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Global prevalence and molecular characterization of extended-spectrum β-lactamase producing-*Escherichia coli* in dogs and cats – A scoping review and meta-analysis

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ABSTRACT

Antimicrobial resistance (AMR) represents a major threat to human and animal health. Part of the AMR dimension is the circulation of extended-spectrum β-lactamases producing-*Escherichia coli* (ESBL-*E. coli*), which is now commonly reported among companion animals. However, the global perspective of the prevalence and population structure of ESBL-*E. coli* circulating in dogs and cats has not been estimated limiting our understanding of their role in the dissemination of ESBL-*E. coli*. The aim of this study was to compare the prevalence of ESBL-*E. coli* between dogs and cats and across countries through meta-analysis. We also performed a scoping review to summarize the current knowledge on ESBL genes and *E. coli* clones circulating among companion animals. A total of 128 studies published in PubMed, Web of Science, and Scopus up to April 2020 were selected and contained information on prevalence and/or molecular characterization of ESBL genes and ESBL-*E. coli* clones. Our review shows an increase in the number of publications between 2000 and 2019, concentrated mainly in Europe. Prevalence varied across continents, ranging from 0.63% (Oceania) to 16.56% (Africa) in dogs and from 0% (Oceania) to 16.82% (Asia) in cats. Although there were twice as many studies reporting prevalence on dogs ($n = 61$) than on cats ($n = 32$), and only 9 studies focused exclusively on cats, our meta-analysis showed no difference in the global prevalence of ESBL-*E. coli* between dogs (6.87% [95% CI: 4.46–10.45%]) and cats (5.04% [95% CI: 2.42–10.22%]). A considerable diversity of ESBL genes ($n = 60$) and sequence types (ST) ($n = 171$) were recovered from companion animals. ESBL-*E. coli* encoded by CTX-M-15 (67.5%, 77/114) and SHV-12 (21.9%, 25/114), along with resistant strains of ST38 (22.7%, 15/66) and ST131 (50%, 33/66) were widespread and detected in all continents. While presence of ESBL-*E. coli* is widespread, the drivers influencing the observed ESBL-*E. coli* prevalence and the clinical relevance in veterinary medicine and public health along with economic impact of ESBL-*E. coli* infections among companion animals need to be further investigated.

1. Background

Antibiotics are considered one of the most beneficial drugs in veterinary and human medicine. However, the increase of antimicrobial resistance (AMR) in hospitals and in the community has become a major public health concern [1,2]. Almost 700,000 human deaths every year due to failure of antibiotic treatments of bacterial infections are estimated [2]. In addition, the AMR burden can provoke economic losses

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reducing countries' Growth Domestic Product (GDP) [3]. AMR represents a threat to animal health as well, with more than 70% of antimicrobial sales intended for use in livestock [4]. However, very few studies have quantified the antibiotic use and AMR among dogs and cats in comparison with research conducted in livestock or humans although the widespread use of antibiotics on companion animals and a very close daily contact with humans [5].

Extended-spectrum β-lactamases (ESBL)-producing *Enterobacterales* are a widely distributed source of AMR, for animals and humans [6]. ESBL confers resistance to 3rd and 4th generation cephalosporins and aztreonam, which are among the last available antibiotics to threat infections against enterobacteria, such as *Escherichia coli* and *Klebsiella pneumonia* [7]. Thus, the use of broad-spectrum cephalosporins in small animal practice is commonly associated with an increase in ESBL producing-*Escherichia coli* (ESBL-*E. coli*) in companion animals [8]. Several studies have demonstrated the presence of ESBL-*E. coli* in clinical samples from dogs and cats. For example, ESBL producing uropathogenic *E. coli* (UPEC) have been identified causing urinary tract infections in dogs and cats [9,10]. Likewise, virulence factors associated with extra-intestinal pathogenic (ExPEC), enteropathogenic (EPEC), and enterohemorrhagic (EHEC) in ESBL-*E. coli* strains have been detected in dogs and cats, including the pandemic strain ESBL-*E. coli* B2-O25b-ST131-H30R, which is frequently associated to human infections [11–14]. ESBL-*E. coli* are also commonly detected in subclinical companion animals, often associated with faecal carriage [15–17,18]. The main ESBL genes associated with *E. coli* obtained from humans and animals are of the groups CTX-M, TEM, and SHV [7], whose have been reported in a large number of *E. coli* from different phylogroups [9,19–21].

Dissemination of ESBL-*E. coli* among companion animals will not only reduce our ability to treat companion animals but could also spread ESBL-*E. coli* to humans. Previous studies have found the same clones of ESBL-*E. coli* in humans and their dogs [22,23]. Although there is initial evidence to support that humans and companion animals are sharing resistant bacterial clones, few studies have conducted simultaneous samplings and molecular characterizations of ESBL-*E. coli* in both species [22–25].

The extension of the problem of ESBL-*E. coli* among companion animals has not received considerable attention, with only few national programs in high-income countries that address the use of antibiotics among companion animals and survey for ESBL-*E. coli* in dogs or cats [26–30]. Furthermore, while some studies are available, many of them do not report prevalence (referred here as the number of animals harboring antimicrobial-resistant bacteria over the total sampled animals) or provide a molecular description of ESBL-*E. coli* [31–37]. However, understanding the prevalence of ESBL-*E. coli* and describing the genetic background responsible for the resistance are crucial to understand the extend of the problem and to develop efficient strategies to reduce the burden of ESBL-*E. coli*.

The purpose of this meta-analysis and scoping review was to summarize and compare the prevalence of ESBL-*E. coli* in clinical and commensal samples between dogs and cats across continents and to identify ESBL-*E. coli* clones circulating among companion animals. To this end, we defined the following research question: "What are the prevalence and the population structure of ESBL-*E. coli* strains reported from clinical and commensal samples of dogs and cats worldwide?". We evaluated the number and geographical location of publications in the 2000–2020 period, compared the prevalence of ESBL-*E. coli* in dogs and cats across continents, characterized the population structure of ESBL-*E. coli* isolated from companion animals, and discussed existing knowledge gaps and future research needs in this field.

2. Methodology

This scoping review followed both the checklists of the Joanna Briggs Institute Reviewer's Manual (JBI Scoping reviews) [38] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [39] (Tables S1 and S2). The scoping review protocol was adapted from a previously published [40]. Research question, objectives, inclusion, and exclusion criteria were prior discussed and defined by all authors.

2.1. Eligibility criteria

The aim of this scoping review was to identify all peer-reviewed publications of studies performed on ESBL-*E. coli* obtained from dogs and/or cats. Data from publications were used to estimate the prevalence and the population structure (sequence type [ST], phylogroup, or virulence genes) of *E. coli* across continents. For inclusion in this scoping review, the studies should provide i) the prevalence (or sufficient information for estimation), defined here as number of dogs or cats that ESBL-*E. coli* were isolated and confirmed by phenotypic or molecular tests over the total number of sampled animals, ii) molecular characterization of ESBL genes detected in *E. coli* isolates, or iii) molecular typing of ESBL-*E. coli* from companion animals (ST, phylogroup, or virulence genes). The search was limited to descriptive (case reports and case series), or observational (cross-sectional and cohort) studies published in English, Spanish, or Portuguese. There were no date or geographical limitations and were included publications up to April 2020.

2.2. Search strategy for identification of relevant studies

The data search was performed on May 6, 2020 from the electronic databases PubMed, Web of Science, and Scopus (gray literature was not included in this scoping review). MeSH and keyword terms in the title, abstract, and keywords included "antimicrobial resistance", "ESBL", "extended spectrum beta lactamase", "dog", "cat", "pet", "companion animals", "canine", "feline", "small animals", "*E. coli*", "*Escherichia coli*". All queries are available as additional file (Table S3). The Microsoft Excel software (Power Query editor) was used for visualization, duplicate removal, and stored of data collected.

2.3. Screening phase and exclusion criteria

We identified a total of 2757 non-duplicate scientific papers (*i.e.*, original articles, letters for editor, and short communications) published between 2000 and April 2020 (Fig. 1). These publications were screened following a specific criterion. Briefly, papers should explicitly include at least one of the words: "ESBL", "lactamase", "CTX-M", "SHV", "TEM", in combination with at least one of these: "dog", "cat", "pet", "canine", "feline", and should also include the term "coli" (Fig. S1). Articles that did not met this criteria, full text were not available, or that were not in English, Spanish, or Portuguese were excluded. Then, the selection process of papers was based on a carefully full-text examination to select only studies presenting ESBL-*E. coli* isolates from clinical or commensal samples of companion animals and in accordance with the inclusion criteria (Fig. S2). Studies including previously published data, reviews, studies of basic or experimental science (*e.g.*, mutations detection, sequencing of specific proteins, *in vitro* analysis, experimental infections, clinical trials), books, and book chapter were excluded.

2.4. Data extraction and information summarizing methods

Data extracted from the manuscript and supplementary material of records were entered into a Microsoft Excel template designed exclusively for this study. Data extraction were performed by one author (MS-C) and verified independently by two authors (AM-S and JAB). Disagreements were resolved through discussion. This form contained predetermined variables: characteristics of publications (search tool, query, doi, title, first author, and year), type of the study, type of samples, animal species included in the study, methodology conducted, number of dogs or cats that ESBL-*E. coli* were isolated along with the

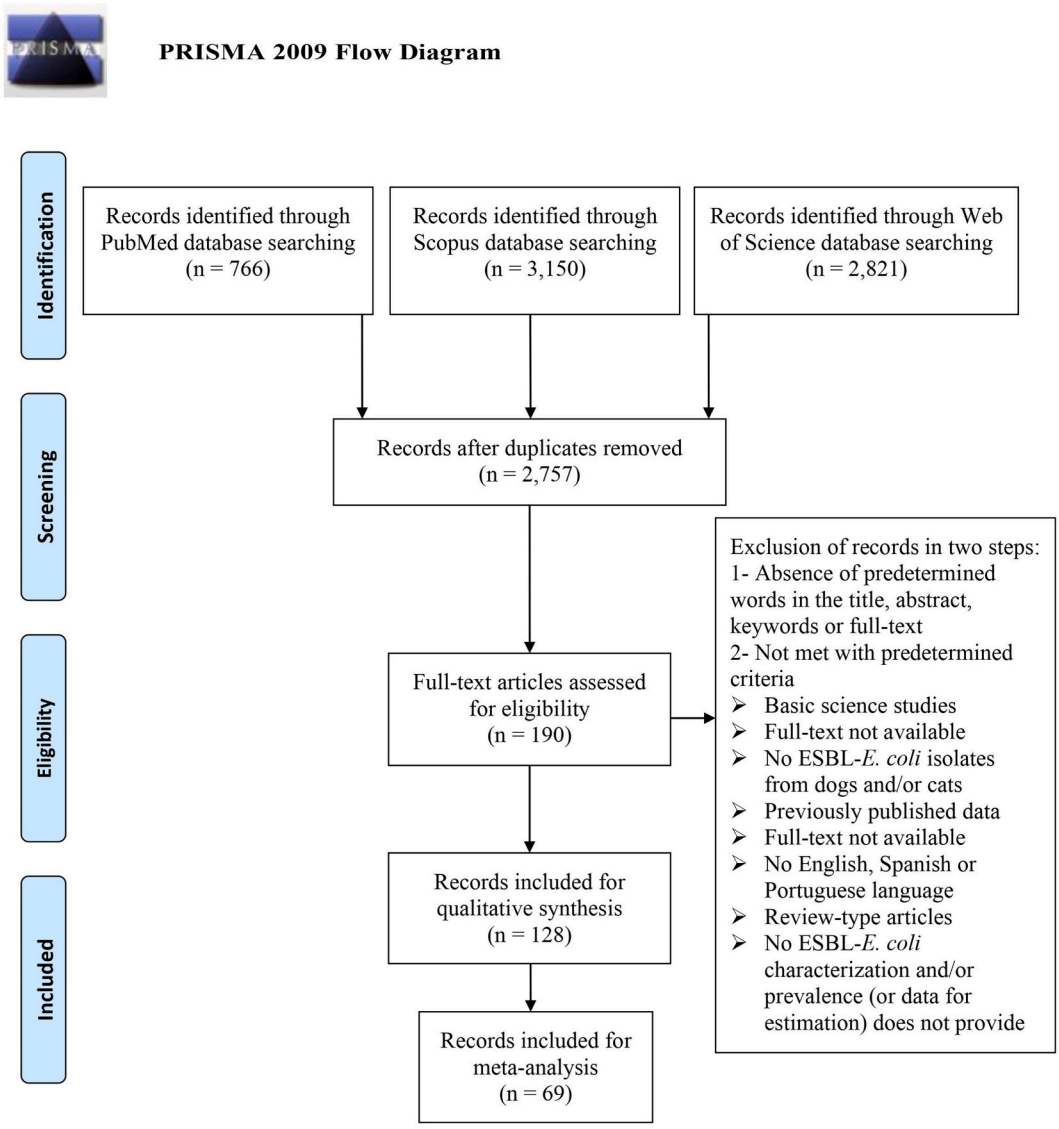

Fig. 1. Flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

total number of animals sampled, genotypes of ESBL genes in *E. coli*, and molecular typing of these isolates (ST, phylogroup, virulence genes) (Table S4).

Here, we presented an overview of four major topics: i) temporal trend in the number of publications, ii) geographic location of reported prevalence, iii) molecular characterization of ESBL genes detected in clinical and commensal *E. coli*, and iv) the population structure of *E. coli* isolates harboring these resistance genes.

2.5. Meta-analysis

Of papers included for qualitative synthesis, we selected those containing the number of positive and total dogs and/or cats to estimate the global prevalence of ESBL-*E. coli* and compared between dogs and cats and across countries. A critical appraisal of these papers was conducted to be included in our meta-analysis. Papers were scored between 0 and 4 according to four questions (1. Was the number of positive dogs/cats provide? / 2. Was the number of total sampled dogs/cats provide? / 3. Was data from dogs or cats provided separately? / 4. Was ESBL-*E. coli* isolates confirmed by phenotypic/molecular tests?) and those that scored 4 were included in the meta-analysis. The meta-analysis was performed using the *meta* and *metafor* libraries in R [41,42]. The overall prevalence and confidence interval of 95% were determined according with the total number of dogs or cats sampled using a random effect model [43]. The effects and impact of variation of species, continent, or year were tested using a meta-regression with the *metareg* function in R [42]. Forest plots were shown using the *forest* function. The heterogenicity in the meta-analysis, referred as the variation in study outcomes between studies that is not due to chance, was measured using the I^2 statistic [44].

3. Results

3.1. Qualitative synthesis and meta-analysis

A total of 190 articles were first selected. Based on the eligibility criteria, 128 studies containing data on ESBL-*E. coli* prevalence, molecular characterization of ESBL genes, or molecular typing of ESBL-*E. coli* isolates from dogs and/or cats were retained (Table 1). The eligibility process and reasons for exclusion in each step were summarized in the flow chart (Fig. 1). Data on each article are given on Table S4.

Table 1
Summary of features of studies included in the scoping review ($n = 128$).

Origin of samples	Total of publications	Species sampled	Number of publications estimating prevalence [a]		Number of publications characterizing ESBL genes [b]		Number of publications performing phylo-typing		Number of publications determining MLST typing		Number of publications screening for virulence genes		References
America	20[c]	dogs and cats	10/20	(50%)	16/20	(80%)	11/20	(55%)	9/20	(45%)	5/20	(25%)	[10,21,22,35,37,45–59]
Europe	60[d]	dogs and cats	32/60	(53%)	55/60	(92%)	23/60	(38%)	36/60	(60%)	13/60	(22%)	[9,12,14,16,17,23,24,32,34,60–110]
Africa	9	dogs and cats	8/9	(89%)	8/9	(89%)	7/9	(78%)	3/9	(33%)	0/9	(0%)	[20,111–118]
Asia	33	dogs and cats	15/33	(45%)	30/33	(91%)	11/33	(33%)	14/33	(42%)	7/33	(21%)	[8,11,13,15,31,36,119–145]
Oceania	6	dogs and cats	3/6	(50%)	5/6	(83%)	0/6	(0%)	4/6	(67%)	0/6	(0%)	[146–151]

[a] Reported in the study or estimated based on the information provide by study.
[b] Molecular characterization of the genes $bla_{\text{CTX-M}}$, bla_{SHV}, and bla_{TEM}
[c] One study analyzed samples originated from United States and Canada.
[d] Six studies analyzed samples originated from two or more countries within Europe.

3.2. Spatio-temporal characteristics in the number of publications

The number of peer-reviewed articles increased from one per year in 2001 to 19 per year in 2019, with an increase in the last ten years (Fig. 2). Most studies were conducted in Europe (46.9%, 60/128) followed by Asia (25.8%, 33/128) (Fig. 3A). China ($n = 11$) and Japan ($n = 10$) contained the largest number of publications (Table S5).

Overall, 67.2% (86/128) of studies were conducted exclusively in companion animals and the remaining 32.8% (42/128) analyzed samples from different animal species besides dogs and cats including livestock ($n = 25$), humans ($n = 15$), and wildlife ($n = 12$). Most studies included only dogs (41.4%) or both dogs and cats (51.6%), and 7% were conducted exclusively in cats (Fig. 3B).

Almost all studies (97.7%, 125/128) confirmed the production of ESBL by using molecular methods to detect the most common ESBL genes (CTX-M, SHV, and TEM) and 47.7% (61/128) used selective media to screen ESBL-*E. coli* before confirmation.

Studies included clinical samples (*i.e.*, from hospitalized or sick animals) (43%, 55/128), samples from healthy animals (*i.e.*, non-clinical samples) (41.4%, 53/128), or both clinical and non-clinical samples specimens (13.3%, 17/128). The remaining studies did not specify the type of samples (2.3%, 3/128). Clinical samples included majority urine specimens (18%, 42/239 from 72 studies) whereas faecal specimens represented 91% of non-clinical specimens (67/74 from 70 studies) (Fig. 4).

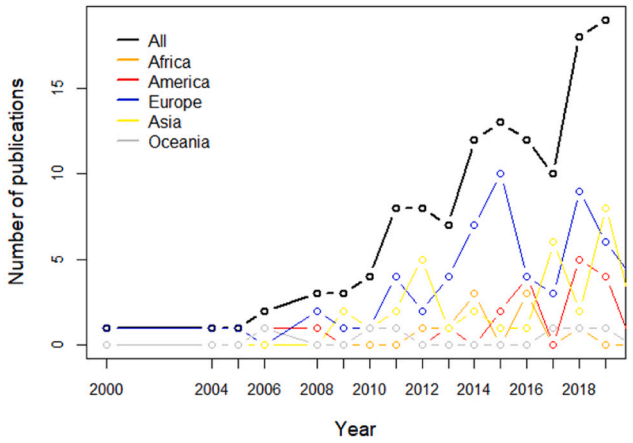

Fig. 2. Number of publications per continent over 2000–2020 period.

3.3. Meta-analysis of global prevalence of ESBL-E. coli in companion animals

Based on the quality assessment performed, meta-analysis was conducted using data from 67 studies, which yielded a total of 8005 dogs and 2263 cats sampled. Remaining studies assigned to a lower score than 4 were still eligible enough for our scoping review based on our inclusion criterion. The prevalence was more reported on dogs (91%, 61/67) compared to cats (47.8%, 32/67). The global prevalence of ESBL-*E. coli* was estimated to be 6.87% [95% CI: 4.46–10.45%] in dogs and 5.04% [95% CI: 2.42–10.22%] in cats (Fig. 5). There was no statistical difference in the prevalence between dogs and cats (meta-regression, $p = 0.5$). In addition, our meta-analysis did not show trends in the prevalence of ESBL-*E. coli* either dogs or cats over 2000–2020 period (meta-regression, $p > 0.1$).

The prevalence of ESBL-*E. coli* varied across continent, ranging from 0.63% [95% CI: 0.02–15.34%] (Oceania) to 16.56% [95% CI: 7.45–32.84%] (Africa) in dogs (Fig. 6). Similarly, it ranged from 0% [95% CI: 0–100%] (Oceania) to 16.82% [95% CI: 5.26–42.45%] (Asia) in cats (Fig. 7). Variation required in estimations and sample size to estimate prevalence varied significantly across studies ($I^2 > 79\%$) and countries, with the highest prevalence reported reaching up to 84% in dogs (The Netherlands) and 74% in cats (Pakistan) (Tables S6, S7, and S8).

3.4. Molecular characterization of ESBL genes detected in E. coli isolates from clinical and non-clinical samples of companion animals

Molecular characterization of ESBL-*E. coli* isolates was performed on 118 studies. Bacterial molecular typing of ESBL-*E. coli* was performed by identification of *E. coli* phylogroup in 52 studies and multi-locus sequence typing (MLST) in 66 studies. Phylogroup was identified mainly in ESBL-*E. coli* from clinical samples (51.9%, 27/52) compared to non-clinical (34.4%, 18/52) and in 13.5% of studies ($n = 7$) the isolates were from both clinical and non-clinical or were not specified. Likewise, MLST was conducted in isolates from 53% of studies containing clinical samples (35/66), 34.9% of studies containing non-clinical samples (23/66), and 12.1% of studies ($n = 8$) isolated ESBL-*E. coli* from both clinical and non-clinical or did not specify the type of sample.

Molecular characterization of the main ESBL genes ($bla_{\text{CTX-M}}$, bla_{SHV}, bla_{TEM}) was performed in 114 studies. ESBL-*E. coli* genes were recovered from 43.8% of studies containing clinical samples (50/114) and from 39.5% of studies containing non-clinical samples (45/114). In 16.7% of studies ($n = 19$), the isolates were obtained from both clinical and non-clinical or the type of specimen was not provided.

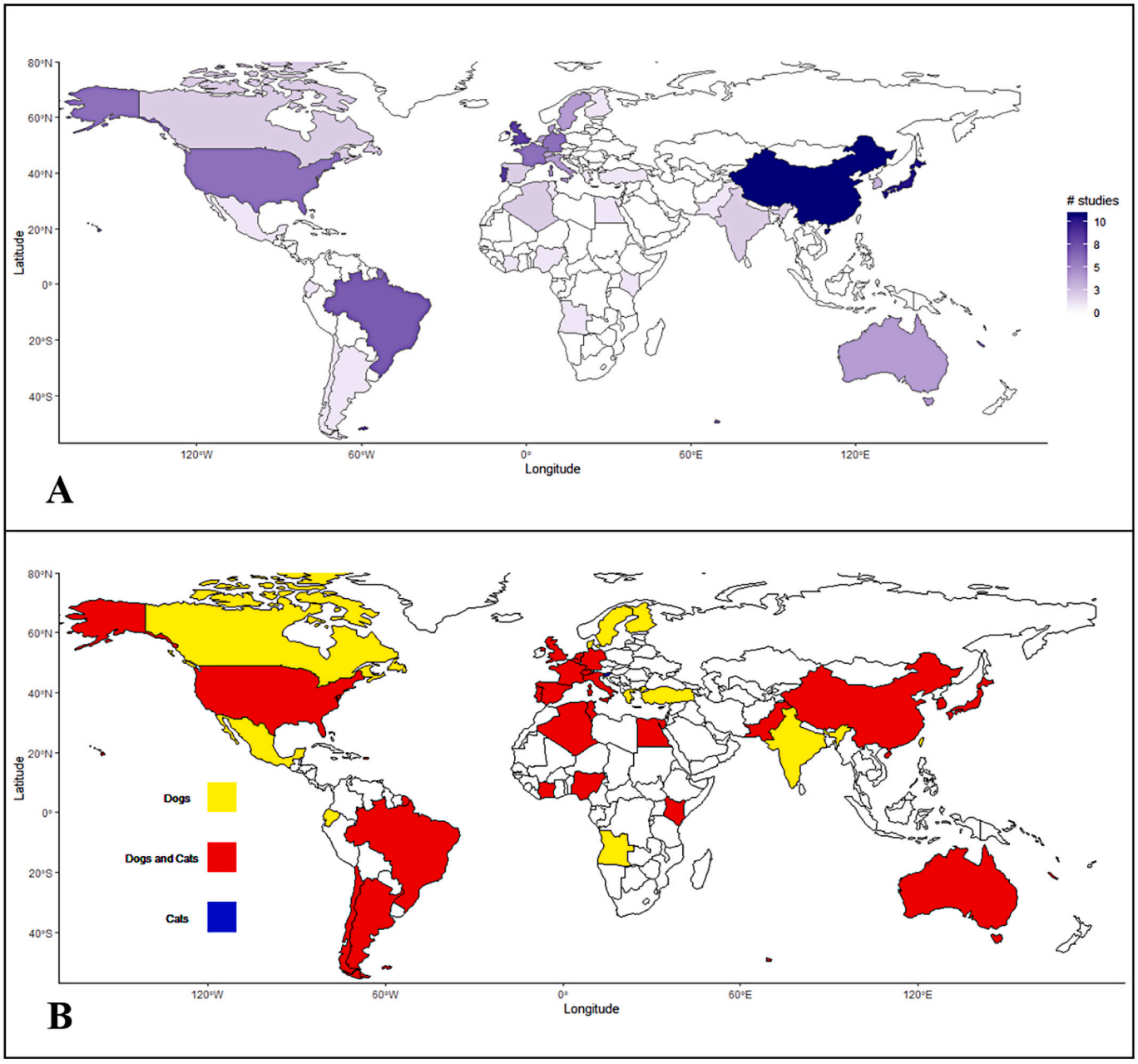

Fig. 3. A: Number of publications of ESBL-*E. coli* in dogs and cats per country in gradient. B: Studies performed exclusively in dogs, or cats, or both per country.

Only 25 studies tested the presence of virulence factors among ESBL-*E. coli* and in 23 of them, virulence genes were detected. Most of studies identified isolates containing virulence genes from clinical samples (73.9%, 17/23) and the remaining from non-clinical (26.1%, 6/23).

3.4.1. Genetic diversity of ESBL genes

Studies detected 60 different ESBL genotypes including 39 of $bla_{\text{CTX-M}}$, seven of bla_{SHV}, and 14 of bla_{TEM}. $bla_{\text{CTX-M-type}}$ was reported in 95% of studies (110/118) and these were relatively evenly distributed among dogs and cats across all continents (Table 2). Fourteen genotypes of $bla_{\text{CTX-M}}$, two genotypes of bla_{SHV}, and three genotypes of bla_{TEM} were present in two or more continents and $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-12}}$ were described in all. Unique genotypes of ESBL were found in all continents, except for Africa, with 13 genotypes exclusively described in Europe, 13 in Asia, seven in America, and one in Oceania.

3.4.2. Population structure of ESBL-E. coli among companion animals

One-hundred seventy-one different STs were identified (Table 3). ST38 and ST131 were found in all continents followed by ST68, ST405, ST617, and ST648 detected in at least four.

All phylogroups (A, B1, B2, C, D, E, and F) were found in ESBL-*E. coli* isolates from America and Europe (Table 3). Studies from Oceania did not perform the identification of phylogroup of ESBL-*E. coli* isolates.

Ninety-three virulence genes were detected in isolates from America, Asia, and Europe (Table 2). Most virulent genes were associated with *E. coli* pathotypes such as extraintestinal pathogenic (EPEC, including uropathogenic [UPEC]), enterohemorrhagic (EHEC), enterotoxigenic (ETEC), diffusely adherent (DAEC), and shiga-toxin producing (STEC).

4. Discussion

ESBL-*E. coli* circulating among dogs and cats have been reported worldwide, but the extend of the circulation of this bacteria among

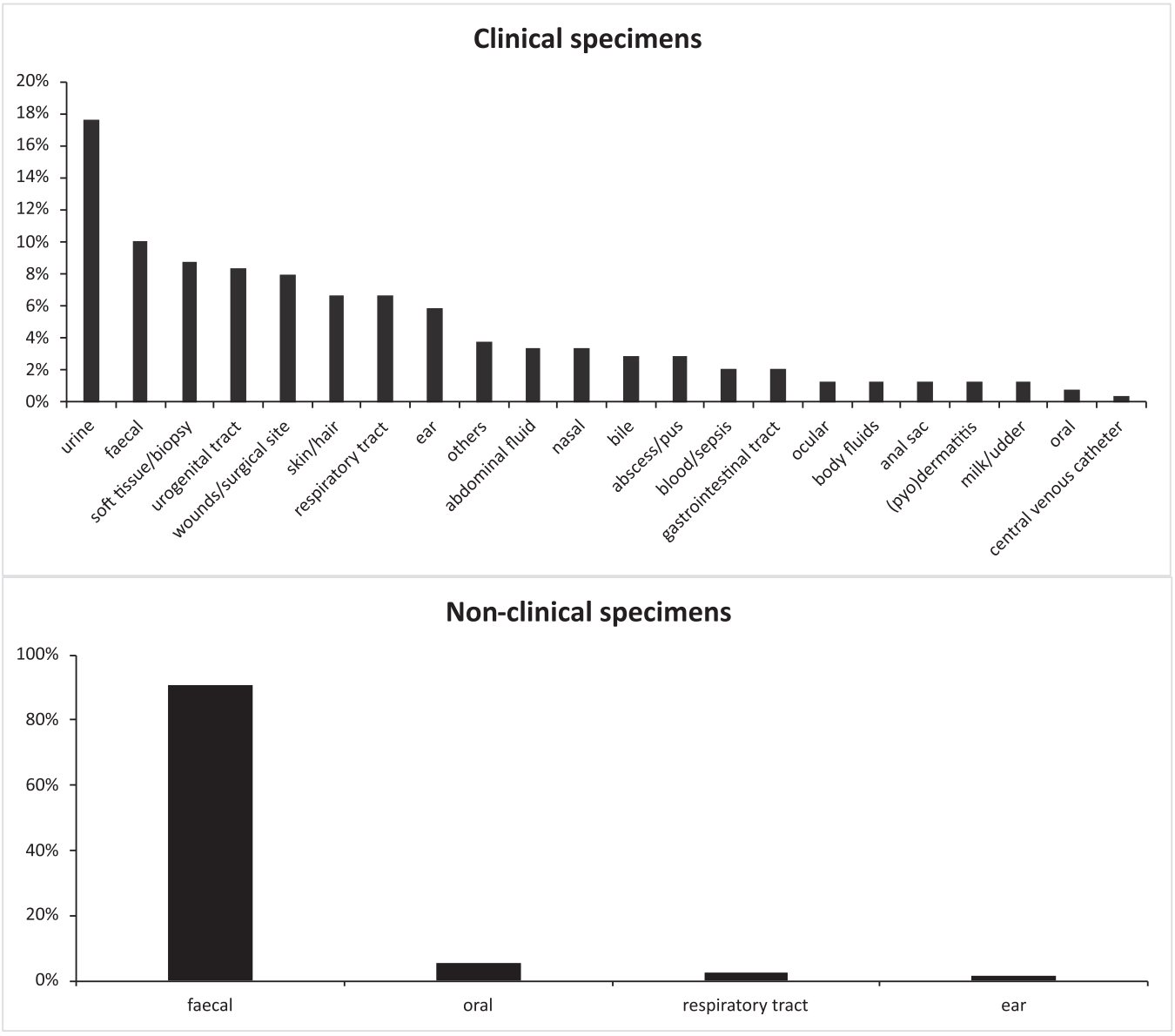

Fig. 4. Type of samples and proportion of specimens that were collected by included studies. Body fluids specimens includes effusions; Faecal specimens includes diarrhea and non-diarrhea; Gastrointestinal tract specimens includes digestive tract, enteritis, vomitus; Ocular specimens includes conjuntive, córnea, and eye; Others specimens referred as type of sample not specified; Respiratory tract [clinical] specimens includes bronchoalveolar lavage, sneeze, pharynx, pleural effusion, throat, and trachea lavage fluids; Respiratory tract [non-clinical] specimens includes nasal, and pharyngeal; Soft tissue/biopsy specimens includes colon, gut, liver, lung, and lymphonodes; Urogenital tract specimens includes uterus, vaginal secretion, intrauterine liquid, preputial secretion, prostate, pyometra, and scrotal fluid; Wounds/surgical sites specimens includes fistula.

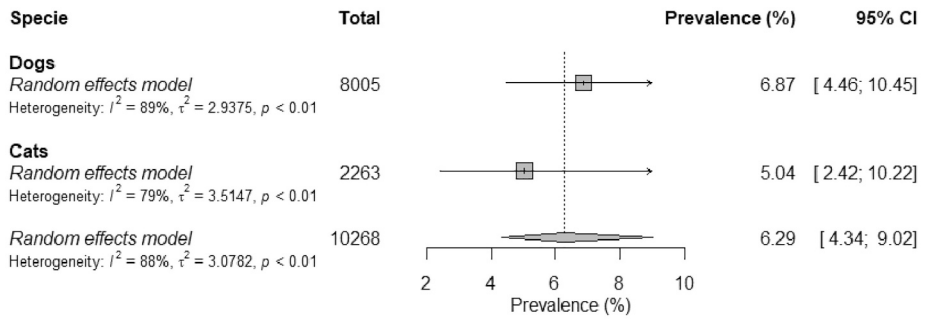

Fig. 5. Forest plot of the global prevalence of ESBL-*E. coli* in dogs and cats.

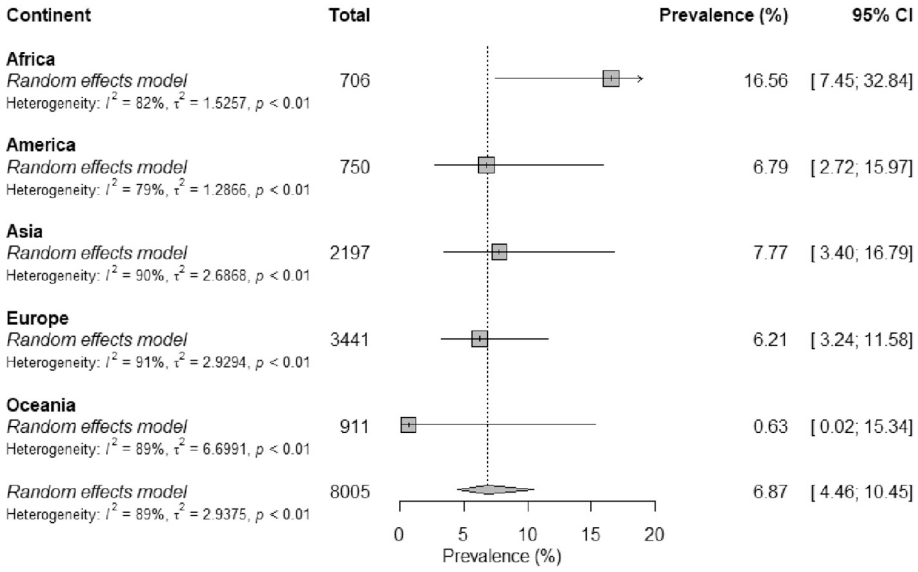

Fig. 6. Forest plot of the prevalence of ESBL-*E. coli* in dogs across continent.

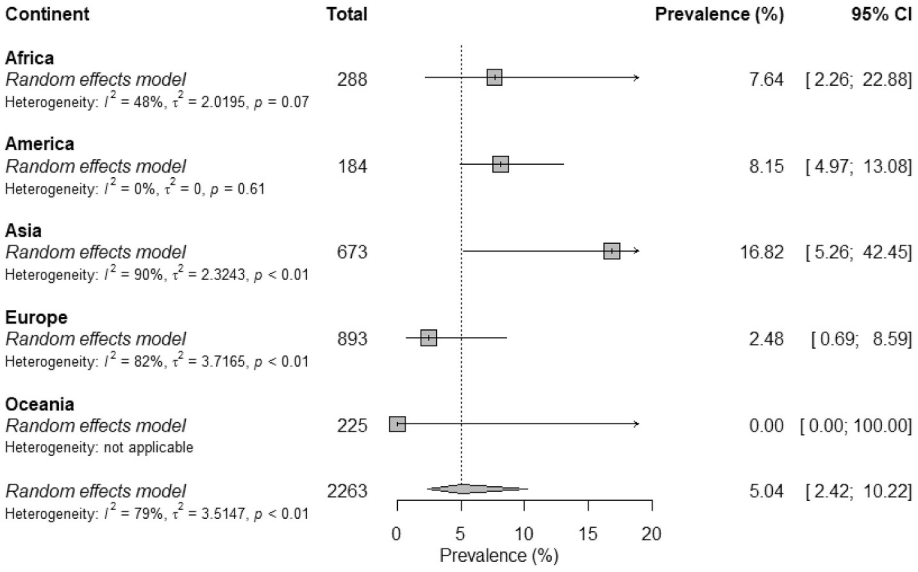

Fig. 7. Forest plot of the prevalence of ESBL-*E. coli* in cats across continents.

companion animals remains unclear. In this review, we showed an increasing number of publications focusing on this topic and estimated a similar global prevalence of ESBL-*E. coli* of 6.87% in dogs and 5.04% in cats. We identified that the number of publications and prevalence varied extensively across continents, countries, and studies. A high diversity of both ESBL genes and *E. coli* clones were found worldwide, with ESBL genes $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-12}}$ and sequence types ST38 and ST131 found in all continents.

The estimated prevalence of 6.29% [95% IC: 4.34–9.02%] of ESBL-*E. coli* in companion animals can be considered lower compared to estimations in livestock (50%–70%) [152–155], and in humans (2%–46%) [156–159]. No statistical differences of prevalence were observed between dogs (6.87%) and cats (5.04%) and we did not observe variation on the prevalence rates of ESBL-*E. coli* either in dogs or cats over years (meta-regression, $p > 0.1$). There were fewer studies conducted exclusively on cats, although we have estimated a similar prevalence in cats and dogs. The smaller number of studies conducted in cats could possibly be related to greater logistical challenges in obtaining samples. For instance, feline handling is difficult during medical examinations, as restraint techniques increase fear and fear aggression in many cats compared to dogs [160], and cats usually bury their feces after defecation [160,161]. Despite a relative low prevalence compared to livestock or humans and no reported increase over the 20-year period, the presence of ESBL-*E. coli* in dogs and cats can have important impacts for the treatment of companion animals. Resistant bacterial infections increase length of hospital stay, mortality, and healthcare costs in humans [162], which would be also expected for companion animals. However, to our knowledge, no study has estimated the cost and burden of ESBL-*E. coli* infections on companion animals.

Significant variation in prevalence estimations were observed across continents and studies. Part of these differences could be associated with differences in study methodologies since the use of selective culture medium might overestimate the prevalence [163]. Alternatively, differences in prevalence across continents and countries could reflect differences in the circulation of ESBL-*E. coli* related, for example, to different levels of antibiotic use among veterinarians and owners and

Table 2
ESBL and virulence genes identified from *E. coli* isolates among dogs and cats.

Continent	ESBL genotypes	Ref.	Virulence genes	Ref.
Africa	CTX-M-1, CTX-M-15, SHV-12, TEM-135	[20,111–114,116–118]	No data	
America	CTX-M-1, CTX-M-2, CTX-M-3, CTX-M-8, CTX-M-9, CTX-M-14, CTX-M-15, CTX-M-24, CTX-M-27, CTX-M-55, CTX-M-65, CTX-M-106, CTX-M-115, CTX-M-123, CTX-M-169, CTX-M-202, SHV-2, SHV-3, SHV-12, TEM-5, TEM-30, TEM-33, TEM-181	[10,35,37,46–58]	*afa/draBC, air, cba, cma, cnf1, cvaC, eilA, fimH, focA, fyuA, gad, hlyA, hlyD, ibeA, ipfA, ireA. iroN, iutA, iss, kpsMTII, kpsMTK5, malX, mchF, PAI, papA, papC, papE, papGIII, rfc, sfa/focDE, tsh, traT*	[10,21,51,55,56]
Asia	CTX-M-1, CTX-M-2, CTX-M-3, CTX-M-8, CTX-M-9, CTX-M-13, CTX-M-14, CTX-M-15, CTX-M-24, CTX-M-27, CTX-M-28, CTX-M-55, CTX-M-57, CTX-M-64, CTX-M-65, CTX-M-90, CTX-M-104, CTX-M-116, CTX-M-123, CTX-M-127, CTX-M-174, SHV-12, SHV-190, TEM-30	[8,11,13,15,31,36,119–131,133,134,136,137,139–145]	*aec, cah, clpV, csgA, csgB, csgC, csgD, csgE, csgF, csgG, eaeA, eaeH, ETTT, ehaB, espl, espR, espX, f17a-A, fimH, fyuA, hlyE, iha, iutA, iucD, kpsmMT, malX, papC, papE, papG, PAI, sat, stx2, traT*	[15,131,133,138,144]
Europe	CTX-M-1, CTX-M-2, CTX-M-3, CTX-M-8, CTX-M-9, CTX-M-14, CTX-M-15, CTX-M-18, CTX-M-20, CTX-M-24, CTX-M-27, CTX-M-28, CTX-M-32, CTX-M-44, CTX-M-55, CTX-M-57, CTX-M-61, CTX-M-65, CTX-M-79, CTX-M-82, CTX-M-138, SHV-2, SHV-2A, SHV-5, SHV-12, SHV-28, TEM-21, TEM-32, TEM-35, TEM-52, TEM-52B, TEM-52C, TEM-52StPaul, TEM-80, TEM-135, TEM-158	[9,12,14,16,17,23,24,32,34,60–66,68,70–92,94–97,99–107,109,110]	*afa/dra, argW, astA, cba, celb, chuA, cif, cma, cnf1, crl, csgA, eae, ecpA, eilA, espA, espB, espF, espJ, fimA, fimC, fimH, fyuA, gad, HPI, hlyA, iha, ireA, iroN, irp2, iss, iucD, iutA, iutD, kpsMTII, lpfA, malX, mat(A), mchF, mcmA, nleA, nleB, prfB, ompA, PAI, papAH, papC, papGII, papEF, sat, senB, sfaDE, sfa/foc, sitA, tir, toxB,* traT, *tsh,* yfcv	[9,12,34,64,66,73,77,81,93,101,102,107,110]
Oceania	CTX-M-11, CTX-M-14, CTX-M-15, CTX-M-27, SHV-12, TEM-33	[147–151]	No data	

other factors influencing bacterial transmission. For example, socio-economic and behavioral components may reflect the differences of AMR ratios observed in low- and middle-income countries [164]. In fact, prevalence was higher in Africa or Asia, and lower in Oceania and Europe, which could be associated with a socio-economic gradient, this requiring further investigation.

A high diversity of ESBL genes and *E. coli* clones were associated with ESBL resistance in dogs and cats. Identification of similar ESBL and STs across continents confirmed the widespread of ESBL-*E. coli* in companion animals also observed in humans [165]. Europe showed the highest molecular diversity, which could be associate both to a higher number of studies and to a more available molecular typing techniques, when compared to low-income countries. Overall, our review shows that ESBL-*E. coli* circulation among companion animals is not necessarily clonal and could result from multiple introductions from other sources (*e.g.*, livestock and humans) or a selective pressure generated by antibiotics usage by veterinarians and owners. For example, owners tend to exert substantial influence on veterinary decisions on the prescription of antibiotics [166]. The inability of companion animals to communicate the severity of their symptoms often leads owners to prioritize preventive measures including the use of antibiotics.

Most studies reporting ESBL-*E. coli* concluded that dogs and cats are

Table 3
Phylogroup and sequence types of ESBL-*E. coli* isolated from dogs and cats.

Continent	Phylogroup	Ref.	Sequence Types	Ref.
Africa	A, B1, B2, D, E, F	[20,112–114,116–118]	ST38, ST44, ST46, ST58, ST131, ST617, ST2852, ST3687, ST3694, ST3726	[20,111,113]
America	A, B1, B2, C, D, E, F	[35,37,49–52,54,55,58]	ST10, ST12, ST23, ST38, ST44, ST58, ST68, ST69, ST73, ST90, ST104, ST117, ST127, ST131, ST155, ST162, ST167, ST224, ST354, ST371, ST372, ST393, ST405, ST410, ST443, ST457, ST617, ST648, ST770, ST961, ST1011, ST1088, ST1193, ST1585, ST1722, ST1730, ST1976, ST2175, ST2541, ST2936, ST3267, ST3395, ST3944, ST4110, ST4891, ST5033, ST5063, ST5174, ST5206, ST5219, ST5220, ST5231, ST5232, ST5612, ST6478	[10,21,37,50,51,54–57]
Asia	A, B1, B2, C, D, F	[13,124,126,127,130,131,133,134,137,141,144]	ST10, ST38, ST44, ST46, ST64, ST68, ST69, ST70, ST73, ST75, ST90, ST93, ST95, ST104, ST101, ST117, ST127, ST131, ST155, ST162, ST165, ST167, ST181, ST224, ST302, ST327, ST345, ST349, ST350, ST351, ST354, ST359, ST372, ST375, ST405, ST410, ST448, ST453, ST457, ST533, ST602, ST617, ST642, ST648, ST746, ST827, ST1125, ST1177, ST1193, ST1262, ST1421, ST1431, ST1642, ST1700, ST1722, ST1820, ST1960, ST2042, ST2178, ST2179, ST2375, ST2509, ST2541, ST2599, ST3058, ST3210, ST3630, ST5176, ST6316	[8,13,15,124–126,131,133,134,137,140,141,143,144]

(*continued on next page*)

Table 3 (*continued*)

Continent	Phylogroup	Ref.	Sequence Types	Ref.
Europe	A, B1, B2, C, D, E, F	[9,32,34,64,66,72–74,77,79,80,82,87,88,91,93,94,96,99,102,104,106,107]	ST3, ST10, ST23, ST38, ST43, ST46, ST57, ST58, ST59, ST68, ST69, ST73, ST88, ST90, ST92, ST93, ST101, ST117, ST127, ST131, ST141, ST155, ST156, ST160, ST162, ST167, ST186, ST209, ST219, ST224, ST227, ST297, ST315, ST349, ST354, ST359, ST361, ST362, ST398, ST405, ST410, ST453, ST457, ST448, ST461, ST493, ST533, ST539, ST555, ST602, ST609, ST617, ST648, ST670, ST744, ST746, ST949, ST963, ST973, ST1126, ST1177, ST1196, ST1249, ST1284, ST1303, ST1340, ST1421, ST1431, ST1485, ST1576, ST1594, ST1665, ST1670, ST1684, ST1730, ST1832, ST1850, ST2067, ST2348, ST2449, ST2607, ST3018, ST3163, ST3381, ST3509, ST3847, ST3848, ST3889, ST4181, ST4184, ST4304, ST4305, ST4340, ST4496, ST4792, ST6998	[9,12,14,16,17,24,32,34,64,66,70–74,76,77,79,81–84,87,88,94,96,97,99–102,104,105,107,109,110]
Oceania	No data		ST12, ST38, ST68, ST106, ST131, ST405, ST648, ST744, ST1408, ST1569, ST2144, ST3268, ST3520, ST4200	[148–151]

'reservoirs' of ESBL. However, no study to our knowledge has fully proven that companion animals are 'reservoirs' of ESBL-*E. coli*, defined as a population that can maintain and subsequently transmit the bacteria to a target population (*e.g.*, humans) without the introduction from another source [167]. Therefore, it remains unclear whether reducing the transmission of ESBL-*E. coli* among companion animals will result in less transmission to humans.

5. Conclusions and future directions

Research on ESBL-*E. coli* in companion animals has increased in the last 20 years, showing that these bacteria is present in dogs from all continents and cats in all continents, except for Oceania. Despite increasing interest, the prevalence of ESBL-*E. coli* is still not reported in many countries, mainly in low-income countries and in cats. A high diversity of ESBL genes and ESBL-*E. coli* clones were detected. Although some studies detected the presence of virulent genes, the pathogenic relevance of these bacteria as well as their impact on animal morbidity, mortality, length of hospitalization, and treatment cost remain poorly understood. Future research should focus on identifying the drivers responsible for the acquisition and dissemination of ESBL-*E. coli* in companion animals including cross-species transmission with humans and livestock, the clinical relevance of these bacteria and their economic impact.

This scoping review identified the prevalence and population structure of ESBL-*E. coli* isolates circulating in dogs and cats. Many studies were excluded due to incomplete or inadequate reporting of data. Also, the comparison between studies with different designs is challenging and can introduced several biases regarding the comparison of prevalence across studies, countries, and continents. Part of this is probably reflected on the high heterogeneity on study results. Therefore, we recommend standardization among methodologies of studies, which could follow consensus of international experts.

Our review also calls for the establishment of national surveillance programs in low- and middle-income countries that will allow monitoring the extension of the ESBL problem in companion animals and evaluate the implementation of different strategies to limit the spread of ESBL including more responsible use of antibiotics by both veterinarians and owners.

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Competing interests

The authors of this paper have no conflicts of interest to report.

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CRediT authorship contribution statement

Conceptualization: M.S.-C., J.A.B., A.M.-S.; Data curation: M.S.-C.; Formal analysis: M.S.-C., J.A.B.; Funding acquisition: M.S.-C., J.A.B., A.M.-S.; Investigation: M.S.-C., J.A.B., A.M.-S., A.D.A, A.C.P.; Methodology: M.S.-C., J.A.B., A.D.A.; Project administration: J.A.B., A.M.-S., A.C.P.; Resources: J.A.B., A.M.-S., A.C.P.; Software: J.A.B.; Supervision: J.A.B., A.M.-S., A.C.P; Validation: M.S.-C., J.A.B., A.M.-S., A.D.A., A.C.P.; Visualization: M.S.-C., J.A.B., A.M.-S., A.D.A., A.C.P.; Writing - original draft: M.S.-C.; Writing - review & editing: M.S.-C., J.A.B., A.M.-S., A.D.A., A.C.P.

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