0
Fusobacterium necrophorum	0
Trueperella pyogenes	0
Campylobacter fetus	0
Pseudomonas aeruginosa	0

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

Figure 1 below provides an overview of the 14 included publications (12 articles and two national reports), some with data on multiple bacterial species, sorted by year of publication.

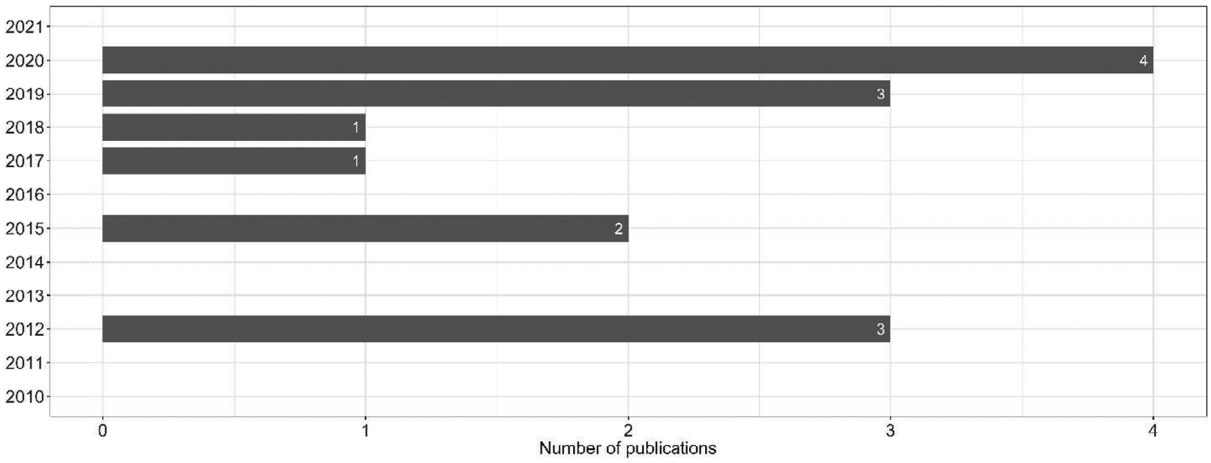


Figure 1: The number of included publications (total 14) arranged by year of publication

Considering geographical distribution, AMR data were reported in six publications from Asia (two from China, two from India and one from Pakistan and Turkey, respectively), six from Europe (two from the UK and one study from France, Greece, Italy and Spain) and two from North America (one study each from Canada and the United States) (Figure 2).

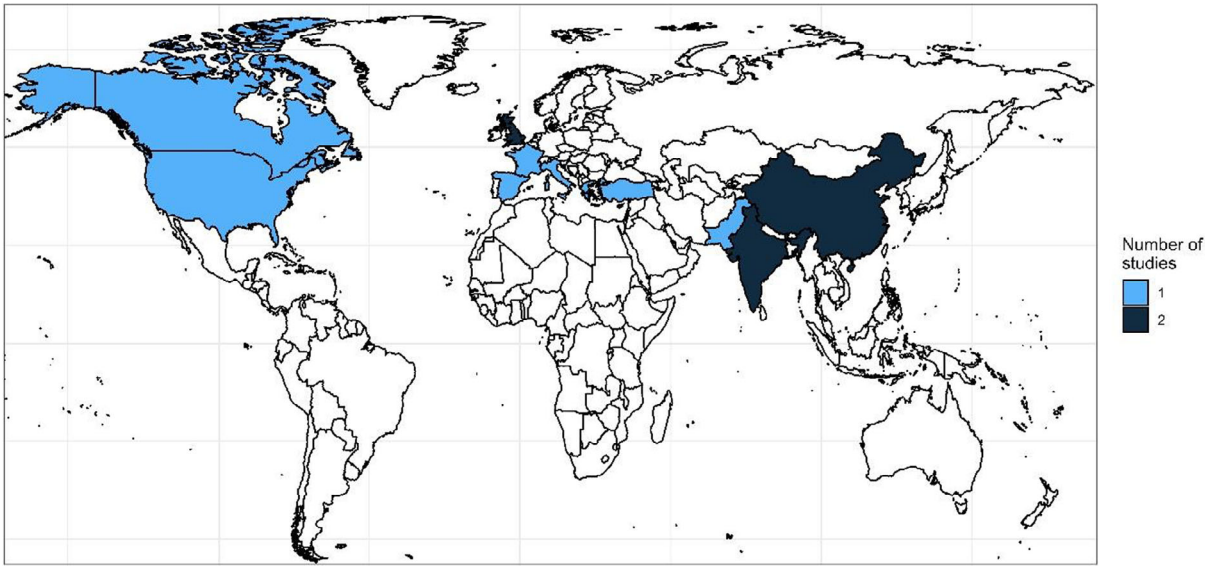


Figure 2: Geographical distribution of the 14 included publications

3.1.1.2. Data from the extensive literature review

Based on the type of isolates analysed in the study, references included were divided into those based on the assessment of isolates from: (a) a clearly defined population of sheep and/or goats in farms, hospitals or clinics; and (b) those without – or with limited – background information on animals (comprising publications with isolates from a diagnostic laboratory or obtained in slaughterhouses). Eight publications had isolates obtained from samples actively collected in farms, whereas four had isolates from diagnostic laboratories without further specification and none included isolates from samples collected at slaughterhouses. In one study, isolates had a mixed origin (farm and diagnostic laboratory), and for the last study, there was no information on sample and isolate origin, except they were from sheep and goats. Information on the application or not of previous antimicrobial treatments in the sampled populations was only reported in two publications (which only reported the absence of treatment of sampled animals in the previous 2 weeks or 5 days).

3.1.1.3. Data from national AMR surveillance reports

Additional details/data on one or more of the pathogens of interest of this opinion that are provided in previous versions of two national AMR monitoring reports retrieved (up to the previous 5 years), namely RESAPATH – France and UK-VARSS – United Kingdom, were also extracted and are presented in the following section (see Table 3). The same terminology used in the report (e.g. proportion of non-susceptible or proportion of resistant isolates) based on the selected breakpoint for defining resistance/susceptibility in each report was used to describe the results provided.

3.1.2. AMR frequency data

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

In general, AMR data from different publications were 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 14 selected references (total of 17,058, Appendix B) was largely due to the number of results found for *E. coli* (9,998, or 58.6% of the total number of AST results) and to a lower degree *S. aureus* (2,990, 17.5%) and *M. haemolytica* (2,837, 16.6%). Fewer than 1,000 AST results were available for *P. multocida* (960, 5.6%) and *B. trehalosi* (273, 1.6%). The laboratory method most commonly used to determine the AST phenotype was disc diffusion (14,720 of all AST results generated through this method, 86.3%) followed by microdilution (1,738, 10.2%), agar dilution (438 tests performed in a single study, 2.6%) and PCR (162 tests also performed in a single study, 1.0%) (Appendix B).

Furthermore, the definition of AMR differed across publications, as the intermediate (I) category defined by clinical breakpoints (CBPs) was included in the calculation of AMR frequencies in some

publications, whereas it was omitted in others. Accordingly, in the figures with resistance data, we have illustrated for each study whether %R or %R + I was reported; therefore, this should be taken into account when comparing publications. When presenting data obtained in the ELR in the text, the results are presented as proportion of resistant isolates irrespective of the cut-off used except in specific cases. It is also important to mention that no infection-specific and host-specific clinical breakpoints (CBPs) existed for pathogens in sheep and goats, even if most AST results (15,388/17,058) were interpreted according to CBPs according to the authors of the publications (Appendix B). This complicates interpretation of data, as for some publications, it was unclear if the CBPs used were adapted from other bacterial or animal species, from humans or even 'self-invented'. Taken together, the outcomes of the present report should be interpreted and cited with caution, as all specificities of individual publications cannot be taken into consideration. To support conclusions made from the figures or tables (e.g. a high proportion of resistance in a certain country/continent), it is strongly recommended that individual papers are consulted and checked in case results would be biased by previous antimicrobial treatment, sampling of animals in a certain environment, the use of certain diagnostic methods or breakpoints, or other factors.

For data included in the national AMR monitoring reports, details/data provided in previous versions of the reports from these monitoring programmes (up to the previous 5 years) were extracted and are presented at the end of each bacterium's specific section to assess the existence of changes over time in the proportion of non-susceptible/resistant isolates when possible. The pathogens included in the two reports included in this opinion were *E. coli* (with data from different pathologies reported together) and *M. haemolytica*, *P. multocida* and *B. trehalosi* from respiratory pathologies (Table 3). Assessment of changes in AMR levels over time in the pathogens under evaluation based on the data in the reports is hampered in certain cases by the lack of consistent reporting over the years (i.e. only data from specific years were reported) and/or because data on isolates retrieved over several years were presented together. Between-country comparisons must be performed carefully as different methodologies were applied to obtain the results presented in each report, number of isolates tested for certain species and countries was limited and results provided here are those presented 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 in Table 3.

Table 3: AST methodology, bacterial species, host species, number of isolates and temporal coverage on pathogens of interest from sheep and goat provided in the two national AMR monitoring reports (up to the last 5 years) reviewed in this opinion. When a monitoring programme does not include a pathogen of interest this is indicated in the table as 'No' marked in red

Programme	UK-VARSS	RESAPATH
Country	UK	France
Laboratory method	Disc diffusion	Disc diffusion
AST interpretation	CBPs[(a)]	ECOFFs[(b)]
E. coli	Yes	Yes
Origin (no. of isolates)	Lambs and adult sheep 29–179/year[(c)]	Digestive (sheep)/all pathologies (goat) 99–334/year in sheep, 117–282/year in goat
Years covered	2015–2019	2014–2018
M. haemolytica	Yes	Yes
Origin (no. of isolates)	Respiratory disease in sheep 35–90/year	Respiratory disease in sheep (76–194/year)
Years covered	2015–2019	2014–2018
P. multocida	Yes	No[d]
Origin (no. of isolates)	Respiratory disease in sheep (3–14/year)	
Years covered	2015–2019	
B. trehalosi	Yes	No
Origin (no. of isolates)	Respiratory disease in sheep (32–95/year)	

Programme	UK-VARSS	RESAPATH
Years covered	2016–2019	

(a): Human breakpoints recommended by the British Society for Antimicrobial Chemotherapy when available and a uniform cut-off point of 13 mm when not available.
(b): Veterinary guidelines of the Antibiogram Committee of the French Society of Microbiology (CA-SFM).
(c): Results are provided separately for England and Wales (60–179 isolates/year), Scotland (29–70 isolates/year) and Northern Ireland (38–80 isolates/year).
(d): Data from *Pasteurella* spp. are available.

3.1.3. *Escherichia coli*

3.1.3.1. Results of the ELR by bacterium

Escherichia coli is a commensal and an opportunistic pathogen residing in the intestinal microbiota of animals and humans. It can cause a variety of infections: certain pathogenic *E. coli* strains are associated with diarrhoea and others with septicaemia in lambs and goat kids (Constable et al., 2016). In addition, *E. coli* strains are associated with environment mastitis in sheep and goat (Gelasakis et al., 2015).

In total, eight studies with ≥ 50 *E. coli* isolates and results for one or more of the relevant antibiotics (ampicillin/amoxicillin, amoxicillin-clavulanic acid, apramycin, colistin, enrofloxacin/ciprofloxacin, gentamicin, neomycin, paromomycin, sulfonamide–trimethoprim, tetracyclines, 3GC) were included. Those studies were distributed as follows: Asia (4), Europe (3) and North America (1).

The distribution of *E. coli* isolates per site of infection is shown in Figure 3.

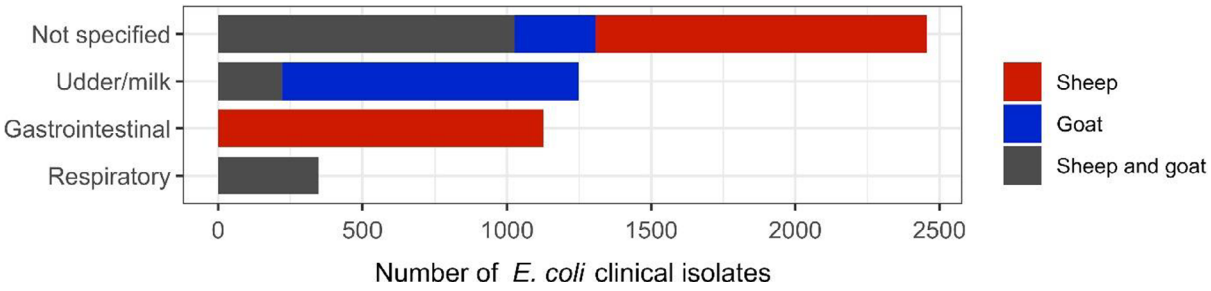


Figure 3: Distribution of *Escherichia coli* isolates per site of infection

Figure 4 shows for each country the proportion of resistance reported in individual studies with at least 50 *E. coli* isolates.

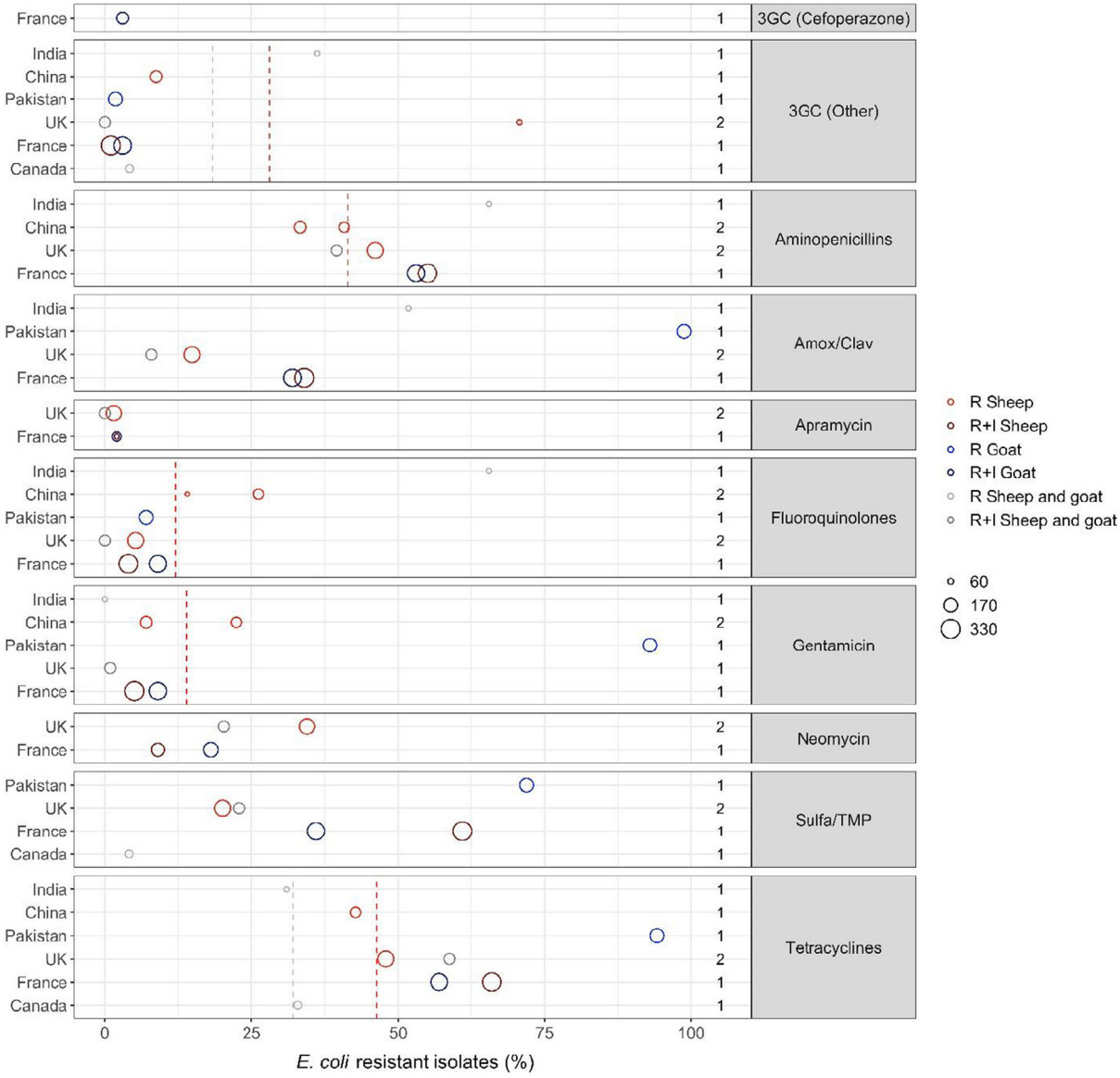


Figure 4: *Escherichia coli* resistance data for each included study sorted by continent. Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance in isolates of sheep origin (red circle), resistance merged with intermediate in isolates of sheep origin (brown circle), resistance in isolates of goat origin (light blue circle), resistance merged with intermediate in isolates of goat origin (dark blue circle), resistance in isolates of mixed origin (light grey circle) and resistance merged with intermediate in isolates of mixed origin (dark grey circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of % R or %R + I with the same colour codes as used for the circles. The exact percentages that 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

Among the beta-lactams, the proportion of resistance to **3GCs** was very high (71%) among 58 isolates from sheep in the UK (UK-VARSS, 2019). This was in contrast with another British study failing to identify 3GC resistance among 114 isolates from goats and sheep (Cheney et al., 2015). The reasons for this discrepancy can be manifold, e.g. the two studies testing different animal populations (sheep vs. sheep/goat), including isolates from different time periods (2019 vs. 2005–2007), and isolates with different origins (since the actual samples from which isolates originated are not detailed). A fairly high proportion of 3GC resistance (36%) was found in isolates from sheep and goat in India (Sonawane et al., 2019), whereas remaining studies reported < 9% resistance to this drug

class. Proportions of resistance to **aminopenicillins** varied from 33% to 74%, whereas for **amoxicillin–clavulanic acid,** the variation was even higher, ranging from 6.5% to 99%. The highest proportion was among 171 goat isolates from Pakistan (Jabbar et al., 2020).

In most studies, proportions of resistance to **fluoroquinolones** were < 15%. Two exceptions include a Chinese study on 103 sheep isolates (26%, Tuo et al. (2020)) and an Indian study on 58 isolates of mixed origin (including goat and sheep isolates) (66%, Sonawane et al. (2019)). Compared with fluoroquinolones, very similar levels of resistance were seen for **gentamicin**, and again the Chinese study by Tuo et al. (2020) was an exception to the low proportions with 22% resistance being reported. The above-mentioned study with exceptionally high resistance to amoxicillin–clavulanic acid had a similar result for gentamicin with 93% of isolates displaying resistance to this drug (Jabbar et al., 2020). Compared with gentamicin, resistance levels for the other aminoglycosides **neomycin** and **apramycin** were in the same range and slightly lower, respectively. However, this was based on only three studies for each of these drugs. For **sulfonamide–trimethoprim**, resistance levels varied considerably from 4% in 74 goat and sheep isolates from Canada (Awosile et al., 2018), to 72% among the goat isolates from Pakistan (Jabbar et al., 2020). The overall highest levels of resistance were detected for **tetracyclines**. For this drug class, the lowest reported proportion was 26% among 127 sheep isolates from China (Tang et al., 2019). As for most other drugs, the highest proportion of resistance (98%) was observed in Pakistan (Jabbar et al., 2020).

Table 4: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *Escherichia coli* for the target antimicrobials in each continent. NA means that SD could not be calculated as only one study was included

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC (Cefoperazone)	Europe	Goat	1	127	3	3	3	NA
3GC (Other)	Asia	Goat	1	171	1.8	1.8	1.8	NA
3GC (Other)	Asia	Sheep	1	127	8.7	8.7	8.7	NA
3GC (Other)	Asia	Sheep and goat	1	58	36.2	36.2	36.2	NA
3GC (Other)	Europe	Goat	1	278	3	3	3	NA
3GC (Other)	Europe	Sheep	2	390	11.4	1	70.7	24.8
3GC (Other)	Europe	Sheep and goat	1	114	0	0	0	NA
3GC (Other)	North America	Sheep and goat	1	74	4.2	4.2	4.2	NA
Aminopenicillins	Asia	Sheep	2	230	36.6	33.3	40.8	3.7
Aminopenicillins	Asia	Sheep and goat	1	58	65.5	65.5	65.5	NA
Aminopenicillins	Europe	Goat	1	280	53	53	53	NA
Aminopenicillins	Europe	Sheep	2	562	51.3	46.1	55	4.4
Aminopenicillins	Europe	Sheep and goat	1	114	39.5	39.5	39.5	NA
Amox/Clav	Asia	Goat	1	171	98.8	98.8	98.8	NA
Amox/Clav	Asia	Sheep and goat	1	58	51.7	51.7	51.7	NA
Amox/Clav	Europe	Goat	1	281	32	32	32	NA
Amox/Clav	Europe	Sheep	2	563	26.2	14.8	34	9.4
Amox/Clav	Europe	Sheep and goat	1	114	7.9	7.9	7.9	NA
Apramycin	Europe	Goat	1	86	2	2	2	NA

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Apramycin	Europe	Sheep	2	265	1.6	1.5	2	0.2
Apramycin	Europe	Sheep and goat	1	114	0	0	0	NA
Fluoroquinolones	Asia	Goat	1	171	7	7	7	NA
Fluoroquinolones	Asia	Sheep	2	160	21.9	14	26.2	5.9
Fluoroquinolones	Asia	Sheep and goat	1	58	65.5	65.5	65.5	NA
Fluoroquinolones	Europe	Goat	1	258	9	9	9	NA
Fluoroquinolones	Europe	Sheep	2	548	4.5	4	5.2	0.6
Fluoroquinolones	Europe	Sheep and goat	1	114	0	0	0	NA
Gentamicin	Asia	Goat	1	171	93	93	93	NA
Gentamicin	Asia	Sheep	2	230	13.9	7	22.3	7.6
Gentamicin	Asia	Sheep and goat	1	58	0	0	0	NA
Gentamicin	Europe	Goat	1	270	9	9	9	NA
Gentamicin	Europe	Sheep	1	332	5	5	5	NA
Gentamicin	Europe	Sheep and goat	1	114	0.9	0.9	0.9	NA
Neomycin	Europe	Goat	1	190	18	18	18	NA
Neomycin	Europe	Sheep	2	363	23.7	9	34.5	12.6
Neomycin	Europe	Sheep and goat	1	114	20.2	20.2	20.2	NA
Sulfa/TMP	Asia	Goat	1	171	71.9	71.9	71.9	NA
Sulfa/TMP	Europe	Goat	1	280	36	36	36	NA
Sulfa/TMP	Europe	Sheep	2	564	44.3	20	61	20.2
Sulfa/TMP	Europe	Sheep and goat	1	114	22.8	22.8	22.8	NA
Sulfa/TMP	North America	Sheep and goat	1	74	4.1	4.1	4.1	NA
Tetracyclines	Asia	Goat	1	171	94.2	94.2	94.2	NA
Tetracyclines	Asia	Sheep	1	103	42.7	42.7	42.7	NA
Tetracyclines	Asia	Sheep and goat	1	58	31	31	31	NA
Tetracyclines	Europe	Goat	1	268	57	57	57	NA
Tetracyclines	Europe	Sheep	2	541	58.3	47.9	66	9
Tetracyclines	Europe	Sheep and goat	1	114	58.8	58.8	58.8	NA
Tetracyclines	North America	Sheep and goat	1	74	32.9	32.9	32.9	NA

3.1.3.2. Results from the national AMR monitoring reports

Information on AMR in clinical *E. coli* retrieved from sheep and/or goat was retrieved from the national surveillance AMR programmes from France (RESAPATH) and the UK (UK-VARSS).

RESAPATH (France): Data on AMR determined on clinical *E. coli* isolates retrieved from sheep (digestive pathologies) and goat (all pathologies reported together) are provided for eight or nine antimicrobials of interest for this opinion (apramycin was included in 4 years in sheep isolates and 3 years in goat isolates) during the 2014–2018 period. The number of isolates tested each year for each

antimicrobial ranged between 99 and 334 for sheep (excluding apramycin, only tested for between 34 and 58 isolates per year) and 117 and 282 for goat (excluding apramycin, only tested for between 39–86 isolates per year). Proportions of non-susceptible isolates from both species followed similar patterns, with higher proportions of resistant isolates (> 50%) to tetracycline and amoxicillin, followed by sulfonamide-trimethoprim and amoxicillin–clavulanic acid (ranging mostly between 20% and 40%) and lower levels found for the remaining antimicrobials (≤ 4% for ceftiofur and apramycin, data not shown) (Figure 5).

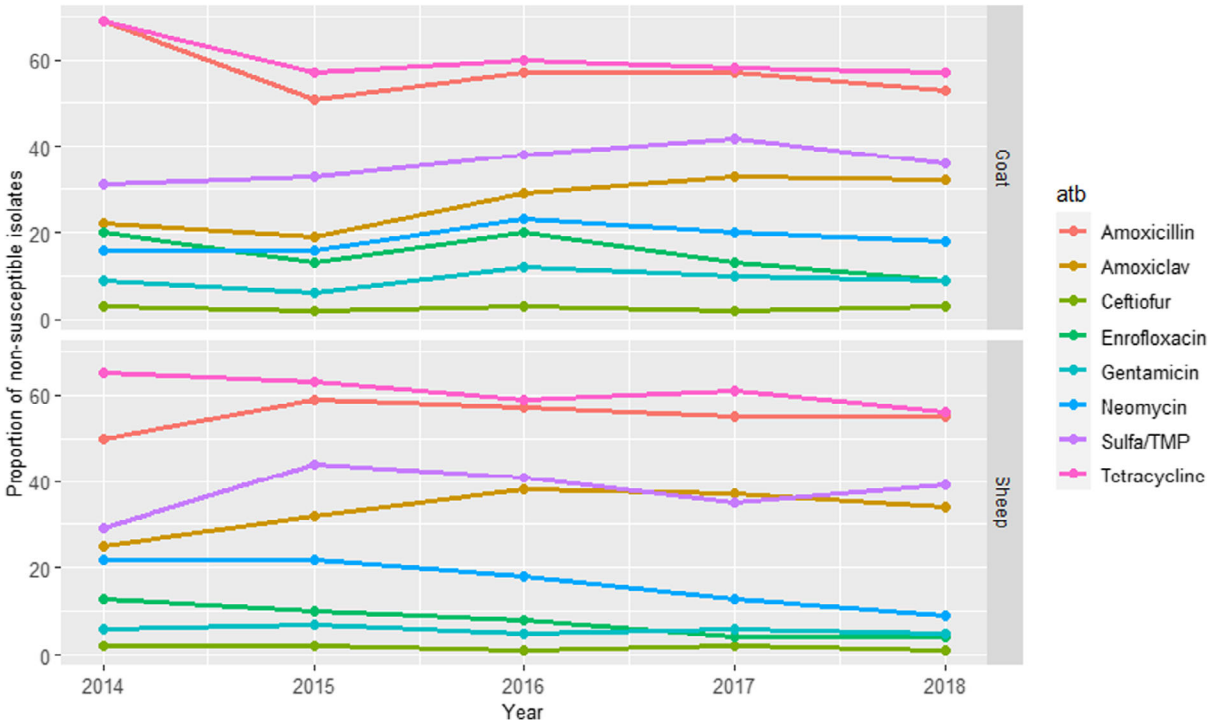


Figure 5: Proportion (%) of clinical *Escherichia coli* isolates retrieved from cases with digestive disorders (sheep) and all pathologies (goat) non-susceptible to eight antimicrobials of interest reported by the RESAPATH monitoring programme

UK-VARSS (United Kingdom): Data on AMR from clinical *E. coli* retrieved from sheep (including isolates from neonatal lambs and adult sheep) were available for isolates from England and Wales (60–179 isolates per year), Scotland (29–70 isolates per year) and Northern Ireland (38–80 isolates per year) in the last reports published, with certain differences in the antimicrobials tested depending on the source of the isolates (mostly on the 3GCs included among tested antimicrobials).

Isolates originating from England and Wales had higher (although decreasing) resistance levels to tetracyclines and ampicillin (35–65%), followed by sulfonamide-trimethoprim, amoxicillin–clavulanic acid and neomycin (ranging between 6% and 28%) and below 4% for the remaining antimicrobials (Figure 6). In addition, 130 isolates were tested using colistin in 2018, and all isolates were considered susceptible (data not shown).

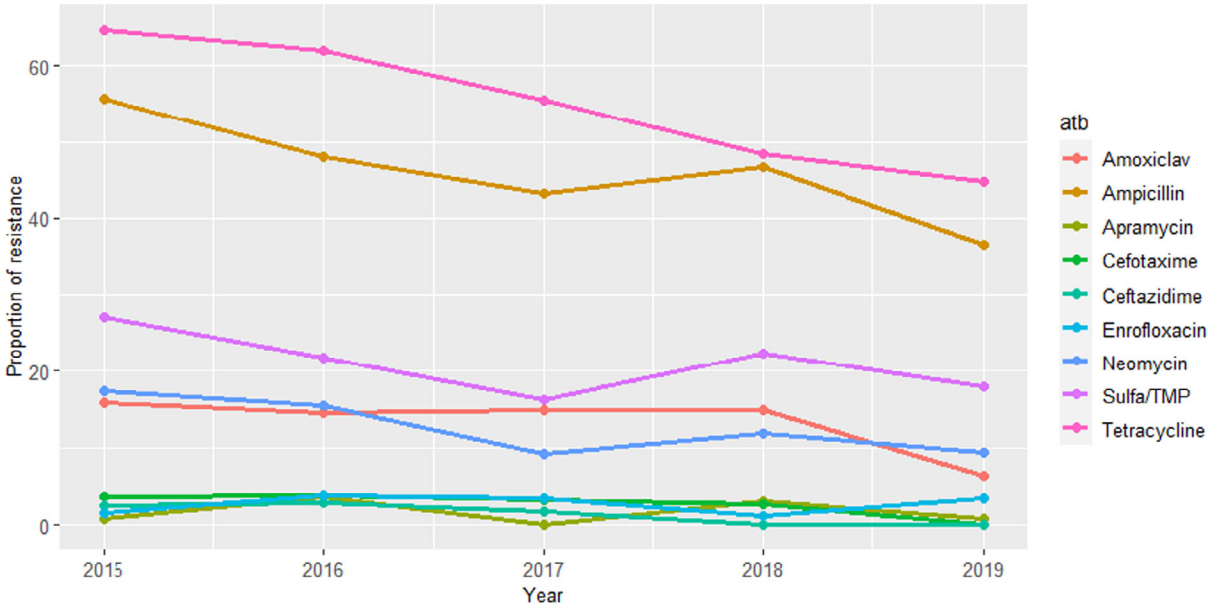


Figure 6: Proportion (%) of clinical *Escherichia coli* isolates retrieved from sheep (all ages) in England and Wales resistant to nine antimicrobials of interest reported by the UK-VARSS monitoring programme

Isolates originating from Scotland followed a similar trend in terms of the proportion of isolates resistant to each antimicrobial, with higher levels of resistance (> 40%) to tetracycline and ampicillin, intermediate (10/40%) for sulfonamide/trimethoprim, amoxicillin–clavulanic acid and neomycin (6–35%) and lower (< 4%) for the remaining antimicrobials (Figure 7). In addition, apramycin was included in 3 years (with 0–2.2% of resistant isolates).

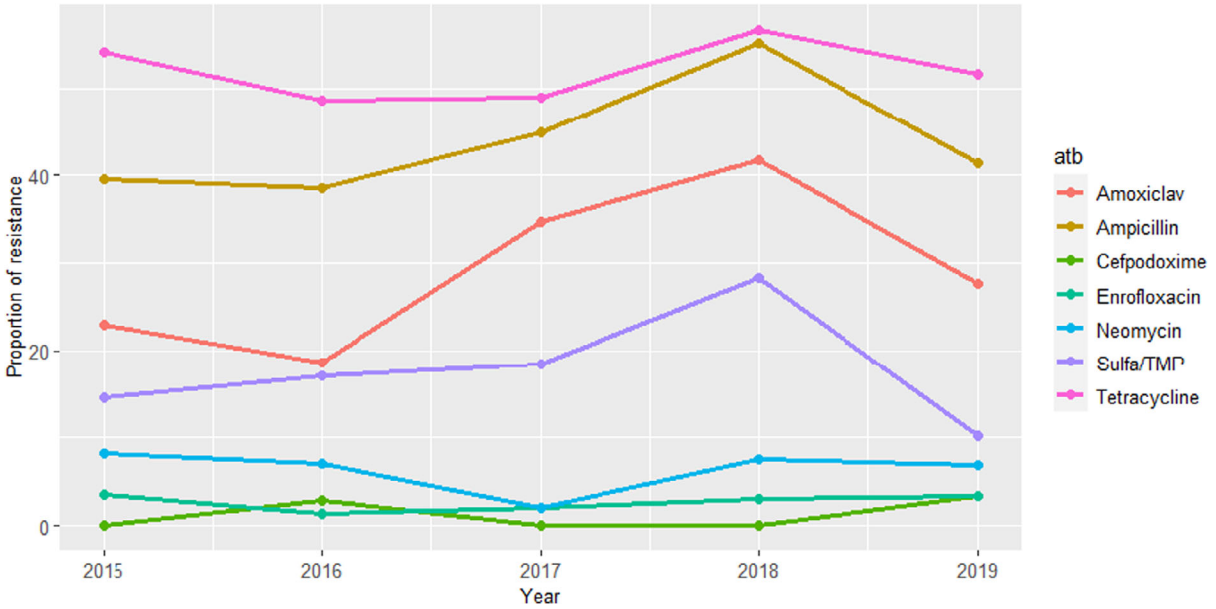


Figure 7: Proportion (%) of clinical *Escherichia coli* isolates retrieved from sheep (all ages) in Scotland resistant to seven antimicrobials of interest reported by the UK-VARSS monitoring programme

Finally, on the isolates from Northern Ireland, the highest level of resistance was found for neomycin (with all isolates reported as resistant consistently over the years, unlike that observed for the rest of the UK, < 20%), and higher levels for most of the remaining antimicrobials (of note, cefpodoxime resistance was above 50% in the last 3 years) (Figure 8), which could suggest that

isolates included in the report (not more than 80 for any given year) may be a biased representation of the clinical *E. coli* isolates in sheep in Northern Ireland.

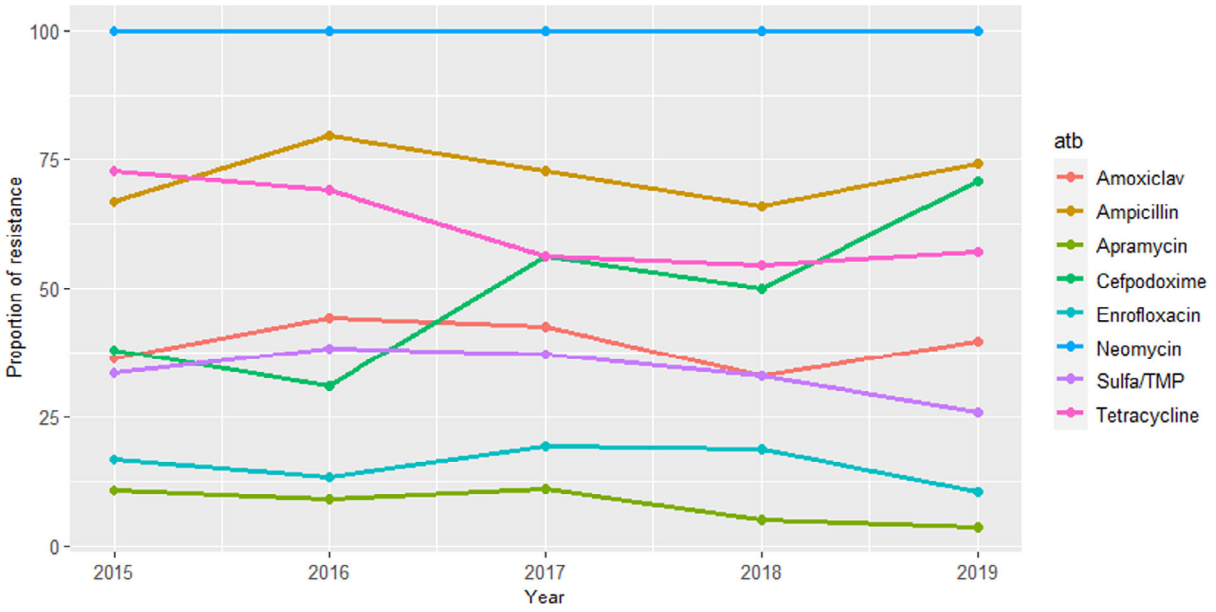


Figure 8: Proportion (%) of clinical *Escherichia coli* isolates retrieved from sheep (all ages) in Northern Ireland resistant to eight antimicrobials of interest reported by the UK-VARSS monitoring programme

3.1.4. *Staphylococcus aureus*

3.1.4.1. Results of the ELR by bacterium

Staphylococci are opportunistic pathogens of the skin and mucosal membranes. *S. aureus* is one of the most common and important *Staphylococcus* species in sheep and goats being primarily associated with mastitis.

In total, four studies with ≥ 50 *S. aureus* isolates and results for one or more of the relevant antibiotics [cefoperazone, ceftiofur, enrofloxacin/ciprofloxacin, erythromycin, methicillin (cefoxitin, oxacillin or presence of *mecA*/*mecC*), neomycin, penicillin, penicillin–novobiocin, pirlimycin, sulfonamide–trimethoprim] were included. Three of these studies included isolates from Europe and one from Asia.

All isolates originated from milk/udder, meaning from cases of either clinical or subclinical mastitis: 440 in sheep, 162 in goat and 267 in sheep and goat.

Figure 9 shows for each country the proportion of resistance reported in individual studies with at least 50 *S. aureus* isolates.

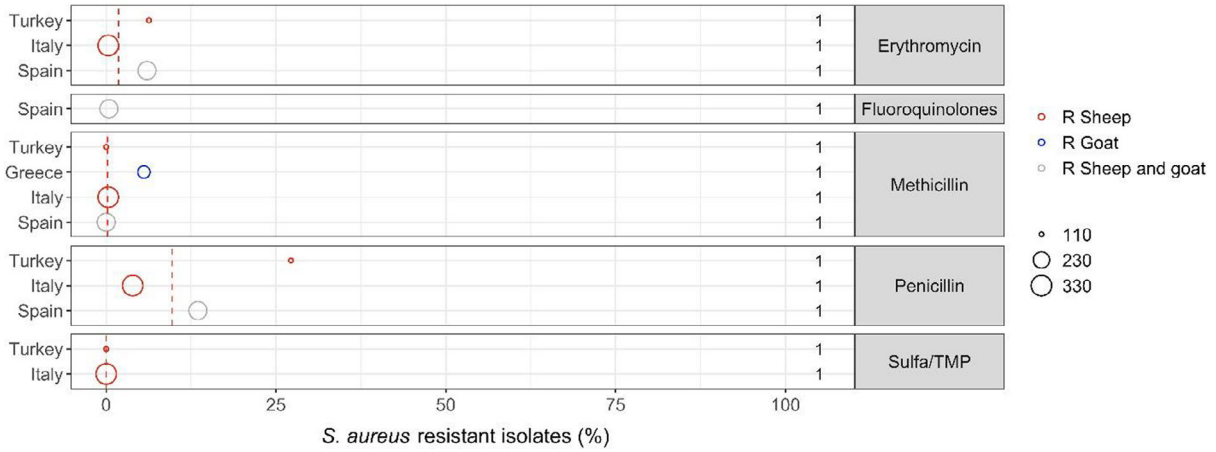


Figure 9: *Staphylococcus aureus* resistance data for each included study sorted by country. Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance in isolates of sheep origin (red circle), in isolates of goat origin (blue circle) and in isolates of mixed origin (grey circles). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of % R with the same colour codes as used for the circles. The exact percentages that 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

Overall, fairly low levels of resistance were reported in *S. aureus* from sheep and goat. Using cefoxitin or oxacillin as indicators, **methicillin resistance** (MR) was not detected in the two studies from Turkey and Spain (Porrero et al., 2012; Tel et al., 2012), whereas the proportion of MR was 0.3% among 330 isolates from sheep in Italy (Azara et al., 2017). The highest proportion (5.5%) was observed among 160 isolates from goats in Greece (Angelidis et al., 2020). Interestingly, an even higher proportion of isolates in that study (8.8%) tested positive for *mecA*, but the authors found that some of the *mecA*-positive isolates had low oxacillin MICs and failed to produce PBP2a, and thus, phenotypic results were preferred to determine the levels of MR. This illustrates that results of MR based on phenotypic and genotypic methods are not always comparable. Resistance to **sulfonamide–trimethoprim** was not detected in the two available studies, whereas the only study testing for fluoroquinolone resistance found only 0.4% of 267 Spanish isolates resistant to **ciprofloxacin** (Porrero et al., 2012). Levels of resistance to **erythromycin** were also low (< 7%), whereas resistance to **penicillin** varied from 3.9% to 27.2%, the highest proportion was observed among 110 sheep isolates from Turkey (Tel et al., 2012).

Table 5: Weighted arithmetic mean, minimum and maximum proportion of resistance and weighted standard deviation (SD) in *Staphylococcus aureus* for the target antimicrobials in each continent. NA means that SD could not be calculated as only one study was included

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Erythromycin	Asia	Sheep	1	110	6.3	6.3	6.3	NA
Erythromycin	Europe	Sheep	1	330	0.3	0.3	0.3	NA
Erythromycin	Europe	Sheep and goat	1	267	6	6	6	NA
Fluoroquinolones	Europe	Sheep and goat	1	267	0.4	0.4	0.4	NA
Methicillin	Asia	Sheep	1	110	0	0	0	NA
Methicillin	Europe	Goat	1	162	5.6	5.6	5.6	NA

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
Methicillin	Europe	Sheep	1	330	0.3	0.3	0.3	NA
Methicillin	Europe	Sheep and goat	1	267	0	0	0	NA
Penicillin	Asia	Sheep	1	110	27.2	27.2	27.2	NA
Penicillin	Europe	Sheep	1	330	3.9	3.9	3.9	NA
Penicillin	Europe	Sheep and goat	1	267	13.5	13.5	13.5	NA
Sulfa/TMP	Asia	Sheep	1	110	0	0	0	NA
Sulfa/TMP	Europe	Sheep	1	330	0	0	0	NA

3.1.5. *Pasteurella multocida, Mannheimia haemolytica* and *Bibersteinia trehalosi*

3.1.5.1. Results of the ELR by bacterium

Pasteurella multocida, Mannheimia haemolytica and Bibersteinia trehalosi are commensals and opportunistic pathogens of the respiratory tract in sheep and goats. These agents primarily cause infection of the respiratory tract, although they may also be involved in other conditions such as mastitis and septicaemia. *M. haemolytica* and *P. multocida* are associated with pneumonic pasteurellosis in sheep and goats, whereas *B. trehalosi* is mainly associated with systemic pasteurellosis in fattening lambs (Donachie, 2007; Cid et al., 2020).

In total, four, four and two studies with ≥ 10 *P. multocida*, *M. haemolytica* or *B. trehalosi* isolates, respectively, were included. Each included study had results for one or more of the following relevant antibiotics: ampicillin/amoxicillin, enrofloxacin/ciprofloxacin/danofloxacin, erythromycin, florfenicol, gamithromycin, gentamicin, 3GC, penicillin, tetracyclines, tildipirosin, tilmicosin, tulathromycin and tylosin. For *P. multocida*, studies included isolates from Asia (1), Europe (1) and North America (2). For *M. haemolytica*, studies included isolates from Europe (2) and North America (2). For *B. trehalosi*, the two included studies represented Europe and North America.

The distribution of *P. multocida*, *M. haemolytica* and *B. trehalosi* isolates per site of infection is shown in Figure 10.

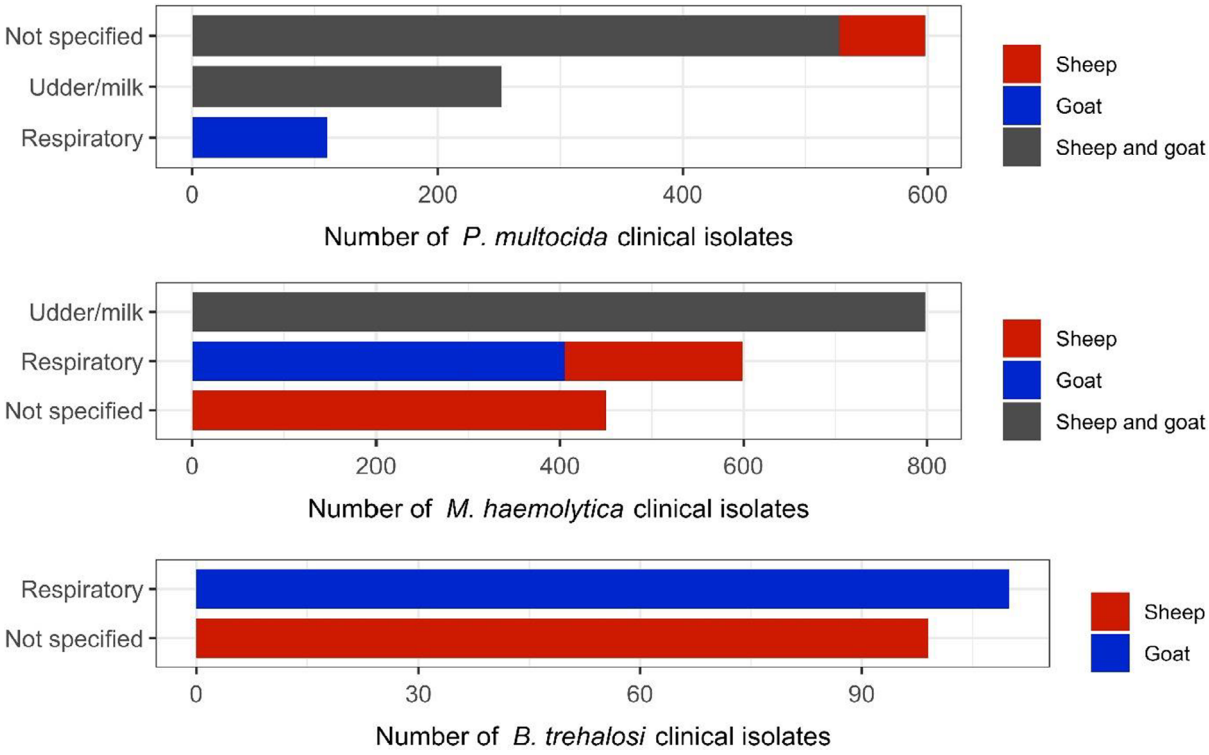
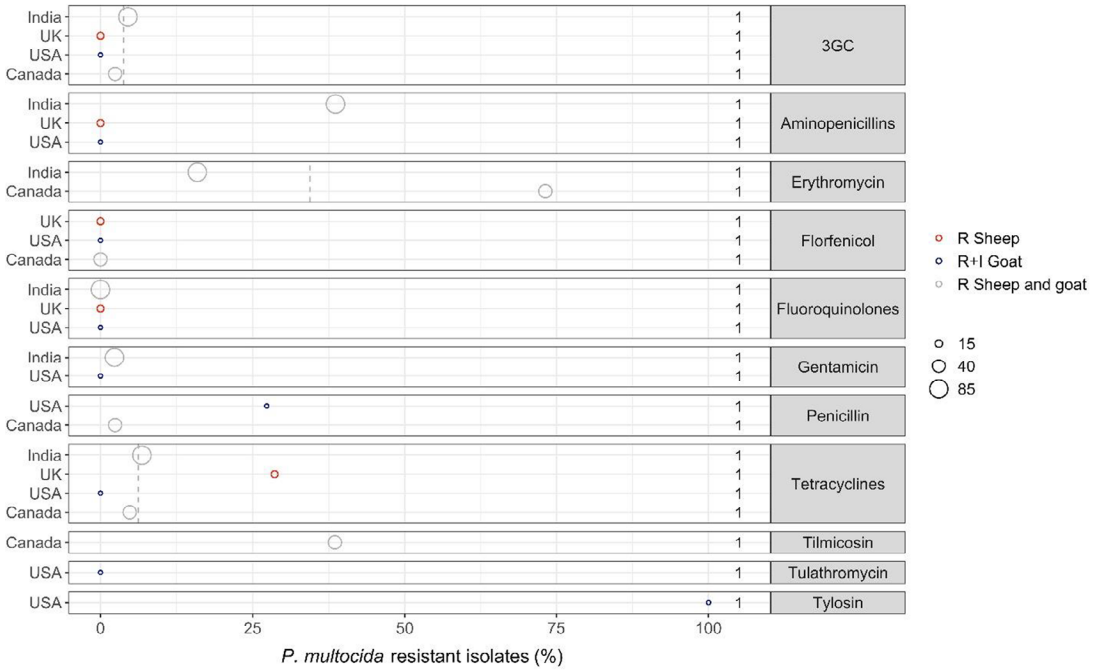
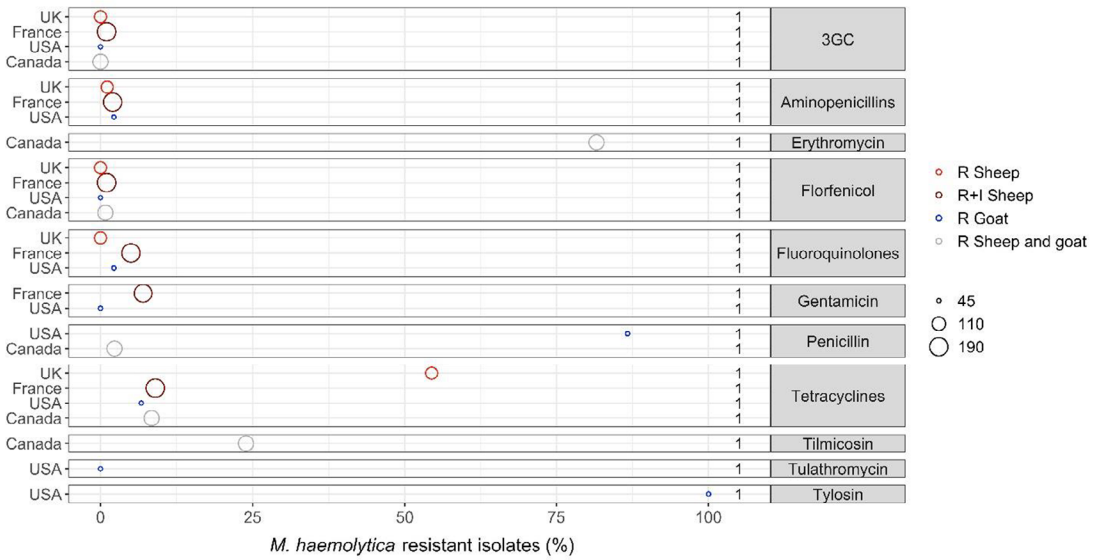


Figure 10: Distribution of *Pasteurella multocida*, *Mannheimia haemolytica* and *Bibersteinia trehalosi* isolates per site of infection

Figure 11 shows for each country the proportion of resistance reported in individual studies with at least 10 *P. multocida*, *M. haemolytica* and *B. trehalosi* isolates.


India
UK
USA
Canada
3GC
Aminopenicillins
Erythromycin
Florfenicol
Fluoroquinolones
Gentamicin
Penicillin
Tetracyclines
Tilmicosin
Tulathromycin
Tylosin
0
25
50
75
100
P. multocida resistant isolates (%)
R Sheep
R+I Goat
R Sheep and goat
15
40
85


UK
France
USA
Canada
3GC
Aminopenicillins
Erythromycin
Florfenicol
Fluoroquinolones
Gentamicin
Penicillin
Tetracyclines
Tilmicosin
Tulathromycin
Tylosin
0
25
50
75
100
M. haemolytica resistant isolates (%)
R Sheep
R+I Sheep
R Goat
R Sheep and goat
45
110
190

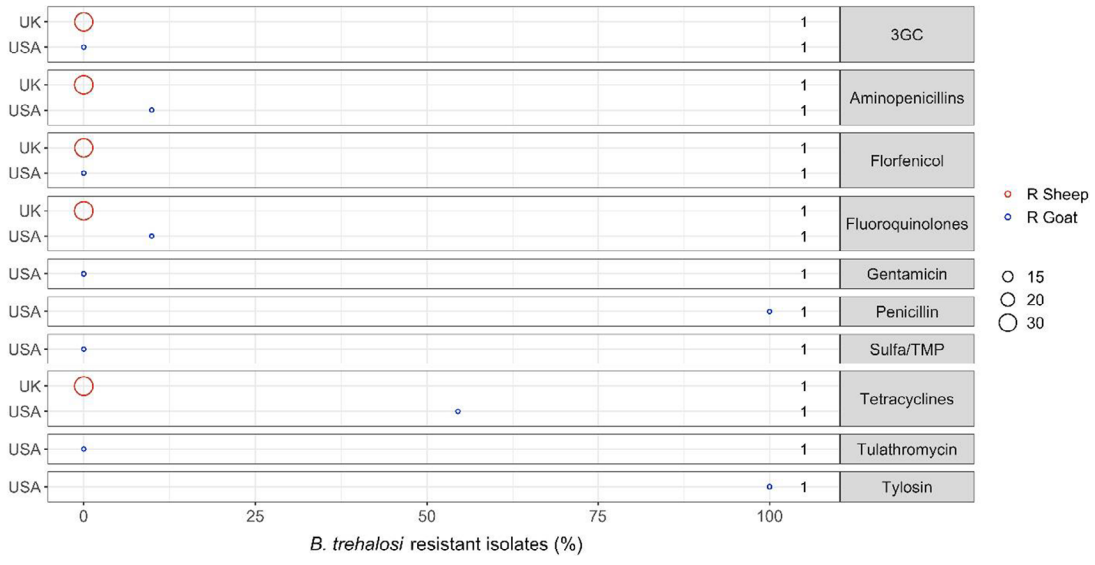

UK
USA
3GC
Aminopenicillins
Florfenicol
Fluoroquinolones
Gentamicin
Penicillin
Sulfa/TMP
Tetracyclines
Tulathromycin
Tylosin
0
25
50
75
100
B. trehalosi resistant isolates (%)
R Sheep
R Goat
15
20
30

Figure 11: *Pasteurella multocida*, *Mannheimia haemolytica* and *Bibersteinia trehalosi* resistance data for each included study sorted by country. Each circle represents one study, and the size of each circle reflects how many isolates were included in the study. The colour of a circle illustrates resistance in isolates of sheep origin (red circle), resistance in isolates of goat origin (light blue circle), resistance in isolates of mixed origin (light grey circle), resistance merged with intermediate in isolates of sheep origin (brown circle) and resistance merged with intermediate in isolates of goat origin (dark blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R or %R + I with the same colour codes as used for the circles. 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

For beta-lactams, most studies reported zero or very little resistance to **3GCs** for the three species. The highest proportion of 3GC resistance (4.5%) was detected for ceftriaxone in 88 *P. multocida* isolates from goat and sheep in India (Sarangi et al., 2015); no information on the organ from which these isolates were retrieved or on the age and production type of the sampled animals was available. Resistance levels for **aminopenicillins** were almost equally low, with the notable exception of – again - Sarangi et al. (2015) reporting a high proportion of resistance (38.6%) in Indian *P. multocida* isolates. Susceptibility to **penicillin** was only tested in two studies. One reported < 3% resistance in 42 *M. haemolytica* and 133 *P. multocida* isolates from goats and sheep in Canada (Awosile et al., 2018). The other reported 27.3%, 86.7% and 100% resistance in 11 *P. multocida*, 45 *M. haemolytica* and 11 *B. trehalosi* isolates, respectively, from goats in the USA (Clothier et al., 2012). The authors of the latter study stated that such high levels were expected, although without explaining this further.

Resistance to **florfenicol** was very rare. In fact, the highest level (non-susceptibility) observed was 1% of 194 *M. haemolytica* isolates from sheep in France (RESAPATH (ANSES), 2020).

Only three studies had tested susceptibility to at least one of the six target **macrolides**. One noteworthy result was that of Clothier et al. (2012) who found tylosin resistance in all isolates belonging to the three target bacterial species, whereas the same isolates were fully susceptible to tulathromycin. An almost similar difference was reported in the Canadian study, but between two other macrolides (Awosile et al., 2018). In that study, 81.6% and 73.2% of *M. haemolytica* and *P. multocida* isolates, respectively, were resistant to erythromycin, whereas corresponding proportions for tilmicosin were 23.9% and 38.5%.

Fluoroquinolone resistance was relatively uncommon with all studies reporting < 10% resistance.

The proportion of **tetracycline** resistance varied considerably between studies and species. The British surveillance system reported, for sheep isolates, proportions of resistant isolates to tetracycline of 54.4% and 0% among 90 *M. haemolytica* and 33 *B. trehalosi* isolates, respectively (UK-VARSS, 2019). A completely opposite picture was seen for goat isolates in the USA with 6.7% and 54.5% of 45 *M. haemolytica* and 11 *B. trehalosi* isolates, respectively, resistant to oxytetracycline (Clothier et al., 2012).

Susceptibility to **gentamicin** was investigated by three studies. Proportions of resistance were mostly < 3%, except for the French surveillance system reporting 7% of 178 *M. haemolytica* isolates (sheep) non-susceptible to this drug (RESAPATH (ANSES), 2020).

Table 6: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *Pasteurella multocida* for the target antimicrobials in each continent. NA means that SD could not be calculated as only one study was included

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC	Asia	Sheep and goat	1	88	4.5	4.5	4.5	NA
3GC	Europe	Sheep	1	14	0	0	0	NA

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC	North America	Goat	1	11	0	0	0	NA
3GC	North America	Sheep and goat	1	42	2.4	2.4	2.4	NA
Aminopenicillins	Asia	Sheep and goat	1	88	38.6	38.6	38.6	NA
Aminopenicillins	Europe	Sheep	1	14	0	0	0	NA
Aminopenicillins	North America	Goat	1	11	0	0	0	NA
Erythromycin	Asia	Sheep and goat	1	88	15.9	15.9	15.9	NA
Erythromycin	North America	Sheep and goat	1	42	73.2	73.2	73.2	NA
Florfenicol	Europe	Sheep	1	14	0	0	0	NA
Florfenicol	North America	Goat	1	11	0	0	0	NA
Florfenicol	North America	Sheep and goat	1	42	0	0	0	NA
Fluoroquinolones	Asia	Sheep and goat	1	88	0	0	0	NA
Fluoroquinolones	Europe	Sheep	1	14	0	0	0	NA
Fluoroquinolones	North America	Goat	1	11	0	0	0	NA
Gentamicin	Asia	Sheep and goat	1	88	2.3	2.3	2.3	NA
Gentamicin	North America	Goat	1	11	0	0	0	NA
Penicillin	North America	Goat	1	11	27.3	27.3	27.3	NA
Penicillin	North America	Sheep and goat	1	42	2.4	2.4	2.4	NA
Tetracyclines	Asia	Sheep and goat	1	88	6.8	6.8	6.8	NA
Tetracyclines	Europe	Sheep	1	14	28.6	28.6	28.6	NA
Tetracyclines	North America	Goat	1	11	0	0	0	NA
Tetracyclines	North America	Sheep and goat	1	42	4.8	4.8	4.8	NA
Tilmicosin	North America	Sheep and goat	1	42	38.5	38.5	38.5	NA
Tulathromycin	North America	Goat	1	11	0	0	0	NA
Tylosin	North America	Goat	1	11	100	100	100	NA

Table 7: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *Mannheimia haemolytica* for the target antimicrobials in each continent. NA means that SD could not be calculated as only one study was included

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC	Europe	Sheep	2	283	0.7	0	1	0.5
3GC	North America	Goat	1	45	0	0	0	NA
3GC	North America	Sheep and goat	1	133	0	0	0	NA
Aminopenicillins	Europe	Sheep	2	281	1.7	1.1	2	0.4
Aminopenicillins	North America	Goat	1	45	2.2	2.2	2.2	NA
Erythromycin	North America	Sheep and goat	1	133	81.6	81.6	81.6	NA
Florfenicol	Europe	Sheep	2	284	0.7	0	1	0.5
Florfenicol	North America	Goat	1	45	0	0	0	NA
Florfenicol	North America	Sheep and goat	1	133	0.8	0.8	0.8	NA
Fluoroquinolones	Europe	Sheep	2	281	3.4	0	5	2.3
Fluoroquinolones	North America	Goat	1	45	2.2	2.2	2.2	NA
Gentamicin	Europe	Sheep	1	178	7	7	7	NA
Gentamicin	North America	Goat	1	45	0	0	0	NA
Penicillin	North America	Goat	1	45	86.7	86.7	86.7	NA
Penicillin	North America	Sheep and goat	1	133	2.3	2.3	2.3	NA
Tetracyclines	Europe	Sheep	2	282	23.5	9	54.4	21.2
Tetracyclines	North America	Goat	1	45	6.7	6.7	6.7	NA
Tetracyclines	North America	Sheep and goat	1	133	8.4	8.4	8.4	NA
Tilmicosin	North America	Sheep and goat	1	133	23.9	23.9	23.9	NA
Tulathromycin	North America	Goat	1	45	0	0	0	NA
Tylosin	North America	Goat	1	45	100	100	100	NA

Table 8: Weighted arithmetic mean, minimum and maximum proportion of resistance (%R or %R + I) and weighted standard deviation (SD) in *Bibersteinia trehalosi* for the target antimicrobials in each continent. NA means that SD could not be calculated as only one study was included

Antibiotic	Continent	Species	No. of papers	No. of isolates	Weighted arithmetic mean proportion of resistance (%)	Minimum resistance % observed	Maximum resistance % observed	Weighted standard deviation
3GC	Europe	Sheep	1	32	0	0	0	NA
3GC	North America	Goat	1	11	0	0	0	NA
Aminopenicillins	Europe	Sheep	1	33	0	0	0	NA
Aminopenicillins	North America	Goat	1	11	9.9	9.9	9.9	NA
Florfenicol	Europe	Sheep	1	32	0	0	0	NA
Florfenicol	North America	Goat	1	11	0	0	0	NA
Fluoroquinolones	Europe	Sheep	1	33	0	0	0	NA
Fluoroquinolones	North America	Goat	1	11	9.9	9.9	9.9	NA
Gentamicin	North America	Goat	1	11	0	0	0	NA
Penicillin	North America	Goat	1	11	100	100	100	NA
Sulfa/TMP	North America	Goat	1	11	0	0	0	NA
Tetracyclines	Europe	Sheep	1	33	0	0	0	NA
Tetracyclines	North America	Goat	1	11	54.5	54.5	54.5	NA
Tulathromycin	North America	Goat	1	11	0	0	0	NA
Tylosin	North America	Goat	1	11	100	100	100	NA

3.1.5.2. Results from the national AMR monitoring reports

Information on AMR in clinical isolates from these three species was found in RESAPATH reports (*M. haemolytica*) and UK-VARSS (all three species).

RESAPATH (France): AST results were available for six antimicrobials of interest determined in between 76 and 194 *M. haemolytica* clinical isolates retrieved from sheep with respiratory pathologies was included for the 2014–2018 period (in addition, between 30 and 34 isolates were tested using danofloxacin in 2015, 2016 and 2018). Proportions of non-susceptibility were below 15% in all years and for all antimicrobials except gentamicin between 2014 and 2016 (Figure 12). Proportions of non-susceptibility to danofloxacin ranged between 6 and 13% (data not shown).

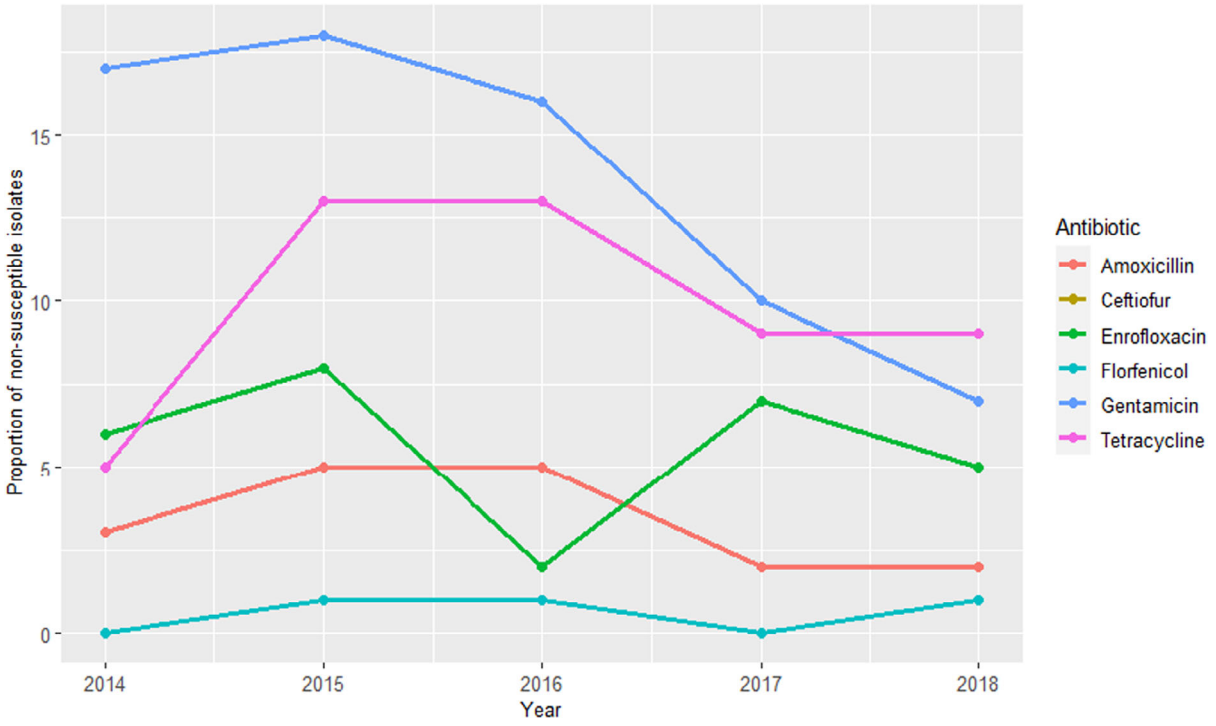


Figure 12: Percentage (%) of clinical sheep *Mannheimia haemolytica* isolates retrieved from respiratory samples non-susceptible to six antimicrobials of interest reported by the RESAPATH monitoring programme

The RESAPATH report also includes AST results determined in isolates identified as *Pasteurella* spp. that have not been included in the literature review in agreement with the exclusion criteria (as data reported at the genus level were to be excluded). Regardless, proportion of non-susceptible isolates in *Pasteurella* spp. isolates tested in 2014–2018 were always ≤ 20% (except for danofloxacin, which was < 30%) (data not shown).

UK-VARSS (United Kingdom): AMR data from *M. haemolytica* (35–90 isolates tested each year), *P. multocida* (3–14 isolates per year) and *B. trehalosi* (32–95 isolates per year) retrieved from respiratory infections in sheep in England and Wales are included in the annual reports. Resistance levels in *M. haemolytica* were very low (< 5%) for all antimicrobials of interest considered except tetracycline, for which increasing levels of resistance were found in the last 3 years (Figure 13).

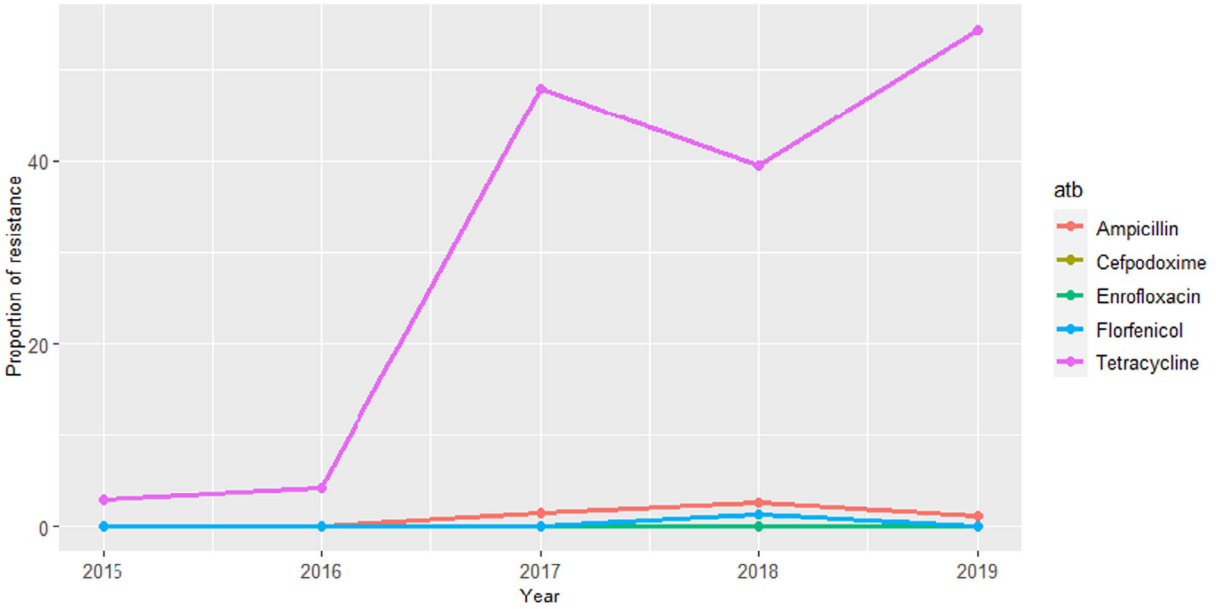


Figure 13: Percentage (%) of clinical sheep *Mannheimia haemolytica* isolates retrieved from respiratory samples resistant to five antimicrobials of interest reported by the UK-VARSS monitoring programme

For the *P. multocida* clinical isolates, resistance was only found to tetracycline and ampicillin (Figure 14), although the very low number of isolates were tested each year (14 in 2019, eight or less the remaining years) precludes from extracting meaningful conclusions from these data.

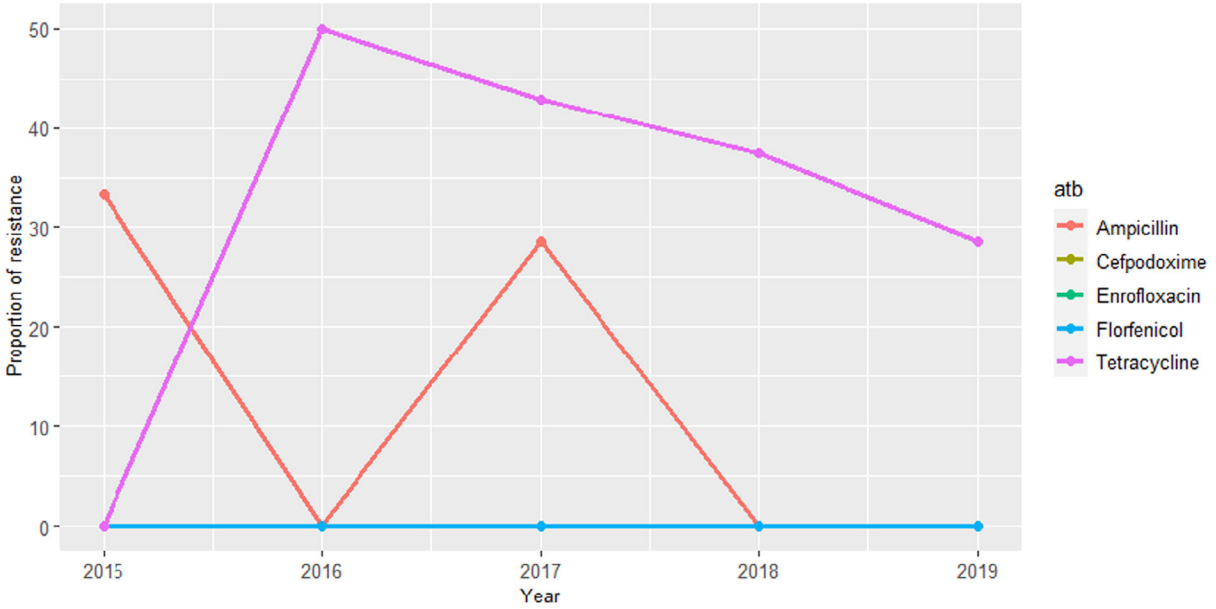


Figure 14: Percentage (%) of clinical sheep *Pasteurella multocida* isolates retrieved from respiratory samples resistant to five antimicrobials of interest reported by the UK-VARSS monitoring programme

Finally, very low (≤ 2.5%) resistance levels were found in the *B. trehalosi* respiratory isolates tested between 2015 and 2019, with only one or two isolates out of the 32–95 tested each year found resistant to tetracycline, florfenicol and enrofloxacin in certain years (Figure 15).

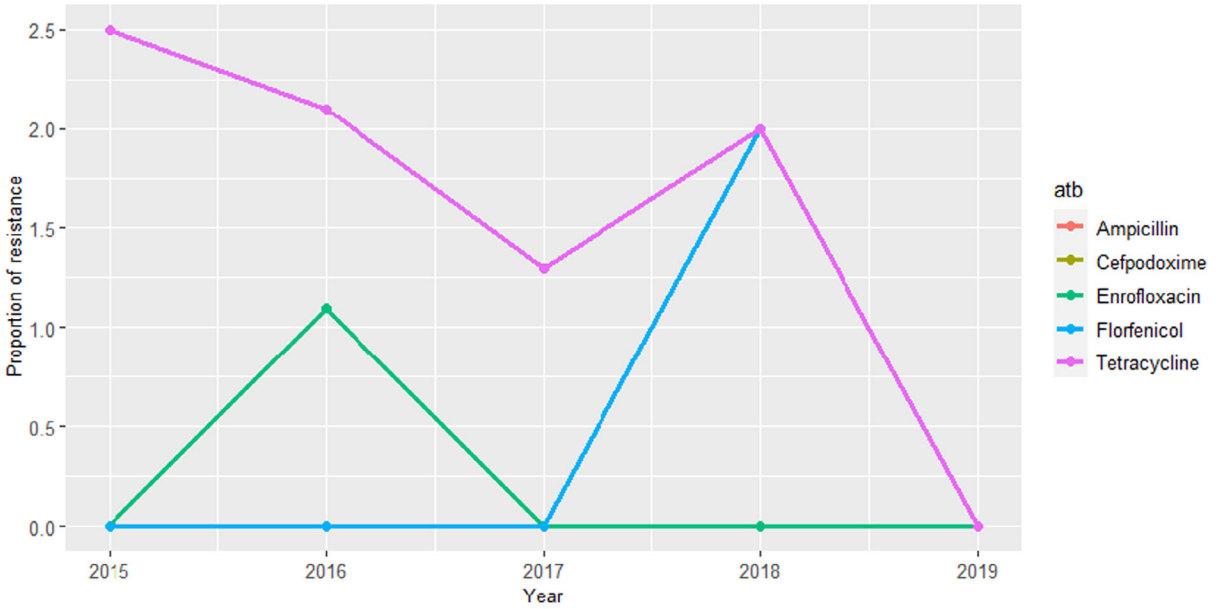


Figure 15: Percentage (%) of ovine clinical *Bibersteinia trehalosi* isolates retrieved from respiratory samples resistant to five antimicrobials of interest reported by the UK-VARSS monitoring programme

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 for the assessment of animal diseases caused by bacteria resistant to antimicrobials within the AHL framework (EFSA AHAW Panel, 2021), the evidence available was assessed individually by all working group members who provided individual judgements on the perceived relevance to the health of sheep and goats of the antimicrobial-resistant bacteria included in the list.

After discussion of the individual judgements for each bacterium, it was agreed with ≥ 66% certainty that the group of the most relevant resistant bacteria in sheep and goat for the EU was composed of only *E. coli* (Figure 16). The rationale for the selection of this species was based on: (a) its perceived importance as a causative agent of relevant diseases with a strong impact on animal health (mainly diarrhoea in young animals and mastitis), which, for digestive problems, typically results in the use of antimicrobials; and (b) on the evidence found consistently suggesting that resistance to several antimicrobials of relevance in the treatment of *E. coli*-related gastrointestinal issues (aminopenicillins, tetracyclines, potentiated sulfonamides) was common, which could lead to the use of antimicrobials in the B AMEG category (e.g. fluoroquinolones). The potential importance of AMR for *E. coli* in sheep and goat is also shown by the number of references/AST results retrieved through the ELR (e.g. almost 60% of all AST results in Appendix B were related to this pathogen, and *E. coli* AST results (n = 9,998) were over three times more numerous than for the following most represented pathogens, *S. aureus* and *M. haemolytica*, with < 3,000). Nevertheless, several sources of uncertainty were identified in this assessment, leading to a wide range in the collective assessment (Figure 16); these included an overall low number of studies identified in the ELR (only six articles and two national monitoring programmes originating from six countries in the world), and the lack of information on the site of infection from which isolates originated (not specified in nearly half of all isolates tested) and the host (it was not possible to differentiate if isolates were from sheep or goat in nearly one-third of the cases), so preventing a more detailed evaluation.

Among the remaining bacterial pathogens considered in this opinion, information was available for only four of them, none of which were included among the most relevant (Figure 16). *Mannheimia haemolytica* and *P. multocida* are important pathogens in sheep and goats, leading to a large proportion of the overall antimicrobial usage in small ruminants. However, they were not selected due to the lack of data suggesting that AMR could be a major issue, since the results retrieved through the ELR did not indicate a large proportion of resistance to most antimicrobial classes. Nevertheless, due to the very limited data retrieved, there was also a large uncertainty associated with this assessment (Figure 16). The same conclusion was reached for the other two pathogens for which information

could be retrieved, *B. trehalosi* and *S. aureus*, although with slightly less uncertainty due to the lower perceived potential role of AMR in treatment failures.

No data were obtained for all the remaining pathogens, which was interpreted as suggesting a lack of relevance of AMR preventing therapeutic success in the treatment of the diseases caused by them. Hence, they were not identified among the most relevant AMR pathogens affecting sheep and goats. Nevertheless, this lack of evidence could be also due to the limited routine use of culture and AST to guide antimicrobial treatment of sheep and goats. Because of this, a large degree of uncertainty was associated with this judgement (Figure 16).

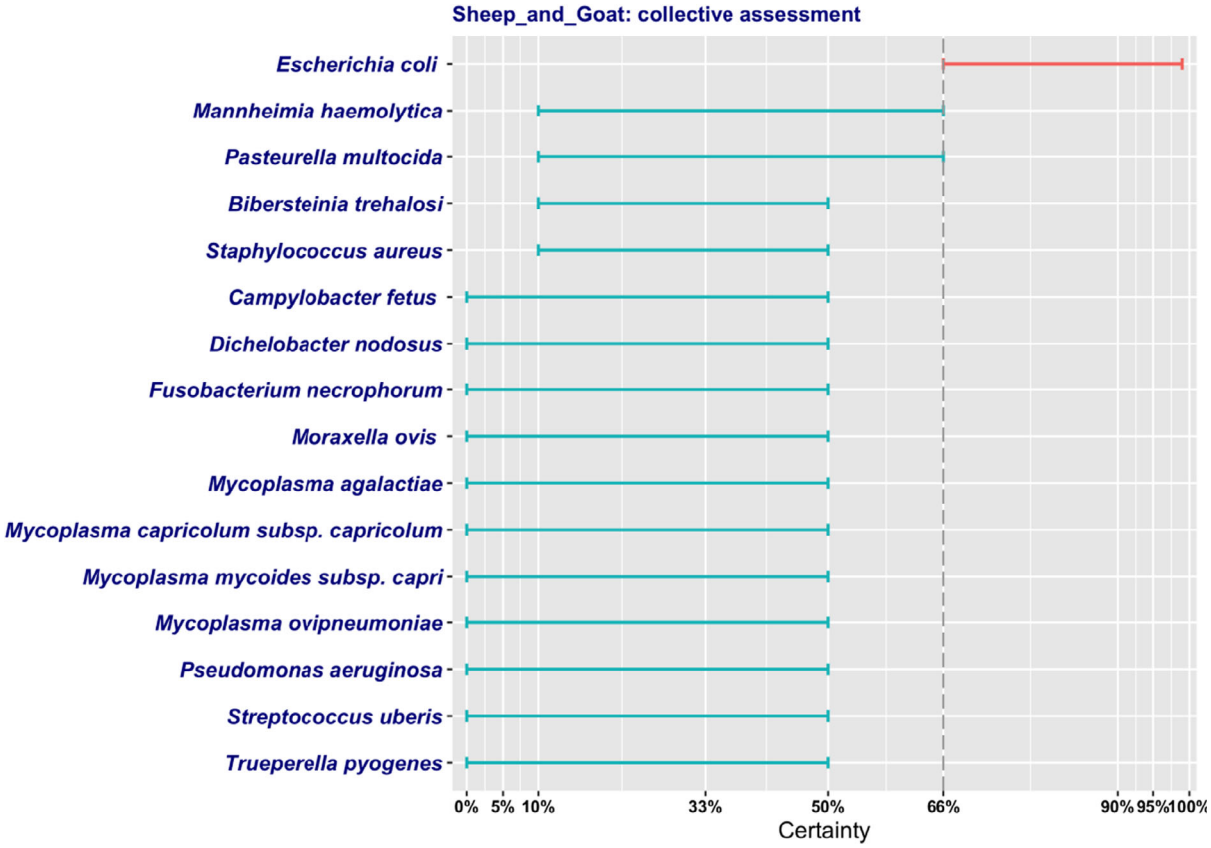


Figure 16: Level of certainty for the inclusion of the selected antimicrobial resistant pathogens of sheep and goat among the most relevant in the EU

4. Conclusions

In this opinion, EFSA presents the results of the assessment conducted to answer ToR 1 (global state of play of antimicrobial-resistant animal bacteria) and the first part of ToR 2 (identifying the most relevant resistant bacteria in the EU) according to 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 sheep and goats in the EU, and their eligibility for being listed and categorised in the framework of the AHL, will be assessed in the next step of this EFSA project.

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

- Due to the scope of the ELR, only studies published in the last 10 years and in English were considered eligible (except for the GERM-VET report, originally in German), therefore adding a possible selection bias.

- A very limited number of studies was found in the ELR, and these related to only five of the 16 pathogens initially considered, so providing a detailed global state of play of the situation on AMR in pathogens from sheep and goats is very difficult.
- Furthermore, 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, between one-third to > 90% of the AST results obtained for the five pathogens for which some data were available and were determined using isolates cultured from non-specified samples/ locations and it was not possible to differentiate sheep from goat strains. Moreover, isolates may have originated from animals subjected to previous antimicrobial treatments, which may lead to higher levels of resistance in tested isolates, but only two studies provided some information on this aspect (indicating the absence of treatments for between 5 and 14 days). Finally, several of the bacterial species included here can also be found in healthy animals (e.g. *E. coli and S. aureus*). Therefore, even if they originated from diseased animals, they may not be the causative agent in a proportion of cases that cannot be quantified.
- Even though only studies exceeding a minimum quality threshold were included (e.g. use of international or national standards), the methodology used was also diverse (e.g. use of disc diffusion or microdilution methods, CBP or ECOFFs, consideration or not of the intermediate category, etc.). Therefore, descriptive statistics provided here (average proportion of resistant isolates for bacterium, country and antimicrobial) should be interpreted with caution as they may not be representative of the true underlying situation, particularly for cases in which the sample size was small.
- AMR data referring to one or more bacterial pathogens of interest in this opinion were retrieved from only two national AMR monitoring reports. However, comparison of data reported in the different countries is difficult due to differences in: (a) the bacterial species, host (sheep and/or goat) and origin of the isolates 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 (disc 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 AMR in sheep and goats for the following bacteria: *Staphylococcus aureus, Escherichia coli* (non-VTEC), *Pseudomonas aeruginosa*, *Dichelobacter nodosus*, *Moraxella ovis*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma ovipneumoniae*, *Mycoplasma agalactiae*, *Trueperella pyogenes*, *Streptococcus uberis*, *Bibersteinia trehalosi*, *Campylobacter fetus*, *Mycoplasma mycoides* subsp. *capri*, *Mycoplasma capricolum* subsp. *Capricolum and Fusobacterium necrophorum.*

Among those bacteria, based on the evidence available and expert opinion, EFSA identified *E. coli* as the most relevant antimicrobial-resistant pathogen in sheep and goat in the EU with ≥ 66% certainty. Based on the limited evidence found for the remaining pathogens and expert opinion, none of the other bacteria were among the most relevant antimicrobial-resistant pathogens in sheep and goat, although the lack of evidence found resulted in a large uncertainty in the assessment. This lack of (or very limited) evidence for the selected species is probably due to the limited routine use of AST to guide antimicrobial therapy in small ruminants, further hampering the assessment of the importance of antimicrobial resistant phenotypes in these pathogens.

Regarding the reports from national monitoring systems from European countries included in the assessment, only two included information on AMR in sheep and goat clinical isolates belonging to the bacterial species of interest in this opinion. Because of the very limited sample sizes, it is difficult to extract definitive conclusions in terms of AMR levels in sheep and goat populations based on the reports from national monitoring systems from European countries assessed in this opinion, although stable AMR trends were found for most pathogen–drug combinations tested, and levels of resistance were in general low for most pathogen–antimicrobial combinations. Nevertheless, the significance of these observations should not be overinterpreted due to the above-mentioned limitations.

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

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

5. Recommendations

Data on AMR in bacterial pathogens are necessary to enhance animal health, promote the rational use of antimicrobials and identify specific therapeutic challenges attributable to AMR. Therefore, and given the scarcity of information available for pathogens in sheep and goats, there is a need for reliable AST data on pathogenic bacteria from sheep and goats in the regions of the world in which these species are abundant, which are obtained through the use of standardised methodologies that allow to make comparisons between locations and over time. These data should be accompanied by sufficient metadata to allow meaningful interpretations (such as age of the animals, previous antimicrobial treatments and details on clinical presentation).

Only two national monitoring programmes for AMR included information from sheep and goat clinical isolates of the pathogens of interest for this opinion. Although there are limitations that hamper the comparability of data reported by different countries (Mader et al., 2021), assuming that sampling and methodological biases are relatively constant over time for a given monitoring programme, longitudinal data from national monitoring programmes can be helpful to detect the potential emergence of new antimicrobial resistant phenotypes of clinical importance or changes in resistance proportions, and therefore help to guide antimicrobial stewardship in sheep and goat. Therefore, inclusion of sheep and goat pathogens in the AMR monitoring programmes from countries where small ruminants are relevant livestock species could provide very valuable information, especially in the case of the main bacterial pathogens contributing to respiratory diseases in sheep and goats (*P. multocida* and *M. haemolytica*) as they are major drivers of on-farm antimicrobial usage.

In the future, standardisation and harmonisation of the methodology used by national monitoring programmes, including selection criteria for collecting bacterial isolates and performance of AST, or development of supranational monitoring systems, would allow more meaningful comparisons between countries (Mader et al., 2021). In addition, access to raw AST data generated by such programmes could enable analysis of data from different countries using the same laboratory methods and interpretive criteria (CBPs or ECOFFs), and facilitate identification of geographical differences in the distribution of specific antimicrobial resistance phenotypes of clinical relevance.

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Abbreviations

3GC	third generation cephalosporin
AHAW	Animal Health and Welfare
AHL	animal health law
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
CBP	clinical breakpoints
CLSI	Clinical and Laboratory Standards Institute
ECOFF	epidemiological cut-off
ELR	extensive literature review
ESBL	extended-spectrum beta-lactamase
ESC	extended-spectrum cephalosporinase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
I	intermediate
MIC	minimum inhibitory concentration
MR	methicillin resistance
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSP	methicillin-resistant *Staphylococcus pseudintermedius*
PCR	polymerase chain reaction
R	resistant
S	susceptible
UTI	urinary tract infection

Appendix A – Search strings applied

A.1. PubMed

Common search string "Antimicrobials"

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

Host-based strings:

“sheep”[Title/Abstract] OR “goat”[Title/Abstract] OR “Goats”[Title/Abstract] OR “small ruminant”[Title/Abstract] OR “small ruminants”[Title/Abstract] OR “ovine”[Title/Abstract] OR “caprine”[Title/Abstract] OR “sheep, domestic”[MeSH Terms] OR “Goats”[MeSH Terms]

“Bacterial species”

“Bibersteinia trehalosi”[Title/Abstract] OR “Campylobacter fetus”[Title/Abstract] OR “Dichelobacter nodosus”[Title/Abstract] OR “Escherichia coli”[Title/Abstract] OR “Fusobacterium necrophorum”[Title/Abstract] OR “Mannheimia haemolytica”[Title/Abstract] OR “Moraxella ovis”[Title/Abstract] OR “Mycoplasma agalactiae”[Title/Abstract] OR “mycoplasma capricolum subsp capricolum”[Title/Abstract] OR “mycoplasma mycoides subsp capri”[Title/Abstract] OR “Mycoplasma ovipneumoniae”[Title/Abstract] OR “Pasteurella multocida”[Title/Abstract] OR “Pseudomonas aeruginosa”[Title/Abstract] OR “Staphylococcus aureus”[Title/Abstract] OR “Streptococcus”[Title/Abstract] OR “Corynebacterium pyogenes”[Title/Abstract] OR “Trueperella pyogenes”[Title/Abstract]OR “Bibersteinia trehalosi”[Supplementary Concept] OR “Campylobacter fetus”[MeSH Terms] OR “Dichelobacter nodosus”[MeSH Terms] OR “Escherichia coli”[MeSH Terms] OR “Fusobacterium necrophorum”[MeSH Terms] OR “Mannheimia haemolytica”[MeSH Terms] OR “Moraxella ovis”[Supplementary Concept] OR “Mycoplasma agalactiae”[MeSH Terms] OR “mycoplasma mycoides subsp capri”[Supplementary Concept] OR “Mycoplasma ovipneumoniae”[MeSH Terms] OR “Pasteurella multocida”[MeSH Terms] OR “Pseudomonas aeruginosa”[MeSH Terms] OR “Staphylococcus aureus”[MeSH Terms] OR “Streptococcus”[MeSH Terms] OR “Corynebacterium pyogenes”[MeSH Terms]

A.2. Embase

Common search string "Antimicrobials"

1) antibiotic resistance/ or exp antibiotic sensitivity/ or exp drug resistance/
2) susceptib*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3) resistan*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4) 2 or 3
5) antibiotic.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6) antibiotics.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7) antimicrobial.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8) antimicrobials.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9) 5 or 6 or 7 or 8
10) antibiotic agent/
11) 10 or 9

12) 11 and 4
13) 12 or 1

Host-based string:

1) sheep/
2) goat/
3) (sheep or goat or goats or caprine or ovine or "small ruminant" or "small ruminants").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) 1 or 2 or 3

"Bacterial species"

1) Campylobacter fetus/
2) Dichelobacter nodosus/
3) Escherichia coli/
4) Fusobacterium necrophorum/
5) Mannheimia haemolytica/
6) Mycoplasma agalactiae/
7) Mycoplasma capricolum/
8) "Mycoplasma mycoides subsp. capri"/
9) Mycoplasma ovipneumoniae/
10) Pasteurella multocida/
11) Pseudomonas aeruginosa/
12) Staphylococcus aureus/
13) Streptococcus/
14) Trueperella pyogenes/
15) ("Bibersteinia trehalosi" or "Campylobacter fetus" or "Dichelobacter nodosus" or "Escherichia coli" or "Fusobacterium necrophorum" or "Mannheimia haemolytica" or "Moraxella ovis" or "Mycoplasma agalactiae" or "Mycoplasma capricolum subsp. capricolum" or "Mycoplasma mycoides subsp. capri" or "Mycoplasma ovipneumoniae" or "Pasteurella multocida" or "Pseudomonas aeruginosa" or "Staphylococcus aureus" or Streptococcus or "Trueperella pyogenes").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]
16) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Appendix B – Excel file with information on all studies for full-text screening

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.5561174

Appendix C – Clinically relevant antibiotics for which data were extracted

Bacterial species	Relevant resistance tested
Escherichia coli	• Ampicillin or amoxicillin • Amox+clav • Apramycin • 3rd gen cephalosporins (Cefpodoxime, cefotaxime, ceftazidime or ceftriaxone, or ceftiofur) • Cefoperazone • Colistin • Enrofloxacin or Ciprofloxacin • Gentamicin • Neomycin • Paromomycin • Sulfa-TMP • Tetracyclines (oxy/doxy/chlor/tet)
Staphylococcus aureus	• Cefoxitin • Cefoperazone • Ceftiofur • Enrofloxacin or Ciprofloxacin • Erythromycin • *mecA* gene • Neomycin • Oxacillin • Penicillin • Penicillin–novobiocin • Pirlimycin • Sulfa-TMP
Pasteurella multocida	• Ampicillin, amoxicillin • Enrofloxacin, ciprofloxacin or danofloxacin • Erythromycin • Florfenicol • Gamithromycin • Gentamicin • 3rd gen cephalosporins (Cefpodoxime, cefotaxime, ceftazidime or ceftriaxone, or ceftiofur) • Penicillin • Tetracyclines (oxy/doxy/chlor/tet) • Tildipirosin • Tilmicosin • Tulathromycin • Tylosin
Mannheimia haemolytica	• Ampicillin, amoxicillin • Enrofloxacin, ciprofloxacin or danofloxacin • Erythromycin • Florfenicol • Gamithromycin • Gentamicin • 3rd gen cephalosporins (Cefpodoxime, cefotaxime, ceftazidime or ceftriaxone, or ceftiofur) • Penicillin • Tetracyclines (oxy/doxy/chlor/tet) • Tildipirosin • Tilmicosin • Tulathromycin • Tylosin

Bacterial species	Relevant resistance tested
Bibersteinia trehalosi	• Ampicillin, amoxicillin • Enrofloxacin, ciprofloxacin or danofloxacin • Erythromycin • Florfenicol • Gamithromycin • Gentamicin • 3rd gen cephalosporins (Cefpodoxime, cefotaxime, ceftazidime or ceftriaxone, or ceftiofur) • Penicillin • Tetracyclines (oxy/doxy/chlor/tet) • Tildipirosin • Tilmicosin • Tulathromycin • Tylosin

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 proportion of resistance (%)	Maximum resistance % observed	Minimum resistance % observed	Weighted standard deviation	Bacterial species/ genus
3GC (Other)	R_Sheep	28.1	70.7	8.7	28.8	*E. coli*
3GC (Other)	R_Sheep and goat	18.3	36.2	4.2	15.9	*E. coli*
Aminopenicillins	R_Sheep	41.4	46.1	33.3	5.4	*E. coli*
Fluoroquinolones	R_Sheep	12	26.2	5.2	9	*E. coli*
Gentamicin	R_Sheep	13.9	22.3	7	7.6	*E. coli*
Tetracyclines	R_Sheep	46.3	47.9	42.7	2.4	*E. coli*
Tetracyclines	R_Sheep and goat	32.1	32.9	31	0.9	*E. coli*
3GC	R_Sheep and goat	3.8	4.5	2.4	1	*P. multocida*
Erythromycin	R_Sheep and goat	34.4	73.2	15.9	26.9	*P. multocida*
Tetracyclines	R_Sheep and goat	6.2	6.8	4.8	0.9	*P. multocida*
Erythromycin	R_Sheep	1.8	6.3	0.3	2.6	*S. aureus*
Methicillin	R_Sheep	0.2	0.3	0	0.1	*S. aureus*
Penicillin	R_Sheep	9.7	27.2	3.9	10.1	*S. aureus*
Sulfa/TMP	R_Sheep	0	0	0	0	*S. aureus*