Antimicrobial resistance of Pasteurella multocida isolated from diseased food-producing animals and pets

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Abstract

Surveillance of *Pasteurella multocida* resistance in food-producing animals is essential to guide the first-line treatment of respiratory diseases and to limit economic losses. Since *Pasteurella* are the most common bacteria isolated from dog and cat bites, this surveillance is also needed to guide treatment in humans in case of bites. The aim of this study was to characterize the phenotypic resistance of *P. multocida* strains isolated from respiratory infections in animals, including both food-producing animals and pets. Data collected between 2012 and 2017 by the French national surveillance network for antimicrobial resistance referred to as RESAPATH were analyzed. The proportions of resistance to antimicrobials of relevance in veterinary and human medicines were estimated for each animal species. For cattle, resistance trends over the period were investigated using non-linear analysis applied to time-series. In total, 5,356 *P. multocida* isolates were analyzed. Proportions of resistance of *P. multocida* were almost all below 20% over the period, and, more precisely, all resistance proportions were below 10% for rabbits, sheep and dogs. The highest resistance proportions to enrofloxacin were identified for cattle (4.5%) and dogs (5.2%). Despite its frequent use in livestock, resistance to florfenicol was less than 1% in *P. multocida* strains, regardless of the animal species considered. Time series analyses revealed continuous increases in resistance to tetracycline, tilmicosin, flumequine and fluoroquinolones in *P. multocida* strains isolated from cattle. These trends contrast with the decrease in use of antibiotics in cattle in France and with the decrease in resistance observed in *E. coli* isolated from diseased cattle.

Keyword: *Pasteurella multocida*; antimicrobial resistance; food-producing animal; dog; cat; time series; RESAPATH

1. INTRODUCTION

Pasteurella multocida is a zoonotic bacterium that can infect a wide range of species, such as mammals and poultry. Humans are mainly contaminated by contact with animals, most often by bites, scratches or licking of abraded skin. They develop local inflammation of the soft tissues that can lead to bacteremia in severe cases (Wilson and Ho, 2013). In animals, *P. multocida* can cause primarily respiratory or systemic diseases (Harper and Boyce, 2017). Particularly in production animals such as cattle, swine and rabbits, *P. multocida* is a major cause of morbidity, leading to significant economic losses all over the world (Davies et al., 2003).

Antibiotics are the most used veterinary products for the management of *P. multocida* infections in animals. The main antibiotic classes approved for treatment of respiratory diseases include first-generation antibiotics, but also critically important antibiotics such as fluoroquinolones (Evira, 2018), which are also used in humans. Despite the frequent use of antibiotics to treat respiratory infections caused by *P. multocida* in animals, data on the epidemiology of its resistance are still rare. Studies have mainly focused to date on the genetic characterization of this bacterium, its phylogenetics, and its virulence (García-Alvarez et al., 2017; Massacci et al., 2018). In the past, *Pasteurella* resistances in animals have mainly been the subject of point-in-time research (Kaspar et al., 2007) or multiple year studies for example in Australia (Dayao et al., 2014), in China (Tang et al., 2009), or in Europe within the framework of European projects such as Vetpath (El Garch et al., 2016) and Compath (Morrissey et al., 2016).

However, regular monitoring of resistance levels of *P. multocida* strains isolated from animals is essential. Public health issues are to: *(i)* guide first-line treatment in animals and limit economic losses, *(ii)* guide treatment in humans in case of infection following exposure to an animal (before antibiogram results), and finally *(iii)* determine the scale of the phenomenon in order to guide control measures. The aim of this study was thus to characterize the epidemiology of phenotypic resistance of *P. multocida* strains isolated from respiratory infections in animals, including both food-producing animals and pets.

2. MATERIALS AND METHODS

2.1 Source of data

This study was performed using the dataset from RESAPATH, the well-established French national surveillance network for antimicrobial resistance (AMR) in pathogenic bacteria from animals. RESAPATH collects antibiogram results, through its member laboratories (74 out of 112 in the country in 2015 (Boireau et al., 2018a)) that are located in all the administrative regions of France. All the antibiogram results collected by the RESAPATH are initially requested by veterinarians in a context of disease for diagnostic purposes. Even if each laboratory has its own strategy for bacterial identification, API galleries are often used and the biggest ones use Maldi-TOF. All laboratories perform antibiograms by the disk diffusion method following the veterinary recommendations of the Antibiogram Committee of the French Society of Microbiology (CA-SFM, https://www.sfm-microbiologie.org/). Results are then compiled in the RESAPATH database and duplicates were systematically traced and deleted.

From this database, data concerning *P. multocida* were extracted from 2012 to 2017. For each animal species, in view of antibiotic use and practices depending on the pathological context (Bourély et al., 2018), we specifically extracted data regarding respiratory disease, which is the major disease caused by *P. multocida.* For duck isolates, septicemia was also considered because extremely acute cases in ducks can include non-specific lesions of sepsis. Samples transmitted initially to laboratories included nasal, tracheal or bronchial swabs, trans-tracheal aspirations and lung tissues. Appropriate antibiotics of relevance in veterinary and human medicine were selected for analysis, according to their spectrum of activity, their use to treat animals, and their public health interest (Table 1).

2.2 Data analysis

Analyses were performed for animal species for which at least one hundred isolates of *P. multocida* were collected over the period 2012-2017 (Supplementary Data). The first step in the analysis was to categorize isolates as susceptible, intermediate or resistant, using their inhibition zone diameters compared with the breakpoints recommended by the veterinary section of the CA-SFM. From an epidemiological point of view, the event of interest is the non-susceptibility to a particular antibiotic, indicating that the isolate is no longer a wild-type strain. Therefore, intermediate isolates were grouped together with resistant isolates in the non-susceptible population, referred to as resistant in this study. For each animal species and antibiotic combination, the indicator of resistance was defined as the ratio between the number of resistant strains and the total number of strains collected. The resistance proportions were calculated over the whole period and their confidence intervals (CIs) were calculated using the exact binomial method. Proportions were then compared using Fisher's exact test.

Secondly, to detect variations in proportions over time, time-series analyses were performed for animal species/antibiotic combinations for which we had sufficient data, i.e. at least 25 antibiograms per time step (Barlow, 2011). To capture trends, we used generalized additive models (GAM), which are flexible and effective techniques for conducting nonlinear regression analysis in time-series studies. The proportion between the number of resistant strains and the total number of strains collected on a three-monthly time step was modelled using binomial regression. The analysis was carried out as described in Boireau et al. (2018b). R, version 3.5.0 was used for all statistical analyses (gamm4 package for GAM implementation). We considered a p-value of ≤ 0.05 as a statistically significant difference. If trend variations were not significant, the trend was stationary.

3. RESULTS

In total, 5,356 *P. multocida* isolates collected between January 2012 and December 2017 were analyzed (Table 2). The proportions of resistance of *P. multocida* isolated from animals were almost all below 20% over the period, and, more precisely, all resistance proportions were below 10% for rabbits, sheep, and dogs.

The proportions of resistance to amoxicillin of *P. multocida* isolated from animals were all below 5% over the whole period. *P. multocida* isolates from rabbits presented the lower proportion of resistance to gentamicin (1.8% [1.0; 3.0]) compared with isolates from other animal species ($p<0.001$), except with isolates from swine ($p=0.1$). The proportion of resistance to tetracycline varied greatly according to animal species and isolates from cattle presented the highest proportion of resistance (23.4% [21.4; 25.5], $p<0.001$), followed by ducks (13.0% [10.1; 16.5], $p<0.01$), whereas all other animal species presented resistance below 7%. Similarly, isolates from cattle presented higher proportion of resistance to tilmicosin (17.2% [15.3; 19.2]) compared with isolates from other animal species ($p<0.002$), except with isolates from cats ($p=0.1$) and resistance proportions for other animal species were below 10%. By contrast, resistance proportions to trimethoprim-sulfamethoxazole were below 10% for the majority of animal species including cattle (6.2% [5.1; 7.4]). Resistance proportions to quinolones were above 10% only for isolates from cattle (14.3% [12.2; 16.6]) and ducks (26.1% [22.1; 30.4]), and ducks presented the highest resistance proportion ($p<0.001$). Resistance proportions to enrofloxacin were very low for swine (0.5% [0.1; 1.3]) and rabbits (0.2% [0.0; 0.8]); though low, they were higher ($p<0.01$) for cats (2.6% [1.6; 4.1]), ducks (3.7% [2.1; 5.8]), cattle (4.5% [3.5; 5.6]) and dogs (5.2% [3.1; 8.1]). Resistance to florfenicol was close to zero for all animal species, without differences among them ($p=0.6$).

From 2012 to 2017, most resistance trends of *P. multocida* isolated from cattle presented significant variations over time. However, resistance trends to trimethoprim-sulfamethoxazole ($p=0.9$), amoxicillin ($p=0.08$), and florfenicol ($p=0.9$) were stationary (Figure 1). Resistance trends to tetracycline ($p>0.001$), tilmicosin ($p>0.001$), flumequine ($p=0.003$), and enrofloxacin ($p=0.008$) increased continuously over the period. More specifically, resistance proportions to tetracycline, tilmicosin and flumequine varied greatly from 2012 to 2017: they were below 15% at the beginning of the period and reached 33.8% [27.0; 40.5], 26.5% [22.2; 30.8] and 21.0% [15.6; 26.4] in December 2017, respectively. Resistance proportions to enrofloxacin increased from 2.0% [0.7; 3.4] in January 2012 up to 7.3% [4.6; 10.0] in December 2017.

4. DISCUSSION

Data on the epidemiology of resistance of *P. multocida* isolates are rare. In these studies, the samples size is very often low and/or the isolates of several animal species are grouped together (Schwarz et al., 2007; Cucco et al., 2017), limiting interpretation by animal species. In Germany, a study on 1,111 *P. multocida* isolated from swine reported similar resistance proportions to ours for enrofloxacin and florfenicol (below 1%), for resistance to trimethoprim-sulfamethoxazole (between 4% and 10%) and to tetracycline (between 11.5% and 19.2%) (Kaspar et al., 2007). In Australia, a more recent study on 51 *P. multocida* isolated from swine reported very low levels of resistance, except for tetracycline (28%) (Dayao et al., 2014). Two studies in swine, one in China on 233 isolates and the other on 454 isolates collected in South Korea also identified high levels of tetracycline resistance (58.0% and 66.5% respectively) (Tang et al., 2009; Oh et al., 2018), higher than those reported in Europe (El Garch et al., 2016), North America (Sweeney, 2017), Australia (Dayao et al., 2014) and in our study (6.7%). Similarly, resistance to florfenicol reached 18.5% in South Korea, whereas it appeared to be very limited in Europe. These differences are likely the result of differing in practices since antibiotic use is considered higher in Korea (Oh et al., 2018).

For rabbits, our results are consistent with a previous study conducted in Brazil on 45 commensal *P. multocida* isolates, which reported low or no resistance to beta-lactam, fluoroquinolones, florfenicol, and tetracyclines (Ferreira et al., 2016).

A study in Europe on 134 *P. multocida* isolated from cattle between 2009 and 2012 already reported that resistance to tetracycline (11.2%) was above other resistance (El Garch et al., 2016). This estimate aligns with the resistance proportion calculated in our study in January 2012 from cattle isolates (12.9% [8.1; 17.8]). The parallel increases of resistance proportions to different antibiotics in *P. multocida* isolated from cattle suggest the joint spread of resistance determinants. *P. multocida* can carry plasmids conferring resistance to different antibiotics: most commonly beta-lactams, tetracycline, streptomycin and sulfonamides (Kadlec et al., 2011). Molecular investigations are needed to confirm this hypothesis. Finally, these increasing resistance trends in *P. multocida* isolates from cattle contrast with the stationary or decreasing resistance trends of *Escherichia coli* isolated from cattle in recent years (Boireau et al., 2018b).

4.1 Analysis in relation to antibiotic use

The differences observed between resistance proportions among animal species were probably due to differences in antibiotic use. For example, gentamicin is generally not used in rabbits due to its nephrotoxicity and the resistance to gentamicin was lower for this species. Besides, some insignificant differences between proportions were likely due to a lack of statistical power, related to a low number of isolates collected for some animals.

Due to a lack of specific data regarding antibiotic use in animals to treat *P. multocida* infections, resistance trends could not be directly analyzed in terms of antibiotic use in the models. Based on antibiotic sales for use in cattle (all diseases combined), exposure to antibiotics has decreased overall between 2011 and 2017 (-23%, all antibiotics considered) and exposure to fluoroquinolones has been decreasing since 2013 (-93%) (Anses-ANMV, 2018). However, several resistance trends in *P. multocida* isolates, including resistance trend to fluoroquinolones, increased from 2012 to 2017 in our study. These differences emphasize the importance of monitoring antibiotic use by animal species and by disease, to better document the use-resistance pattern.

Despite the frequent use of florfenicol in food-producing animals since its first usage in 1995 in France, resistance of *P. multocida* to florfenicol was below 1%, regardless of the animal species considered. However, a recent study reported that gastro-intestinal exposure of the microbiota to florfenicol leads to resistance selection in commensal *E. coli* (De Smet et al., 2018). These results underscore the importance of always using antibiotics prudently, and of continued monitoring of changes in resistance in bacteria, whether commensal or pathogenic.

4.2 Limitations

The major strength of our study was the availability of data regarding the susceptibility of *P. multocida* from an ongoing nationwide surveillance system for AMR in animals. Nevertheless, this study had several limitations due to potential selection bias, because laboratories join the

RESAPATH on a voluntary basis and antibiograms rely on decisions taken by veterinarians during their veterinary practice. Because RESAPATH laboratories performed antibiograms by disk diffusion, which is a qualitative method, no information regarding the minimal inhibitory concentrations is collected. Despite a good standardization, isolates could be misclassified because this method remains manual. Nevertheless, the annual participation of laboratories to quality assurance proficiency tests contributes to control data and limit such misclassifications. The proportions of samples from previously untreated compared to treated animals were unknown and could potentially impact the resistance results. In addition, it was not possible to differentiate first and subsequent sample submissions and we simply assumed that multiple sampling from the same animal did not occur frequently considering the cost of the analysis. All these biases can lead to a lack of representativeness and a misestimation of resistance levels. However if biases do not vary over time, the observed resistance trends remain meaningful. A recent assessment of the RESAPATH network concluded that the antibiograms collected were representative of the antibiograms performed in animals in France (Boireau et al., 2018a).

4.3 Public health issues

P. multocida is the main bacterial species responsible for pasteurellosis in humans, especially in cases of severe infections. In almost all reported cases, evidence of upstream contact with an animal was mentioned (Wilson and Ho, 2013). Zoonotic transmission to humans usually occurs through domestic animal bites, which can lead to significant morbidity and often require specialized care and specific antibiotic treatments (Bula-Rudas and Olcott, 2018). Although bites are often polymicrobial, *Pasteurellae*, and particularly *P. multocida*, are the most commonly isolated bacteria from dog and cat bites (Freshwater, 2008). Since the 1950s, penicillins have generally been used as empirical treatments of cat and dog bites, before antibiogram results are obtained (Freshwater, 2008). According to the results of our study, given the low resistance of *P. multocida* isolates from dogs and cats to penicillins, the use of these antibiotics is still a valid therapeutic option.

5. CONCLUSION

This study provides an overall view of the antimicrobial resistance epidemiology of *Pasteurella multocida* strains isolated from food-producing animals and pets in a context of respiratory disease in France. It highlighted that resistance to florfenicol was very low for all species. Time series analyses revealed continuous increases in resistance to tetracycline, tilmicosin, and flumequine in *P. multocida* strains isolated from cattle, whereas the overall use of antibiotics in cattle decreased over this same period in France. Furthermore, these trends contrast with decreasing resistance trends of *E. coli* strains isolated from cattle in recent years. These differences likely reflect differing practices according to the pathological contexts, stressing the importance of monitoring bacteria other than *E. coli*, which is commonly monitored. Since *Pasteurellae* are the most common bacteria isolated from dog and cat bites in humans, these results are also useful in guiding the therapeutic choices of physicians in case of bite wounds or scratches.

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Conflicts of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data used for this study was obtained from the RESAPATH network and the access to data is controlled by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). Conditions of approval (respecting the anonymity of farms and laboratories) do not allow us to distribute or make available data directly to other parties.

Author contributions

All the authors read and approved the final manuscript.

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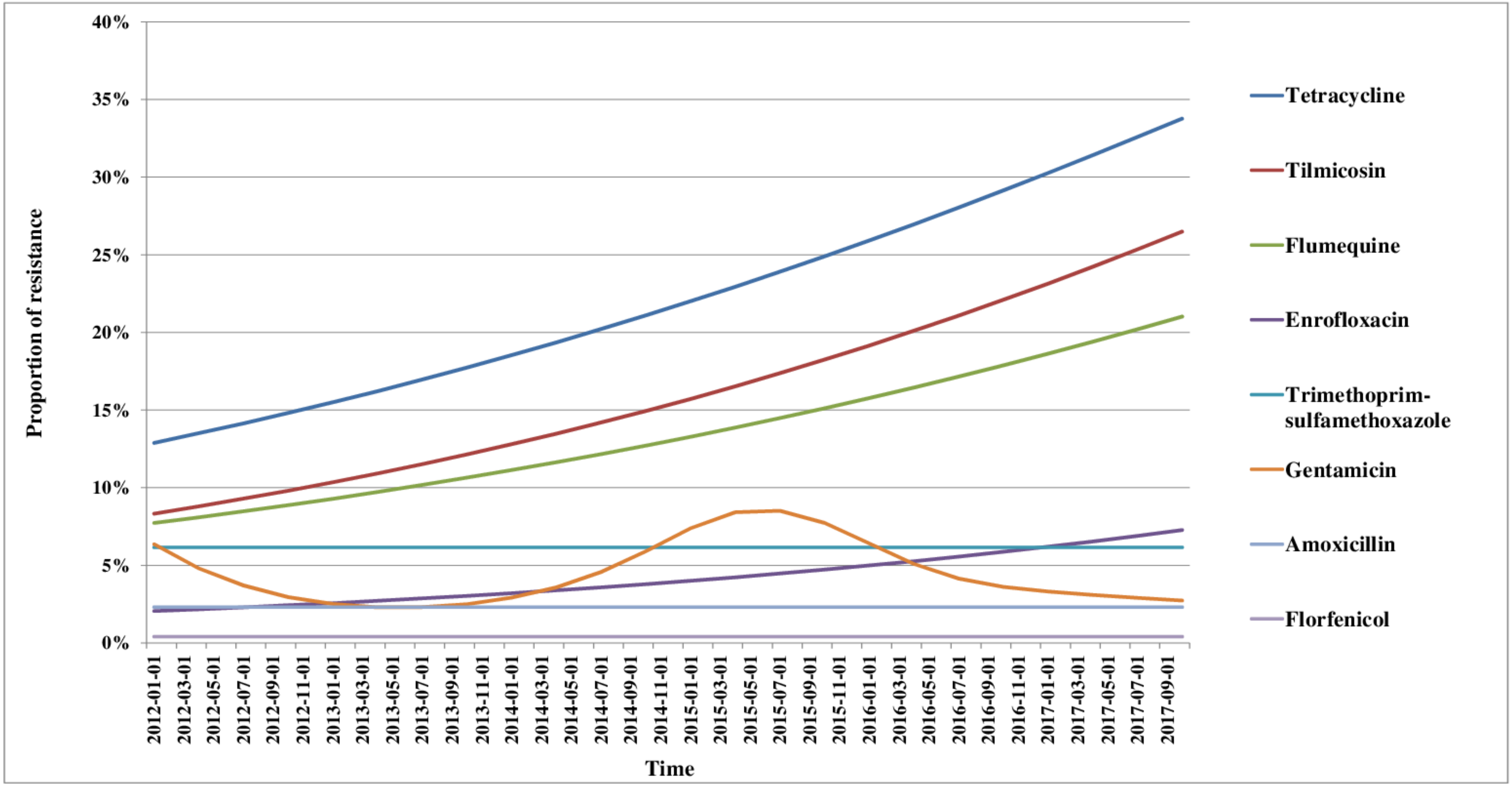
Tables

Table 1. Selected antibiotics and the corresponding antibiotic classes

Table 2. Antimicrobial resistance (in % with 95% CI) in *P. multocida* isolated from diseased food-producing animals and pets in a context of respiratory disease in France over the 2012- 2017 period

Figure

Figure 1. Trends for antimicrobial resistance in *P. multocida* isolates from cattle with respiratory diseases over the period 2012-2017, on a three-monthly time scale (at least 25 isolates per time step)



40%
35%
30%
25%
20%
15%
10%
5%
0%
Proportion of resistance
2012-01-01
2012-03-01
2012-05-01
2012-07-01
2012-09-01
2012-11-01
2013-01-01
2013-03-01
2013-05-01
2013-07-01
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2016-05-01
2016-07-01
2016-09-01
2016-11-01
2017-01-01
2017-03-01
2017-05-01
2017-07-01
2017-09-01
Time
Tetracycline
Tilmicosin
Flumequine
Enrofloxacin
Trimethoprim-sulfamethoxazole
Gentamicin
Amoxicillin
Florfenicol

Table 1. Selected antibiotics and the corresponding antibiotic classes

Antibiotic classes	Antibiotics
Beta-lactams	Amoxicillin
Aminoglycosides	Gentamicin
Tetracyclines	Tetracycline
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole
Phenicols	Florfenicol
Macrolides	Tilmicosin
Quinolones	Nalidixic acid/Flumequine
Fluoroquinolones	Enrofloxacin

Table 2. Antimicrobial resistance (in % with 95% CI) in *P. multocida* isolated from diseased food-producing animals and pets in a context of respiratory disease in France over the 2012-2017 period

Antibiotic		Cat	Dog	Cattle	Duck[2]	Sheep	Swine	Rabbit
Amoxicillin	Number of isolates	657	325	1,635	464	302	796	224
	Proportion	4.1 [2.7; 5.9]	4.9 [2.8; 7.9]	2.3 [1.6; 3.1]	0.9 [0.2; 2.2]	2.3 [0.9; 4.7]	0.3 [0.0; 0.9]	1.3 [0.3; 3.9]
Gentamicin	Number of isolates	690	352	1,511	Not-tested	300	458	789
	Proportion	9.3 [7.2; 11.7]	6.0 [3.7; 9.0]	4.6 [3.6; 5.8]		6.7 [4.1; 10.1]	3.5 [2.0; 5.6]	1.8 [1.0; 3.0]
Tetracycline	Number of isolates	440	192	1,702	460	311	784	935
	Proportion	4.1 [2.4; 6.4]	4.2 [1.8; 8.0]	23.4 [21.4; 25.5]	13.0 [10.1; 16.5]	4.5 [2.5; 7.4]	6.7 [5.1; 8.7]	3.5 [2.4; 4.9]
Trimethoprim-sulfamethoxazole	Number of isolates	679	345	1,705	465	311	839	935
	Proportion	13.0 [10.5; 15.7]	7.5 [5.0; 10.8]	6.2 [5.1; 7.4]	11.4 [8.7; 14.6]	7.1 [4.5; 10.5]	15.4 [13.0; 18.0]	3.2 [2.2; 4.5]
Florfenicol	Number of isolates	206	85	1,695	371	298	811	327
	Proportion	0.5 [0.0; 2.7]	0.0 [0.0; 4.2]	0.4 [0.2; 0.8]	0.3 [0.0; 1.5]	0.0 [0.0; 1.2]	0.8 [0.3; 1.6]	0.0 [0.0; 1.1]
Tilmicosin	Number of isolates	54	Not-tested	1470	447	193	795	876
	Proportion	7.4 [2.1; 17.9]		17.2 [15.3; 19.2]	0.9 [0.2; 2.3]	7.3 [4.0; 11.9]	2.1 [1.3; 3.4]	5.1 [3.8; 6.8]
Nalidixic acid / Flumequine [1]	Number of isolates	531	253	1,014	449	257	522	494
	Proportion	3.6 [2.2; 5.5]	8.7 [5.5; 12.9]	14.3 [12.2; 16.6]	26.1 [22.1; 30.4]	2.7 [1.1; 5.5]	2.7 [1.5; 4.5]	6.9 [4.8; 9.5]
Enrofloxacin	Number of isolates	685	347	1,672	465	294	780	906
	Proportion	2.6 [1.6; 4.1]	5.2 [3.1; 8.1]	4.5 [3.5; 5.6]	3.7 [2.1; 5.8]	1.4 [0.4; 3.4]	0.5 [0.1; 1.3]	0.2 [0.0; 0.8]

[1] Nalidixic acid for dog, cat and sheep, flumequine otherwise

[2] In a context of respiratory disease and septicemia