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

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Abstract

In this opinion, the antimicrobial-resistant bacteria responsible for transmissible diseases that constitute a threat to the health of farmed rabbits have been assessed. The assessment has been performed following a methodology based on information collected through 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 *Pasteurella multocida*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bordetella bronchiseptica*, *Clostridium difficile*, *Clostridium perfringens* and *Clostridium spiroforme* is provided. Among these bacteria, none were identified as being the most relevant antimicrobial-resistant bacteria in rabbits in the EU due to the very limited scientific evidence available.

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

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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 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 rabbits 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 rabbits.

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 through an extensive literature review (ELR)] 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 rabbits had been agreed upon by the EFSA working group: *Bordetella bronchiseptica*, *Escherichia coli*, *Pasteurella multocida*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. In a second stage, *Clostridioides (Clostridium) difficile*, *Clostridium perfringens* and *Clostridium spiroforme* were also included in the scope of the opinion.

The ELR was carried out by the University of Copenhagen under the contract OC/EFSA/ALPHA/2020/02 – LOT 1.[2] On 5 May 2021, two different search strings (Appendix A) were applied in PubMed and Embase, respectively, resulting in a search result of 668 unique abstracts published since 2010. Two additional searches for the same time period were performed afterwards: one to add the three *Clostridium* species, which were not part of the original search string, and the other to assess the impact of a spelling error in the initial search. This led to a total of 704 abstracts. Upon import into Rayyan software, 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 abstracts was downloaded into the EndNote software. In addition, the most recent national antimicrobial resistance (AMR) monitoring report from France was downloaded and used in the ELR. Only the latest version of the AMR monitoring report was included in the ELR as isolates included in these reports can be assumed to originate from the same sampled populations and most recent versions would therefore include the most up-to-date antimicrobial resistant data. The previous

[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

versions of the national AMR monitoring reports, i.e. up to the previous 5 years, were not included in the ELR but were downloaded and analysed separately to assess changes over time when possible. Antimicrobial resistant 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:

1) Exclusion criterion 8 (minimum number of isolates in a study to be considered acceptable): This number was set at 50 for *E. coli* and *S. aureus* and at the default of 10 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.
2) Exclusion criterion 16 (studies in which AMR was only assessed genotypically): Studies in which *mecA* and/or *mecC* was used to infer the proportion of methicillin-resistant *S. aureus* (MRSA) were considered eligible.
3) Exclusion criterion 17 (others): Only studies dealing with AMR in the selected bacterial species in farmed rabbits were considered eligible (i.e. studies on pet and wild rabbits were not in the scope of the opinion).

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 if only data from a certain time period within a study were extracted.

Information extracted from the eligible assessed full-text reports/publications is described in the scientific opinion describing the ad hoc method applied in the assessment (EFSA AHAW Panel, 2021). Information on all the full-text studies that were assessed, including the reason for exclusion for those that were excluded at the full-text screening, is presented in 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 rabbits 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 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 cephalosporins (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, the one for which more isolates were tested was included.
- For fluoroquinolones, the order of preference was enrofloxacin > ciprofloxacin, meaning that enrofloxacin was always selected if resistance data for both drugs were available.
- For tetracyclines, the order of preference was tetracycline > oxytetracycline > doxycycline > chlortetracycline, therefore tetracycline was always selected if resistance data for all four drugs, or tetracycline + one of the other drugs, were present.

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

- When no information on the I category was provided in a study, it was 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 epidemiologic cut-off values (ECOFFs) reported %R, this was considered this as %R + I, as the I category is always part of the non-wild-type population.
- When %I was reported separately, it was extracted along with %R and calculated as %R + I.
- For some drugs and presence of *mecA* and/or *mecC* genes, there is no I category for the bacterial species included, therefore only %R was reported, irrespective of the assumptions mentioned above.

2.2. Data on AMR from the Istituto Zooprofilattico Sperimentale delle Venezie (IZSVe)

In addition to the data retrieved through the ELR, data available at the online public interactive report on AMR generated by the IZSVe (2021) and collected between 2017 and 2020 were also used in this opinion and are presented in the appropriate pathogen-specific section.

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 704 abstracts, 20 publications were selected for evaluation according to the criteria under Methods. Of these, 15 publications were excluded with the reasons for exclusion highlighted in columns D and E of Appendix B. The reasons for exclusion of studies are summarised in Table 1. The most common reason for exclusion was failure to find a full-text publication (n = 3) followed by another three reasons encompassing two studies each.

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

Reason	Code in Appendix B	Number of studies
Full text not available at server of the University of Copenhagen	10	3
Study does not follow a standard for antimicrobial susceptibility testing or a standard is not reported	4	2
Inclusion of non-clinical isolates that cannot be distinguished from clinical isolates	5	2
Biased data presented (only a certain subset of isolates was tested)	17[(a)]	2
AMR data from multiple host species (other than rabbit) or from non-farmed rabbits reported together	2	3
AMR data reported at bacterial genus level or above	3	1
Same animals sampled repeatedly	6	1
Fewer than the minimum number of isolates are included in the study	8	1
Study not in English	11	1
Criteria for selection of isolates unclear and/or high risk of data duplication	14	1
AMR assessed genotypically (except *mecA* used to infer methicillin resistance in staphylococci)	16	1

(a): Specified in column E, Appendix B.

In total, six eligible publications were selected for data extraction. In addition, one national report of France was selected, as it contained eligible AMR data for rabbits.

An overview of the number of eligible references for each target bacterium is shown in Table 2.

Table 2: Number of references obtained through the ELR from which AMR data were extracted

Bacterial species	Number of eligible studies for data extraction
Pasteurella multocida	4
Staphylococcus aureus	2
Escherichia coli	1
Bordetella bronchiseptica	1
Clostridium perfringens	0
Clostridium spiroforme	0
Pseudomonas aeruginosa	0
Clostridium difficile	0

Figure 1 below provides an overview of the six included references sorted by year of publication.

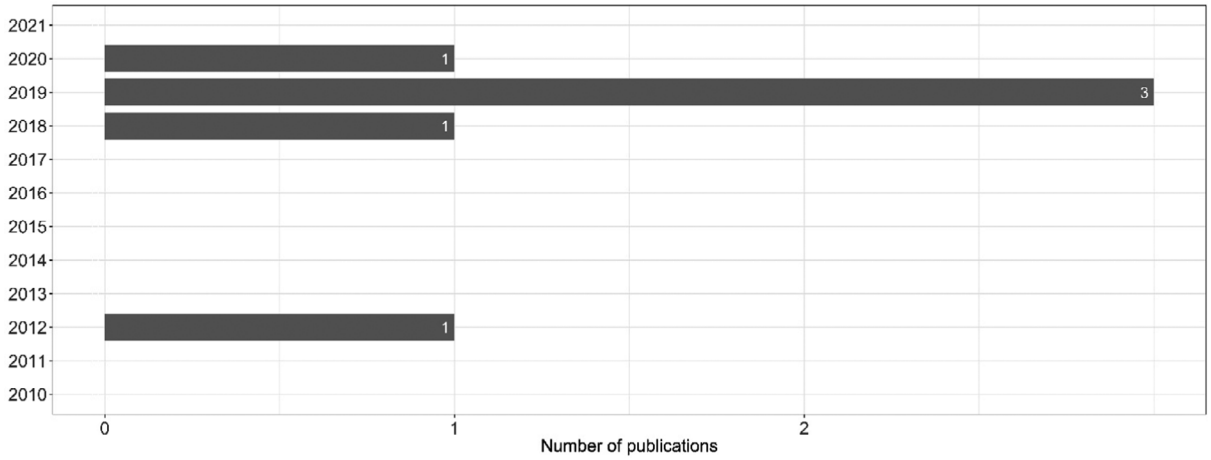


Figure 1: The six included references retrieved through the ELR arranged by year of publication

Considering geographical distribution of the references, AMR data were reported in one reference from Africa (Egypt), two from Asia (both from China), two from Europe (France and Spain) and one from South America (Brazil) (Figure 2).

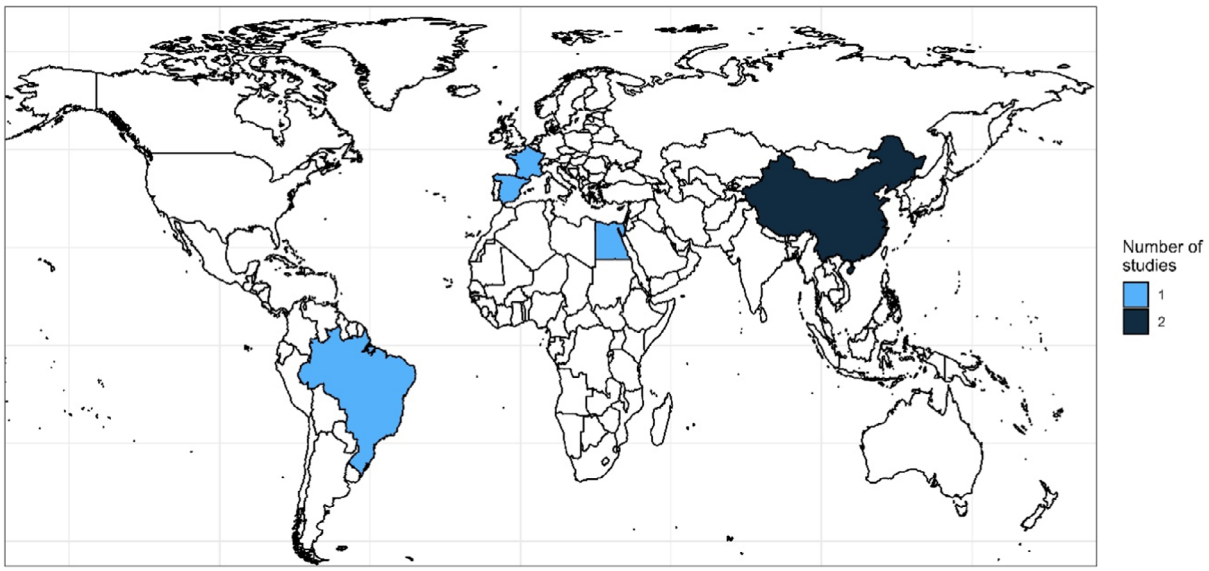


Figure 2: Geographical distribution of the six included references retrieved through the ELR

Based on the type of isolates analysed, references were divided into those with isolates deriving from a defined population of farmed rabbits, and those without – or with limited – background information on sampled rabbits (i.e. studies with isolates from a diagnostic laboratory). The latter category comprised studies with isolates from a diagnostic laboratory. Five studies had isolates obtained from samples actively collected in rabbit farms, whereas two studies had isolates from a diagnostic laboratory.

3.1.1.2. Data from national AMR monitoring reports

Additional data on AMR in clinical isolates from farmed rabbits could be only retrieved from two sources: one national AMR monitoring system [RESAPATH – France (2020), including data on *P. multocida*, *E. coli* and *S. aureus*] and from one online interactive AMR report for Italy provided by the IZSVe (2021) (including data from on *P. multocida*, *S. aureus*, *E. coli*, *B. bronchiseptica*, *C. perfringens* and *C. spiroforme)*. These data were extracted and are presented in relevant sections. For the purpose of this scientific opinion, the same terminology used in the original reports (i.e. proportion of non-susceptible isolates or proportion of resistant isolates) based on the selected breakpoint for defining resistance/susceptibility was used to here describe and report the results provided.

3.1.2. Occurrence of AMR

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

In general, AMR data from different studies are extremely difficult to compare due to differences in study design, populations, methods, interpretive criteria, etc. The number of antimicrobial susceptibility testing (AST) results for any given antimicrobial extracted from the seven references selected (a total of 4,804; Appendix B) was largely due to the number of results found for *P. multocida* (n = 1,722; 35.8% of the total number of results) and *E. coli* (1,710; 35.6%), followed by *S. aureus* (934; 19.4%) and *B. bronchiseptica* (438; 9.1%). All results were obtained using the disk diffusion method (Appendix B).

Furthermore, the definition of AMR differed across studies, as the intermediate category defined by clinical breakpoints was included in the calculation of AMR frequencies in some studies, whereas it was omitted in others. Accordingly, in the figures with resistance data, we describe AMR occurrence for each study with %R or %R + I; therefore, this should be taken into account when comparing studies. It is also important to mention that no infection- and host-specific clinical breakpoints (CBPs) exist for bacterial pathogens isolated from rabbits. This makes data interpretation and comparison of studies more complex, as for some studies, it was unclear if the CBPs used were adapted from other bacterial species or other animal species, from humans or even defined by the author.

Taken together, the outcomes of the present report should be interpreted and cited with caution, as all specificities of individual studies cannot be taken into consideration. To support conclusions made from the figures or tables (e.g. a high proportion of resistance in a certain country/continent), it is strongly recommended to consult individual papers and check if results may be biased by previous antimicrobial treatment (very likely for commercial rabbitries except in the case of antibiotic-free production systems), sampling of animals in a certain environment, the use of certain diagnostic methods or breakpoints or other factors.

For the RESAPATH French AMR monitoring report (2020), AMR data on clinical isolates retrieved in 2014–2018 for the three bacterial species of interest for this opinion (*P. multocida*, *E. coli* and *S. aureus*) included are provided in the pathogen-specific sections. The AST data were generated by disk diffusion, and results were interpreted as susceptible/non-susceptible based on the veterinary guidelines of the Antibiogram Committee of the French Society of Microbiology (CA-SFM). Assessment of changes in AMR levels over time in the pathogens under evaluation based on the data in the report is hampered by the inclusion of certain antimicrobials only in certain years and the limited sample size reached, and therefore, results must be analysed carefully.

Finally, data on AMR on several pathogens of interest for this opinion (*P. multocida*, *S. aureus*, *E. coli*, *B. bronchiseptica*, *C. perfringens* and *C. spiroforme)* were available at the online interactive AMR report generated by the IZSVe (2021). These data are generated through the routine monitoring activities conducted at the veterinary diagnostic laboratories in the Italian regions of Veneto, Friuli Venezia Giulia and Trentino Alto Adige, where over 70% of the Italian rabbit production is located, and includes AST results from clinical isolates retrieved from 245 rabbit commercial farms between 2017 and 2021. For interpretation of the AST data, human or animal-derived breakpoints from the Clinical

and Laboratory Standards Institute (CLSI M100, CLSI VET01S) were used when available and, for pathogens/antimicrobials lacking those, the ECOFFs from the veterinary guidelines of the Antibiogram Committee of the French Society of Microbiology (CA-SFM) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were preferred. MIC values of tiamulin, valnemulin and bacitracin obtained for *C. perfringens* and *C. spiroforme* were interpreted on the basis of ECOFFs determined at the IZSVe.

3.1.3. *Pasteurella multocida*

3.1.3.1. Results of the ELR by bacterium

P. multocida is an opportunistic pathogen residing in the upper respiratory tract of rabbits. Especially under stressful conditions (e.g. overcrowding, high speed of cold air, hot dry air), it may cause snuffles, which is productive rhinitis. This disorder can be followed by sequels such as conjunctivitis, otitis, subcutaneous abscesses, bronchopneumonia, metritis and pyometra.

In total, four studies with ≥ 10 *P. multocida* isolates were included. The studies represented Brazil, China, Egypt and France, respectively. The distribution of *P. multocida* isolates per site of infection is shown in Figure 3.

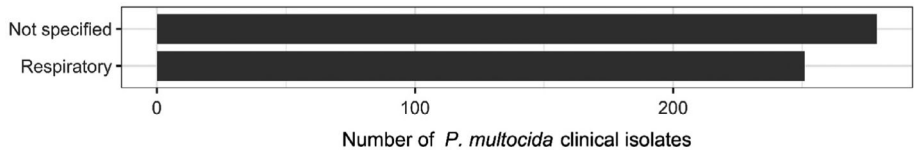
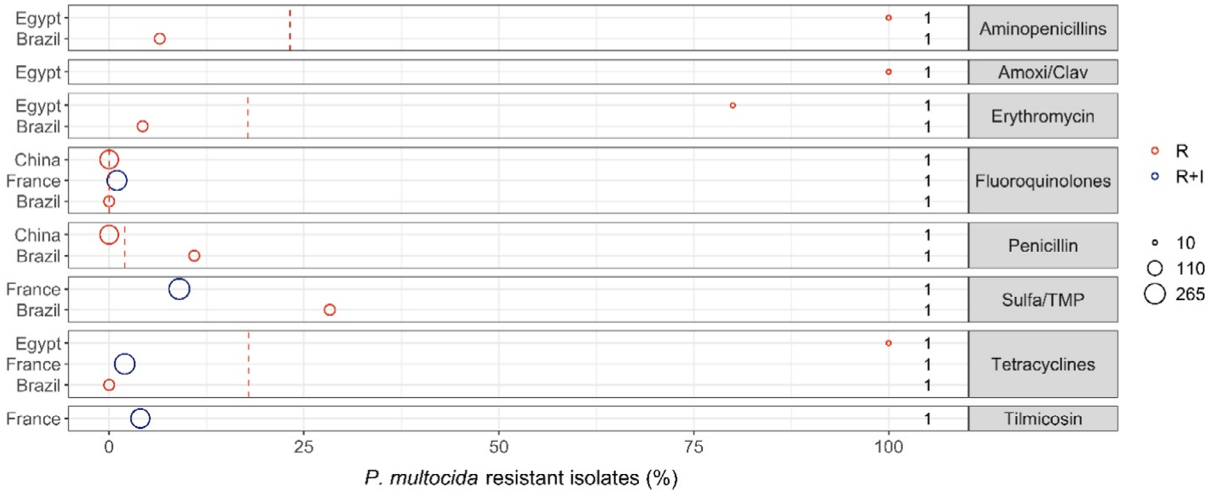


Figure 3: Distribution of *P. multocida* isolates per site of infection

Figure 4 shows for each country the proportion of resistance reported in individual studies with at least 10 *P. multocida* 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 (red circle) or resistance merged with intermediate (blue circle). The dashed lines indicate, for each antibiotic, the weighted arithmetic mean of %R. 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 4: *Pasteurella multocida* resistance data for each included study sorted by country

Overall, fairly low levels of resistance were reported in *P. multocida* isolates. For **penicillins**, one study from Egypt reported that all of 10 included isolates were resistant to both ampicillin (included as a surrogate for penicillin/amoxicillin, used only by the parenteral route in rabbits) and amoxicillin–clavulanic acid (Awad and Abd El-Hamid, 2019). Another study from Brazil (Ferreira et al., 2012) found 10.9% and 6.5% of 45 isolates resistant to penicillin and amoxicillin, respectively, whereas a Chinese study found all 205 included isolates susceptible to penicillin (Wang et al., 2019). All isolates from the

Brazilian and Chinese studies were susceptible to **fluoroquinolones** (enrofloxacin), whereas 1% of isolates from the French surveillance system were resistant to this drug (RESAPATH, 2020). Similarly, low proportions of resistance were observed for tetracyclines in two of three studies, the one exception again being the Egyptian study reporting resistance in all 10 isolates (Figure 4). More variable levels of resistance were observed for **sulfonamides–trimethoprim**, whereas resistance levels for the macrolides **erythromycin** and **tilmicosin** were close to zero with the exception of the Egyptian study reporting 80% erythromycin resistance.

3.1.3.2. Results from the national AMR monitoring reports

Information on AMR in rabbit clinical *P. multocida* originating mainly from respiratory disorders and skin and mucous membrane disorders was included in the RESAPATH (France) national reports (results provided for all isolates together irrespective of the specimen type). Between 110 and 396 isolates were tested each year from 2014 to 2018 (> 340 isolates per year the first 3 years) using four antimicrobials of interest in this opinion (amoxicillin was tested only in 2018 with 1% of the isolates classified as non-susceptible, data not shown). Proportions of non-susceptible isolates (%R + I) were always below 10% (Figure 5). Over the study period, an increasing trend was seen for sulfonamides–trimethoprim. For tilmicosin, there was an increasing trend although a decrease was noticed in 2018. The trend for enrofloxacin is stable with proportions of non-susceptible isolates always at 1%. Results for doxycycline, although based on two data points, indicated a decreasing trend (Figure 5).

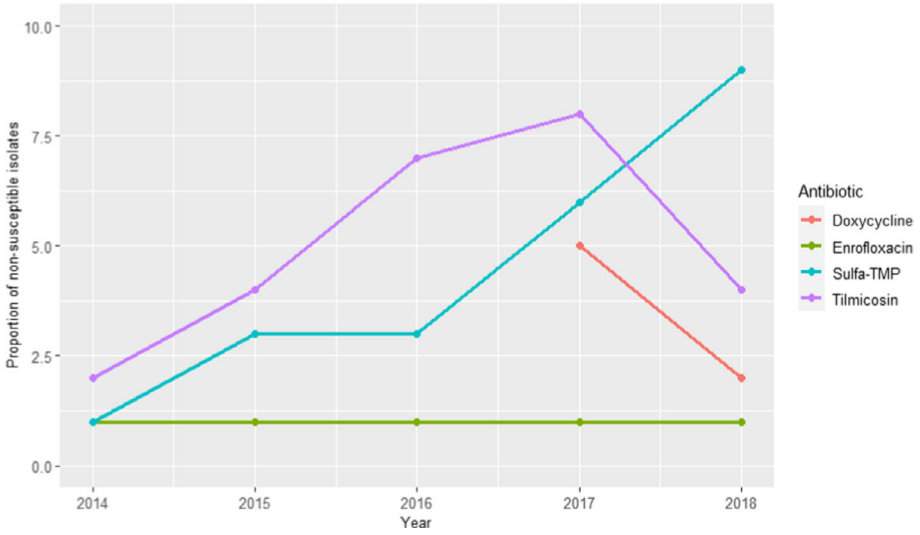


Figure 5: Proportion (%) of clinical *P. multocida* isolates retrieved from rabbit (all pathologies) non-susceptible to four antimicrobials of interest reported by the RESAPATH monitoring programme

In addition, the online AMR report provided by the IZSV includes AST data on four antimicrobials of interest for this opinion on 896 *P. multocida* isolates collected from young animals with multiple pathologies (pneumonia, otitis, abscesses and metritis). Results indicate also a very low proportion of non-susceptible isolates to enrofloxacin (< 1%), and higher levels of non-susceptible isolates for sulfonamides–trimethoprim (< 5%), tilmicosin (11%) and tetracycline (15%) (Figure 6).

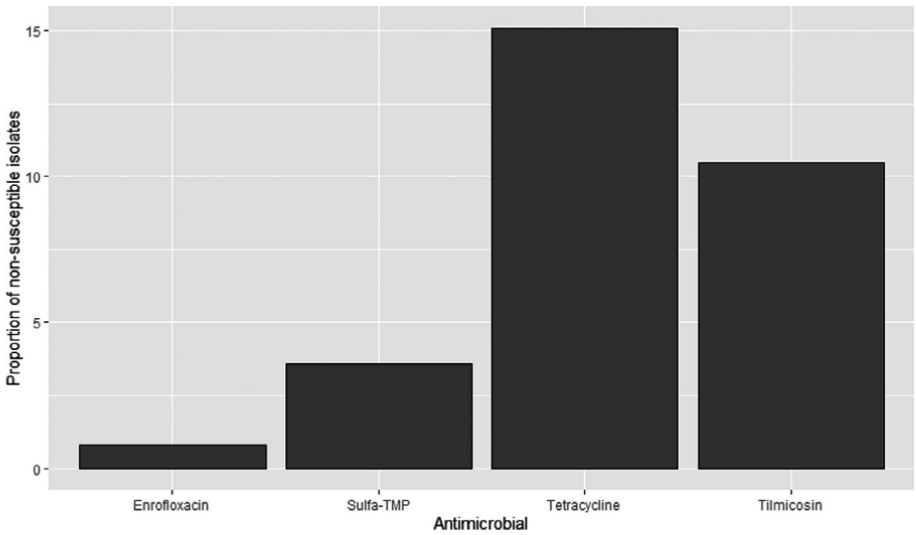


Figure 6: Proportion (%) of clinical *P. multocida* isolates retrieved from rabbit (all pathologies) non-susceptible to four antimicrobials of interest included in the online AMR IZSVe report (2021)

3.1.4. *Staphylococcus aureus*

3.1.4.1. Results of the ELR by bacterium

Staphylococcus aureus is an opportunistic pathogen that might colonise various body sites in rabbits. It can cause pyoderma and, upon invasion of subcutaneous tissues, a range of other infections such as mastitis, abscesses, pneumonia, metritis/pyometra or pododermatitis.

Two studies with ≥ 50 *S. aureus* isolates were included. One study from Spain (Moreno-Grua et al., 2018) found cefoxitin resistance in 12.5% of 240 isolates from various disorders in rabbits. All cefoxitin-resistant isolates were confirmed as MRSA, with 27 and three isolates having *mecA* and *mecC*, respectively. The other reference, the French surveillance system (RESAPATH, 2020), also reported data for *S. aureus* isolated in 2018 from rabbits, with the majority (46.3%) of 162 isolates being from skin and soft tissue infections. RESAPATH reported a much lower proportion of cefoxitin resistance (4% of 129 isolates) compared with the Spanish study. Resistance proportions for other drugs varied from 13% (penicillin) to 54% (spiramycin).

3.1.4.2. Results from the national AMR monitoring reports

Antimicrobial susceptibility data for four antimicrobials of interest in rabbit isolates were available for at least 2 years between 2014 and 2018 in RESAPATH reports. Isolates were mainly sampled from rabbits with skin or mucous membrane diseases, and ranged between 102 and 287 tested each year. Proportions of non-susceptible isolates (%R + I) were higher for spiramycin (49–64%) compared with sulfonamides–trimethoprim and doxycycline (tested only 2 years), which remained between 28 and 50%, while they remained below 22% for penicillin G. Decreasing trends were seen for the four drugs from 2015 to 2018 (Figure 7).

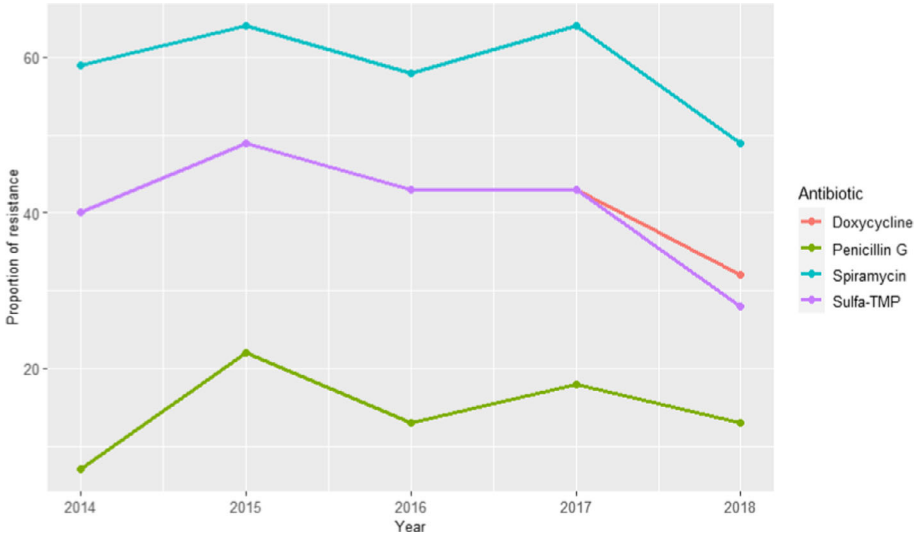


Figure 7: Proportion (%) of clinical rabbit *S. aureus* isolates retrieved from all pathologies non-susceptible to four antimicrobials of interest reported by the RESAPATH monitoring programme

In the online IZSVe AMR report (2021), AST results from 537 coagulase-positive *Staphylococcus* sp. isolates, most of which could be assumed to be *S. aureus*, and that were retrieved from breeders and young animals with mastitis, dermatitis or pneumonia, are provided for four antimicrobials of interest for this opinion. The highest proportions of non-susceptible isolates were found for tylosin (76%) and tiamulin (34%), while proportion of non-susceptibility to penicillin and doxycycline were ~ 12% and 1%, respectively (Figure 8).

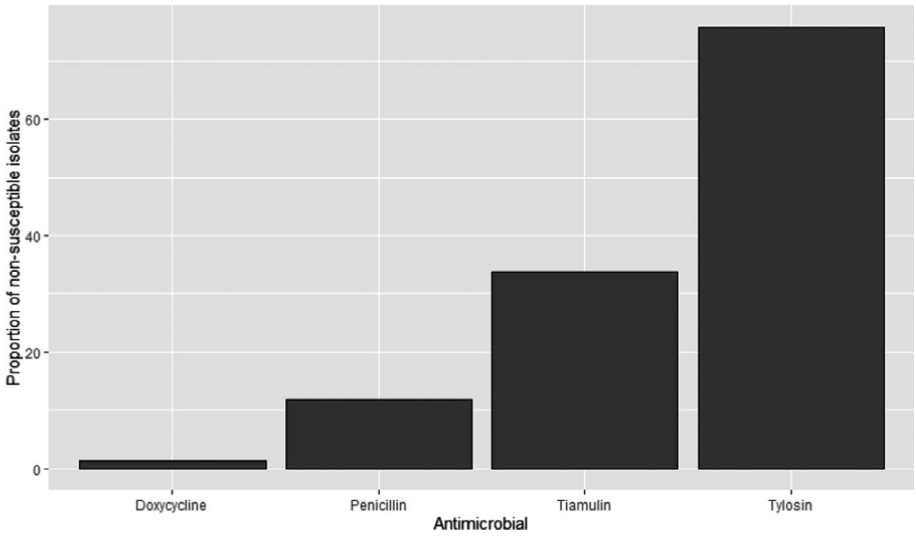


Figure 8: Proportion (%) of clinical coagulase-positive *Staphylococcus* isolates retrieved from rabbit (all pathologies) non-susceptible to four antimicrobials of interest included in the online AMR IZSVe report (2021)

3.1.5. *Escherichia coli*

3.1.5.1. Results of the ELR by bacterium

In rabbits, *E. coli* has primarily been associated with neonatal as well as post-weaning colibacillosis accompanied by enteritis–diarrhoea.

According to the ELR, only the French surveillance system RESAPATH (2020) reported eligible susceptibility data for *E. coli* in rabbits (isolates tested in 2018). The 277 isolates of that report were mostly (70.8%) from digestive pathology, which may be treated using sulfonamides, fluoroquinolones

and aminoglycosides. Proportions of non-susceptible isolates to **aminoglycosides** were 9%, 10%, 18% and 40% for gentamicin, apramycin, neomycin and streptomycin, respectively. A higher proportion of non-susceptible isolates (66%) was reported for sulfonamides–trimethoprim, while fluoroquinolone resistance was uncommon, with only 3% of isolates being non-susceptible to enrofloxacin. Overall 1% of the isolates were non-susceptible to ceftiofur. This 3GC is not the best indicator of extended-spectrum beta-lactamase (ESBL), but the result still suggests that very few *E. coli* from rabbits are ESBL producers.

3.1.5.2. Results from the national AMR monitoring reports

When the AMR results included in up to the five previous RESAPATH reports are considered, between 117 and 564 isolates were tested with one or more of the antimicrobials of interest for this opinion in the 2014–2018 period (Figure 9). Proportions of non-susceptible isolates (%R + I) were high for sulfonamides–trimethoprim (65–74%) and streptomycin (40–66%) and below 25% for the other drugs. Decreasing trends were seen for streptomycin and enrofloxacin in particular, while proportions remained fairly stable for other drugs.

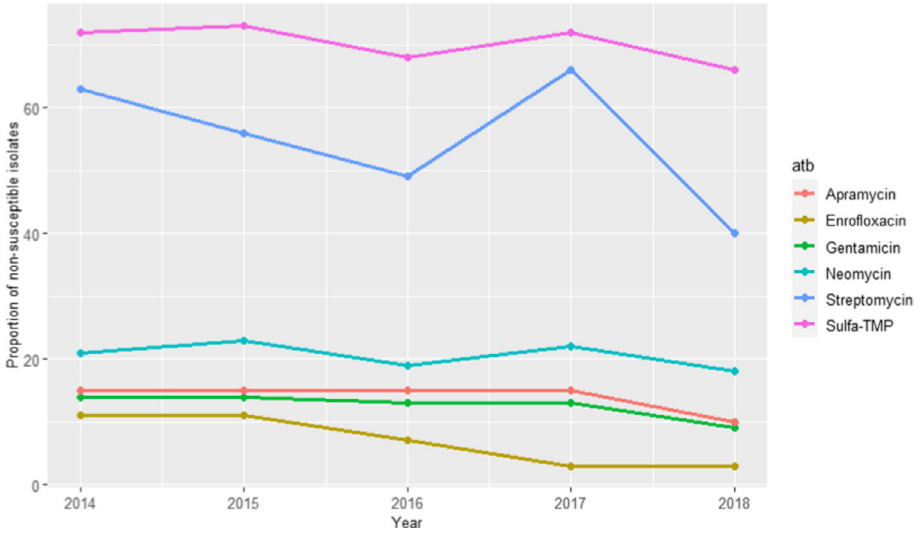


Figure 9: Proportion (%) of clinical rabbit *E. coli* isolates retrieved from all disorders non-susceptible to six antimicrobials of interest reported by the RESAPATH monitoring programme

The online IZSVe AMR report (2021) provides AST results between 1,985 and 1,987 *E. coli* clinical isolates retrieved from young animals with digestive pathologies and tested with two antimicrobials of interest for this opinion. Similar to what was observed in the RESAPATH collection, proportions of non-susceptible isolates were particularly high for sulfonamides–trimethoprim (87%) and lower for enrofloxacin (29%).

3.1.6. *Bordetella bronchiseptica*

3.1.6.1. Results of the ELR by bacterium

Similar to *P. multocida*, *B. bronchiseptica* is an upper respiratory tract pathogen associated with snuffles in rabbits.

One Chinese study was included (Wang et al., 2020). The study comprised 219 isolates from lung samples of rabbits with respiratory disease. All isolates were susceptible to fluoroquinolone (ciprofloxacin), whereas 3.2% of isolates were resistant to aminopenicillin (ampicillin).

3.1.6.2. Results from the national AMR monitoring reports

The online IZSVe AMR report (2021) provides AST data on 57 *B. bronchiseptica* isolates retrieved from cases of pneumonia and upper respiratory tract infections in young animals, which were tested using four antimicrobials of interest for this opinion. Proportions of non-susceptible isolates ranged between 58% (tilmicosin) and 2% (enrofloxacin), with tetracycline and sulfonamides–trimethoprim showing intermediate levels (16 and 11%, respectively) (Figure 10).

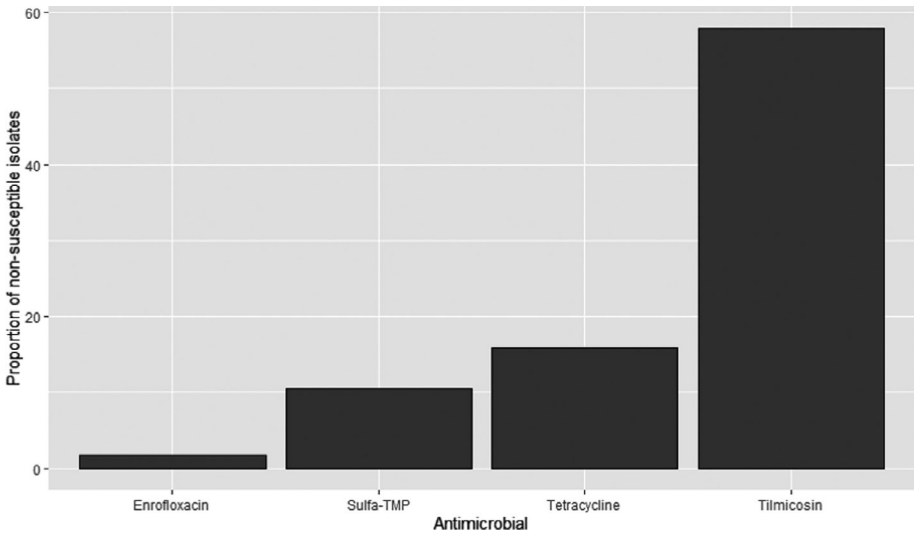


Figure 10: Proportion (%) of clinical *B. bronchiseptica* isolates retrieved from rabbit (respiratory pathologies) non-susceptible to four antimicrobials of interest included in the online AMR IZSVe report (2021)

3.1.7. *Clostridium perfringens* and *C. spiroforme*

Clostridium perfringens causes intestinal disorders and enterotoxaemia in rabbits through the production of exotoxins. Although *C. perfringens* type E (alpha and iota toxins producer) has been traditionally associated with typhlitis in rabbits, type A (alpha toxin producer) is the most prevalent toxinotype isolated from diseased subjects (Agnoletti et al., 2009). Well-known binary toxins similar to the iota toxin of *C. perfringens* are produced by *C. spiroforme*, which causes severe diarrhoea and a high mortality rate, mainly in post-weaned rabbits.

No eligible references were retrieved in the ELR, but the online IZSVe AMR report (2021) includes AST data on four antimicrobials of interest tested for between 682 and 694 *C. perfringens* isolates retrieved from young animals with enteric disorders and between 818 and 841 *C. spiroforme* isolates from typhlitis cases in young animals. Proportions of non-susceptible isolates were much higher for *C. spiroforme* isolates for bacitracin, tiamulin and valnemulin, with proportions close to or above 75% compared with less than 35% for the three antimicrobials in *C. perfringens* cases (Figure 11). In contrast, proportions of non-susceptible isolates for doxycycline were very low for both species (Figure 11).

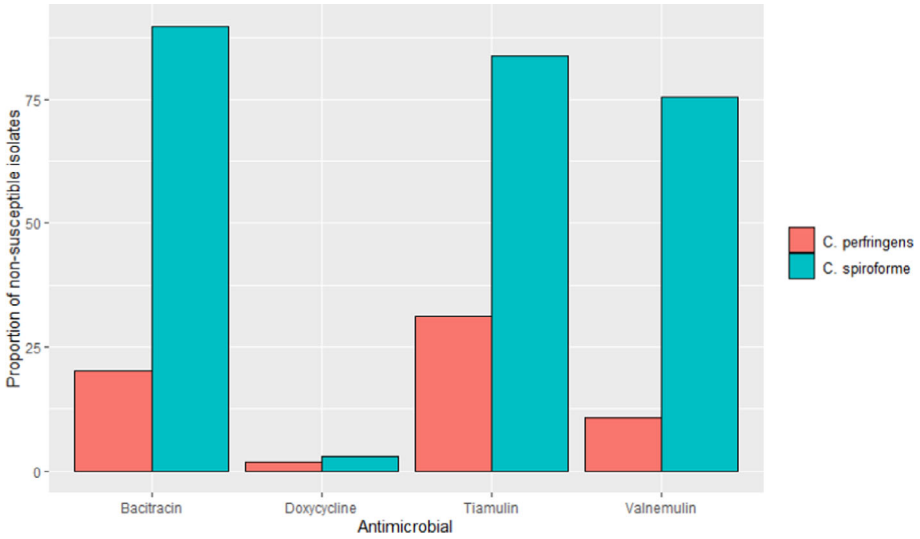


Figure 11: Proportion (%) of clinical *C. perfringens* and *C. spiroforme* isolates retrieved from rabbit (digestive disorders) resistant to four antimicrobials of interest included in the online AMR IZSVe report (2021)

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 rabbits of the antimicrobial-resistant bacteria included in the list.

After discussion of the individual judgements for each bacterium, it was agreed that based on the available evidence it was not possible to identify with sufficient certainty (i.e. > 66%) any of the pathogens assessed among the most relevant antimicrobial-resistant bacteria in rabbits in the EU (Figure 12). *Escherichia coli*, *Staphylococcus aureus* and *Pasteurella multocida* were the three highest ranked relevant bacteria with the lower uncertainty ranges compared to the other bacteria assessed. This was a result of their perceived clinical importance as pathogens involved in major health issues for rabbits (mainly gastrointestinal disorders for *E. coli* and a wide spectrum of disorders, including mastitis and pododermatitis in *S. aureus* and *P. multocida*) (Corpa et al., 2009; Kylie et al., 2017; Solans et al., 2019), of their role as drivers of antimicrobial usage in farmed rabbits and of the availability of some data (mostly coming from the RESAPATH and IZSVe monitoring systems, that includes > 100 isolates tested each year in the 2017–2020 period using a range of antimicrobials of interest for this opinion) indicating the presence of large (> 40%) proportions of non-susceptible isolates to certain clinically relevant antimicrobials in the last years (Figures 4–9). Nevertheless, the limited amount of data and results found (originating mainly from only two countries, France and Italy), along with the absence of consistent reports on antimicrobial failures associated with these two pathogens and the lack of rabbit-adapted clinical breakpoints that could help to assess the clinical significance of *in vitro* AST results resulted in a high uncertainty that prevented their inclusion among the most relevant antimicrobial-resistant bacteria in rabbits in the EU.

Pasteurella multocida was the pathogen for which a larger number of eligible references and AST results were retrieved in the ELR, probably reflecting its clinical importance as a pathogen in farmed rabbits causing respiratory diseases, a major issue in breeding rabbits for which it is the main aetiologic agent (García-Alvarez et al., 2015; Massacci et al., 2018), and also other disorders such as reproductive problems (Boucher et al., 2001), although these consisted only in three scientific publications and two national monitoring programmes including data from four countries (only France and Italy in Europe). Most results suggested that resistance to the relevant antimicrobial classes assessed here was not as common as for *E. coli* and *S. aureus* with the only exception of one study from Egypt that described very high (80–100%) proportions of resistant isolates to several antimicrobials although in a very small (n = 10) sample size, while almost all the remaining results reported resistance levels approximately or below 10% (Figure 4). Based on these data, this pathogen was ranked lower than *E. coli* and *S. aureus*, although again the lack of evidence resulted in a relatively large uncertainty range (Figure 12).

For the remaining pathogens, very little to no data were available through the ELR, and therefore, there was a very large uncertainty in the assessment of their relevance as antimicrobial-resistant pathogens in rabbits in the EU. *Clostridium spiroforme* is also a relevant rabbit pathogen involved in digestive disorders, sometimes in cases of antibiotic-associated colitis and other forms of antibiotic treatment-related dysbiosis. This clinical presentation is very relevant in farmed rabbits (particularly in combination with other pathogens, mainly *E. coli*) (Kylie et al., 2017; Solans et al., 2019) and is in fact associated with the use of antimicrobials. However, very limited information on the prevalence of resistance was available for the assessment, and the role of such resistance on the treatment of animals could therefore not be evaluated adequately therefore preventing their inclusion among the most relevant AMR pathogens in rabbits. Similarly, the lack of data on the prevalence of AMR in *Bordetella bronchiseptica* also hampered their assessment.

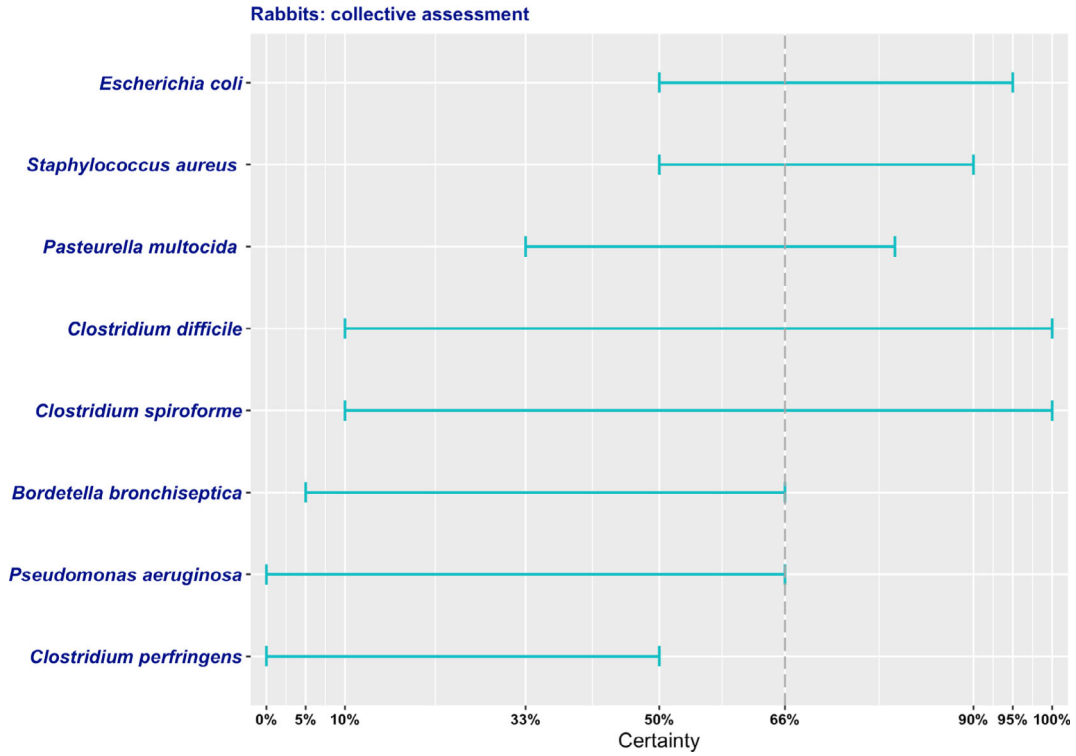


Figure 12: Level of certainty for the inclusion of the selected antimicrobial-resistant pathogens of rabbit among the most relevant in the EU

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 rabbits in the EU, and their eligibility for being listed and categorised in the framework of the AHL—will not be assessed in later steps of this EFSA mandate given that none of the pathogens in the scope of this opinion was included among the most relevant antimicrobial-resistant pathogens in rabbits for the EU.

EFSA has summarised the global state of play on AMR in rabbits for the following bacteria: *Escherichia coli*, *Pasteurella multocida*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bordetella bronchiseptica*, *Clostridium spiroforme*, *Clostridium perfringens*, and *Clostridium difficile*. Based on the evidence available and expert opinion, none of the evaluated bacterial species were included among the most relevant antimicrobial-resistant rabbit pathogens in the EU (lower uncertainty ranges for all pathogens were lower than 66%). Still, *E. coli* and *S. aureus* were ranked higher than other pathogens based on the limited evidence retrieved suggesting that resistance to certain clinically relevant antimicrobials may not be uncommon, as well as their clinical importance as rabbit pathogens, and the common use of antimicrobials to treat infections caused by them.

The scientific assessment of the global state of play of the resistant bacterial pathogens of rabbits included in this opinion and of their EU relevance was hampered by several important sources of uncertainty mainly due to a lack of data and to 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:

- The strategy used to retrieve relevant information on AMR data for the rabbit bacterial pathogens of interest resulted in a reduced number of eligible references, probably reflecting the more limited economic importance of farmed rabbits compared with other livestock species, which in turn would result in a low number of studies on infectious diseases in general (and AMR in particular) in this species under farm conditions (Boucher et al., 2001; Marlier et al., 2006).

- Due to the scope of the ELR, only studies published in the last 10 years and in English were considered eligible, therefore introducing a possible selection bias.
- Information on the rationale and study design for the references retrieved in the ELR was limited and heterogeneous, making the detailed assessment of the representativeness of the isolates included in each study very difficult. Furthermore, several of the bacterial species included here can also be found in healthy animals (e.g. *E. coli*, *P. multocida*, *S. aureus*). Therefore, even if they originated from diseased animals, they may not be the causative agent in a proportion of cases and could not be quantified. Finally, it was often not possible to assess whether multiple isolates may have originated from single epidemiological units (i.e. farms), which could have led to overrepresentation of certain strains (and phenotypes), further limiting the representativeness of the isolates considered.
- Even though only studies exceeding a minimum quality threshold were included (e.g. use of international or national standards) and in this case, most of the AST data retrieved in the ELR were obtained through the disk diffusion method and referred the use of CBPs, different references to support the CBPs were provided and the specific concentrations used were not evaluated here, what could have resulted in the use of different breakpoints. Therefore, descriptive statistics 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 in which the sample size was small.
- Few rabbit-adapted CBPs exist for any of the pathogens and antimicrobials evaluated here (Tao et al., 2017); therefore, the significance of the AST results obtained in the ELR for predicting the success of antimicrobial treatment is unknown; therefore, further stressing that results presented in this opinion should be interpreted carefully.
- AMR data referring to one or more of the bacterial pathogens of interest were retrieved from only two national AMR monitoring systems. Therefore, it was not possible to assess reliably whether country-specific differences exist, and within-country trends over time must be assessed carefully due to the large yet limited sample sizes that may not be representative of the whole country, and other potential biases associated with the process by which the panels of isolates were built each year.

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. Therefore, there is a need for reliable data on pathogenic bacteria from rabbits from different regions of the world obtained through the use of standardised methodologies that would allow making comparisons between locations and over time. This need is particularly critical given the scarce information currently available in the peer-reviewed scientific literature and the lack of inclusion of clinical isolates from rabbits in most national AMR monitoring programmes, as well as the absence of rabbit-adapted clinical breakpoints that allow the identification of clinically relevant resistant phenotypes in rabbit pathogens.

Generating reliable AMR data for highly relevant rabbit pathogens for which some evidence on the occurrence of antimicrobial-resistant phenotypes exist, such as *E. coli* and *S. aureus*, is critical to correctly assess the current situation in the EU and worldwide, given that the currently available information does not allow a reliable evaluation. Similarly, availability of this type of data for other clinically relevant pathogens in which resistance may be less common such as *P. multocida* would be also very valuable to ensure that most isolates remain susceptible to the most commonly used antimicrobial treatments. Monitoring AMR in farmed rabbits is important given that compared with other food-producing animals and relative to the body weight of each species, there is a higher level of antimicrobial consumption in intensive rabbit production than in any other livestock species (Agnoletti et al., 2018; ANSES, 2020). In this sense, inclusion of AMR data from rabbit pathogens in additional national monitoring programmes would lead to the generation of data that could allow the evaluation of trends over time (i.e. detection of increases/decreases in resistance levels) if the methodological biases that may occur in a given country remain more or less constant over time for a given national programme.

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Abbreviations

3GC	Third-generation cephalosporin
AHL	Animal Health Law
AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
CBP	clinical breakpoint
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
ToR	Term of Reference
UTI	Urinary tract infection

Appendix A – Search strings applied

1) **PubMed**:

Common search string "Antimicrobials"

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

Host-based strings

(rabbit[Title/Abstract] OR rabbits[Title/Abstract] OR laurex[Title/Abstract] OR laurices[Title/Abstract] OR laurice[Title/Abstract] OR cuniculture[Title/Abstract]) OR ("Rabbits"[Mesh]) AND (2010:2021[pdat])

"Bacterial species"

"Bordetella bronchiseptica"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR "Pasteurella multocida"[Title/Abstract] OR "Pseudomonas aeruginosa"[Title/Abstract] OR "Staphylococcus aureus"[Title/Abstract] OR (("Bordetella bronchiseptica"[MeSH Terms] OR "Escherichia coli"[MeSH Terms] OR "Pasteurella multocida"[MeSH Terms] OR "Pseudomonas aeruginosa"[MeSH Terms] OR "Staphylococcus aureus"[MeSH Terms]) AND 2010/01/01:2021/12/31[Date - Publication])

Additional search for Clostridium species in rabbits performed in August 2021 (the aim was C. perfringens, C. difficile and C. spiroforme):

("Clostridium perfringens"[Title/Abstract] OR "Clostridium spiroforme"[Title/Abstract] OR "Clostridium difficile"[Title/Abstract]) OR ((("Clostridium perfringens"[Mesh]) OR "Clostridioides difficile"[Mesh]) OR "Clostridium spiroforme" [Supplementary Concept])

2) **Embase**:

Common search string "Antimicrobials"

3) antibiotic resistance/ or exp antibiotic sensitivity/ or exp drug resistance/
4) 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]
5) 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]
6) 2 or 3
7) 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]
8) 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]
9) 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]
10) 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]
11) 5 or 6 or 7 or 8
12) antibiotic agent/
13) 10 or 9
14) 11 and 4

15) 12 or 1

Host-based string

16) leporidae/ or domestic rabbit/ or infant rabbit/ or oryctolagus/ or rabbit breed/ or sylvilagus/
17) (Rabbit or Rabbits or Cuniculture or Laurices or Laurex or Laurice).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]
18) 1 or 2

"Bacterial species"

19) Bordetella bronchiseptica/
20) Escherichia coli/
21) Pasteurella multocida/
22) Pseudomonas aeruginosa/
23) Staphylococcus aureus/
24) 1 or 2 or 3 or 4 or 5
25) ("Bordetella bronchiseptica" or "Escherichia coli" or "Pasteurella multocida" or "Pseudomonas aeruginosa" or "Staphylococcus aureus").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]
26) 6 or 7

Additional search for *Clostridium* species performed in August 2021 (the aim was *C. perfringens*, *C. difficile* and *C. spiroforme*. Note that there was no mesh term for *C. spiroforme* in Embase):

27) Clostridium perfringens/
28) clostridioides difficile/
29) ("clostridium spiroforme" or "clostridium difficile" or "clostridium perfringens").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]
30) 1 or 2 or 3

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.5575775.

Appendix C – Clinically relevant antibiotics for which data were extracted

Bacteria	Treatment
***Clostridium* spp. (*C. difficile*, *C. perfringens*, *C. spiroforme*)**	Oral: doxycycline, bacitracin zinc, tiamulin, valnemulin
Escherichia coli	Enteritis–diarrhoea: neomycin, dihydrostreptomycin, apramycin, gentamicin, sulfonamides, enrofloxacin
Pasteurella multocida ***Bordetella bronchiseptica***	Parenteral: amoxicillin, penicillin, oxytetracycline, macrolides (spiramycin, tulathromycin, tilmicosin) Oral: sulfonamides, doxycycline, oxytetracycline, tilmicosin, tiamulin, tylosin, enrofloxacin
Pseudomonas aeruginosa	Parenteral: macrolides (spiramycin, tulathromycin, tilmicosin) Oral: doxycycline, oxytetracycline, tilmicosin, enrofloxacin
Staphylococcus aureus	Parenteral: amoxicillin, penicillin, oxytetracycline, macrolides (spiramycin, tulathromycin, tilmicosin) Oral: sulfonamides, doxycycline, oxytetracycline, tilmicosin, tiamulin, tylosin
***Enterococcus* spp. (*E. faecalis*, *E. hirae*)**	Tilmicosin, gentamicin, bacitracin zinc

Appendix D – Exact percentages of weighted arithmetic means of %R and %R + I, respectively

Antibiotic	How resistance is reported (% R or %R + I)	Weighted arithmetic mean proportion of resistance (%)	Maximum resistance % observed	Minimum resistance % observed	Standard deviation (SD)	Bacterial species/ genus
Aminopenicillins	R	23.2	100	6.5	36.1	*P. multocida*
Erythromycin	R	17.8	80	4.3	29.3	*P. multocida*
Fluoroquinolones	R	0	0	0	0	*P. multocida*
Penicillin	R	2	10.9	0	4.2	*P.* multocida
Tetracyclines	R	17.9	100	0	38.6	*P. multocida*
Cefoxitin	R	9.5	12.5	4	4.1	*S. aureus*