One Health 16 (2023) 100522

Contents lists available at ScienceDirect

One Health

journal homepage: www.elsevier.com/locate/onehlt

Antimicrobial resistance in bacteria isolated from peridomestic *Rattus* species: A scoping literature review

Theethawat Uea-Anuwong [a], Kaylee A. Byers [b,c], Lloyd Christian Wahl [d], Omid Nekouei [a,d], Yrjo Tapio Grohn [e], Ioannis Magouras [a,d,f,*]

[a] Department of Infectious Diseases and Public Health, Jockey Club College of Veterinary Medicine, City University of Hong Kong, Kowloon Tong, Hong Kong Special Administrative Region, China
[b] Canadian Wildlife Health Cooperative, Animal Health Centre, Abbotsford, British Columbia, Canada
[c] Pacific Institute on Pathogens, Pandemics and Society, Simon Fraser University, Burnaby, British Columbia, Canada
[d] Centre for Applied One Health Research and Policy Advice, City University of Hong Kong, Kowloon Tong, Hong Kong Special Administrative Region, China
[e] Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA
[f] Veterinary Public Health Institute, Department of Clinical Research and Veterinary Public Health, Vetsuisse Faculty, University of Bern, Bern, Switzerland

ARTICLE INFO

Keywords:
Antimicrobial resistance
Rattus
ESBL
MRSA
Peridomestic wildlife
Public health

ABSTRACT

Rattus spp. may acquire and disseminate antimicrobial resistant bacteria or antimicrobial resistance (AMR) genes. We conducted a scoping review to synthesize available research findings on AMR in *Rattus* spp. and to describe the size and scope of available literature on AMR epidemiology in *Rattus* spp. The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR). The search focused on scientific peer-reviewed publications focusing on AMR in peridomestic *Rattus* spp. The review was limited to publications in English available in PubMed, Web of Science and Scopus between 2000 and 2021. The results were summarized descriptively. Thirty-four studies conducted in twenty-one countries were included in this scoping review. Twelve bacterial species with AMR were identified with *Escherichia coli* and *Staphylococcus aureus* being the two most commonly reported. The resistant bacteria were isolated from species of peridomestic *Rattus* spp. in which *R. norvegicus* and *R. rattus* were the two most commonly studied. Rats were also found to carry multi-drug resistant (MDR) bacteria including extended-spectrum beta (β)-lactamase (ESBL), methicillin-resistant *Staphylococcus aureus* (MRSA), colistin-resistant Enterobacteriaceae (CoRE), and vancomycin-resistant Enterococci (VRE). This scoping review suggests that peridomestic *Rattus* spp. can carry multiple antimicrobial resistant bacteria, indicating their potential to serve as reservoirs and spreaders of AMR thus posing a threat to human and animal health.

1. Introduction

Antimicrobial resistance (AMR) creates significant challenges in treating bacterial infections in both animals and humans. The rise and spread of antimicrobial resistant microbes, in the past several decades pose a serious threat to global health [1,2]. Antimicrobial resistance increases morbidity and mortality, and has a significant impact on the treatment duration and costs [3]. It was estimated that infections with antimicrobial resistant bacteria claimed the lives of a million people worldwide in 2019 and this number was predicted to become 10 times higher by 2050 [4]. The epidemiology of AMR is complex and still not entirely understood. While several studies have focused on AMR in humans and domestic animals, little is known about the potential role of wildlife in the maintenance and transmission of AMR [5]. Peridomestic animals, such as various species of rodents and birds, could be particularly of interest as they may serve as reservoirs and spreaders of resistant bacteria that they uptake from their environment [1].

Cosmopolitan *rattus* species, such as brown rats (*R. norvegicus*) and black rats (*R. rattus*) are well adapted to living alongside people in a variety of rural and urban habitats [6]. They are known carriers of several zoonotic pathogens including *Yersinia pestis*, the etiologic agent of the plague, and *Leptospira interrogans*, the causative agent of leptospirosis [7]. Several studies have demonstrated that rats can carry antimicrobial resistant bacteria. These include extended-spectrum beta

* Corresponding author at: Department of Infectious Diseases and Public Health, Jockey Club College of Veterinary Medicine, City University of Hong Kong, Kowloon Tong, Hong Kong Special Administrative Region, China
E-mail address: ioannis.magouras@cityu.edu.hk (I. Magouras).

https://doi.org/10.1016/j.onehlt.2023.100522
Received 20 October 2022; Received in revised form 27 February 2023; Accepted 1 March 2023
Available online 4 March 2023

(β)-lactamases (ESBL) [8] and methicillin-resistant *Staphylococcus aureus* (MRSA) [9,10]. As rats live in close association with people, they could potentially carry human-derived antimicrobial resistant bacteria and further disseminate these in the environment and to other people or animals.

The majority of resistant bacteria carried by peridomestic rats is considered to be of anthropogenic origin [11,12]. Misuse and overuse of antimicrobial agents in both human and veterinary healthcare promote the evolution of AMR among different bacteria [13]. For example, inappropriate disposal of antimicrobial products leads to the contamination of antimicrobial residues in the environment and results in further selective pressure [11]. Wastewater from residential areas, sewage effluent from hospitals, farm animal slurry and manure (including aquaculture) are sources of antimicrobial resistant bacteria and AMR genes, which are disseminated in the environment and can be acquired by rats [1,2,14].

The objective of this scoping literature review is to consolidate and describe the published research on AMR in peridomestic *Rattus* spp. as well as to resolve areas of interest and knowledge gaps on the potential role of rats in the complex epidemiology of AMR. Specifically, this review aims to: 1) identify the species and frequency of antimicrobial resistant bacteria carried by peridomestic rats globally; and 2) describe the phenotypic and/or molecular profile of AMR in these bacteria.

2. Materials and methods

2.1. Literature sources and search strategies

A systematic search of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) [15]. We searched for scientific peer-reviewed publications available in the following electronic databases: PubMed, Web of Science and Scopus. Gray literature was not included in this scoping review because there is no standard method for performing gray literature search [16]. In order to obtain the most recent epidemiological data, searches were limited to studies in English that were published from January 1st, 2000 to July 2nd, 2021, because the number of studies about AMR in wildlife began to increase just over a decade ago [17]. Moreover, molecular methods for AMR identification and characterization, such as DNA sequencing, became widely available using standard protocols after 2000 [18]. The search included medical subject headings (MeSH) and keywords from three domains: "AMR", "rat", and "bacteria", present in the title and/or the abstract. The combination of terms from the three domains is shown in Table S1.

2.2. Inclusion and exclusion criteria

An article was included if it fulfilled the following criteria: 1) presented primary research (observational study) on AMR in bacteria; 2) the study population included peridomestic *Rattus* spp. caught in their natural habitats; 3) described the methods used to characterize the AMR phenotype or genotype; and 4) reported the presence of AMR in bacteria from rats.

An article was excluded if: 1) it was an experimental study or a review; 2) the study population was laboratory, captive, or transgenic rats; or 3) it used bacterial isolates derived from other independent studies.

2.3. Study selection

Every document retrieved from the bibliographic databases was uploaded to rayyan.ai [19]. Duplicates were removed, and the remaining articles were screened by two reviewers following a two-step approach. In the first step, the titles and abstracts were screened based on the exclusion criteria. Publications were excluded through mutual agreement. The second step included a full-text review for the eligibility of publications based on the inclusion criteria. The process of study selection is presented in Fig. 1.

2.4. Data extraction

Data from the articles included for the final analysis were extracted into a spreadsheet using Microsoft Excel [20] with 22 pre-determined variables (i.e., rat species, sample types, bacterial species, and methods for detecting AMR (Table S2). Data extraction and results verification were done by the first author.

The extracted data of antimicrobial resistant bacteria were grouped into two broad categories, including drug-resistant (DR), which was defined as being resistant to one or two antimicrobial classes, and multidrug resistant (MDR) for those bacteria resistant to at least one antimicrobial in three or more antimicrobial classes [21]. In this review, MDR was divided into specific and non-specific MDR. The term "specific MDR" was applied to ESBL, MRSA, Vancomycin-resistant *Enterococcus* (VRE), Colistin-resistant Enterobacteriaceae (CoRE), Fluoroquinolones-resistant Enterobacteriaceae (FQRE), and Methicillin-resistant *S. pseudintermedius* (MRSP). All remaining MDR were defined as "non-specific". The results for DR and MDR bacteria are presented separately. In this review, the term "rats" is used collectively for all *Rattus* spp. when the species are not specified.

3. Results

The initial literature search identified a total of 2413 records of which 69 articles were included for full-text review. An additional 35 articles were removed because they did not meet the inclusion criteria; e.g., *Rattus* spp. were not in the study population or bacterial isolates originated from other studies. As a result, 34 articles were included in the scoping review (Fig. 1).

Most studies on AMR in peridomestic rats were published after 2011 (31/34 articles) [6,9–12,22–47]. The countries of the selected studies are presented in Fig. 2. *Rattus norvegicus* or brown rats were the most commonly studied *Rattus* spp. (30/34) [6,9–12,23–30,32–36,38–45,47–50], followed by *R. rattus* or black rats (15/34) [6,10,11,25–27,31,33–36,40,46,47,49]. Four studies reported other rat species, including *R. tanezumi* (Asian house rat), *R. argentiventer* (ricefield rat), *R. exulans* (Polynesian rat), *R. andanamensis* (Indochinese forest rat), *R. losea* (lesser ricefield rat), and *R. nitidus* (Himalayan rat) (Table 1).

3.1. Rat sampling and antimicrobial resistance testing

Rat collection was performed using live traps in more than half of the studies (22/34) [6,9,10,22–30,32,35,36,40,41,45–48,50] while kill trapping was used in only four studies [12,25,39,49]. Rats in four studies were collected as part of pest control programs [33,34,38] or rodent-borne pathogen surveillance systems [50]. Four studies did not mention how rats were collected [11,31,37,40]. Most of the rats were collected from areas inhabited by humans, such as city centers (downtowns), touristic areas, and around hospitals, markets, ports, treatment plants, and garbage sites. Seven studies specifically reported livestock farms, such as pig and chicken farms, as the rat collection sites (Table 1).

Twenty-four articles studied AMR only in peridomestic rats [6,10,22,24,26,27,29–32,35,36,38–44,46–50] and nine studies included other species such as livestock (chicken, duck, pig, and cattle) [28,33,34,37], humans [9,23,25], companion animals (dog and cat) [33,34], and wildlife (shrew and iguana) [9,11,12]. One study also integrated data on rat abundance, weather, and microenvironmental characteristics [45]. Rat species were identified morphologically (19/34) [10,11,23–27,31,33–36,38–40,43,45–47], or using DNA sequencing of the mitochondrial cytochrome *b* gene (3/34) [6,9,12], or molecular sequencing of cytochrome oxidase I (1/34) [28].

The most common samples collected from rats were gastrointestinal samples (31/34), including caecal and colon contents, fecal pellets, and

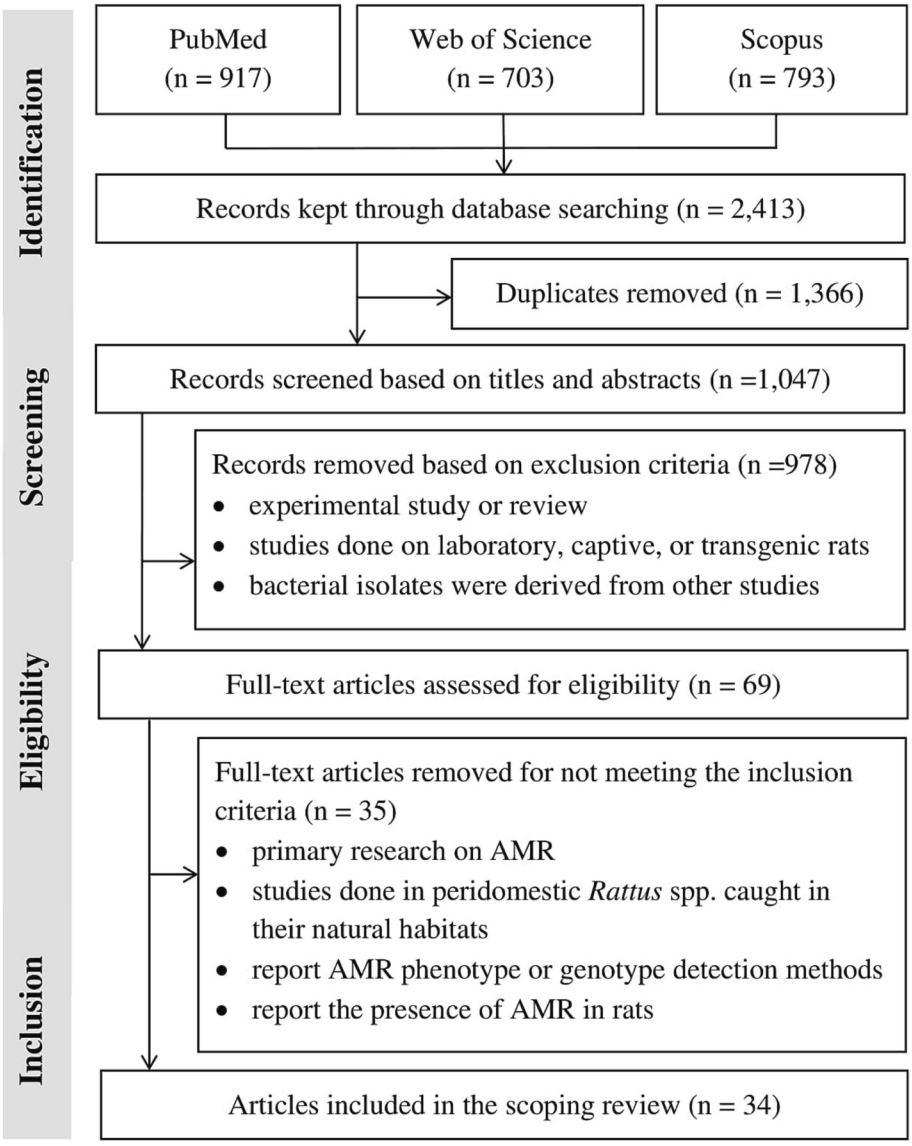

Fig. 1. PRISMA-ScR diagram of the selection process of studies included in the scoping review, for antimicrobial resistance in peridomestic rats, 2000–2021.

rectal swabs [6,9–12,22–24,26–32,34–46,48,50]. Studies on Enterobacteriaceae accounted for 51% of all bacteria (Fig. 3) and most focused on *E. coli* (61%), followed by *Klebsiella* spp., *Salmonella* spp., *Proteus* spp., and *Enterobacter* spp. (Table 1).

Samples from the respiratory tract (13/34) included nasal parts, nasal/ nasopharyngeal swabs, oropharyngeal swabs, tracheal swabs, and lung tissues [9,10,24,25,33,36,38,39,41,45–47,49]. Respiratory samples were used to isolate gram-positive bacteria, such as *Staphylococcus* spp. (30% of all bacteria), especially *Staphylococcus aureus*, which was the most common studied. Other species within the same genus described included *S. pseudintermedius, S. epidermis, S. fleurettii, S. haemolyticus, S. sciuri, S. xylosus*, and *S. lugdunensis* [24]. Other samples, such as blood, urine, and kidney tissue, were used to isolate *Leptospira* spp. in only one study [48].

Drug-resistant bacteria isolated from rats were reported in 15 studies. Twenty-nine studies reported MDR, 24 of which identified the specific types of MDR, including ESBL (16/34), MRSA (11/34), CoRE (1/34), VRE (1/34), FQRE (1/34), and MRSP (1/34) (Fig. 4 and Table 1).

Twenty-four studies investigated both the phenotypes and the genotypes of antimicrobial resistant bacteria. Eight studies characterized the antimicrobial resistant bacteria only phenotypically, and one study only conducted molecular analyses. The disk diffusion test (23/34) and minimum inhibitory concentration (MIC) methods (13/34) were used to characterize the AMR phenotypes. Twenty-one studies used polymerase chain reaction (PCR) to detect the AMR genes. Other molecular methods used in these studies included multi-locus sequence typing (MLST), whole genome sequencing (WGS), and microarrays (Table 1).

3.2. Drug resistance (DR) and non-specific type of multidrug resistance (MDR)

Fifteen studies reported DR in rats, nine of which included a non-specific type of MDR. There were 10 *Rattus* spp. reported in DR studies, including *R. norvegicus*, *R. rattus*, *R. rattus sladeni*, *R. rattus diardii*, *R. tanezumi*, *R. argentiventer*, *R. exulans*, *R. andamanensis*, *R. losea*, and *R. nitidus*. Four studies included other species such as livestock [28,37], and wildlife [11,12]. Most rats were captured alive and euthanized later for sample collection except in two studies where no information on rat capture was provided [11,43]. Fecal content was the main sample in these studies. Several other samples were collected, including fragment/tissue of colon [11,48], urine, kidney tissue [48], buccal swabs [45,48], and lung tissue [47]. *Escherichia coli* was the most

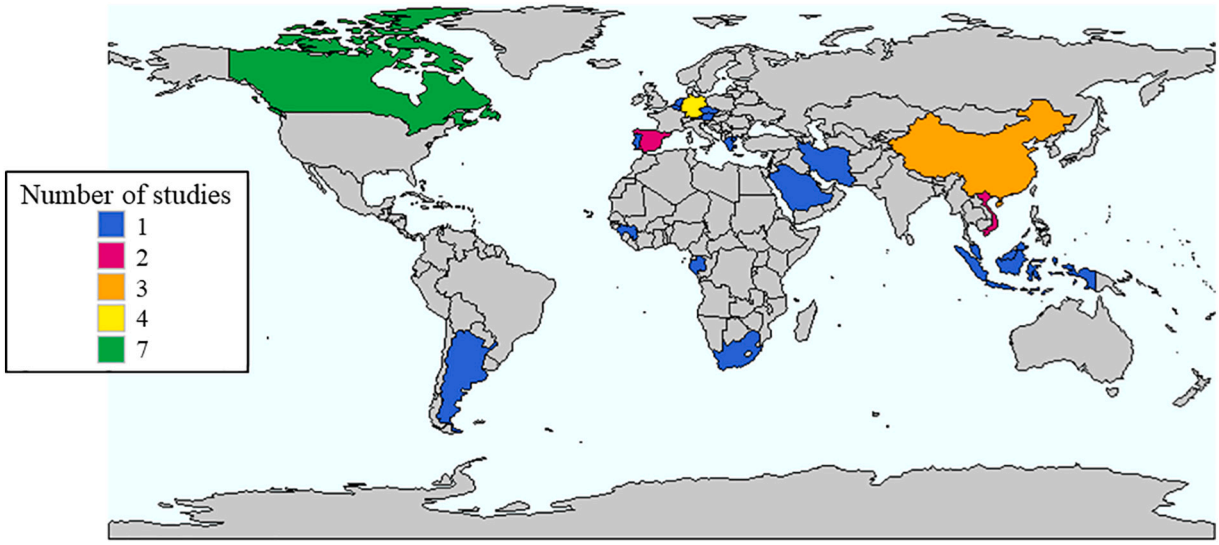

Fig. 2. Geographical distribution and number of studies per country on antimicrobial resistance in peridomestic rats, 2000–2021.

commonly studied bacterial species (35% of all isolates), followed by *Salmonella* spp. [27,37,46,48], *Proteus* spp. [32,46,48], *Klebsiella* spp. [32,48], *Enterobacter* spp. [24,32], *Leptospira* spp. [48], *Shigella* spp. [32], *Listeria* spp. [43], *Bordetella* spp. [47], *Serratia* spp., and *Citrobacter* spp. [32]. One study reported gram-positive and gram-negative resistant bacteria without specifying the species [46].

The disk diffusion test (Kirby-Bauer disk diffusion method) was the most commonly used method for AMR phenotype testing (9/15) [11,12,26,28,30,32,37,43,48], followed by MIC testing (5/15) [27,29,45–47], including the agar dilution test, agar broth microdilution [29], and broth microdilution [27]. One study used both techniques [6]. The antimicrobial susceptibility tests were performed on up to 40 different antimicrobial drugs covering 13 antimicrobial classes (Table S3).

The molecular characterization of AMR genotypes was predominantly conducted with PCR (7/15) [6,11,12,27,29,32,37]. Other molecular approaches used were MLST [29,32,47], plasmid sequencing [11,32], and WGS [11]. The most common AMR phenotypes (44.1%) detected were against β-lactam antimicrobials, namely penicillins (22.8%), cephalosporins (13.4%), carbapenems (7.4%), and monobactams (0.5%) (Fig. 5). Overall, resistance against penicillins in *E. coli* was the most common phenotype detected, followed by resistance against cephalosporins, quinolones, aminoglycosides, sulfonamides, tetracyclines, phenicols, macrolides, carbapenems, and monobactams. No resistance against nitrofurantoins, rifamycins, or lincosamides was found in *E. coli*. Resistance against representative antimicrobials of other bacterial species is shown in Fig. 6 except for one study which did not report the AMR results on individual species level but on group level (gram-positive and gram-negative bacteria) [46]. In that study, gram-negative bacteria were predominantly resistant to cephalosporins, followed by penicillins, quinolones, sulfonamides, and nitrofurantoins. Gram-positive bacteria were resistant only to the β-lactam class (penicillins and carbapenems).

Of all detected genes, the β-lactamase resistance gene, *bla*, was the most prevalent one (53%) [6,11,12,29,32], followed by the *str* gene and gene cassettes conferring aminoglycosides resistance (14%) [11,37], *sul* (sulfonamide resistance genes, 13%) [6,11,12,29,37], *tet* (tetracycline resistance gene, 11%) [37], gene cassettes conferring trimethoprim resistance (4%) [11], *qnr* (quinolone resistance gene, 3%) [6,37], *cat* (chloramphenicol resistance gene, 1%), and others (1%) [37]. A summary of the resistance genes is given in Table 2. The most common resistance gene detected was bla_{TEM} and was reported in *E. coli*. Both DR and non-specific types of MDR were mostly detected within cities (69% of studies), including residential buildings [11,26,27,29,32,45], markets, hospitals [6,12,47], and ports/cargo [6,27,48] followed by livestock farms (25% of studies) [11,28,30,37,43,46]. In four studies, AMR was studied in other animal species in addition to rats, such as farm animals (chickens, ducks, and pigs) [28,37], and wildlife (reptiles and shrews) [11,12].

3.3. Specific types of multidrug resistance (MDR)

3.3.1. Extended-spectrum β-lactamase (ESBL)

Occurrence of ESBL in *Rattus* spp. was reported in 12 studies. Rats were mostly trapped alive and euthanized later for sample collection. All rats carrying ESBL-producing bacteria were captured from cities and human communities, including streets, parks, markets, hospitals, residential buildings, hawkers, and touristic places. Three *Rattus* spp. (*R. norvegicus*, *R. rattus*, and *R. argentiventer*) were identified in the ESBL studies. Three studies also investigated samples from other animal species, such as livestock (chickens, pigs, and cattle), companion animals (dogs and cats) [34], wildlife (birds, anoles, iguanas, and shrews) [11,23], and humans [23]. All studies isolated Enterobacteriaceae primarily from feces. Colon tissues were collected in two studies [11,24]. *Escherichia coli* was the most commonly reported bacterial spp. in 11 articles [6,11,22,24,27,29,34,35,40,42,50], two of which also included other species, such as *Klebsiella pneumoniae* [23] and *Enterobacter xiangfangensis* [24].

The combination disk diffusion test, using both cefotaxime and ceftazidime with and without clavulanate [51], was used for the confirmation of the ESBL phenotype in five ESBL studies in rats [24,29,35,42,50]. The double-disk synergy test, using amoxicillin-clavulanic acid with three different cephalosporin disks[52], was used to confirm the ESBL phenotype in another five ESBL studies [6,11,22,34,40]. Two studies screened for ESBL gene through PCR [23,27].

Polymerase chain reaction using primers with specificity for all three ESBL subgroups (CTX-M (Cefotaximase), SHV (Sulfhydryl variable), and TEM (Temoniera)) was the most commonly applied molecular technique for ESBL genotyping (11/12) [6,11,22–24,27,29,34,40,42,50], followed by MLST (6/12) [24,29,34,40,42,50]. Additional molecular methods included WGS (3/12) [11,24,35], plasmid sequencing (2/12) [11,34], and microarrays (1/12) [24].

Among all bacteria isolated in ESBL studies, the predominant ESBL genotype was bla_{CTX} (61%), followed by bla_{TEM} (26%) and bla_{SHV} (13%). A summary of all ESBL genotypes is presented in Fig. 7.

Table 1
Summary description of the reviewed 34 studies included in the present scoping review.

Type of resistance	Bacteria	Rat habitat	Rat species and number	Phenotypic method	Molecular method	Ref.
DR[1] and non-specific type of MDR[2]	*E. coli, Salmonella* spp., *Proteus* spp., *Klebsiella* spp., and *Leptospira* spp.	The commercial port-front of Piraeus, Greece	25 *Rn*[9]	Disk diffusion	–	[48]
	E. coli[*]	Urban areas in Berlin, Germany	87 *Rn*	MIC[11]	PCR[12], MLST[13]	[29]
	E. coli and *Salmonella* spp.[*]	Inner-city neighborhood of Vancouver and shipping port, Canada	633 rats (*Rn* and *Rr*[10])	MIC	PCR	[27]
	E. coli[*]	Pig, chicken, and duck farms, forests, and the perimeters of rice fields in Cao Lanh District, Dong Thap Province, Vietnam	59 rats (*Rn*, *R. tanezumi, R. argentiventer,* and *R. exulans*)	Disk diffusion	–	[28]
	E. coli[*]	A chicken hatchery in Abbotsford, British Columbia, Canada	7 *Rn*	Disk diffusion	–	[30]
	E. coli	Shantytowns, residential sites riverside, railways, and any accessible points in Buenos Aires, Argentina	96 *Rn* and 22 *Rr*	Disk diffusion	–	[26]
	E. coli	Vancouver Downtown Eastside, Canada	665 *Rn*	MIC	–	[45]
	E. coli[*]	Urban, suburban, and agriculture and livestock area in Guadeloupe and nearby islands, French West Indies	162 *Rn* and 187 *Rr*	Disk diffusion	PCR, WGS[14] and plasmid sequencing	[11]
	E. coli, S. aureus, S. lugdunensis, P. aeruginosa, Salmonella, P. oryzihabitans, and *P. mirabilis*	Around farms in villages at Al-Ahsa, Saudi Arabia	6 *Rr*	MIC	–	[46]
	E. coli[*]	Hospitals, markets, and a cargo station in Hanoi, Vietnam	135 *Rn*, 8 *Rr*, and 1 *R. argentiventer*	Disk diffusion and MIC	PCR	[6]
	E. coli[*]	Four markets in Bogor, Indonesia	79 *Rn*	Disk diffusion	PCR	[12]
	E. coli, Klebsiella spp., *Enterobacter* spp., *Proteus* spp., *Shigella* spp., *Serratia* spp., and *Citrobacter* spp.[*]	Alleys behind the residential building in Tehran, Iran	100 *Rn*	Disk diffusion	PCR, sequencing, and MLST	[32]
	Listeria spp.	Areas of farms, woodland, cassava field, and grassland in 5 regions (Tibet, Hainan, Guangdong, Fujian, and Shanxi province), China	19 *Rn*, 1 *R. rattus sladeni*, 18 *R. andamanensis*, 89 *R. losea,* and 3 *R. nitidus*	Disk diffusion	–	[43]
	Bordetella bronchiseptica and *B. pseudohinzii*	Wet markets in Ohor, Kedah, Kelantan and Terengganu, Malaysia	177 *Rn* and 100 *R. rattus diardii*	MIC	MLST	[47]
	Salmonella spp.[*]	Poultry farms in Mafikeng, South Africa	154 rats	Disk diffusion	PCR	[37]
	E. coli	Urban areas in Berlin, Germany	66 *Rn*	Disk diffusion and MIC	PCR and MLST	[50]
	E. coli	Urban areas in Berlin, Germany	87 *Rn*	MIC	PCR and MLST	[29]
	E. coli	Inner-city areas of Berlin, Germany	56 *Rn*	Disk diffusion	PCR and MLST	[42]
	E. coli and *Salmonella* spp.	Inner-city neighborhood of Vancouver and shipping port, Canada	633 rats	MIC	PCR	[27]
	E. coli	Urban areas in Hong Kong	5 *Rn* and 1 *Rr*	Disk diffusion	PCR, MLST, and plasmid sequencing	[34]
	E. coli	Urban areas in Hong Kong	452 *Rn* and 39 *Rr*	Disk diffusion	PCR and MLST	[40]
ESBL[3]	*E. coli and K. pneumoniae* ssp. *pneumoniae*	Inside and outside the houses in 3 densely populated districts of Conakry, Guinea	6 *Rn* and 22 *Rr*	ESBL-producing confirmatory test	WGS	[35]
	E. coli, Enterobactor xiangfangensis, S. fleurettii, S. sciuri, S. aureus, S. pseudintermedius, S. epidermis, S. haemolyticus, and *S. xylosus*	Touristic areas and along Danube canal in the centre of Vienna, Austria	76 *Rn*	Disk diffusion	PCR, microarrays, MLST, and WGS	[24]
	K. pneumoniae	Around human community in Baiyun District, Guangzhou, China	80 *Rn*	Disk diffusion	PCR	[23]
	E. coli	Urban, suburban, and agriculture and livestock area in Guadeloupe and nearby islands, French West Indies	162 *Rn* and 187 *Rr*	Disk diffusion	PCR, WGS and plasmid sequencing	[11]
	E. coli	Inside the Makokou Regional hospital and outpatient houses near the hospital Makokou Gooue Ivindo province, Gabon	161 rats	Disk diffusion	PCR	[22]
	E. coli	Hospitals, markets, and a cargo station in Hanoi, Vietnam	135 *Rn*, 8 *Rr*, and 1 *R. argentiventer*	Disk diffusion and MIC	PCR	[6]
MRSA[4]	*S. aureus*	Pig farms in Netherlands and Belgium	3 *Rn* and 40 *Rr*	–	Multiplex PCR and MLST	[49]
	S. aureus	Urban areas in Hong Kong	281 *Rn* and 22 *Rr*	Disk diffusion	PCR and MLST	[33]
	S. aureus		637 rats	MIC		[10]

(*continued on next page*)

Table 1 (*continued*)

Type of resistance	Bacteria	Rat habitat	Rat species and number	Phenotypic method	Molecular method	Ref.
		Vancouver Downtown Eastside, Canada			latex agglutination test	
	S. aureus	North-central and southern Spain	6 *Rn*	Disk diffusion and MIC	PCR and MLST	[44]
	S. aureus	Pig farms in the southwest of Ontario, Canada	21 *Rn*	–	Latex agglutination test and spa[15] typing	[38]
	S. aureus	Vancouver downtown eastside, Canada	665 *Rn*	MIC	–	[45]
	S. aureus	Touristic areas and along Danube canal in the centre of Vienna, Austria	76 *Rn*	Disk diffusion	PCR, microarrays, MLST, and WGS	[24]
	S. aureus	Vancouver Downtown Eastside, Canada	595 *Rn*	Disk diffusion	–	[39]
	S. aureus	Around human community in Baiyun District, Guangzhou, China	197 *Rn*	Disk diffusion and MIC	PCR	[9]
	S. aureus	Livestock farms, pheasant farms, and towns in Germany and Czech Republic	145 rats	MIC	PCR, spa genotyping, MLST	[25]
	S. aureus	Port and surrounding areas of Lisbon and Ponta Delgada, Portugal	120 *Rn* and 75 *Rr*	Disk diffusion	PCR, sequencing, and MLST	[36]
MRSP[5]	*S. pseudintermedius*	Vancouver Downtown Eastside, Canada	237 *Rn*	MIC	dru[16] typing	[41]
VRE[6]	*Enterococcus* spp.	South of Palencia Province (where rats coexist with livestock and human) and Cádiz Province (where rats coexist with wildlife), Spain	46 *Rr*	Disk diffusion and MIC	PCR and MLST	[31]
FRE[7]	*E. coli* and *Enterobacter xiangfangensis*	Touristic areas and along Danube canal in the centre of Vienna, Austria	76 *Rn*	Disk diffusion	PCR, microarrays, MLST, and WGS	[24]
CoRE[8]	*E. coli*	Hospitals, markets, and a cargo station in Hanoi, Vietnam	135 *Rn*, 8 *Rr*, and 1 *R. argentiventer*	Disk diffusion and MIC	PCR	[6]

[*] non-specific type of MDR.
[1] DR: drug-resistant bacteria.
[2] MDR: multi-drug resistant bacteria
[3] ESBL: extended-spectrum β-lactamase Enterobacteriaceae
[4] MRSA: methicillin-resistant *Staphylococcus aureus*
[5] MRSP: methicillin-resistant *Staphylococcus pseudintermedius*
[6] VRE: vancomycin-resistant *Enterococcus* spp.
[7] FRE: fluoroquinolone-resistant *Enterobacteriaceae*
[8] CoRE: colistin-resistant Enterobacteriaceae
[9] *Rn*: *Rattus norvegicus*
[10] *Rr*: *Rattus rattus*
[11] MIC: minimum inhibitory concentration
[12] PCR: polymerase chain reaction
[13] MLST: multi-locus sequence typing
[14] WGS: whole genome sequencing
[15] spa: *S. aureus*-specific staphylococcal protein A
[16] dru: direct repeat uni.

The rat *E. coli* isolates carried all three subgroups of ESBL genes. The CTX-M subgroup was the most common, followed by the TEM and the SHV subgroup. Eight genes belonging to CTX-M subgroup detected in *E. coli* were $bla_{\text{CTX-M}}$ [22,27], $bla_{\text{CTX-M-1}}$ [6,11,24,34,40,42], $bla_{\text{CTX-M-3}}$ [24], $bla_{\text{CTX-M-9}}$ [24,29,34,40,50], $bla_{\text{CTX-M-15}}$ [24,35], $bla_{\text{CTX-M-64}}$, $bla_{\text{CTX-M-123}}$, and $bla_{\text{CTX-M-132}}$ [34]. Five genes of the TEM subgroup identified were $bla_{\text{TEM-1}}$ [24,50], $bla_{\text{TEM-1B}}$ [35], $bla_{\text{TEM-1-like}}$ [29], $bla_{\text{TEM-52}}$ [11], $bla_{\text{TEM-176}}$ [24]. The study by Le Huy et al. also detected the TEM subgroup but did not report any specific gene type. One gene of the SHV subgroup ($bla_{\text{SHV-12}}$) was also found in *E. coli* [42]. An additional gene of the ampicillin C (AmpC) β-lactamases group, $bla_{\text{CMY-2}}$ was also identified [24].

Klebsiella pneumoniae was considered in only one study, reporting the identification of three subgroups of ESBL genes: CTX-M ($bla_{\text{CTX-M-9}}$, $bla_{\text{CTX-M-14}}$, and $bla_{\text{CTX-M-15}}$), TEM ($bla_{\text{TEM-1B}}$), and SHV ($bla_{\text{SHV-11-like}}$, $bla_{\text{SHV-28}}$, and $bla_{\text{SHV-62}}$). Two additional β-lactamase genes $bla_{\text{DHA-1}}$ and $bla_{\text{OXA-1}}$ were detected and categorized in the AmpC and oxacillinase groups, respectively [35].

Enterobacter xiangfangensis was also screened for ESBL genes in one study that reported to carry two ESBL genes: $bla_{\text{CTX-M-15}}$ and $bla_{\text{TEM-176}}$. There were two more genes belonging to different β-lactamases groups discovered in *En. xiangfangensis*: $bla_{\text{NDM-1}}$ (metallo-β-lactamase (MBL) group) and $bla_{\text{OXA-1}}$ (oxacillinase group) [24].

3.3.2. Methicillin-resistant Staphylococcus aureus (MRSA)

Rats were the main focus of some studies on MRSA, except in one study where rats were included with the sampling of pigs, chickens, dogs, and cats [33]. Rats were primarily live-trapped and later euthanized for sample collection. In some studies, rats were trapped using lethal methods [25,49] or caught and released for longitudinal analysis [39]. Rats were trapped from urban ports [10,36], underserved neighborhoods [10,39], touristic areas [24] as well as from farms [38,49]. In three cases, samples were also obtained from humans, including hospital patients [9,36], residents of the neighborhood where rats were caught [10], or from people who participated in other research studies related to *S. aureus* colonization [25].

Sampling for MRSA primarily involved swabbing rats' nasopharyngeal, oropharyngeal, or tracheal area [9,10,24,33,36,38,39,49]. In one

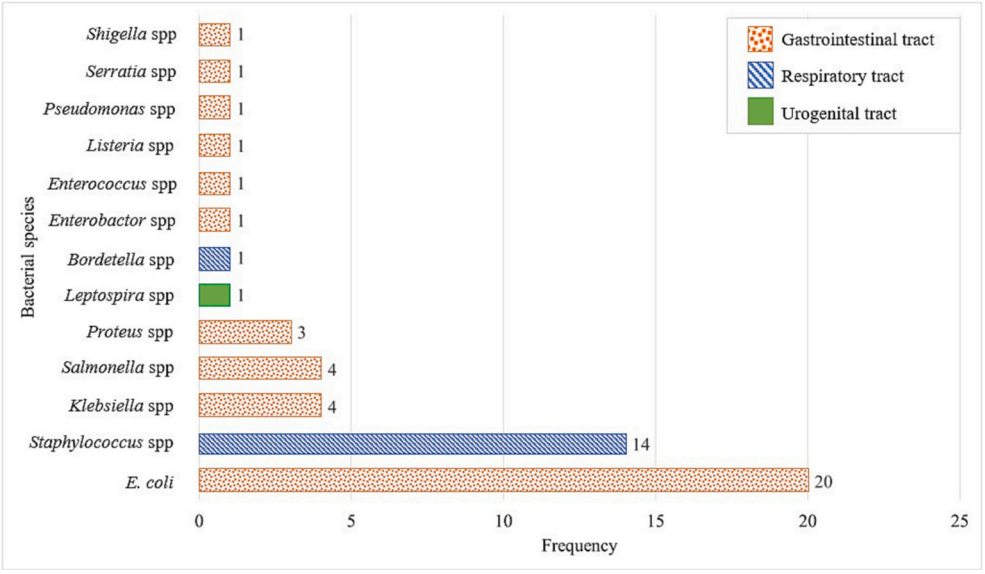

Fig. 3. The frequency and site of isolation of bacterial species described in studies on antimicrobial resistance in peridomestic rats, 2000–2021.

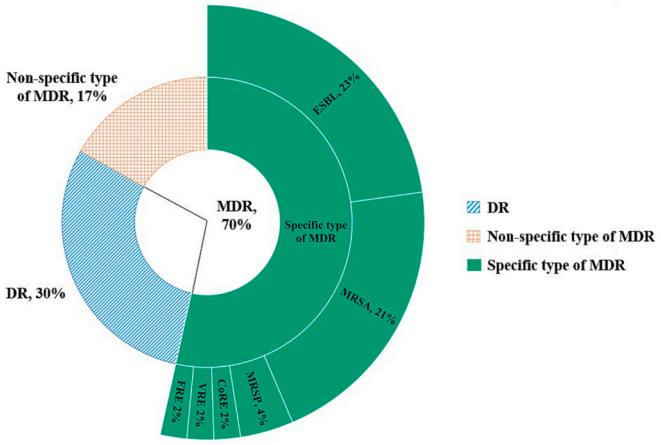

Fig. 4. The proportion of resistance types reported in the 34 studies on antimicrobial resistance in rats, 2000–2021. (DR: Drug-resistance, MDR: Multidrug resistance, ESBL: Extended -spectrum β-lactamase Enterobacteriaceae, MRSA: Methicillin-resistant *S. aureus*, FQRE: Fluoroquinolones-resistant Enterobacteriaceae, VRE: Vancomycin-resistant Enterococcus, MRSP: Methicillin-resistant *S. pseudintermedius*, CoRE: Colistin-resistant Enterobacteriaceae).

instance, the entire nose was used for analysis [25]. Methicillin-resistant *S. aureus* was also investigated in rat feces by collecting fecal samples [44] and rectal swabs [36,39]. Samples collected from rats were stored in an incubation broth containing sodium chloride for approximately 24 h and then inoculated onto a variety of agar media for bacterial growth and identification.

Detection of MRSA first required establishing the presence of *S. aureus*. Colonies demonstrating staphylococcal morphology were assessed using a variety of microbiological techniques including gram staining, and catalase, coagulase and hemolysin tests, as well as by detecting DNAse production [9,10,25,38,39,44]. In some cases, *S. aureus* was also identified by PCR amplification of the species-specific *nuc* gene [9,25,44].

Positive *S. aureus* samples were assessed for antimicrobial resistance by various methods. Several studies identified methicillin-resistance based on the presence of penicillin-binding protein 2a antigen using a latex agglutination test [10,25,38]. Penicillin resistance was also evaluated through broth microdilution [10,25]. Other studies used the agar disk diffusion method [24], such as the Kirby-Bauer method, which included testing up to 14 [9,36] or 16 antimicrobial agents [44]. Resistance was further assessed through PCR by amplification of the resistance and virulence genes *mec*A [24,44,49], *mec*C [9,24,36,44], *gyr* [25], and *bla*Z [44]. Genes encoding the Panton-Valentine leucocidin toxin [36,49] and toxic shock syndrome [49] were also investigated. In some instances, isolates were also characterized by Immune Evasion Cluster (IEC), based on the presence or absence of the *scn* gene [36,44]. Identified MRSA isolates were characterized through Multi-Locus Sequence Typing (MLST) [9,25,36,44,49], *spa* typing [9,10,24,25,36,38,44,49], *agr* typing [36,44], and *dru* typing [24].

MRSA was detected in rats in all of the reviewed studies except for two [33,44]. The MRSA prevalence ranged from 0% [33,44] to 11.6% [49]. While some studies did not detect a difference in MRSA prevalence across trapping locations [24], studies in Vancouver, Canada, found marked variations in the prevalence at a small spatial scale, with prevalence varying significantly by the city block (0–50%) [10].

Several studies found that the MRSA strains carried by rats were similar to those found in people [9,10]. For example, in Guangzhou, China, brown rats and human patients were colonized with the same MRSA clonal complexes: (CC)59 (sequence type (ST)59-t437), CC5 (ST1-t127), and CC45 (ST45-t116) [9].

3.3.3. Other specific types of MDR

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) was investigated in *Rattus norvegicus* [24,41]. The brown rat samples were captured from urban areas, such as downtown Vancouver [41] and tourist areas along the Danube canal in Vienna [24]. Pharyngeal and nasal samples were collected in both of these studies. Polymerase chain reaction was performed and found *mecA* gene from Staphylococcal chromosome cassette (SCC) type V (*mecA*/SCC*mec*V) [24]. Single locus typing techniques, like staphylococcal protein A (*spa*) typing, were performed and discovered *spa* type t02 [24]. Other AMR genes were also detected, such as *blaZ*, *blaI*, *blaR*, *tet*(K), *tet*(M), *erm*(B), *aacA-aphD*, *aphA1*, and *sat* [24]. Direct repeat unit (dru) typing was used in both studies and showed dru type (dt) 11a, dt7ac,[41], and dt11av [24].

Colistin-resistant Enterobacteriaceae (CoRE) from rat fecal samples was reported in one study by LE Huy et al. [6]. This study included three *Rattus* spp.; *R. norvegicus*, *R. rattus*, and *R. argentiventer*. All rats were trapped in human communities, including hospitals, wet markets, and a cargo station in the city of Hanoi. *Escherichia coli* was cultured from rectal swabs and identified by several biochemical tests. Detection of the

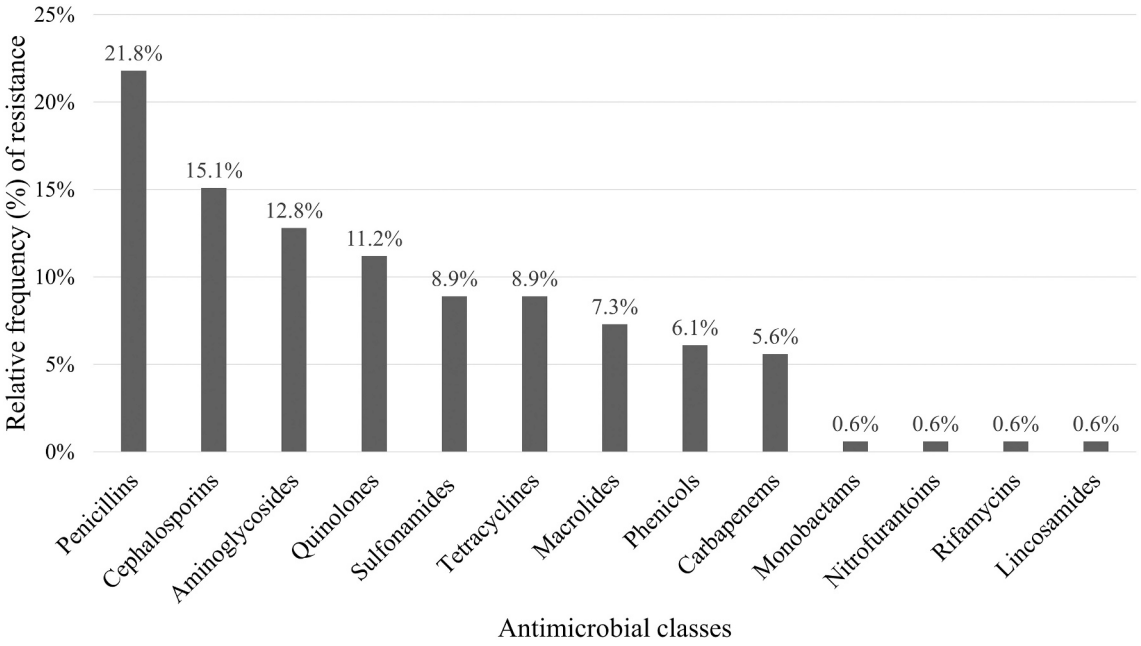

Fig. 5. The relative frequency (%) of antimicrobial resistance by antimicrobial classes described in drug resistance (DR) and non-specific type of multidrug resistance (MDR) studies in rats, 2000–2021.

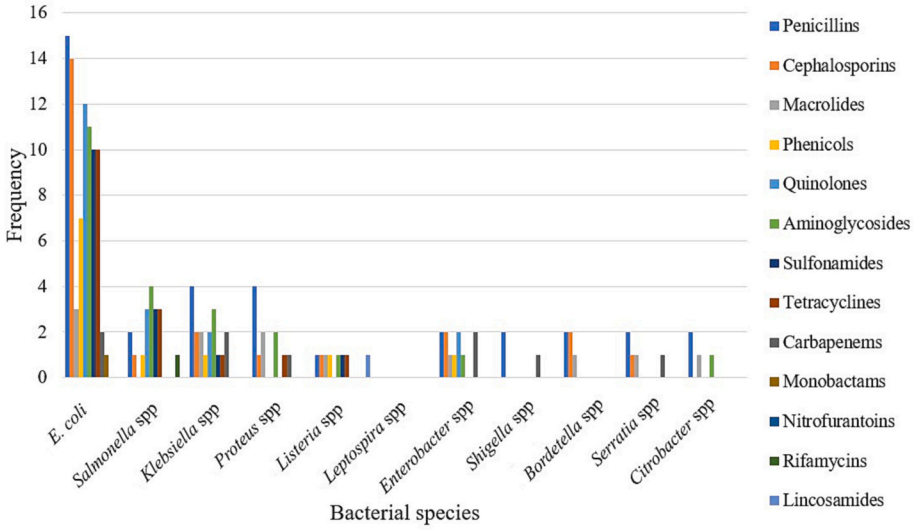

Fig. 6. The frequencies of 11 antimicrobial resistant bacterial species (from DR and non-specific type of MDR studies) against 13 classes of antimicrobials, in rat studies, 2000–2021.

yaiO gene by PCR was chosen for the confirmation of *E. coli*. Broth microdilution and macrodilution methods were used for the colistin susceptibility test. Polymerase chain reaction was used with the primers for the CoRE genes (*mcr-1*, *mcr*-2, and *mcr-3*) and detected the *mcr-1* gene in *E. coli.* Other AMR genes detected included bla_{TEM}, *tet*(A), *tet*(B), *sul1*, *sul2*, and *sul3* [6].

One study focused on fecal vancomycin-resistant Enterococci (VRE) in 7 small mammal species, including *R. rattus*. Rats were from two regions of Spain, representing the areas where rats coexisted with livestock, humans, and wildlife. Four species of Enterococci (*E. faecium*, *E. fecalis*, *E. gallinarum*, and *E. casseliflavus*) were studied. The agar dilution method was chosen to assess the susceptibility of vancomycin and teicoplanin, while ten other antimicrobials were tested for susceptibility by the disk diffusion method. Polymerase chain reaction was primarily used to detect the VRE genes. Then, MLST was carried out and detected ST915-*vanA* in *E. faecium,* ST6-*vanB2* in *E. fecalis, vanC1* in *E. gallinarum,* and *vanC2* in *E. casseliflavus*. Other non-VRE genes were also detected mostly in *E. faecium*, including *erm*(B), *tet*(M), *aac*(6′)-Ie-aph(2″)-Ia, *ant*(6)Ia, aph(3′)-IIIa, and *dfrF*. *Enterococcus gallinarum* and *E. casseliflavus* carried only *erm*(B) and *tet*(M), respectively [31].

Fluoroquinolones-resistant Enterobacteriaceae (FQRE) was detected from *R. norvegicus* in one study by Desvars-Larrive et al. [24]. All brown rats were trapped alive from the touristic areas and along the Danube canal in Vienna. Both small and large intestinal tissues were collected as pooled samples. *Enterobacter xiangfangensis* (*En. cloacae complex*) and *E. coli* were confirmed by matrix-assisted laser desorption/ionisation-time-of-flight (MALDI-TOF) mass spectrometry. Polymerase chain reaction was used to detect the quinolone resistance gene (*qnr*). *QnrS* and *qnrB1* were detected in *E. coli* and *En. xiangfangensis*, respectively. Other AMR genes and gene cassettes were also identified, including *sul*, *cat*, *str*,

Table 2
Antimicrobial resistance genes detected in eight bacterial species in drug resistance (DR) and non-specific type of multidrug resistance (MDR) studies in rats, 2000–2021.

Bacteria	Resistance genes or gene cassettes* or integrons[+]
E. coli	bla_{TEM}, $bla_{TEM\text{-}1\text{-}like}$, bla_{TEM2}, $bla_{NDM\text{-}1}$, bla_{SHV}, bla_{VIM}, bla_{IMP}, bla_{aadA}, bla_{aphA}, $bla_{CTX\text{-}M}$, $bla_{CTX\text{-}M\text{-}1}$, *strA*, *strB*, *aadA*[*1], *aadA1*[*1], *aadA5*[*1], *aph(3″)-Ib*[*1], *aph(6)-Id*[*1], *aac(3)-IV*[*1], *aac(6′)-Ib-cr*[*1], *sul1*, *sul2*, *sul3*, *tetA*, *tetB*, *tet34*, *dfrA1*[*2], *dfrA17*[*2], *dfr14*[*2], and *qnrB1*
Klebsiella spp.	bla_{TEM}, $bla_{NDM\text{-}1}$, bla_{SHV}, bla_{IMP}, bla_{aadA}, and bla_{aphA},
Enterobacter spp.	bla_{TEM}, bla_{VIM}, bla_{IMP}, bla_{aadA}, and bla_{aphA},
Shigella spp.	bla_{TEM}, bla_{IMP}, and bla_{aadA},
Proteus spp.	bla_{TEM}, bla_{aadA}, and bla_{aphA},
Serratia spp.	bla_{TEM} and bla_{IMP},
Citrobacter spp.	bla_{TEM}, $bla_{NDM\text{-}1}$, bla_{VIM}, bla_{IMP}, and bla_{aadA},
Salmonella spp.	bla_{TEM}, *aadA*[*1], *qnrA*, *cat*, *tet*, and *intl1*[+3]

[1] gene cassettes mediated aminoglycoside resistance.
[2] gene cassettes mediated trimethoprim resistance.
[3] integrons mediated other antimicrobial resistance

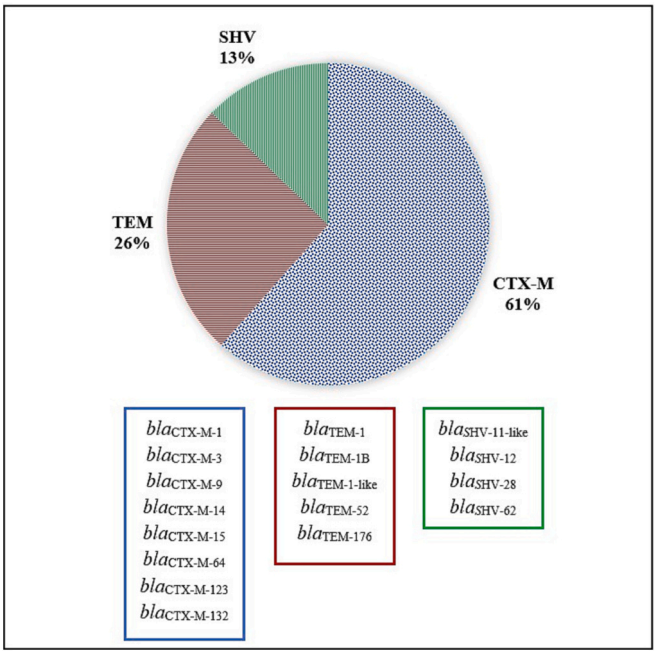

Fig. 7. The proportion of three subgroups of extended-spectrum β-lactamase (ESBL) genes and their gene members studied in rats, 2000–2021.

tet, *floR*, *ramA*, *aac*(6′)-Ib-cr, *aadA1*, *aadA2*, *aphA*, *cmlA1*, *dfrA1*, *dfrA12*, and *dfrA14*. Moreover, two isolates of *En. xiangfangensis* in this study were resistant to at least one antimicrobial drug in every class. [24].

4. Discussion

This review describes the species, frequency, phenotypic and genotypic characteristics of antimicrobial resistant bacteria isolated from peridomestic *Rattus* spp. between 2000 and 2021. To the best of our knowledge, this is the first scoping review on AMR in peridomestic *Rattus* spp.

Antimicrobial resistance in *Rattus* spp. has been mostly reported in urban and livestock settings which provide opportunities for antimicrobial resistant bacteria to circulate between people, livestock, and rats. The most common rat species studied were *Rattus norvegicus* (brown rat) and *R. rattus* (black rat) due to their worldwide distribution. Rats carried multiple species of resistant bacteria highlighting their potential role as reservoirs and spreaders of AMR bacteria. Rats could also serve as a mixing bowl for the evolution of new resistant pathogens.

4.1. Anthropogenic activities and AMR in rats

Cities and livestock farms were likely the focus of these studies because of the opportunities for rats to acquire human and livestock associated AMR. Indeed, anthropogenic influence in areas where rats thrived was the key factor in AMR development in a Canadian study [11]. In another study from South Africa, a high prevalence of rifampicin resistance was observed in rats living around a gold mine where people used rifampicin to treat their pulmonary tuberculosis [37,53]. Some studies found a higher AMR prevalence in rats living in towns compared to other places [11,42]. Peridomestic rats in urban areas feed around garbage sites and move within the sewage tunnels, and wastewater drains, where they are readily exposed to human waste, polluted water, and sewage sludge [6,22,29,32]. They may also directly ingest antimicrobial residues improperly discarded from households or clinics, resulting in the development of AMR in their own gut flora [22,54]. However, a study in Hong Kong did not find a correlation between the number of sewage treatment plants and the prevalence of AMR in rats [40]. These findings highlight that rats in cities may find numerous routes of acquiring antimicrobial resistant bacteria [27].

It is generally accepted that farms are one of the most important sites of AMR development and dispersal. The use of antimicrobials to promote growth in farm animals is still a common practice in several countries. The discharge from farms into the environment may hasten the evolution of AMR [55]. Rats residing in livestock farms are characterized by similar AMR exposure pathways as the ones in towns. Rats could obtain antimicrobial resistant bacteria indirectly from the animal slurry and manure, or they can directly consume antimicrobials disposed by farmers or in animal feed and water containing antimicrobial agents [28]. In some parts of the world, such as in Southeast Asian countries, traditional practices where farmers discharge excreta from the farm directly to the fishpond (integrated fish farming), further support the dissemination of AMR into the environment. Although antimicrobials are generally not stable in the environment, the AMR genes can persist for a long time [28].

4.2. Antimicrobial resistant bacteria species carried by rats

This review showed that AMR bacteria isolated from peridomestic rats were mostly *E. coli*, which is considered an ideal indicator bacterial species to monitor and characterize AMR in the environment [2]. In rats, *E. coli* is carried in the guts and shed by defecation like in other animals, which represents the main dissemination pathway [56]. Other Enterobacteriaceae bacteria were isolated from rats in urban areas except for *Salmonella* spp., which were equally from rats in cities and poultry farms.

Staphylococcus spp. were also commonly described in the reviewed studies, with *S. aureus* being isolated the most, followed by *S. pseudintermedius*. All *S. aureus* were isolated for the purpose of MRSA studies. Although the prevalence of MRSA varied between the studies, it was generally found to be low (0–12.5%). Rats likely acquire MRSA from the environment, such as through direct contact with livestock manure and inhalation of contaminated air in the farms, as *S. aureus* frequently colonizes the nasal epithelium [25,49]. However, rats can shed MRSA into the environment through their feces, which may increase the risk of transmission to people [39].

Other bacteria species isolated from peridomestic rats were *Pseudomonas* spp., *Proteus* spp., *Serratia* spp., *Shigella* spp., *Citrobacter* spp., *Listeria* spp., and *Bordetella* spp. *Pseudomonas aeruginosa* is considered as one of the most common resistant bacteria linked with nosocomial infections which was isolated from rats living around human settings in Saudi Arabia [46]. Burriel et al. [48] found a high prevalence of *Proteus* spp. isolated from rat intestines exhibiting resistance to 12

antimicrobials commonly used in animals. This was in agreement with another study that described MDR *Proteus mirabilis*, *P. vulgaris*, and *Serratia* spp. from rats [32]. Antimicrobial-resistant *Shigella* spp. and *Citrobacter* spp. were identified in rats, but in only one isolate of each species [32]. *Listeria* spp. is associated with a high mortality rate, especially *L. monocytogenes*, which is commonly found in contaminated food products. Wang et al. [43] isolated antimicrobial resistant *Listeria* from rats in China that were resistant to oxacillin, cefuroxime, and trimethoprim-sulfamethoxazole, but were susceptible to most drugs commonly used to treat human listeriosis. *Bordetella* spp. are considered opportunistic bacteria of both humans and animals. Rats are not natural hosts of *B. bronchiseptica,* but they can be colonized with the bacterium. Loong et al. [47] detected resistant *B. bronchiseptica* from the lung tissue of brown and black rats collected in markets in Malaysia. They were resistant to amoxicillin-clavulanic acid, ampicillin, ceftriaxone, cefotaxime, and erythromycin. Both brown and black rats carried the same genotype (ST82, *nrdA* locus162), suggesting a transmission of resistant *B. bronchiseptica* between rat species living in the same area. *Leptospira* spp. is another zoonotic pathogen known to be carried by rats. One report intended to study AMR in *Leptospira* spp., but all rats were found to be free of *Leptospira* spp. [48]. *Clostridium difficile* was detected in brown rats from two studies in Canada, but none had been tested for antimicrobial resistance [38,45].

4.3. Rats may support the evolution of antimicrobial resistant bacteria

In addition to carrying a number of antimicrobial resistant bacteria, we found that several of the isolates from rats had plasmid-mediated AMR genes which could allow for the horizontal transmission of AMR genes among bacterial strains. Resistance to broad-spectrum antimicrobials like tetracycline was one of the most prevalent types of AMR found in this review. The tetracycline resistance gene *tet* is typically encoded in plasmids and transposons which can be transmitted by conjugation [57]. Several studies identified *tet* genes in bacteria isolated from peridomestic rats, such as *tet* in *Salmonella* spp. [37], *tetA* and *tetB* in *E. coli* [6,12,29], and *tet34* in *E. coli* [11]. Sulfonamide resistance genes (*sul*) were found frequently in the bacteria isolated from rats. Plasmid-mediated genes like *sul1*, *sul2*, and *sul3* were also detected in *E. coli* isolated from rats [6,11,29]. Streptomycin resistance genes (*str*) were previously detected on plasmids from bacteria of both domestic animals and human origins [58]. These genes, in particular *strA* and *strB* have also been detected in *E. coli* from rats [29]. Fluoroquinolone resistance genes (*qnr*) that are plasmid-mediated have also been detected in Enterobacteriaceae isolated from rats, such as *qnrA* in *Salmonella* spp. [37] and *qnrB1* in *E. coli* [29] and *En. xiangfangensis* [24]. Moreover, it was found that *qnr* genes frequently coexisted on the same plasmid with β-lactamases genes such as ESBL and AmpC [59].

4.4. Extended-spectrum β-lactamases

Beta-lactamase enzymes and their encoding genes have been continuously studied for decades, and almost a thousand of them have been identified [60]. Genes from the $bla_{CTX\text{-}M}$ group, especially CTX-M-15, are considered to be the most widely spread β-lactamase found in humans (in both clinical and non-clinical settings) and animals [11,35,50]. $Bla_{CTX\text{-}M\text{-}15}$ was also detected in *E. coli* isolated from peridomestic rats in Guinea [35] and Austria [24]. This gene was also found in other bacteria isolated from rats, such as *K. pneumonia* [35] and *En. xiangfangensis* [24]. Others CTX-M subgroups, such as CTX-M-1, which was commonly detected in livestock and human isolates in European countries, were also detected in brown rats caught in Berlin [42]. CTX-M-64, previously found in humans, livestock, and companion animals in China, was detected in rats captured in Hong Kong [34]. Furthermore, studies indicated that some strains of *E. coli* harbored more than one resistance gene. An *E. coli* isolate from a brown rat in the city of Berlin had both $bla_{CTX\text{-}M\text{-}9}$ and $bla_{TEM\text{-}1}$ with other non-ESBL genes, including *sul* and *str* [29]. Several *E. coli* isolates from brown rats caught in an Indonesian market carried bla_{TEM}, *sul*, and *tet* [12]. Some *E. coli* isolates from brown rats in Iran carried all three groups of ESBL genes; $bla_{CTX\text{-}M}$, bla_{TEM}, and bla_{SHV} [32].

Beta-lactamase genes like ESBL are frequently plasmid-mediated, and can be transmitted between bacteria through horizontal gene transfer [6,34,48]. This is believed to be a key mechanism of the spread of ESBL genes [24]. It is noteworthy that peridomestic rats were colonized by a number of *E. coli* strains which could facilitate the horizontal transfer of ESBL genes [27]. This would be an intractable problem if it occurred with some highly pathogenic strains, such as *E. coli* O157 H7. A study by Guenther et al. [42] reported that several ESBL *E. coli* isolates exhibited combined resistance to other antimicrobial classes including fluoroquinolone, tetracyclines, and aminoglycosides.

Extended-spectrum β-lactamase genes were also identified in other species of bacteria such as *K. pneumoniae.* A study in the south of China found that 7.94% of *K. pneumoniae* in brown rats were ESBL producers [23]. Another study conducted in Guinea showed *K. pneumoniae* subsp. pneumoniae isolated from black rats harbored $bla_{CTX\text{-}M}$, bla_{TEM}, and bla_{SHV}. Other β-lactamase genes (non-ESBL), such as bla_{OXA}, and bla_{DHA} were also detected in *K. pneumoniae* isolated from *R. rattus* [35].

Other bacteria species, such as *En. xiangfangensis*, isolated from brown rats in the city of Vienna were found to carry ESBL genes. Two ESBL genes; $bla_{CTX\text{-}M\text{-}15}$ and $bla_{TEM\text{-}176}$ and other types of β-lactamase genes, such as bla_{OXA} and bla_{NDM}, were also detected [24]. Bla_{TEM} was detected in *Salmonella* spp. in rats and chickens on a farm. It was interesting that isolates from both animal species carried the same class 1 integrons. This may suggest that rats acquired the AMR gene cassette from the environment on the poultry farm [37].

4.5. Methicillin-resistant Staphylococcus species

Methicillin-resistant *Staphylococcus aureus* is another multiresistant bacterial species responsible for an increasing number of human deaths every year [46]. Originally, MRSA began as a nosocomial infection restricted to hospital environments. It was generally known as hospital-acquired MRSA (HA-MRSA) [36]. Twenty years after the first report of HA-MRSA in UK, community-acquired MRSA (CA-MRSA) was reported for the first time in the US without any association with healthcare facilities [36,61]. Recently, livestock-associated MRSA (LA-MRSA) was reported in several animal species, including rats [36]. The carriage rate of MRSA in rats varied among the studies in this review. This could be due to differences in sampling locations and sample types. Interestingly, a study has reported evidence of seasonal variation in MRSA prevalence in rats. Himsworth et al. [10] found that brown rats collected in winter and spring exhibited lower MRSA carriage rates compared to summer and fall. In one study where rats were captured, released, and re-caught, MRSA carriage was found to change between capture events such that a rat might be positive for MRSA on its first capture and test negative upon a subsequent capture or vice versa. This suggested that rats may shed MRSA intermittently or clear the bacterium and subsequently be re-colonized [39]. A detailed environmental analysis in one study also suggested that rats were more likely to carry MRSA when they were caught in areas with more institutional buildings and food gardens [45]. One study found that rats were more likely to carry MRSA if they were “fatter” [10], which may be due to larger rats occupying more dominant roles in rat social structures, with more frequent aggressive interactions with other rats.

A study conducted in Vancouver discovered four genetically similar clusters of MRSA collected from brown rats. Among these, one cluster aligned with CC5-ST105, which is the leading cause of HA-MRSA infection in Canada, while the most common cluster aligned with strain USA300, the most common strain of MRSA identified among people living in the area where these rats were trapped [10]. Livestock-associated MRSA, such as ST398 known to colonize livestock, in particular swine, were detected in both farm and city rats [10]. A study

in the south of China also found that ST398 was dominant among MRSA isolated from brown rats collected in the town [33]. Similarly, in Ontario, Canada, the MRSA type detected in one rat was ST398 – t034, a livestock associated strain believed to had been acquired from pigs on the farm on which the rat was caught [38]. These findings demonstrate how microenvironmental features and characteristics could promote the clustering of strains in some areas.

Methicillin-resistance in *Staphylococcus aureus* is mediated by a gene called *mecA* located in the mobile genetic element (SCCmec). Silva et al. [36] detected some *mecA* in MRSA isolated from rats in Portugal. One of them was ST22-t747-*agrI* which was associated with HA-MRSA. It was found to be linked with trapping locations close to human hospitals. This result emphasizes that rats could carry a variety of MRSA strains. Other *Staphylococcus* spp. isolated from rats and identified as methicillin-resistant by the detection of *mecA* were *S. pseudintermidius*, *S. epidermis*, *S. hemolyticus*, *S. fleurittii*, and *S. sciuri* [24]. In the case of MRSP, a study conducted on brown rats collected from Vancouver found that three isolates were *dru* type dt11a. This strain was common in dogs. This finding indicated that MRSP could be transmitted between dogs and rats [41]. Another gene, namely *mecC*, which is 30% different from *mecA* was detected in 2011 [10,44]. *MecC*-carrying MRSA was identified in rats and belonged to CC130. This clonal complex is believed to originate in ruminants [36]. *MecC* was detected not only in *S. aureus*, but also in *S. xylosus*. A five-year study of *mecC*-carrying *Staphylococci* in Austria identified *mecC*-positive MR *S. xylosus* in brown rats [24].

4.6. Other types of multi- and extensive drug resistance

Colistin-resistant Enterobacteriaceae are another highly concerning MDR. Colistin is considered the last resort for the treatment of multi-resistant gastrointestinal infections in humans [62]. The colistin resistance gene: *mcr-1* was discovered a decade ago and has been since detected worldwide in animals and humans [63]. A study in Vietnam identified *mcr-1* from *E. coli* isolated from five urban rats caught in the market and around the hospital in Hanoi, Vietnam [6].

Vancomycin-resistant Enterococci is believed to be a result of using avoparcin to promote growth in livestock farms [64]. Even though the prevalence of VRE has decreased due to a ban on using avoparcin as a growth promoter, the problem persists. *VanA* and *vanB* had been detected in humans, animals, and food products [31,65]. Those genes were also identified in *Enterococcus* spp. isolated from rats. *VanA* and *vanB2* were found in *E. faecium* and *E. faecalis* in black rats collected in Spain [31].

Extensively drug-resistant (XDR) bacteria were not susceptible to at least one antimicrobial drug in every antimicrobial class [66]. It is interesting to note that these *En. xiangfangensis* isolated from brown rats in Vienna were considered as XDR [24].

It could be assumed that rats were a reservoir of MDR and XDR. They could cause the emergence of clinical infections in human and animals by spreading the resistant bacteria both directly and indirectly.

4.7. Limitations and suggestions

The main limitation of this review is the low amount of available literature on most types of AMR (such as CoRE, VRE, FQRE) and most bacteria species from peridomestic rats. Another constraint is the variety of methodologies used in each study which makes the comparison difficult. For example, some studies investigated several isolates from a rat, while others used only a single isolate per rat. The result of resistance phenotypes in the latter studies may have been underestimated because a rat could be colonized with several strains of bacteria [27]. The references used for antimicrobial susceptibility testing and resistance interpretation varied between studies. The Clinical and Laboratory Standard Institute (CLSI) guidelines and the European Committee on Antimicrobial Susceptibility Test (EUCAST) were mainly used. However, some studies relied on other guidelines, such as the Canadian Integrated Programme for Antimicrobial Resistance (CIPAR) [27], Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) [11], and European Food Safety Authority [40]. The exact species characterization of rats was often lacking, especially for rats belonging to the *R. rattus* complex group which includes several closely related species [67]. This is important in epidemiologic studies because different species have different habitat preferences, behaviors, and population dynamics which result in specific pathogens and hosts [67,68]. The lack of diversity of places and sampling locations could be another limitation of some studies in this review. The inclusion of more diverse sampling locations could provide more information on the spatial distribution, variability, and risk factors of AMR in different environments.

5. Conclusions

Peridomestic rats, especially *Rattus* spp. carried multiple antimicrobial resistant bacteria, indicating their potential to serve as reservoirs and spreaders of antimicrobial resistant bacteria. Many antimicrobial resistant bacteria detected in rats, such as ESBL and CoRE, confer resistance to critically important antimicrobials and pose a threat to public health. Several AMR genes detected in rats (i.e., *str*, $bla_{\text{CTX-M}}$, *vanA,* and *vanB*) were previously found in human and domestic animals suggesting that rats could serve as reservoirs of those AMR genes, posing a serious transmission threat to humans and other animals through interactions in shared environments, such as cities/towns and livestock farms. Among AMR genes, plasmid-mediated AMR genes (i.e., *tet*, *sul*, *qnr, bla,* and *mecA*) are of particular concern because they could horizontally be transfer between bacterial strains. This phenomenon could occur in the rat gut, where several strains of bacteria reside, and it could highlight the role of rats in the evolution of antimicrobial resistant bacteria and genes.

More studies in ecologically diverse locations and molecular comparisons of rat AMR data with that of humans and livestock are needed to better understand the role that synanthropic rats and other peridomestic wildlife might play on the complex epidemiology of AMR.

Funding

This work was partially supported by the City University's start-up grant for new Faculty (project No 9610449).

Ethical approval

Not applicable.

CRediT authorship contribution statement

Theethawat Uea-Anuwong: Methodology, Validation, Visualization, Writing – review & editing. **Kaylee A. Byers:** Writing – review & editing. **Lloyd Christian Wahl:** Methodology, Validation. **Omid Nekouei:** Writing – review & editing. **Yrjo Tapio Grohn:** Investigation, Writing – review & editing. **Ioannis Magouras:** Conceptualization, Investigation, Methodology, Validation, Methodology, Validation.

Declaration of Competing Interest

The authors declare no conflicts of interest in this scoping review.

Data availability

Material has been shared as supplementary files

Appendix A. Supplementary data

Table S1, S2, and S3 are available as supplementary data.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2023.100522.

References

[1] K.E. Arnold, N.J. Williams, M. Bennett, 'Disperse abroad in the land': the role of wildlife in the dissemination of antimicrobial resistance, Biol. Lett. 12 (8) (2016) 20160137, https://doi.org/10.1098/rsbl.2016.0137.

[2] L.E. Furness, Wild small mammals as sentinels for the environmental transmission of antimicrobial resistance, Environ. Res. (2017) 7. Published online.

[3] D. Ait Ouakrim, A. Cassini, M. Cecchini, D. Plachouras, The health and economic burden of antimicrobial resistance, in: E. Mossialos, M. Anderson, M. Cecchini (Eds.), Challenges to Tackling Antimicrobial Resistance: Economic and Policy Responses. European Observatory on Health Systems and Policies, Cambridge University Press, 2020, pp. 23–44, https://doi.org/10.1017/9781108864121.003.

[4] C.J. Murray, K.S. Ikuta, F. Sharara, et al., Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, Lancet 399 (10325) (2022) 629–655, https://doi.org/10.1016/S0140-6736(21)02724-0.

[5] I. Magouras, L.P. Carmo, K.D.C. Stärk, G. Schüpbach-Regula, Antimicrobial usage and -resistance in livestock: where should we focus? Front. Vet. Sci. 4 (2017) 148, https://doi.org/10.3389/fvets.2017.00148.

[6] L.E. Huy, N. Koizumi, T.T.H. Ung, et al., Antibiotic-resistant Escherichia coli isolated from urban rodents in Hanoi, Vietnam, J. Vet. Med. Sci. 82 (5) (2020) 653–660, https://doi.org/10.1292/jvms.19-0697.

[7] N.A. Jahan, L.L. Lindsey, P.A. Larsen, The role of peridomestic rodents as reservoirs for zoonotic foodborne pathogens, Vector-Borne Zoonotic Dis. (February 24, 2021), https://doi.org/10.1089/vbz.2020.2640. Published online.

[8] S. Guenther, C. Ewers, L.H. Wieler, Extended-spectrum beta-lactamases producing *E. coli* in wildlife, yet another form of environmental pollution? Front. Microbiol. 2 (2011) 246, https://doi.org/10.3389/fmicb.2011.00246.

[9] J. Ge, X.S. Zhong, Y.Q. Xiong, et al., Methicillin-resistant *Staphylococcus aureus* among urban rodents, house shrews, and patients in Guangzhou, Southern China, BMC Vet. Res. 15 (1) (2019) 260, https://doi.org/10.1186/s12917-019-2012-8.

[10] C.G. Himsworth, R.R. Miller, V. Montoya, et al., Carriage of methicillin-resistant *Staphylococcus aureus* by wild urban Norway rats (Rattus norvegicus), PLoS One 9 (2) (2014), e87983, https://doi.org/10.1371/journal.pone.0087983.

[11] S. Guyomard-Rabenirina, Y. Reynaud, M. Pot, et al., Antimicrobial resistance in wildlife in Guadeloupe (French West Indies): distribution of a single *bla* (CTX-M-1)/IncI1/ST3 plasmid among humans and wild animals, Front. Microbiol. 11 (2020) 1524, https://doi.org/10.3389/fmicb.2020.01524.

[12] H.L. Huy, N. Koizumi, H. Nuradji, et al., Antimicrobial resistance in *Escherichia coli* isolated from brown rats and house shrews in markets, Bogor, Indonesia, J. Vet. Med. Sci. 83 (3) (2021) 531–534, https://doi.org/10.1292/jvms.20-0558.

[13] H.K. Allen, J. Donato, H.H. Wang, K.A. Cloud-Hansen, J. Davies, J. Handelsman, Call of the wild: antibiotic resistance genes in natural environments, Nat. Rev. Microbiol. 8 (4) (2010) 251–259, https://doi.org/10.1038/nrmicro2312.

[14] S.I. Polianciuc, A.E. Gurzău, B. Kiss, M.G. Ştefan, F. Loghin, Antibiotics in the environment: causes and consequences, Med. Pharm. Rep. 93 (3) (2020) 231–240, https://doi.org/10.15386/mpr-1742.

[15] A.C. Tricco, E. Lillie, W. Zarin, et al., PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation, Ann. Intern. Med. 169 (7) (2018) 467–473, https://doi.org/10.7326/M18-0850.

[16] A. Paez, Gray literature: an important resource in systematic reviews, J. Evidence-Based Med. 10 (3) (2017) 233–240, https://doi.org/10.1111/jebm.12266.

[17] M. Vittecoq, S. Godreuil, F. Prugnolle, et al., Antimicrobial resistance in wildlife, J. Appl. Ecol. 53 (2) (2016) 519–529, https://doi.org/10.1111/1365-2664.12596.

[18] C.D. Sibley, G. Peirano, D.L. Church, Molecular methods for pathogen and microbial community detection and characterization: current and potential application in diagnostic microbiology, Infect. Genet. Evol. 12 (3) (2012) 505–521, https://doi.org/10.1016/j.meegid.2012.01.011.

[19] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan—a web and mobile app for systematic reviews, Syst. Rev. 5 (1) (2016) 210, https://doi.org/10.1186/s13643-016-0384-4.

[20] Microsoft Corporation, Microsoft Excel, Accessed March 14, 2022, https://office.microsoft.com/excel, 2018.

[21] A.P. Magiorakos, A. Srinivasan, R.B. Carey, et al., Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance, Clin. Microbiol. Infect. 18 (3) (2012) 268–281, https://doi.org/10.1111/j.1469-0691.2011.03570.x.

[22] R. Onanga, P.P. Mbehang Nguema, G.R. Ndong Atome, et al., Prevalence of extended-Spectrum β -lactamases in *E. coli* of rats in the region north east of Gabon, Vet. Med. Int. 2020 (2020) 1–6, https://doi.org/10.1155/2020/5163493.

[23] X.S. Zhong, Y.Z. Li, J. Ge, et al., Comparisons of microbiological characteristics and antibiotic resistance of *Klebsiella pneumoniae* isolates from urban rodents, shrews, and healthy people, BMC Microbiol. 20 (1) (2020) 12, https://doi.org/10.1186/s12866-020-1702-5.

[24] A. Desvars-Larrive, W. Ruppitsch, S. Lepuschitz, et al., Urban brown rats (*Rattus norvegicus*) as possible source of multidrug-resistant Enterobacteriaceae and meticillin-resistant *Staphylococcus* spp., Vienna, Austria, 2016 and 2017, Eurosurveillance. 24 (32) (2019), https://doi.org/10.2807/1560-7917.ES.2019.24.32.1900149.

[25] D. Raafat, D.M. Mrochen, F. Al'sholui, et al., Molecular epidemiology of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* in wild, captive and laboratory rats: effect of habitat on the Nasal S. aureus population, Toxins. 12 (2) (2020) 80, https://doi.org/10.3390/toxins12020080.

[26] X. Blanco Crivelli, M.P. Bonino, Castillo P. Von Wernich, A. Navarro, O. Degregorio, A. Bentancor, Detection and characterization of Enteropathogenic and Shiga toxin-producing *Escherichia coli* strains in *Rattus* spp. from Buenos Aires, Front. Microbiol. 9 (2018) 199, https://doi.org/10.3389/fmicb.2018.00199.

[27] C.G. Himsworth, E. Zabek, A. Desruisseau, et al., Prevalence and characteristics of *Escherichia coli* and *Salmonella* spp. in the feces of wild urban Norway and black rats (*Rattus Norvegicus* and *Rattus Rattus*) from an Inner-City neighborhood of Vancouver, Canada, J. Wildl. Dis. 51 (3) (2015) 589–600, https://doi.org/10.7589/2014-09-242.

[28] N.T. Nhung, N.V. Cuong, J. Campbell, et al., High levels of antimicrobial resistance among *Escherichia coli* isolates from livestock farms and Synanthropic rats and shrews in the Mekong Delta of Vietnam. Elkins CA, ed, Appl. Environ. Microbiol. 81 (3) (2015) 812–820, https://doi.org/10.1128/AEM.03366-14.

[29] S. Guenther, A. Bethe, A. Fruth, et al., Frequent Combination of Antimicrobial Multiresistance and Extraintestinal Pathogenicity in *Escherichia coli* Isolates from Urban Rats (*Rattus norvegicus*) in Berlin, Germany. Gordon SV, ed, PLoS One 7 (11) (2012), e50331, https://doi.org/10.1371/journal.pone.0050331.

[30] C.G. Himsworth, E. Zabek, A. Desruisseau, et al., Avian pathogenicity genes and antibiotic resistance in *Escherichia coli* isolates from wild Norway rats (*Rattus norvegicus*) in British Columbia, Canada, J. Wildl. Dis. 52 (2) (2016) 418–421, https://doi.org/10.7589/2015-09-238.

[31] C. Lozano, D. González-Barrio, J.T. García, et al., Detection of vancomycin-resistant *Enterococcus faecalis* ST6-vanB2 and *E. faecium* ST915-vanA in faecal samples of wild *Rattus rattus* in Spain, Vet. Microbiol. 177 (1–2) (2015) 168–174, https://doi.org/10.1016/j.vetmic.2015.02.025.

[32] T. Azimi, L. Azimi, F. Fallah, et al., Detection and characterization of Enterobacteriaceae family members carried by commensal *Rattus norvegicus* from Tehran, Iran, Arch. Microbiol. 203 (4) (2021) 1321–1334, https://doi.org/10.1007/s00203-020-02126-0.

[33] P.L. Ho, K.H. Chow, E.L. Lai, et al., Clonality and antimicrobial susceptibility of *Staphylococcus aureus* and methicillin-resistant *S. aureus* isolates from food animals and other animals, J. Clin. Microbiol. 50 (11) (2012) 3735–3737, https://doi.org/10.1128/JCM.02053-12.

[34] P.L. Ho, M.C.J. Liu, W.U. Lo, et al., Prevalence and characterization of hybrid bla_{CTX-M} among *Escherichia coli* isolates from livestock and other animals, Diagn. Microbiol. Infect. Dis. 82 (2) (2015) 148–153, https://doi.org/10.1016/j.diagmicrobio.2015.02.010.

[35] K. Schaufler, K. Nowak, A. Düx, et al., Clinically relevant ESBL-producing *K. pneumoniae* ST307 and *E. coli* ST38 in an urban west African rat population, Front. Microbiol. 9 (2018) 150, https://doi.org/10.3389/fmicb.2018.00150.

[36] V. Silva, S.I. Gabriel, S.B. Borrego, et al., Antimicrobial resistance and genetic lineages of *Staphylococcus aureus* from wild rodents: first report of *mecC*-positive methicillin-resistant *S. aureus* (MRSA) in Portugal, Animals. 11 (6) (2021) 1537, https://doi.org/10.3390/ani11061537.

[37] M.O. Taioe, O.M.M. Thekisoe, M. Syakalima, T. Ramatla, Confirmation of antimicrobial resistance by using resistance genes of isolated *Salmonella* spp. in Chicken Houses of North West, South Africa, jwpr. 9 (3) (2019) 158–165, https://doi.org/10.36380/scil.2019.wvj20.

[38] Rothenburger JL, Rousseau JD, Weese JS, Jardine CM. Livestock-Associated Methicillin-Resistant *Staphylococcus aureus* and *Clostridium difficile* in Wild Norway Rats (*Rattus norvegicus*) from Ontario Swine Farms:4.

[39] M.J. Lee, K.A. Byers, C.M. Donovan, et al., Methicillin-resistant *Staphylococcus aureus* in urban Norway rat (*Rattus norvegicus*) populations: epidemiology and the impacts of kill-trapping, Zoonoses Public Health 66 (3) (2019) 343–348, https://doi.org/10.1111/zph.12546.

[40] P.L. Ho, W.U. Lo, E.L. Lai, et al., Clonal diversity of CTX-M-producing, multidrug-resistant *Escherichia coli* from rodents, J. Med. Microbiol. 64 (2) (2015) 185–190, https://doi.org/10.1099/jmm.0.000001.

[41] C.G. Himsworth, D.M. Patrick, K. Parsons, A. Feng, J.S. Weese, Methicillin-resistant *Staphylococcus pseudintermedius* in rats, Emerg. Infect. Dis. 19 (1) (2013) 169–170, https://doi.org/10.3201/eid1901.120897.

[42] S. Guenther, J. Wuttke, A. Bethe, et al., Is fecal carriage of extended-spectrum-β-lactamase-producing *Escherichia coli* in urban rats a risk for public health? Antimicrob. Agents Chemother. 57 (5) (2013) 2424–2425, https://doi.org/10.1128/AAC.02321-12.

[43] Y. Wang, L. Lu, R. Lan, et al., Isolation and characterization of *Listeria* species from rodents in natural environments in China: isolation and characterization of *Listeria* species, Emerg. Microb. Infect. 6 (1) (2017) 1–6, https://doi.org/10.1038/emi.2017.28.

[44] P. Gomez, D. Gonzalez-Barrio, D. Benito, et al., Detection of methicillin-resistant *Staphylococcus aureus* (MRSA) carrying the *mecC* gene in wild small mammals in Spain, J. Antimicrob. Chemother. 69 (8) (2014) 2061–2064, https://doi.org/10.1093/jac/dku100.

[45] J.L. Rothenburger, C.G. Himsworth, N.M. Nemeth, D.L. Pearl, C.M. Jardine, Environmental factors associated with the carriage of bacterial pathogens in Norway rats, EcoHealth. 15 (1) (2018) 82–95, https://doi.org/10.1007/s10393-018-1313-x.

[46] L. Badger-Emeka, Y. Al-Mulhim, F. Al-Muyidi, M. Busuhail, S. Alkhalifah, N. AlEid, An investigation of potential health risks from zoonotic bacterial pathogens associated with farm rats, Environ. Health Insights. 14 (2020), 1178630220942240, https://doi.org/10.1177/1178630220942240.

[47] S.K. Loong, N.A.A. Che-Mat-Seri, O. Abdulrazak, et al., Recovery of *Bordetella bronchiseptica* sequence type 82 and *B. pseudohinzii* from urban rats in Terengganu, Malaysia. *The*, J. Vet. Med. Sci. 80 (1) (2018) 77–84, https://doi.org/10.1292/jvms.17-0218.

[48] A.R. Burriel, S.K. Kritas, V. Kontos, Some microbiological aspects of rats captured alive at the port city of Piraeus, Greece, Int. J. Environ. Health Res. 18 (2) (2008) 159–164, https://doi.org/10.1080/09603120701358432.
[49] A.W. van de Giessen, M.G. van Santen-Verheuvel, P.D. Hengeveld, T. Bosch, E. M. Broens, C.B.E.M. Reusken, Occurrence of methicillin-resistant Staphylococcus aureus in rats living on pig farms, Prevent. Vet. Med. 91 (2–4) (2009) 270–273, https://doi.org/10.1016/j.prevetmed.2009.05.016.
[50] S. Guenther, M. Grobbel, J. Beutlich, et al., Detection of pandemic B2-O25-ST131 *Escherichia coli* harbouring the CTX-M-9 extended-spectrum -lactamase type in a feral urban brown rat (*Rattus norvegicus*), J. Antimicrob. Chemother. 65 (3) (2010) 582–584, https://doi.org/10.1093/jac/dkp496.
[51] CLSI, Performance Standards for Antimicrobial Susceptibility Testing 31st Edition CLSI Supplement M100, Published online, 2021.
[52] EUCAST, Eucast Guidelines for Detection of Resistance Mechanisms and Specific Resistances of Clinical and/or Epidemiological Importance, Published online, 2017.
[53] E. Hnizdo, J. Murray, Risk of pulmonary tuberculosis relative to silicosis and exposure to silica dust in South African gold miners [published erratum appears in Occup Environ Med 1999 Mar;56(3):215-6], Occup. Environ. Med. 55 (7) (1998) 496–502.
[54] M. Cycoń, A. Mrozik, Z. Piotrowska-Seget, Antibiotics in the soil environment—degradation and their impact on microbial activity and diversity, Front. Microbiol. 10 (2019). Accessed June 2, 2022, https://www.frontiersin.org/article/10.3389/fmicb.2019.00338.
[55] J.L. Martinez, The role of natural environments in the evolution of resistance traits in pathogenic bacteria, Proc. R. Soc. B Biol. Sci. 276 (1667) (2009) 2521–2530, https://doi.org/10.1098/rspb.2009.0320.
[56] C.G. Himsworth, K.L. Parsons, C. Jardine, D.M. Patrick, Rats, cities, people, and pathogens: a systematic review and narrative synthesis of literature regarding the ecology of rat-associated Zoonoses in urban centers, Vector-Borne Zoonotic Dis. 13 (6) (2013) 349–359, https://doi.org/10.1089/vbz.2012.1195.
[57] M. Jahantigh, K. Samadi, R.E. Dizaji, S. Salari, Antimicrobial resistance and prevalence of tetracycline resistance genes in *Escherichia coli* isolated from lesions of colibacillosis in broiler chickens in Sistan, Iran, BMC Vet. Res. 16 (1) (2020) 267, https://doi.org/10.1186/s12917-020-02488-z.
[58] C. Pezzella, A. Ricci, E. DiGiannatale, I. Luzzi, A. Carattoli, Tetracycline and streptomycin resistance genes, transposons, and plasmids in Salmonella enterica isolates from animals in Italy, Antimicrob. Agents Chemother. 48 (3) (2004) 903–908, https://doi.org/10.1128/AAC.48.3.903-908.2004.
[59] M. Rezazadeh, H. Baghchesaraei, A. Peymani, Plasmid-mediated quinolone-resistance (*qnr*) genes in clinical isolates of Escherichia coli collected from several hospitals of Qazvin and Zanjan provinces, Iran, Osong Public Health Res Perspect. 7 (5) (2016) 307–312, https://doi.org/10.1016/j.phrp.2016.08.003.
[60] J. Davies, D. Davies, Origins and evolution of antibiotic resistance, Microbiol. Mol. Biol. Rev. 74 (3) (2010) 417–433, https://doi.org/10.1128/MMBR.00016-10.
[61] A review of community-associated methicillin resistant *Staphylococcal aureus* (CA-MRSA) cases in Hong Kong.9.
[62] CDC, *mcr −1*, Threatens Last-Resort Antibiotics. Centers for Disease Control and Prevention, Published April 15,. Accessed July 6, 2022, https://www.cdc.gov/drugresistance/solutions-initiative/stories/gene-reported-mcr.html, 2022.
[63] R. Wang, L. van Dorp, L.P. Shaw, et al., The global distribution and spread of the mobilized colistin resistance gene *mcr-1*, Nat. Commun. 9 (1) (2018) 1179, https://doi.org/10.1038/s41467-018-03205-z.
[64] M. Levitus, A. Rewane, T.B. Perera, Vancomycin-resistant enterococci, in: In: StatPearls, StatPearls Publishing, 2022. Accessed June 12, 2022, http://www.ncbi.nlm.nih.gov/books/NBK513233/.
[65] Y. Cetinkaya, P. Falk, C.G. Mayhall, Vancomycin-resistant enterococci, Clin. Microbiol. Rev. 13 (4) (2000) 686–707.
[66] S. Basak, P. Singh, M. Rajurkar, Multidrug resistant and extensively drug resistant bacteria: a study, J. Pathog. 2016 (2016) 4065603, https://doi.org/10.1155/2016/4065603.
[67] K.P. Aplin, Australian centre for international agricultural research, in: Field Methods for Rodent Studies in Asia and the Indo-Pacific, Australian Centre for International Agricultural Research, 2003. Accessed July 6, 2022, http://www.aciar.gov.au/web.nsf/doc/ACIA%2D5UFV6V.
[68] South East Asian Murines Field Guide. calameo.com. Accessed June 9, 2022, https://www.calameo.com/read/001494710bc6243baa59c.