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Unveiling the emergence of multidrug-resistant pathogens in exotic pets from France: a comprehensive study (2017-2019)

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Abstract

Aim: This study intends to assess the occurrence of multi-drug resistant (MDR) resistant pathogens among exotic pets from France (2017-2019).

Methods: Isolates were identified using MALDI-TOF-MS. Antimicrobial susceptibility testing was conducted for 21 antimicrobials and was assayed by disk diffusion methods. Statistical analyses were carried out using GraphPad Prism® (version 9.4.1).

Results: Isolates (n = 2,100) recovered from samples of 10 small mammals (n = 1,555), 23 birds (n = 287), and 18 reptiles (n = 208) species were identified as *Enterobacterales* (n = 634), *Pseudomonadaceae* (n = 176), *Pasteurellacea*

(*n* = 276), *Staphylococcaceae* (*n* = 563), *Streptococcaceae* (*n* = 259), and *Enterococcaceae* (*n* = 186). Consistent high resistance rates were observed among diverse genera and/or species to beta-lactams, tetracyclines, and macrolides. Notably, a significant prevalence of MDR bacteria was identified, with 22.8% (*n* = 479/2,100, $P < 0.05$). Furthermore, 23.5% ($P < 0.05$) of these MDR bacteria displayed resistance to all tested antimicrobials: *E. faecalis* (*n* = 47/49; 95.0%), *E. coli* (*n* = 19/52; 36.5%), *Klebsiella* spp. (*n* = 12/32; 37.5%), *S. epidermidis* (*n* = 7/25; 28.0%), *Streptococcus* spp. (*n* = 6/68; 8.8%), *Enterococcus* spp. (*n* = 6/23; 26.0%), *Staphylococcus* spp. (*n* = 4/51; 7.8%), *Lactococcus* spp. (*n* = 4/8; 50.0%), *Citrobacter* spp. (*n* = 3/7; 42.8%), *Raoultella* spp. (*n* = 2/3; 66.6%), *Serratia* spp. (*n* = 1/9; 11.1%), *Pasteurella* spp. (*n* = 1/14; 7.1%), and *S. xylosus* (*n* = 1/28; 3.5%).

Conclusions: This study emphasizes exotic pets as an emergent reservoir of MDR bacteria, focusing on *E. faecalis* as a potential route of transmission of MDR bacteria to humans, other animal species and environment. Urgent measures, including the establishment of mandatory monitoring for antimicrobial resistance (AMR) and the enforcement of restrictive antibiotic use policies in exotic pets, should be implemented to mitigate the risk of further spread and safeguard public and animal health.

Keywords: Exotic pets, antimicrobial resistance, multidrug-resistance, pathogens, public health, One Health

INTRODUCTION

Antimicrobial resistance (AMR) is one of the foremost global public health threats, capturing a position within the top ten concerns worldwide. AMR affects human, animal, and environmental health, making it an urgent issue that requires a comprehensive One Health approach[1]. This focuses on the risk assessment of AMR's emergence, transmission, and maintenance at the interface between all sectors (human, animal, agriculture, and environment)[2]. Additionally, resistant bacteria are mainly determined by selective events related to environments with high selective pressure, such as the hospital and animal-production setting, due to the misuse of antimicrobials[3-6].

Furthermore, in recent years, a new paradigm is currently emerging - the adoption of a wide range of exotic species, including many with origins in the wild. This trend has facilitated unprecedented interactions and contact between wildlife, domestic animals, and humans, leading to potential ramifications[7]. Nevertheless, the AMR is poorly reported worldwide in this niche[8-10].

Noteworthy, approximately 60% of existing human pathogens and over 75% of those that have appeared during the past two decades can be traced back to animals. Among these pathogens, a considerable number have been directly linked to wildlife[11].

Furthermore, the current misunderstanding of antimicrobial use and the prevalence of AMR in exotic animals, among other pets, led the European Union (EU) to adopt Regulation (EU) 2019/6, which establishes specific provisions for veterinary medicinal prescribing. One notable provision is the introduction of electronic prescriptions, which play a crucial role in enhancing the monitoring and control of antimicrobial consumption across different animal species. These ensure that pivotal information regarding the consumption of these compounds per animal group is captured.

Previously, the monitoring of antimicrobial consumption and AMR in veterinary medicine was primarily outlined in Directive No. 2003/99/EC. However, this predominantly concentrated on food-producing animals such as livestock and aquatic animals[12]. Notably, the scarce information available on AMR in pets comes from a few studies conducted by research groups, which mainly cover dogs and cats[13,14].

In order to effectively tackle the misuse of antimicrobials, EMA updated its categorization in 2017, where Critically Important Antimicrobials (CIA) for Human Medicine are classified into two of four categories, i.e., A (Avoid), which is not authorized in veterinary medicine in the EU, and B (Restrict) applied to those which are critically important in humans, and their use in animals should be restricted and considered only when no antimicrobials of the remaining categories C or D are clinically effective. Nevertheless, these antimicrobials can be used in pets under exceptional circumstances, supported by justification[15].

Despite the inherent risks of using those categories of antimicrobials in pets, the stringent regulations surrounding their usage bring notable advantages.

It should be noted that France is among the European Union member states that have implemented an epidemiological network surveillance program to monitor AMR in animal pathogenic bacteria. This program includes data from various pets, including dogs, cats, and other species. However, the information related to the last mentioned group is not reported by specific species or category due to the limited number of antimicrobial susceptibility testing (AST) performed[16].

This study aimed to assess the prevalence of MDR pathogens between 2017 and 2019 from exotic pets originating from France and highlight if exotic pets are a reservoir of MDR bacteria and possess antimicrobial profiles that are relevant to human health.

METHODS

Database source and management

The data used for this retrospective study was provided by a veterinary clinic specializing in caring for new species of pets, "Clinique des NAC", based in Toulouse, France.

The dataset details comprise information on clinical samples (animal species, sample collection date, and origin) and microbiology outcomes (bacterial identification and antimicrobial susceptibility testing results). Duplication samples, repeated results, or data with confidential information were removed to comply with Regulation (EU) 2016/679.

Study design and samples characterization

A total of 2050 samples were collected during clinical practice between 2017 and 2019. Clinical specimens were classified according to exotic pets' division: 23 birds (n = 287), 10 small mammals (n = 1555), and 18 reptiles (n = 208) species [Table 1]. Different clinical specimens were analyzed, such as nasal (n = 563), oral (n = 296), cutaneous (n = 287), ocular (n = 240), ear (n = 222), gastrointestinal tract (n = 163), musculoskeletal (n = 115), internal organs (n = 67), lungs (n = 59), urinary tract (n = 23), and reproductive tract (n = 15) [Supplementary Table 1].

Bacterial identification and study of antimicrobial agents susceptibility

Etiologic agents' identification was performed by Maldi-ToF MS at the Human Medical Biology Laboratory "BIOLAB" Avenir, Toulouse, France. Antimicrobial Susceptibility Testing (AST) was held to 21 antimicrobials [penicillins (P), amoxicillin-clavulanic acid (AMC), cefalexin (CL), ceftiofur (CTF), fusidic acid (FUS), gentamycin (GEN), tobramycin (TOB), neomycin (NC), framycetin (FCT), tylosin (TL), azithromycin (AZM), tiamulin (TIA), tetracycline (TET), doxycycline (DOX), enrofloxacin (ENR), marbofloxacin (MRB), clindamycin (CLM), lincomycin (LMC), chloramphenicol (CHL), florfenicol (FN), sulfamethoxazole-trimethoprim (SXT)] and was determined by disc diffusion method according to national standards (*Comité de l'antibiogramme de la société française de microbiologie. Recommendations vétérinaires*, 2018, 2019) by disk diffusion methods following European guidelines[18].

Table 1. Distribution of clinical specimens by animal species[17]

Mammals (*n* = 1,555)		**Birds (*n* = 287)**		**Reptiles (*n* = 208)**	
Oryctolagus cuniculus	1,173	*Phasianidae*	53	*Testudines*	85
Cavia porcellus	122	*Psittacus erithacus*	42	*Pogona vitticeps*	22
Murinae	120	*Ara*	29	*Iguanidae*	15
Mustela putorius furo	75	*Cacatua*	21	*Python regius*	14
Chinchilla	25	*Falco peregrinus*	17	*Chamaeleonidae*	13
Erinaceus europaeus	14	*Columbidae*	16	*Boa constrictor*	11
Meriones unguiculatus	9	*Amazona*	13	*Gekkonidae*	9
Octodon degus	8	*Melopsittacus undulatus*	12	*Varanidae*	7
Phodopus	7	*Nymphicus hollandicus*	12	*Elaphe*	6
Mustela lutreola	2	*Parabuteo unicinctus*	12	*Python molurus*	5
		Ecletus roratus	11	*Gongylophis colubrinus*	4
		Agapornis	8	*Physignathus cocincinus*	4
		Anatidae	7	*Naja*	3
		Aquila chrysaetos	5	*Pantherophis guttatus*	3
		Aquila rapax	4	*Atheris hispida*	2
		Falco rusticolus	4	*Crocodylia*	2
		Hieraaetus pennatus	4	*Morelia spilota*	2
		Serinus canaria domestica	4	*Epicrates cenchria*	1
		Strigiformes	4		
		Gyps rueppellii	3		
		Aratinga	2		
		Cyanoramphus auriceps	2		
		Falco jugger	2		

"*n*": Number of isolates.

Due to the lack of representativeness of some isolates to perform AST, a cut-off was used, which excluded genera/species with less than 20 isolates. However, all isolates were considered for the analysis of the MDR profile. Additionally, the classification of isolates as susceptible, resistant, or with intermediate susceptibility was done according to EUCAST (2019) guidelines. MDR was considered when isolates were resistant to three or more antimicrobial agents of different families[19].

Statistical analysis

The prevalence of AMR across genera and/or species, along with the distribution of MDR bacterial profiles, was assessed through statistical analysis employing the Chi-square test ($P < 0.05$), within GraphPad Prism® (version 9.4.1.).

RESULTS

Bacterial diversity

In this study, 2,100 isolates were identified as Gram-negative (n = 1,086) and Gram-positive (n = 1,014) bacteria from the collection of 2,050 samples between 2017 and 2019.

A high diversity of bacterial genera and species was found in both bacterial groups. In the Gram-negative bacteria, 15 Genera were identified: 634 isolates belonging to *Enterobacterales*: *Escherichia coli* (n = 155),

Enterobacter spp. (*n* = 131), *Klebsiella* spp. (*n* = 111), *Serratia* spp. (*n* = 66), *Proteus* spp. (*n* = 65), *Pantoea* spp. (*n* = 30), *Citrobacter* spp. (*n* = 23), *Providencia rettgeri* (*n* = 15), *Morganella* spp. (*n* = 14), *Raoultella* spp. (*n* = 10), *Salmonella* spp. (*n* = 6), *Rahnella* spp. (*n* = 4), *Yersinia pseudotuberculosis* (*n* = 2) *Erwinia pyrifolia* (*n* = 1) and *Tatumella ptyseos* (*n* = 1); 176 isolates were identified as *Pseudomonadaceae*: *Pseudomonas aeruginosa* (*n* = 127) and *Pseudomonas* spp. (*n* = 49); and 276 belonged to *Pasteurellaceae*: *Pasteurella* spp. (*n* = 226), *Haemophilus* spp. (*n* = 26), *Mannheimia* spp. (*n* = 16), *Actinobacillus* spp. (*n* = 6), and *Chelonobacter oris* (*n* = 2) [Supplementary Table 2][17].

Regarding to Gram-positive bacteria, 563 isolates were identified within the *Staphylococcaceae*: *Staphylococcus* spp. (*n* = 212), *S. xylosus* (*n* = 143), *S. aureus* (*n* = 122), *S. epidermidis* (*n* = 47), *Gemella* spp. (*n* = 38) and *Macrococcus caseolyticus* (*n* = 1); 259 isolates belonged to *Streptococcaceae*: *Streptococcus* spp. (*n* = 249) and *Lactococcus* spp. (*n* = 10), and finally *Enterococcaceae* with 192 isolates: *Enterococcus faecalis* (*n* = 125), *Enterococcus* spp. (*n* = 58), and *Vagonococcus fluvialis* (*n* = 3) [Supplementary Table 3][17].

According to the sample's origin, nasal, oral, cutaneous, and ear were the most frequent, followed by the gastrointestinal tract, musculoskeletal, lungs, and internal organs specimens [Supplementary Table 1].

The most predominant Gram-negative bacteria were *Escherichia coli*, followed by *Enterobacter* spp., *Klebsiella* spp., *Serratia* spp., and *Proteus* spp., whereas Gram-positive bacteria were *Streptococcus* spp., followed by *Staphylococcus* spp., *S. xylosus*, *S. aureus*, and *Enterococcus faecalis*[17].

Antimicrobial susceptibility testing

Gram-negative bacteria susceptibility profile

Over the triennium spanning 2017-2019, isolates exhibited high resistance levels to beta-lactams (80% to 100%: *Enterobacter* spp.; *E. coli*; *P. aeruginosa*; *Klebsiella* spp.) as well as to tetracyclines (76% to 96.3%: *Klebsiella* spp; *E. coli*; *Enterobacter* spp.; *Serratia* spp.) [Figure 1].

It is noteworthy that *Enterobacterales* demonstrated a notable resistance percentage to tetracyclines, notably to DOX (*E. coli:* 94%/92%/97%; *Enterobacter* spp.: 91%/94%/100%; *Klebsiella* spp.: 89%/92%/89% and *Serratia* spp.: 100%/95%). In contrast, *Pasteurella* spp., from 2017 to 2018, showed a marked decline in the percentage of resistant isolates (43% and 13%, respectively)[17].

Regarding the susceptibility profile of *E. coli*, an increase in resistant isolates was observed in the 2017/18 biennium to fluoroquinolones (ENR: 26%/21%/28%; MRB: 20%/18%/26%), the same was observed for *Serratia* spp. (ENR: 4%/11%; MRB: 0%/4%; 2018-2019)[17].

Enterobacterales and *Pseudomonadaceae* showed a high distribution of isolates carrying resistance to beta-lactams (AMC - *E. coli*: 90%/91%/95%; *Klebsiella* spp.: 100%; CFT - *Enterobacter* spp.: 80%; *P. aeruginosa*: 90%/100%/100%). It is also worth noting that in 2017/18, both *Proteus* spp. and *Klebsiella* spp. had an increase in resistance to SXT (30%/41%; 33%/43%, respectively). However, it was observed a reduce in resistance to aminoglycosides and fluoroquinolones between 2017-2018: GEN - *E. coli*: 58%/42%/40%; *Enterobacter* spp.: 75%/55%/50%; *Klebsiella* spp.: 81%/43%/40%; *Proteus* spp.: 38%/7%; *P. aeruginosa*: 33%/28%/10%; *Pasteurella* spp.: 33%/15%/11%; MRB - *Enterobacter* spp.: 31%/20%/6%; *Klebsiella* spp.: 26%/34%/15%; *Proteus* spp.: 20%/7%; ENR - *Enterobacter* spp.: 47%/31%/33%; *Klebsiella* spp.: 55%/57%/30%; *Proteus* spp.: 25%/18%. Additionally, *Pasteurella* spp. showed a positive evolution in its susceptibility profile to most of the antibiotic families tested [Table 2][17].

Table 2. Antimicrobial resistance of Gram-negative bacteria recovered from exotic pet specimens[17]

Year/Sample	Antimicrobials														
	P	AMC	CL	CFT	AZM	GEN	TET	DOX	ENR	MRB	CHL	FLF	SXT	CLD	TIA
E. coli															
2017, *n* = 43/188		18/20				7/12		34/36	10/38	9/34	7/10		8/41		
2018, *n* = 72/271		32/35	15/18			11/26	6/11	54/59	14/67	11/62	11/12	2/12	15/56		
2019, *n* = 40/175		20/21		1/10		6/15	8/13	31/32	11/40	10/38			9/34		
***Enterobacter* spp.**															
2017, *n* = 39/188						18/24	9/10	31/34	17/36	12/39			13/35		
2018, *n* = 56/271						17/31	15/20	44/47	16/51	10/49			9/38		
2019, *n* = 36/175				8/10		10/20		33/33	11/33	2/34			9/31		
***Klebsiella* spp.**															
2017, *n* = 34/188						13/16	5/12	25/28	18/33	9/34	2/10		10/30		
2018, *n* = 49/271		12/12				13/30	8/15	35/38	27/47	16/47			18/42		
2019, *n* = 28/175						8/20	5/13	17/19	8/27	4/27			3/19		
***Proteus* spp.**															
2017, *n* = 20/188						5/13			5/20	4/20			3/10		
2018, *n* = 29/271						1/15			5/28	2/28			9/22		
***Serratia* spp.**															
2018, *n* = 25/271						1/15	9/10	23/23	1/24	0/23			1/21		
2019, *n* = 29/175						2/19		20/21	3/28	1/28			0/20		
Pseudomonas aeruginosa															
2017, *n* = 38/58				9/10		7/21									
2018, *n* = 58/77				16/16		14/50									
2019, *n* = 31/41				12/12		3/29									
***Pasteurella* spp.**															
2017, *n* = 77/84	17/38		1/10			6/18	5/37	31/72	9/74	3/76	0/15	0/16	2/68		3/11
2018, *n* = 88/109	18/49		1/11	0/14		7/48	2/42	10/79	7/83	3/87			2/69		7/28
2019, *n* = 61/83	8/30		1/13	3/18		4/36	1/21	8/54	5/55	2/59			1/44		1/16

P: Penicillin; AMC: amoxicillin-clavulanic acid; CL: cefalexin; CFT: ceftiofur; AZM: azithromycin; GEN: gentamycin; TET: tetracycline; DOX: doxycycline; ENR: enrofloxacin; MRB: marbofloxacin; CHL: chloramphenicol; FLF: florphenicol; SXT: sulfamethoxazole-trimethoprim; CLD: clindamycin; TIA: tiamulin; "*n*": number of isolates.

Gram-positive bacteria susceptibility profile

Over the study period from 2017 to 2019, all isolates exhibited elevated resistance rates to macrolides ranging from 50.9% to 98.9%, with a focus on *E. faecalis* and *S. xylosus*, followed by *Enterococcus* spp and *S. aureus*. Additionally, high levels of resistance were observed for beta-lactams (38.6% to 80.7%: *Enterococcus faecalis*, *S. aureus*, and *S. xylosus*) as well as tetracyclines (45.5% to 74.2%: *S. epidermidis*, *S. xylosus*, and *E. faecalis*), as depicted in Figure 2.

The observed resistance levels to fluoroquinolones displayed by Enterococci are also a cause for concern(ENR - *E. faecalis*: 92%/98%/100%; *Enterococcus* spp.: 85%/80%, 2017/18). In addition, a slight enhancement in susceptibility to MRB was detected (*E. faecalis*: 90%/96%/85%; *Enterococcus* spp.: 81%/74%, 2018/19 and 2017/18, respectively).

Staphylococcaceae demonstrated an upward trend of resistance to beta-lactams and tetracyclines during 2017/18 (*Staphylococcus* spp. - P: 57%/43%/55%; AMC: 13%/13%/38%; CFX: 19%/8%/25%; CFT: 9%/23%; TET: 24%/26%/40%, 2017-2018; *S. epidermidis* - DOX: 50%/59%)[17].

Staphylococcaceae, *Streptococcaceae,* and *Enterococcaceae* showed increased resistance to macrolides at high rates (AZM - *S. aureus*: 59%/72%/87%; *S. epidermidis*: 53%/82%; *S. xylosus*: 81%/86%; *Satphylococcus* spp.: 51%/64%/71%; *Streptococcus* spp.: 38%/52%/63%; *Enterococcus faecalis*: 96%/100%/100%; *Enterococcus* spp.: 67%/80%, 2017/18). However, the *Staphylococaceae* evolved favorably in its susceptibility profile to the remaining antibiotic classes[17].

Streptococcus spp. revealed a rise in resistance profile to lincosamides (CLD: 21%/38%, 2017/18). A positive evolution in susceptibility to beta-lactams, tetracyclines, and fluoroquinolones has also been detected (MRB: 58%/48%/41%)[17].

It is noteworthy that Enterococci have exhibited a gradual decline in resistance to tetracyclines (TET - *E. faecalis*: 79%/60%/55%; DOX - *E. faecalis*: 82%/78%/71%; *Enterococcus* spp.: 80%/33%, 2017/18) [Table 3][17].

Multidrug-resistant profiles of Gram-negative and positive bacteria

It should be noted that a high percentage of isolates were MDR profile carriers: *E. faecalis* (63.2%, *n* = 79/125) followed by *S. epidermidis* (53.2%, *n* = 25/47), *Enterococcus* spp. (39.7%, *n* = 23/58), *E.coli* (33.5%, *n* = 52/155), *Citrobacter* spp. (30.4%, *n* = 7/23), *Enterobacter* spp. (29.7%, *n* = 39/131), *Klebsiella* spp. (28.8%, *n* = 32/111), *Streptococcus* spp. (27.3%, *n* = 68/249), *Staphylococcus* spp. (24.0%, *n* = 51/212), *S. xylosus* (19.6%, *n* = 28/143), *S. aureus* (18.9%, *n* = 23/122), *Serratia* spp. (13.6%, *n* = 9/66), *Pasteurella* spp. (6.2%, *n* = 14/226), and *Proteus* spp (4.6%, *n* = 3/65) [Figure 3][17].

Other isolates with low sample representativeness were also MDR carriers: *Gemella* spp. (7/38) *Lactococcus* spp. (*n* = 8/10), *Raoultella* spp., *Salmonella* spp. and *Mannheimia* spp. (*n* = 3/10, 3/6, and 3/16, respectively), *Vagonococcus fluvialis* (*n* = 2/3), and *Rahnella* spp., *Actinobacillus* spp., and *Chelonobacter oris* (*n* = 1/4, 1/6, and 1/2, respectively)[17].

The most prevalent co-resistance pattern observed in the MDR bacteria was the simultaneous resistance to both tetracyclines and fluoroquinolones (*n* = 194) [Tables 4 and 5]. Among the gram-negative bacteria, the most prominent co-resistance profile was the B-lactams-tetracyclines-fluoroquinolones combination (*n* = 52), followed by the aminoglycosides-tetracyclines-fluoroquinolones profile (*n* = 40). The first profile may also be associated with resistance to aminoglycosides [Table 4][17].

Table 3. Antimicrobial resistance of Gram-positive bacteria recovered from exotic pet specimens[17]

Year/Sample	Antimicrobials														
	P	AMC	CL	CFT	AZM	GEN	TET	DOX	ENR	MRB	CHL	FLF	SXT	CLD	TIA
S. aureus															
2017, *n* = 44/193	11/17				23/39	8/18	3/11	11/39	18/42	10/43	15/15		3/34		
2018, *n* = 52/198	7/21				31/43	9/26	2/19	4/42	7/49	7/50			2/40		
2019, *n* = 26/122	4/13				20/23	0/13	0/10	1/20	3/25	3/25			0/21		
S. epidermidis															
2017, *n* = 18/193					9/17			8/16	13/18	10/18			4/13		
2018, *n* = 20/198					14/17			7/17	8/18	7/19			2/10		
S. xylosus															
2017, *n* = 42/193	13/15				26/32	2/21	7/12	20/38	27/39	13/41			5/31		
2018, *n* = 37/198	8/11				24/28	0/20	5/14	14/32	4/35	2/34			5/28		
Staphylococcus spp.															
2017, *n* = 70/193	13/23	2/16	3/16		26/51	16/35	7/29	13/57	31/69	18/69	12/18		2/50	7/12	
2018, *n* = 78/198	12/28	2/16	1/12	1/11	44/69	7/46	9/34	15/62	18/74	12/72			15/54		5/11
2019, *n* = 64/122	12/22	6/16	4/16	3/13	32/45	6/41	6/15	12/49	9/60	8/60	9/17		7/45		
Streptococcus spp.															
2017, *n* = 84/87			4/13	1/11	27/72		7/16	36/76	54/77	49/84	9/20	0/14	16/68	3/14	2/12
2018, *n* = 96/103			7/23	2/16	46/88		10/26	36/87	60/87	40/83	5/17		19/69	6/16	2/11
2019, *n* = 69/69			4/18	1/18	43/68		4/18	13/59	42/63	27/66	3/10		13/47		
Enterococcus faecalis															
2017, *n* = 40/62	9/10	6/18			25/26		11/14	28/34	35/38	36/40	11/11				
2018, *n* = 58/89	8/15	4/28			43/43		9/15	35/45	55/56	48/50		6/11			
2019, *n* = 27/41		5/12			18/18		6/11	12/17	26/26	22/26					
Enterococcus spp.															
2017, *n* = 22/62		2/13			8/12			12/15	17/20	17/21					
2018, *n* = 28/89		5/19			20/25			7/21	24/30	20/27					

P: Penicillin, AMC: amoxicillin-clavulanic acid; CL: cefalexin; CFT: ceftiofur; AZM: azithromycin; GEN: gentamycin; TET: tetracycline; DOX: doxycycline; ENR: enrofloxacin; MRB: marbofloxacin; CHL: chloramphenicol; FLF: florphenicol; SXT: sulfamethoxazole-trimethoprim; CLD: clindamycin; TIA: tiamulin; "*n*": number of isolates.

Table 4. Phenotypic features of Gram-negative bacteria carriers of heterogeneous MDR profiles[17]

Escherichia coli	*n*	*Enterobacter* spp.	*n*	*Klebsiella* spp.	*n*	*Salmonella* spp.	*n*
BLC-TET-FL	8	AMN-TET-FL-SUL	6	BLC-TET-FL	10	BLC-AMN-FL-ANF	1
BLC-TET-ANF	4	BLC-TET-FL	4	AMN-TET-FL-SUL	7	AMN-TET-FL	1
BLC-TET-POL-FL	4	BLC-AMN-TET-FL	3	TET-POL-FL	5	TET-POL-FL	1
BLC-FL-ANF	3	AMN-TET-ANF-PL	3	TET-FL-SUL	3		
BLC-TET-PL	3	AMN-TET-POL-FL-SUL-PL	3	TET-POL-FL-SUL	3	***Actinobacillus* spp.**	
AMN-TET-FL	3	TET-FL-SUL-PL	3	BLC-AMN-TET-FL	2	BLC-TET-FL-PL	1
TET-FL-SUL	3	BLC-AMN-TET	2	BLC-AMN-TET-FL-SUL	1		
BLC-AMN-TET	2	AMN-FL-ANF	2	AMN-TET-POL	1	***Chelonobacter oris***	
BLC-AMN-TET-FL-SUL	2	AMN-TET-SUL	2			BLC-AMN-TET	1
BLC-TET-FL-SUL	2	TET-FL-ANF	2	***Serratia* spp.**			
BLC-TET-POL	2	TET-FL-SUL	2	TET-FL-SUL	3	***Mannheimia* spp.**	
BLC-TET-SUL	2	BLC-AMN-TET-ANF-PL	1	TET-FL-PL	2	BLC-TET-FL	2
AMN-TET-ANF	2	BLC-AMN-TET-POL-FL-SUL	1	BLC-TET-FL	1	BLC-AMN-TET-FL	1
AMN-TET-FL-SUL	2	BLC-TET-FL-SUL	1	AMN-TET-FL-ANF	1		
TET-FL-ANF	2	BLC-TET-POL-FL-ANF	1	AMN-TET-FL-ANF-SUL	1	***Pasteurella* spp.**	
TET-POL-FL	2	BLC-TET-POL-FL-ANF-SUL	1	AMN-TET-FL-SUL	1	BLC-AMN-TET	3
AMN-POL-ANF	1	TET-FL-ANF-SUL	1			BLC-TET-FL	3
AMN-POL-PL	1	TET-POL-ANF	1	***Morganella* spp.**		BLC-AMN-FL	1
AMN-TET-POL	1			TET-FL-SUL	1	BLC-TET-FL-SUL	1
TET-ANF-PL	1	***Citrobacter* spp.**				BLC-TET-SUL	1
TET-FL-ANF-SUL	1	BLC-POL-AMN-TET-POL-FL-ANF	1	***Rahnella* spp.**		AMN-FL-SUL	1
TET-FL-SUL-PL	1	BLC-POL-AMN-TET-POL-FL-ANF-SUL-PL	1	AMN-TET-FL-ANF	1	AMN-TET-FL	1
		BLC-TET-FL	1			AMN-TET-FL-SUL	1
***Proteus* spp.**		AMN-TET-FL-SUL	1	***Raoultella* spp.**		TET-FL-PL	1
BLC-AMN-FL-SUL	1	AMN-TET-POL	1	BLC-TET-SUL	1	TET-FL-SUL	1
BLC-AMN-FL-SUL-PL	1	TET-FL-ANF-SUL	1	BLC-TET-POL-FL-SUL	1		
AMN-FL-SUL	1	TET-POL-SUL	1	BLC-AMN-TET-POL-FL-ANF-SUL	1		

MDR: Multi-drug resistant; BLC: beta-lactams; AMN: aminoglycosides; TET: tetracyclines; POL: polymyxins; FL: fluoroquinolones; ANF: anphenicols; SUL: sulphonamides; PL: pleuromutilines; "*n*": number of isolates.

Table 5. Phenotypic features of Gram-positive bacteria carriers of heterogeneous MDR profiles[17]

S. aureus	*n*	*Staphylococcus* spp.	*n*	*Gemella* spp.	*n*	*E. faecalis*	*n*
MAC-AMN-FL-ANF	3	BLC-MAC-TET	7	MAC-TET-SUL	3	MAC-TET-FL	29
BLC-AMN-FL-ANF	2	BLC-MAC-FL-SUL	6	MAC-AMN-FL	2	BLC-MAC-TET-FL	22
BLC-AMN-TET	2	BLC-MAC-AMN-FL	5	MAC-TET-FL-SUL	1	MAC-TET-FL-ANF	10
BLC-MAC-AMN	2	AMN-TET-FL	5	TET-FL-ANF	1	BLC-MAC-TET-FL-ANF	9
MAC-TET-FL	2	BLC-MAC-ANF	4			MAC-TET-FL-ANF-PL	4

BLC-MAC-AMN-TET-FL-ANF-SUL-PL	1	BLC-MAC-TET-FL	4	***Lactococcus* spp.**		TET-FL-ANF	3
BLC-MAC-ANF	1	FUS-AMN-FL	4	BLC-TET-FL-SUL	5	MAC-FL-ANF	2
BLC-MAC-TET-FL	1	BLC-AMN-TET	3	MAC-FL-SUL	2		
BLC-MAC-TET-FL-ANF	1	BLC-MAC-TET-SUL	3	MAC-TET-FL	1	***Enterococcus* spp.**	
BLC-TET-FL-ANF	1	MAC-AMN-TET-FL-ANF	3			MAC-TET-FL	5
AMN-FL-ANF	1	MAC-TET-FL-PL	3	***Streptococcus* spp.**		BLC-MAC-TET-FL	4
AMN-TET-FL	1	BLC-MAC-AMN-TET-FL-SUL	1	MAC-TET-FL	19	MAC-FL-ANF	4
FUS-BLC-MAC-AMN-TET-FL-ANF-SUL	1	FUS-BLC-MAC-AMN-TET-FL	1	TET-FL-SUL	8	BLC-FL-ANF	2
FUS-MAC-FL	1	FUS-FL-ANF	1	BLC-MAC-TET-FL	7	BLC-MAC-FL	2
MAC-AMN-ANF	1	FUS-MAC-AMN	1	MAC-TET-FL-ANF-SUL	6	BLC-MAC-FL-ANF	2
MAC-TET-FL-SUL	1			MAC-TET-SUL	6	MAC-TET-FL-ANF	2
TET-FL-ANF	1	***S. epidermidis***		MAC-TET-FL-SUL	5	FL-TET-ANF	1
		BLC-MAC-TET-FL	7	BLC-MAC-TET-FL-SUL	4	TET-ANF-PL	1
S. xylosus		BLC-MAC-FL	5	MAC-TET-FL-LIN	4		
MAC-TET-FL	10	BLC-AMN-TET-FL	2	BLC-MAC-FL	3	***Vagococcus spp.***	
BLC-MAC-FL	6	BLC-MAC-AMN-TET-FL-SUL	2	MAC-FL-SUL-PL	3	MAC-TET-FL	2
BLC-MAC-TET-FL	5	FUS-BLC-MAC-AMN-TET-FL-SUL	2	BLC-FL-ANF-SUL	1		
BLC-TET-FL-ANF	3	MAC-AMN-TET-FL-SUL	2	BLC-MAC-TET-FL-ANF-SUL	1		
MAC-TET-FL-SUL	3	MAC-TET-FL	2	MAC-TET-PL	1		
MAC-AMN-FL	1	BLC-TET-FL-ANF	1				
		AMN-TET-FL	1				
		MAC-AMN-FL	1				

MDR: Multi-drug resistant; BLC: beta-lactams; MAC: macrolides; AMN: aminoglycosides; TET: tetracyclines; FL: fluoroquinolones; ANF: amphenicols; SUL: sulphonamides; PL: pleuromutilins; LIN: lincosamides; "*n*": number of isolates.

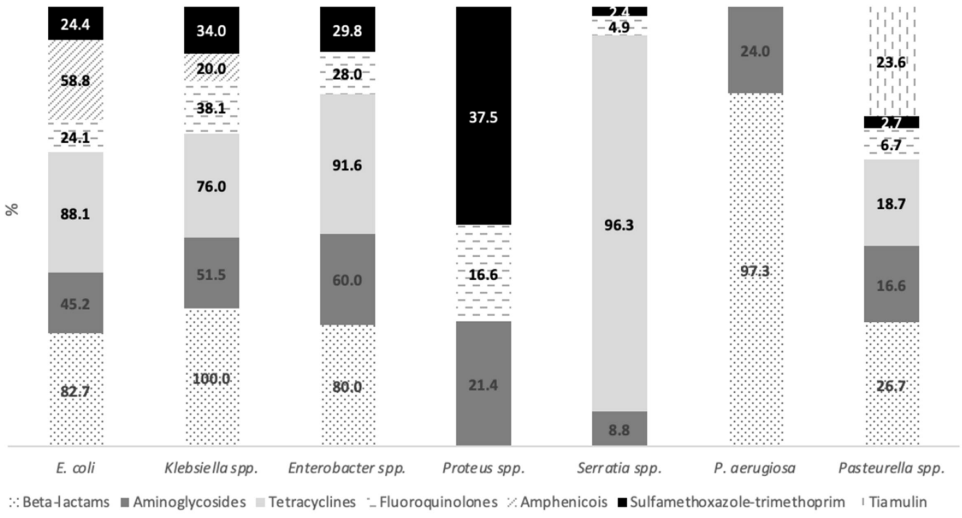

Figure 1. Distribution of antimicrobial resistance among Gram-negative bacteria collected from exotic pet specimens ($P < 0.05$; Chi-square test).

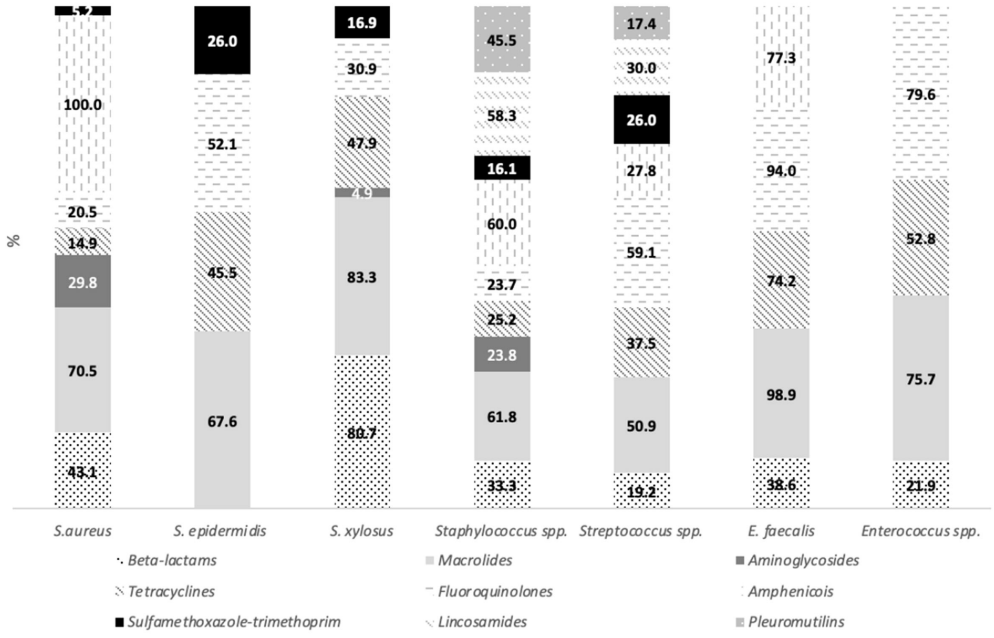

Figure 2. Distribution of antimicrobial resistance among Gram-positive bacteria collected from exotic pet specimens ($P < 0.05$; Chi-square test).

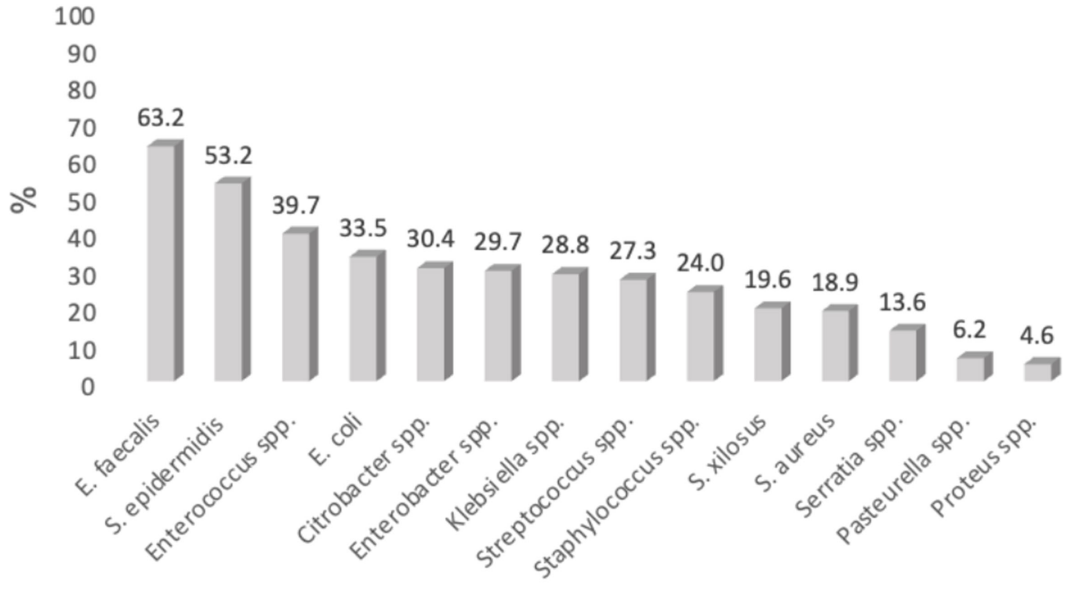

Figure 3. Distribution of MDR profile by genera or species ($P < 0.05$; Chi-square test)[17]. MDR: Multi-drug resistant .

While Gram-positive isolates demonstrate a notable co-resistance profile to macrolides-tetracyclines-fluoroquinolones (n = 102), that may also be linked to high rate resistance against macrolides [Table 5][17].

Concerned results should also be highlighted within these MDR profiles, where a high number of isolates carrying resistance to all antimicrobials tested was detected with emphasis on *Enterococcus faecalis* (n = 47/79), followed by *E.coli* (n = 19/52), *Klebsiella* spp. (n = 12/32), *S.epidermidis* (n = 7/25), *Streptococcus* spp (6/68), *Enterococcus* spp. (n = 6/23), *Staphylococcus* spp. (n = 4/51), *Lactococcus* spp. (n = 4/8), *Citrobacter* spp. (n = 3/7), *Raoultella* spp. (n = 2/3), *Serratia* spp (1/9), *Pasteurella* spp (1/14) and *S. xylosus* (n = 1/28) [Figure 4][17].

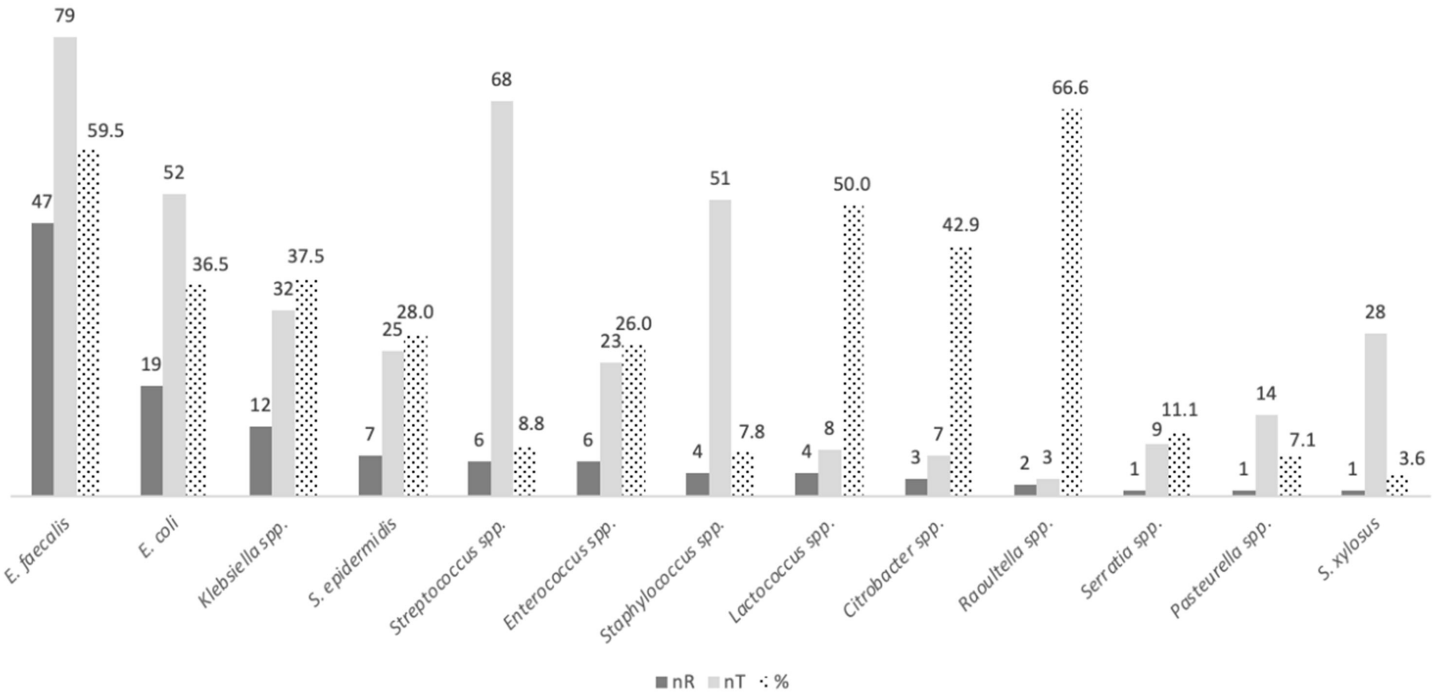

Figure 4. Prevalence of MDR bacteria resistant to all antimicrobials tested ($P < 0.05$; Chi-square test). MDR: Multi-drug; nT: total number of MDR isolates; nR: number of isolates resistant to all antimicrobials tested; %: percentage of MDR isolates.

DISCUSSION

Gram-negative and Gram-positive bacteria-resistant carriers to critically or highly important antimicrobial agents (e.g., aminopenicillins with beta-lactamase inhibitors, Cephalosporins, fluoroquinolones, aminoglycosides, macrolides, and amphenicols), as considered by World Health Organization and recognized by European Medicines Agency, were detected in this study[15,17,20].

A parallel study on exotic pets from the Iberian Peninsula reported similar results on high rates of AMR to different antimicrobial classes. Nevertheless, data on the MDR profile was not consistent with our study concerning the distribution of bacterial genera/species that stand out most frequently (study of Muñoz-Ibarra *et al*., 2022: *S. marcescens* - 94.4% followed by *C. freundii* - 50%, *M. morganii* - 47.4%, *K. pneumoniae* - 46.6%, *E. cloacae* - 44% and *E. coli* - 38.3% *vs*. in this study *E. faecalis* - 63.2%, followed by *S.epidermidis* - 53.2%, *Enterococcus* spp. -39.65%, *E.coli* - 33.5%, *Citrobacter* spp. - 30.4% *Enterobacter* spp. - 29.7%, *Klebsiella* spp. - 28.8%, *Streptococcus* spp. - 27.3%, *Staphylococcus* spp. - 24.0%, *S.xylosus* - 19.5%, *S.aureus* - 18.9%, *Gemella* spp. - 18.4%, *Serratia* spp. - 13.6%, *Pasteurella* spp. - 6.2%, and *Proteus* spp 4.6%)[8,17].

Furthermore, the distribution of resistance profiles observed in this study highlighted certain disparities compared to the official results published by France. Notably, the official reports solely encompass food-producing animals, horses, cats, and dogs, while this work extends its focus to include exotic pets, which hinders the possibility of making direct comparisons with the findings of this study[16,17]. In our work, Gram-negative bacteria revealed high rates of resistance to cefalexin, disagreeing with data reported by the *Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail* (83% *vs*. 13%)[16,17]. The same was observed for the fluoroquinolones, sulphonamides, and tetracyclines (ENR: 4%-8%; SXT: 66%; TET/DOX: 80%; food-producing animals/cats/horses). Nevertheless, some *Enterobacterales*, *P. aeruginosa*,

and *Pasteurella* spp. approached the officially reported data, and an increase in the distribution of susceptible isolates was observed above the national average[16,17]. However, other studies from Italy and Lebanon reported higher resistance rates in *E. coli* (rabbits: ENR- 67%; poultry: GEN: 70%, SXT: 59%, respectively)[21,22].

It is worth noting that a positive evolution in the distribution of susceptible isolates from *Enterobacterales*, *P. aeruginosa*, and *Pasteurella* spp. to aminoglycosides agreed with the National Report and other studies[16,17,23].

In contrast, *Enterobacter* spp., currently emerging in human and veterinary medicine, showed a high rate of resistance to aminoglycosides (GEN - 50% to 75%) in our data, contrary to what has been reported by other studies and National Report (dog, cat, and equines)[16,17,24]. Isolates of *Enterobacterales* and *Pseudomonadaceae* stood out for their high resistance rate to beta-lactams (AMC - 100%), and thus do not fit with official data (cuniculture)[16,17].

Concerning Gram-positive isolates, they revealed an alarming increase in resistance rates to macrolides, fluoroquinolones, amphenicols, and tetracyclines, where *E. faecalis* stood out. In fact, several authors widely described this resistance profile, spanning across the animal production environment, companion animals, general environmental contexts, and healthy and hospitalized humans[3,5,25,26].

This work has provided valuable data to shed light on acknowledging AMR prevalence in exotic pets. The resistance rates documented are noticeably higher compared to those reported at the national level. However, it is worth highlighting that the National Report does not present specific data concerning the species that were investigated in this study. Furthermore, it is noteworthy to mention that the genus Enterococci, which stands out for the high occurrence of MDR isolates, is not included or reported[16].

It can be justified by the policies of each country in the strictness of the implementation of guidelines, in some cases, being almost exclusively dependent on the responsibility of the veterinarian. However, specific measures have been undertaken for the CIA through a Decree publication limiting the use of 3rd- and 4th-generation cephalosporins and fluoroquinolones, and AST is mandatory for veterinarians before using or prescribing those molecules. The goal of reducing the use of fluoroquinolones and 3rd and 4th-generations cephalosporins by 25% (between 2013 and 2016) was regulated in law and has been exceeded. Between this period, sales of 3rd- and 4th-generation cephalosporins and fluoroquinolones decreased by 94% and 84%, respectively. Tetracyclines, penicillins, sulfonamides, and macrolides are the highest-selling antimicrobials in France. Additionally, between 2010 and 2021, a marked decline in the consumption of antimicrobials used in animals in France was observed[27].

Despite global efforts to implement preventive measures, there is currently a lack of comprehensive monitoring through epidemiological surveillance regarding the transmission routes of MDR strains. Furthermore, the documented colonization events between humans and pets are not being adequately monitored or recorded[28]. Scientific literature has described that one of the most significant hazards to human health is the transfer of methicillin-resistant strains of *S. aureus*, vancomycin-resistant *Enterococcus*, or carbapenemases from pets[3,29]. Indeed, carbapenemases from companion animals have been extensively reported worldwide (19 countries from Asia, Americas, Europe, Africa, and Oceania)[29]. Nevertheless, large-scale data on the genotype MDR profile is not available. In this regard, a recent study underscores the urgent requirement to prioritize scientific research and effective communication to establish a solid evidence base for antimicrobial treatment practices in exotic species that will play a crucial key in formulating appropriate recommendations for antimicrobial use in these species[30].

Of particular concern is the simultaneous use of metal-based food additives, particularly copper compounds, in the diets of both food-producing animals and pets. This practice demands attention as it has the potential to contribute to the co-selection, persistence, and transference of AMR genes intra and inter-species, promoting its dissemination to animals, humans, and the environment[5,25].

Our findings emphasize the emergence of exotic animals as a reservoir for MDR isolates, particularly focusing on *E. faecalis* and *E. coli.* Among the identified MDR profiles, resistance to CIAs was observed.

These results suggest that exotic animals could serve as potential hotspots for bacterial diversification. To comprehensively address this global issue, large-scale studies encompassing antimicrobial susceptibility and genotyping of MDR profiles in exotic pets are essential. Additionally, veterinarians play a pivotal role in antimicrobial consumption control as key leaders in recognizing and implementing recommendations by official bodies to fight AMR. This work presents the first extensive study conducted on exotic pets from France, providing valuable insights into the status of AMR.

DECLARATIONS

Acknowledgments

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Authors' contributions

Conceptualization: Cardoso S, Silveira E
Methodology: Silveira E
Resources: Le Loc'h A
Writing-original draft preparation: Cardoso S, Silveira E
Writing-review and editing: Marques I, Almeida A, Sousa S, Saavedra MJ, Anastácio S, Silveira E
Supervision: Silveira E
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The following supporting information can be downloaded at: Supplementary Materials.

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None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The samples were obtained as part of veterinary clinical practice. Following Regulation (EU) 2016/679 of the European Parliament and the Council, dated April 27, 2016, which addresses the protection of natural persons regarding the processing of personal data and the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), any data containing confidential information has been diligently excluded from the dataset.

Consent for publication

Not applicable.

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