International Journal of Infectious Diseases 128 (2023) 325–334

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Extended-spectrum β-lactamase- and AmpC β-lactamase-producing Enterobacterales associated with urinary tract infections in the New Zealand community: a case-control study

Leah J. Toombs-Ruane[1], Jonathan C. Marshall[1,2], Jackie Benschop[1], Dragana Drinković[3], Anne C. Midwinter[1], Patrick J. Biggs[1,4,5], Zoë Grange[1,#], Michael G. Baker[6], Jeroen Douwes[7], Mick G. Roberts[8], Nigel P. French[1,5,7], Sara A. Burgess[1,*]

[1] mEpiLab, School of Veterinary Science, Massey University, Palmerston North, New Zealand
[2] School of Mathematical and Computational Sciences, Massey University, Palmerston North, New Zealand
[3] Microbiology Department, North Shore Hospital, Auckland, New Zealand
[4] School of Natural Sciences, Massey University, Palmerston North, New Zealand
[5] New Zealand Food Safety Science and Research Centre, Massey University, Palmerston North, New Zealand
[6] Department of Public Health, University of Otago, Wellington, New Zealand
[7] Research Centre for Hauora and Health, Massey University, Wellington, New Zealand
[8] New Zealand Institute for Advanced Study, Massey University, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 25 July 2022
Revised 28 October 2022
Accepted 9 December 2022

Keywords:
ESBL
AmpC
Enterobacterales
E. coli
Antimicrobial resistance
Urinary tract infection

ABSTRACT

Objectives: To assess whether having a pet in the home is a risk factor for community-acquired urinary tract infections associated with extended-spectrum β-lactamase (ESBL)- or AmpC β-lactamase (ACBL)-producing Enterobacterales.

Methods: An unmatched case-control study was conducted between August 2015 and September 2017. Cases (n = 141) were people with community-acquired urinary tract infection (UTI) caused by ESBL- or ACBL-producing Enterobacterales. Controls (n = 525) were recruited from the community. A telephone questionnaire on pet ownership and other factors was administered, and associations were assessed using logistic regression.

Results: Pet ownership was not associated with ESBL- or ACBL-producing Enterobacterales-related human UTIs. A positive association was observed for recent antimicrobial treatment, travel to Asia in the previous year, and a doctor's visit in the last 6 months. Among isolates with an ESBL-/ACBL-producing phenotype, 126/134 (94%) were *Escherichia coli*, with sequence type 131 being the most common (47/126).

Conclusions: Companion animals in the home were not found to be associated with ESBL- or ACBL-producing Enterobacterales-related community-acquired UTIs in New Zealand. Risk factors included overseas travel, recent antibiotic use, and doctor visits.

Introduction

Extended-spectrum β-lactamase (ESBL)- and AmpC β-lactamase (ACBL)-producing Enterobacterales are oxyimino-cephalosporin–resistant bacteria of importance commonly associated with urinary tract and blood infections, presenting ongoing challenges for treatment options [1,2]. Historically, these bacteria were primarily acquired through hospital exposures, but have since become associated with community-acquired infections [3–5]. ESBL and ACBL enzymes, which hydrolyze a range of β-lactam antibiotics, are often encoded by genes within mobile elements (i.e., plasmids), and are increasingly found in bacteria with virulence traits that make the bacteria likely to cause disease [6–9]. ESBL-producing Enterobacterales are also animal pathogens, isolated from clinical samples of companion and production animals around the world [10–13], including New Zealand [14].

* Corresponding author
E-mail address: s.burgess1@massey.ac.nz (S.A. Burgess).
Present address: Zoë Grange, Public Health Scotland, Glasgow, United Kingdom

https://doi.org/10.1016/j.ijid.2022.12.013

Person-level risk factors for ESBL-producing Enterobacterales carriage or infection include travel to higher-prevalence countries, frequent healthcare contact, and recent antimicrobial use [15,16]. There have also been some instances of people becoming ill after exposure to companion animals that carry or become infected with multidrug-resistant (MDR) pathogens [17–20], or companion animals that carry the same strain of ESBL-producing *Escherichia coli* as humans [21–23]. In New Zealand, companion animals visiting veterinary clinics may carry human-associated strains of ESBL-producing Enterobacterales [14,24]. In Japan and Europe, human-associated ESBL-producing Enterobacterales were found in clinical bacterial isolates from companion animals [25–27]. These bacteria may contain plasmid-encoded ESBL genes commonly associated with human community infections (such as $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-27}}$ or $bla_{\text{CTX-M-15}}$); the bacteria may also be from human-associated sequence types (STs), such as ST131.

As MDR infections become more common in the community, the risk factors for exposure and subsequent infection (via intestinal carriage) are likely changing [16,28]. In New Zealand, approximately 64% of households have a pet, with 44% having at least one cat and 28% having at least one dog [29]. Given the high pet ownership and the potential for pets to be carrying ESBL- and ACBL-producing Enterobacterales [14,23,30], it is plausible that pets may play a role in community-acquired ESBL- and ACBL-caused infections in people [31].

The aim of this case-control study was to assess whether companion animals, alongside other households, health, and travel variables, are a risk factor for community-acquired urinary tract infections (UTIs) associated with ESBL- and ACBL-producing Enterobacterales in humans. We also describe the genomic epidemiology of ESBL- and ACBL-producing Enterobacterales cultured from these infections.

Methods

Recruitment and sampling

Case and control definitions

A case was defined as a person aged 16 years or older with a community-acquired UTI, who submitted a urine sample to the recruiting community laboratory (Labtests, Healthscope, Auckland, New Zealand) from which an ESBL- or ACBL-producing Enterobacterales was cultured. Case participants were excluded from the study if they had been admitted overnight to a hospital or lived in a residential care facility in the 12 months before the urine sample collection. Control participants were eligible to be part of the study if they had not been a patient overnight in a hospital or lived in a residential care facility in the previous 12 months and were 16 years of age or older.

Recruitment and data collection

This case-control study was approved by the New Zealand Health and Disability Ethics Committee. Case participants were recruited between September 2015 and September 2017 from the Auckland, Northland, and Waikato regions (the northern part of the North Island) of New Zealand from four district health board areas (Auckland, Northland, Waitemata, and Counties Manukau). Controls were recruited by a research company (UMR Research, Wellington, https://umr.co.nz/) using a combination of random digit dialing and verified phone numbers (landline only) in UMR's polling database (the response rate for controls was 32.1% of those eligible). Controls were randomly drawn from the Auckland and Northland regions and were otherwise unmatched. The proportions of controls reflected the population in these two regions. All control participants were recruited between August 2015 and March 2017. Participants consented to a 20-minute telephone interview (see Supplementary data for questionnaire), to collect exposure information during the 6 months preceding the MDR UTI for cases or the previous 6 months for controls. Pretesting of the questionnaire, including cognitive testing, was undertaken by UMR before the recruitment began. The questionnaire covered demographic, health, animal, travel, occupational, and household factors. Demographic details included the decile of the nearest primary school (a measure of socioeconomic position), whether that school was in an urban or a rural area, region (Auckland, Northland, or Waikato), gender, ethnicity, whether the participant lived alone, worked in healthcare, and had been a visitor to a hospital or rest-home in the past six months. Pet-related questions were asked about food, hygiene, contact with animals, and vet visits (including any antimicrobial treatment). Participants were asked to recall recent antimicrobial treatment; for case participants, this was intended to be any treatments before their current infection. Case participants were asked for permission to access government health data (through the New Zealand National Health Index number) for prescriptions of antimicrobials and hospitalizations for MDR infection.

Statistical analyses

Statistical analysis of questionnaire data was performed using RStudio (v. 3.4.3). To assess risk factors both multivariable logistic regression (as described below) and least absolute shrinkage and selection operator (LASSO) logistic regression (Supplementary Methods) were conducted [32,33]. The LASSO modeling was carried out on all variables (Supplementary Methods) using a conservative model to avoid overfitting and to reduce the effect of multicollinearity [34]. Random forest (Supplementary Methods) was used as an independent analysis and provided information on the importance of a variable to the outcome (i.e., case vs control). Random forest was applied to the same 85 variables assessed using the multivariable logistic regression.

Multivariable regression models. Logistic regression was used to assess the relationship between the outcome variable (case or control) and each variable of interest. A preliminary multivariable model was constructed from variables where at least one factor (or level) in the variable had a P-value ≤ 0.2. Upon moving to a final multivariable logistic regression model, variables were excluded using a stepwise approach. Variables were excluded when the covariate did not reach the significance of $P < 0.05$, provided they were not a confounder or the exposure of interest. Model fit was assessed using likelihood ratio tests, area-under receiver operating characteristic (c-statistic), and pseudo-R-squared (Nagelkerke R-squared) with the R package "rms" [32]. These tests, in addition to P-values, residual deviance, and Akaike information criterion were used to describe and assess multivariable model(s) (calculated with the R function "glm").

Subset analysis with National Health Index prescription data. As previous antimicrobial use was an exposure variable of interest, prescription data (accessed through the National Health Index) for the 6 months preceding the submission of the urine sample of the case participant were requested and were available for 70% of case participants ($n = 99$). For multivariable modeling, the most recent prescription was used if there were multiple recorded prescriptions. This subset was used with the full control dataset for repeated regression modeling. The sensitivity and specificity of the questionnaire were assessed using National Health Index prescription data as the true exposure status of case participants.

Population-attributable fractions. Attributable fractions for variables included in the final multivariable logistic regression model were calculated with confidence intervals (CIs) computed via bootstrapping.

Table 1
Summary of demographic and health variables based on questionnaire data of 141 case and 525 control participants and their univariable association with case or control status.

Variable	Level	Control	Case	Unadjusted odds ratio	*P*-value
Home	Lives alone	56/524 (10.7%)	20/139 (14.3%)	Ref	
	Lives with others	468/524 (89.3%)	119/139 (85.6%)	0.71 (0.42, 1.3)	0.23
Sex	Male	251/525 (47.8%)	8/141 (5.7%)	Ref	
	Female	274/525 (51.4%)	133/141 (94.3%)	15 (7.8, 34)	<0.001
Age	Age 16-44	275/525 (22.0%)	31/141 (52.4%)	Ref	
	Age 45-64	161/525 (37.6%)	53/141 (30.7%)	2.9 (1.8, 4.8)	<0.001
	Age 65 plus	89/525 (40.4%)	57/141 (17.0%)	5.7 (3.5, 9.4)	<0.001
Ethnicity[a]	Māori	39/525 (74.2%)	8/141 (5.7%)	0.75 (0.32, 1.6)	0.47
	Asian	37/525 (70.4%)	12/141 (8.5%)	1.2 (0.60, 2.4)	0.56
	Pacifika	10/525 (1.9%)	2/141 (1.4%)	0.74 (0.11, 2.9)	0.70
	European	389/525 (74.1%)	105/141 (74.4%)	1.0 (0.67, 1.6)	0.93
	MELAA [a]	22/525 (41.9%)	5/141 (3.5%)	0.84 (0.28, 2.1)	0.73
Healthcare work	Not health worker	468/525 (89.1%)	109/136 (80.1%)	Ref	
	No patient contact	15/525 (28.6%)	15/136 (11.0%)	4.3 (2.0, 9.1)	<0.001
	Yes patient contact	42/525 (8.0%)	12/136 (8.8%)	1.2 (0.60, 2.3)	0.55
School decile[b]	1 to 3	115/486	18/119 (15.1%)	Ref	
	4 to 7	160/486 (32.9%)	44/119 (37.0%)	1.8 (1.0, 3.3)	0.065
	8 to 10	211/486 (43.4%)	57/119 (47.9%)	1.7 (1.0, 3.1)	0.064
Rural urban	Non-urban	74/487 (15.2%)	12/119 (10.1%)	Ref	
	Urban	413/487 (84.8%)	107/119 (89.9%)	1.6 (0.87, 3.2)	0.16
Overall health	Good to excellent	487/525 (92.8%)	113/140 (80.7%)	Ref	
	Fair or poor	38/525 (72.4%)	27/140 (19.3%)	3.1 (1.8, 5.2)	<0.001
Any chronic disease	None reported	394/524 (75.2%)	60/136 (44.1%)	Ref	
	Yes	130/524 (24.8%)	76/136 (55.9%)	3.8 (2.6, 5.7)	<0.001
Asthma	None reported	495/524 (94.5%)	126/136 (92.6%)	Ref	
	Yes	29/524 (5.5%)	10/136 (7.4%)	1.4 (0.61, 2.8)	0.42
Cardiac disease	None reported	506/524 (96.6%)	127/137 (92.7%)	Ref	
	Yes	18/524 (3.4%)	10/137 (7.3%)	2.2 (1.0, 4.8)	0.051
Diabetes	None reported	514/524 (98.1%)	126/136 (92.6%)	Ref	
	Yes	10/524 (1.9%)	10/136 (7.4%)	4.1 (1.6, 10)	0.002
Other chronic disease	None reported	445/524 (84.9%)	75/136 (55.1%)	Ref	
	Yes	79/524 (15.1%)	61/136 (44.9%)	4.6 (3.0, 6.9)	<0.001
Chronic disease score[c]	None reported	394/523 (75.3%)	59/136 (16.4%)	Ref	
	1	116/523 (22.2%)	59/136 (43.4%)	3.4 (2.2, 5.2)	<0.001
	2	10/523 (1.9%)	15/136 (11.0%)	10 (4.3, 24)	<0.001
	3 plus	3/523 (0.6%)	3/136 (2.2%)	6.7 (1.2, 37)	0.022
>1 urinary tract infection last 6 months	No	509/524 (97.1%)	64/134 (47.1%)	Ref	
	Yes	15/524 (2.9%)	70/134 (52.2%)	37 (21, 71)	<0.001
Doctors visit last 6 months[d]	No	260/525 (49.5%)	10/138 (7.2%)	Ref	
	Yes	265/525 (50.5%)	128/138 (92.8%)	13 (6.8, 26)	<0.001
Antibiotics last 6 months[e]	No	385/521 (73.9%)	28/129 (96.6%)	Ref	
	Yes last 3 to 6 months	72/521 (13.8%)	19/129 (14.7%)	3.6 (1.9, 6.8)	<0.001
	yes last 0 to 3 months	64/521 (12.3%)	82/129 (63.6%)	18 (11, 30)	<0.001
Visitor to hospital last 6 months[f]	No	290/523 (55.4%)	60/139 (43.2%)	Ref	
	Yes	233/523 (44.6%)	79/139 (56.8%)	1.6 (1.1, 2.4)	0.010
Visitor to hospital last 6 months - other household member	Lives alone	56/519 (10.8%)	19/135 (14.1%)	Ref	
	No	372/519 (71.7%)	88/135 (65.1%)	0.70 (0.40, 1.3)	0.21
	Yes	91/519 (17.5%)	28/135 (20.7%)	0.91 (0.47, 1.8)	0.78
Antibiotics last 6 months - other household member	Lives alone	56/506 (11.1%)	19/117 (16.2%)	Ref	
	No	284/506 (56.1%)	48/117 (41.0%)	0.50 (0.28, 0.93)	0.024
	Yes	166/506 (32.8%)	50/117 (42.7%)	0.89 (0.49, 1.7)	0.70
Multidrug resistant infection reported by another household member	Lives alone	56/514 (10.9%)	19/119 (16.0%)	Ref	
	No	444/514 (86.4%)	96/119 (80.7%)	0.64 (0.37, 1.1)	0.12
	Yes	14/514 (27.2%)	4/119 (3.4%)	0.84 (0.22, 2.7)	0.78
Travel	None reported	271/524 (51.7%)	51/140 (36.4%)	Ref	
	All travel	253/524 (48.3%)	89/140 (63.6%)	1.9 (1.3 - 2.8)	0.001
Travel to Africa	None reported	519/524 (99.1%)	133/140 ((95.0%)	Ref	
	Yes	6/524 (11.5%)	7/140 (5.0%)	4.6 (1.5 - 14.4)	0.007
Travel to Asia	None reported	463/524 (88.4%)	98/140 (70.0%)	Ref	
	Yes	62/524 (11.8%)	43/140 (30.7%)	3.3 (2.1 - 5.1)	<0.001
Travel to the European Union	None reported	488/524 (93.1%)	122/140 (87.1%)	Ref	
	Yes	37/524 (59.2%)	19/140 (13.6%)	2.1 (1.1 - 3.7)	0.016
All travel - other household member	None reported	221/523 (42.3%)	48/137 (35.0%)	0.6 (0.4 - 1.2)	0.15
	Yes	246/523 (47.0%)	70/137 (51.1%)	0.8 (0.5 - 1.5)	>0.2
Pet in home[a]	None	267/525 (50.9%)	71/139 (51.1%)	Ref	
	Yes	258/525 (49.1%)	68/139 (48.9%)	1.0 (0.7 - 1.4)	>0.2
Pet type	None	267/525 (50.9%)	71/137 (51.8%)	Ref	
	Cat(s) only	95/525 (18.1%)	26/137 (19.0%)	1.0 (0.6 - 1.7)	>0.2
	Dog(s) only	51/525 (9.7%)	16/137 (11.7%)	1.2 (0.6 - 2.2)	>0.2
	Cat(s) and dog(s)	44/525 (8.4%)	15/137 (10.9%)	1.3 (0.7 - 2.4)	>0.2
	Other pets included	68/525 (13.0%)	9/137 (6.6%)	0.5 (0.2 - 1.0)	0.066
Animal contact:	None reported	455/525 (86.7%)	130/141 (92.2%)	Ref	
- farm	Yes	70/525 (13.3%)	11/141 (7.8%)	0.6 (0.3 - 1.0)	0.078
- wild or other	None reported	506/525 (96.4%)	129/141 (91.5%)	Ref	
	Yes	19/525 (3.6%)	12/141 (8.5%)	2.5 (1.1 - 5.2)	0.018

[a] Ethnicity was reported with multiple answers allowed, ethnicities were compared to "not ethnicity"; MELAA – Middle Eastern, Latin American, and African.
[b] The decile of the nearest school was used as a proxy for social deprivation, with decile one being the 10% of schools that have the greatest proportion of children from a low socioeconomic background and decile ten being the 10% of schools that have the lowest proportion. Refer to https://parents.education.govt.nz/secondary-school/secondary-schooling-in-nz/deciles/.
[c] Chronic disease score was the number of chronic diseases (asthma, chronic obstructive pulmonary disease, cardiac disease, and diabetes) reported.
[d] This includes a medical visit with a general practitioner or with a specialist as an outpatient (including imaging or radiology).
[e] Questionnaire data was used.
[f] Where the case or other household member visited a hospital as a visitor, volunteer or employee but not as a patient.

Bacterial culture and antimicrobial susceptibility testing. ESBL-positive isolates originating from the case urine samples were collected by Labtests Auckland microbiology laboratories. The bacterial isolates were identified using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (Biotyper, Bruker, Billerica, MA, USA) and confirmed to have an ESBL-or AmpC production phenotype according to European Committee on Antimicrobial Susceptibility Testing guidelines using Kirby-Bauer disc diffusion assays [23,35,36]. A saline solution suspension, of each isolate, was swabbed onto Mueller-Hinton agar (Fort Richard Laboratories, Auckland, New Zealand) as a lawn and D62C ESBL cefotaxime and D64C ESBL ceftazidime Paired ID Disks (Mast Group Ltd., Liverpool, U.K.), placed on to the lawn and incubated at 35°C for 16-18 hours. Isolates were also tested for an AmpC-producing phenotype using a three-disk comparison assay (D69C AmpC disk test; Mast Group Ltd.) and screened against an additional panel of fourteen antimicrobials to determine multidrug resistance as previously described [23].

DNA extraction, sequencing, and bioinformatics analyses

Where available, one clinical UTI isolate was sequenced from each case participant. Extraction of genomic DNA, library preparations, and next-generation sequencing were carried out as previously described [23]. Raw sequence reads were processed using the Nullarbor2 bioinformatics pipeline (v. 2.0.20191013) [37]. Thirteen clinical UTI isolates had been sequenced as part of previous studies [23,38].

Whole genome multi-locus sequence typing (wgMLST) of *E. coli* clinical isolates was carried out using Fast-GeP (v.1.0) [39]. The distance matrix tree output from wgMLST was presented as a neighbor-joining tree in SplitsTree [40], and annotated using iTOL [41]. Resistance genes were identified with ABRicate (v.1.0.1) [42] using the National Center for Biotechnology Information (NCBI) AMRFinderplus (v.2021-03-28) [37,43]. Single nucleotide polymorphism (SNP) analysis of the ST131 and ST38 isolates was carried out using Snippy (v. 4.3.6) [44].

Results

Overview of cases and controls

A total of 141 cases and 525 controls were recruited between August 1, 2015, and September 30, 2017, most of whom identified as European or New Zealand European (controls: 74.1% and cases: 74.5%). Females were overrepresented in the cases (94.3%) compared to the controls (52.2%). The age distribution also differed between cases and controls as indicated in Table 1. Most participants lived with other people, 89.3% and 85.6% of control and case participants, respectively. Further descriptions of the demographic and health variables of cases and controls along with the univariable results are provided in Table 1. Home, hygiene, food, and other animal-related variables and univariable results are presented in Supplementary Tables 1 and 2.

Risk factors

In the univariate analysis, we found the strongest associations for ESBL/ACBL- associated UTI with being female, having had more than one UTI, and antimicrobial use within the previous three months (Table 1 and Supplementary Tables 1 and 2). Other health-related factors such as chronic disease and travel to either Africa or Asia had an increased risk. Having a pet in the home was not identified as a risk factor. However, there were increased odds with

Table 2
OR and PAF from a multivariable logistic regression model of factors associated with UTIs caused by extended spectrum β-lactamase- or AmpC β-lactamase-producing Enterobacterales in the community, based on questionnaire data from 141 case and 525 control participants.

Variable	Level	Control	Case	Crude OR	Adjusted OR	PAF
Gender	Male	251/525	8/141	Ref	Ref	Ref
	Female	274/525	133/141	15 (7.8, 34)	24 (7.9, 95)	0.92 (0.81, 1.0)
Age	Age 16 to 44	275/525	31/141	Ref	Ref	Ref
	Age 45 to 64	161/525	53/141	2.9 (1.8, 4.8)	8.4 (3.0, 27)	0.70 (0.48, 0.93)
	Age 65 plus	89/525	57/141	5.7 (3.5, 9.4)	14 (4.7, 51)	0.70 (0.51, 0.95)
Healthcare work	Not healthcare worker	468/525	109/136	Ref	Ref	Ref
	No patient contact	15/525	15/136	4.3 (2.0, 9.1)	4.0 (0.83, 19)	0.08 (-0.02, 0.51)
	Yes patient contact	42/525	12/136	1.2 (0.60, 2.3)	1.1 (0.27, 3.9)	0.00 (-0.07, 0.20)
Diabetes	None reported	514/524	126/136	Ref	Ref	Ref
	Yes	10/524	10/136	4.1 (1.6, 10)	4.1 (0.77, 23)	0.06 (-0.01, 0.53)
Other chronic disease	None reported	445/524	75/136	Ref	Ref	Ref
	Yes	79/524	61/136	4.6 (3.0, 6.9)	2.7 (1.2, 6.2)	0.21 (0.01, 0.51)
>1 UTI last 6 months	No	509/524	64/134	Ref	Ref	Ref
	Yes	15/524	70/134	37 (21, 71)	37 (12, 143)	0.51 (0.31, 0.90)
Doctors visit last 6 months	No	260/525	10/138	Ref	Ref	Ref
	Yes	265/525	128/138	13 (6.8, 26)	24 (7.4, 102)	0.92 (0.82, 1.0)
Antibiotics last 6 months	No	385/521	28/129	Ref	Ref	Ref
	Yes 3 to 6 months	72/521	19/129	3.6 (1.9, 6.8)	2.4 (0.78, 7.0)	0.16 (-0.07, 0.58)
	Yes 0 to 3 months	64/521	82/129	18 (11, 30)	14 (5.5, 38)	0.61 (0.40, 0.90)
Travel to Asia	No	463/525	98/141	Ref	Ref	Ref
	Yes	62/525	43/141	3.3 (2.1, 5.1)	9.1 (3.7, 24)	0.49 (0.27, 0.82)
Travel to Africa	No	519/525	134/141	Ref	Ref	Ref
	Yes	6/525	7/141	4.5 (1.5, 14)	21 (0.54, 449)	0.16 (-0.01, 0.73)
Handwash before eating	Always	259/525	46/141	Ref	Ref	Ref
	Often	104/525	47/141	2.5 (1.6, 4.1)	4.1 (1.6, 11)	0.38 (0.12, 0.73)
	Sometimes	137/525	39/141	1.6 (1.0, 2.6)	2.6 (1.0, 6.9)	0.29 (-0.04, 0.71)
	Never	25/525	9/141	2.0 (0.85, 4.5)	1.3 (0.26, 5.9)	0.01 (-0.04, 0.17)
Pet in home	No pet	267/525	71/139	Ref	Ref	Ref
	Yes	258/525	68/139	1.0 (0.68, 1.4)	0.82 (0.37, 1.8)	-0.10 (-0.55, 0.36)
Animal contact: farm	No contact	455/525	130/141	Ref	Ref	Ref
	Yes	70/525	11/141	0.55 (0.27, 1.0)	0.23 (0.05, 0.86)	-0.12 (-0.17, 0.01)
Animal contact: wild	No contact	506/525	129/141	Ref	Ref	Ref
	Yes	19/525	12/141	2.5 (1.1, 5.2)	3.4 (0.84, 13)	0.08 (0.00, 0.31)

OR, odds ratio; PAF, Population Attributable Fractions; Ref, reference; UTI, urinary tract infections.

Table 3
Summary of *Escherichia coli* isolates across the fifteen sequence types (with multiple isolates) from community-acquired urinary tract infections.

Phylogenetic group[a]	Sequence type[b]	*E. coli* isolates n (total = 126)	Extended spectrum β-lactamase/AmpC type (n isolates)
A	744	2	CTX-M-8 (1)
			CTX-M-14 (1)
C	410	2	CTX-M-15 (1)
			CTX-M-55 (1)
F	648	3	CTX-M-15 (2)
			CTX-M-55 (1)
B1	345	2	CTX-M-14 (1)
			cAmpC[c] (1)
B1	58	2	CTX-M-14 (1)
			CTX-M-55 (1)
B2	12	3	CTX-M-15 (1)
			cAmpC[c] (2)
B2	80	2	cAmpC[c] (2)
B2	131	48	CTX-M-14 (2)
			CTX-M-15 (22)
			CTX-M-27 only (22)
			CTX-M-27 and CMY-2 (1)
			CTX-M-27 and CMY-138 (1)
B2	998	2	CTX-M-15 (2)
B2	1193	5	CTX-M-15 (2)
			CTX-M-27 (2)
			CMY-2 (1)
D	38	16	CTX-M-9 (1)
			CTX-M-14 (1)
			CTX-M-15 (7)
			CTX-M-24 (1)
			CTX-M-27 (6)
D	69	8	CTX-M-14 (1)
			CTX-M-15 (2)
			CTX-M-27 (3)
			CTX-M-55 (1)
			CMY-2 (1)
D	349	2	CMY-2 (1)
			DHA-1 (1)
D	405	3	CTX-M-14 (1)
			CTX-M-15 (1)
			cAmpC[c] (1)
D	963	4	CMY-2 (4)

[a] As in Clermont et al. [69].
[b] Refer to Supplementary Table 7 for singleton STs.
[c] cAmpC refers to chromosomal *ampC* with a mutation in the promoter region.

some pet-associated variables (e.g., picking up pet feces), and contact with wildlife was associated with an increased risk (Table 1 and Supplementary Table 2). Having non-cat/dog pets (e.g., rodents, fish, or birds) or contact with livestock was inversely associated with an ESBL/ACBL-associated UTI. Additional results of the univariate analysis for other hygiene and food or pet-related variables are presented in Supplementary Tables 1 and 2.

Adjusted odds ratios (ORs) for variables included in the multivariable models are shown using the questionnaire data only (Table 2). Having a pet in the home was not found to be a significant risk factor (OR: 0.82 [95% CI 0.37-1.8]). As with the univariate analysis, being older and female were associated with having an ESBL-/ACBL-producing UTI ($OR_{age45to65}$ = 8.4 [95% CI 3.0-27] and OR_{age65+} = 14 [95% CI 4.7-51]; OR_{female} = 24 [95% CI 7.9-95]), as was having more than one UTI in the preceding six months before the incident UTI (OR = 37 [95% CI 12-143]) and antimicrobial treatment in the previous 3 months (OR = 14 [95% CI 5.5-38]). Travel to Asia (OR = 9.1 [95% CI 3.7 - 24]) and some health and hygiene-related exposures of interest were also found to be associated with an increased risk. Population-attributable fractions gave an estimation of the population-level effect of exposures on the outcome, accounting for the rarity of exposures as shown in Table 2.

Antimicrobial prescription data in the previous 6 months was available for 88 of the 99 cases. The questionnaire test sensitivity for this question was estimated to be 87%, while the specificity was 44% (i.e., >50% false positives where people reported antimicrobial use, but no prescriptions were recorded in the New Zealand government database; Supplementary Table 3). Results of the univariable and multivariable analysis for this subset of data are presented in Supplementary Table 4. Despite cases reporting more antimicrobial use than prescriptions recorded, antimicrobial use within the previous three months was associated with having an ESBL-/ACBL-producing UTI.

The variables important to multivariable logistic regression as well as both LASSO regression, and random forest were (i) being over 65 years old; (ii) being female; (iii) having more than one UTI in the previous 6 months; (iv) travel to Africa and/or Asia in the previous 12 months; (v) a doctor's visit in the previous 6 months; (vi) contact with wild animals in the previous 6 months; (vii) having an "other" chronic disease (not asthma, diabetes, chronic obstructive pulmonary disease, or cardiac disease); (viii) not "always" washing hands before eating (Supplementary Tables 5 & 6).

Phenotypic and genomic descriptions of isolates

From 141 cases, clinical isolates were available from 134 people. Of the isolates that were available for sequencing, 126/134 were *E. coli*, 7/134 were *Klebsiella pneumoniae*, and 1/134 was *Morganella morganii*; 114/134 had ESBL genes (of which 111 were the CTX-M type), and 15/134 had plasmid-associated ACBL genes (excluding

Figure 1. Neighbor-joining tree, of 126 clinical *Escherichia coli* isolates, generated from 2654 shared-loci alleles identified using the whole genome multi-locus sequence typing tool Fast-Gep. The first colored strip denotes the phylogroup, followed by the absence (white) or presence of antimicrobial resistance genes where blue is extended spectrum β-lactamase, purple is AmpC, and green is other resistance genes.
ST, sequence type.

four ESBL-producing *E. coli* or *K. pneumoniae* isolates that were also co-producers of ACBL) (Table 3, Supplementary Table 7). A multidrug resistance phenotype (resistance to three or more classes of antibiotics) was observed in 76/134 (57%) of all clinical isolates (Supplementary Table 8).

Eight $bla_{\text{CTX-M}}$ variants (CTX-8, CTX-M-9, CTX-M-14, CTX-M-24, CTX-M-27, CTX-M-55, and CTX-M-65) were identified by whole genome sequencing, in 105 of the 126 *E. coli* isolates, with CTX-M-15 (49/126, 39%) and CTX-M-27 (38/126, 30%) being the dominant variants and one isolate had the SHV-12 variant. Plasmid-associated ACBL types CMY (13/126, 10%) and DHA (4/126, 3%) were also identified. Seven *E. coli* isolates had no plasmid-associated ACBL genes but were putative AmpC hyperproducers with mutations in the promoter region of the chromosomal *ampC* gene.

A comparison of wgMLST profiles for 126 *E. coli* showed that the ESBL/ACBL-producing *E. coli* associated with UTIs were diverse (Figure 1). Phylogroup B2 accounted for 65/126 of all *E. coli* isolates, with ST131 being the dominant ST (48/126, 38%), followed by ST38 (16/126, 13%). In total, 37 different STs were identified, including 22 singleton STs. To further investigate the genetic diversity within the two dominant STs, ST131 and ST38, we compared the SNP profiles (Figure 2). Overall, six ST131 isolates had a difference in ten or fewer SNPs, suggesting community transmission.

The seven *K. pneumoniae* isolates belonged to six different STs, with ST562 isolated from two different individuals (Supplementary Table 7). Of the *K. pneumoniae* isolates, four had a $bla_{\text{CTX-M-15}}$ gene; one a $bla_{\text{CTX-M-14}}$ gene; and one a $bla_{\text{SHV-106}}$ gene. An ACBL gene ($bla_{\text{DHA-15}}$) was found in one isolate. The one *M. morganii* isolate contained both ESBL and ACBL genes, $bla_{\text{VEB-1}}$ and $bla_{\text{DHA-4}}$ respectively.

Discussion

Companion animals in the home were not found to be a risk factor for community-acquired ESBL-/ACBL-producing UTIs in our case population. Although, companion animals have frequently been identified as a source of ESBL-/ACBL-producing *Enterobacteriaceae*, with some studies suggesting that transmission of these bacteria occurs between companion animals and humans within households [21-23,31,45], our work is consistent with a previous New Zealand and Australian study, which assessed risk factors

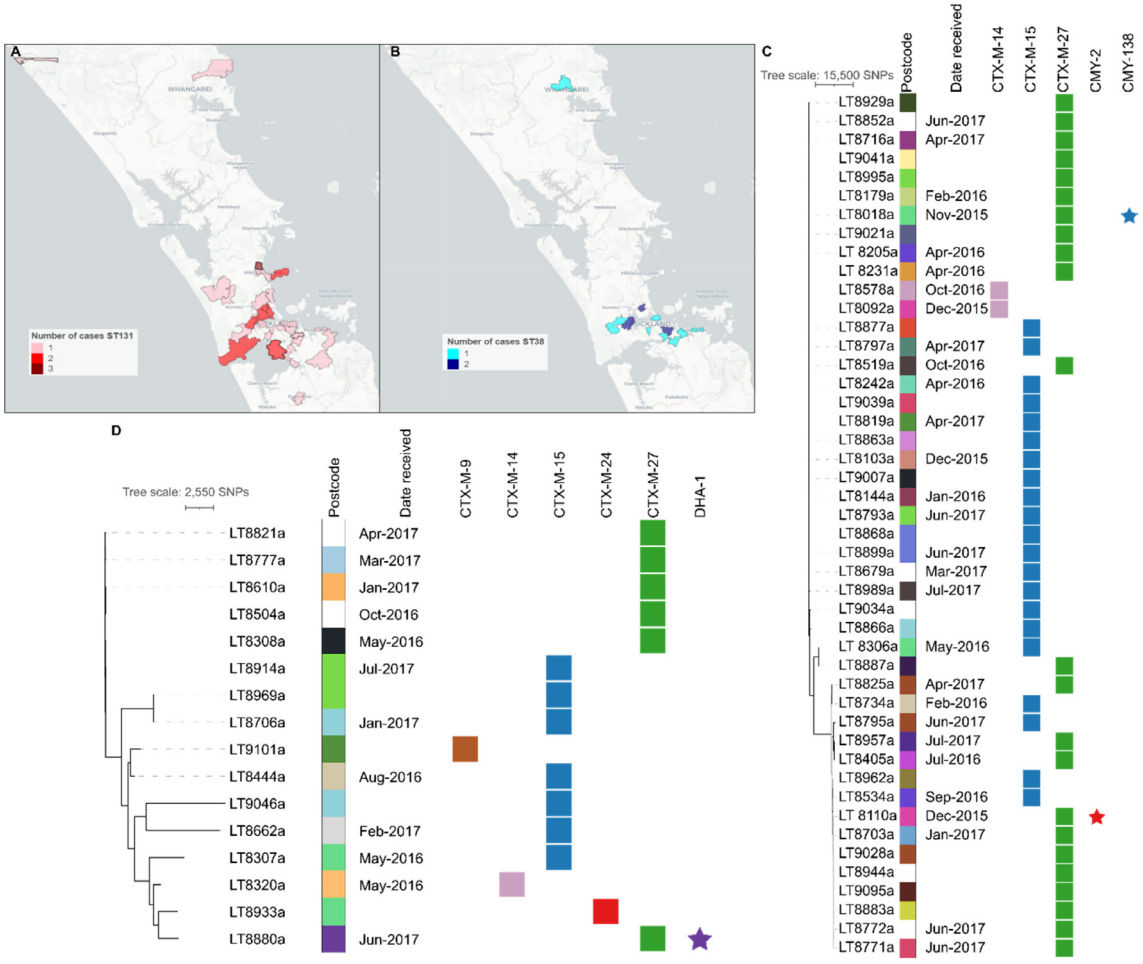

Figure 2. Location of cases and phylogeny of their respective ST131 and ST38 *E. coli* isolates. The number of cases in each postcode region from which ST131 (a) and ST38 (b) *E. coli* were isolated. Postcodes were not available for five of the ST131 and two of the ST38 isolates. A thicker border is around the four regions (1 case per region) that share similar ST131 haplotypes (≤ 10 SNPs difference). Neighbor-joining phylogenetic trees of ST131 were constructed using 15,511 core SNPS (c) and ST38 constructed using 25,529 core SNPs (d).
SNP, single nucleotide polymorphisms; ST, sequence type

for community-acquired third-generation cephalosporin-resistant *E. coli* infections in patients recruited from tertiary care hospitals [28]. To our knowledge, contact with companion animals has not been reported to be a risk factor for community-acquired ESBL-/ACBL-producing infections in other countries; although it is not frequently assessed as a risk factor [46,47].

Previous UTIs, being female, older (age 65+), having a medical visit, having a chronic disease, and traveling to Asia or Africa were associated with increased odds of having a community-acquired ESBL-/ACBL-producing UTI in our study. These findings are consistent with previous studies from both Europe and the United States [48–51]. Travel to high-risk global regions such as North Africa, the Indian subcontinent, Southeast Asia, and China is associated with higher rates of gastrointestinal colonization with ESBL-producing *Enterobacteriaceae* [16], and is associated with carriage in travelers returning from visiting such places [52–54]. In an Australasian study conducted in 2011/2012, travel increased the odds of having an *E. coli* infection resistant to third-generation cephalosporins [28].

There was some internal disagreement noted between the models when examining travel-associated risk factors. LASSO logistic regression modeling found increased odds associated with travel to Asia (all parameters and both datasets). However, travel to Africa was not associated with increased risk in the conservative model (λ_{min} + 1SE) when using the questionnaire dataset. Travel to Asia (but not travel to Africa) was also among the top ten variables (in terms of the effect on the outcome) within the random forest regression. The recurrence of Asian travel in all these modeling modalities reinforces the inference of increased risk associated with travel to this continent within this study. This finding is in concordance with results from other low-prevalence countries [16,28,47,52].

Healthcare exposures, including antimicrobial treatment, are well-described as risk factors for the carriage of ESBL-producing bacteria [16]. They have also been described in a study looking at risks for community-acquired infection, where healthcare exposure in the previous 6 months, UTI in the previous year, and antimicrobial treatment in the previous 6 months were all associated with increased risk [28]. All these risk factors were also identified by multiple modeling methods in our study. However, antimicrobial treatment in the previous 3 months was not statistically significant in the more conservative LASSO regression model (λ_{min} + 1 SE), although it was significantly associated with risks in other models. In multivariable regression models when prescription data were available (for the subset of cases accessed through the National Health Index database), an adjusted OR of 2.8 (95% CI 1.1-7.3) was observed for the risk factor of antimicrobial prescription in the previous 3 months. This is much less than the adjusted OR of 15.3 (95% CI 6.0 – 43.1) for the same risk factor when case participants self-reported this exposure. This difference could be

because patients self-reported the prescription for the current infection (rather than previous infections) and show the importance of validating self-reporting of medication data, especially when it is considered an exposure of interest. Alternatively, patients may have been prescribed antibiotics but did not use the antibiotics or cases may have received antibiotics in the hospital (which are not included in the prescription dataset). Discrepancies in reporting prescription data have been reported elsewhere [55].

The outputs from random forest regression and LASSO regression, where all variables were used, compared to the multivariable regression, varied slightly in the order of the most important variables for predicting the outcome. Some variables such as companion animal contact (handwashing behavior) and animal contact with veterinary care identified in the random forest regression as important were not detected as significant in either the multivariable or the LASSO regressions. These findings may indicate some low or marginal level of risk associated with animals. The degree of risk may be underestimated due to social desirability bias, which may affect replies to questions about personal hygiene [56]. However, there were areas of crossover between the random forest regression and the LASSO model outputs, and the results of the multivariable logistic regression indicated that the main risk factors are consistent across different model frameworks.

Our study showed that there is substantial diversity among ESBL-/ACBL-producing *E. coli* isolates causing UTI in the New Zealand community, despite, one-third of isolates being *E. coli* ST131. This finding is consistent with previous reports on community-acquired infection in New Zealand [1,57–59]. Plasmid-mediated AmpC-producing *E. coli* were approximately ten times less common than ESBLs among *E coli* isolates from community-acquired UTIs as previously reported [58]. Additionally, these ESBL-/ACBL-producing bacteria generally contained multiple antimicrobial resistance genes. The genes encoding ESBLs are often associated with other antimicrobial resistance encoding genes, resulting in a MDR strain, which may result in clinical implications for ESBL-associated infections, including treatment failure, hospitalization, and in some cases increased mortality [60–62].

Both ST131 and ST38 (the second most common ST in our study) strains have previously been found to be shared by humans and their dogs [23]. Previous studies have found ESBL-producing *E. coli* from dogs and cats to be very diverse [63–65], with a New Zealand study identifying strains belonging to more than 25 different STs [66] and a recent global meta-analysis identifying 171 different STs [12]. Some of these, including ST10, ST38, ST57, ST58, and ST963 were found in this present study. Cross-sectional studies in Europe suggest some similar strains of *E. coli* and *K. pneumoniae* are circulating between humans and animals [65,67].

There were several limitations within this study including sources of bias such as possible inaccurate reporting of antimicrobial use in the subset of 70% (99/141) of case participants and social desirability biases influencing replies to questions about hygiene and behaviors. Another source of bias could be through the recruitment of controls if there were differences (i.e., lifestyle, health, or demographic) between those who declined to take part in the study and those who agreed. All controls were assumed to be non-carriers of ESBL/ACBL-producing Enterobacterales, although it is possible that up to 10% had fecal carriage of ESBL-producing *E. coli* [68]. The community carriage prevalence of ESBL/ACBL-producing Enterobacterales in New Zealand was not known at the time of this research, and too few control participants volunteered to give fecal samples to assess this. The results of this study indicate that future work with a focus on the prevalence of ESBL-ACBL-producing bacteria in both humans and pets is needed, to better align pet-related risk factors with the incidence of ESBL/ACBL-producing Enterobacterales in pets.

Conclusions

No pet-related factors were found to be significantly associated with ESBL- and/or ACBL-producing Enterobacterales UTI in people. This study reinforces that overseas travel, previous antibiotic use, and healthcare contact with doctors are the main risk factors for community-acquired ESBL/ACBL-associated UTIs. The genomic epidemiology of ESBL/ACBL-producing *E. coli* is diverse, although over one-third of the isolates analyzed in this study were ST131. Our results suggest that some community transmission of ST131 strains is occurring.

Conflict of interest

The authors have no conflicts of interest.

Funding

This work was supported by the Health Research Council of New Zealand (grant number 14-331).

Ethical approval statement

This case-control study, with a cross-sectional stool-sampling component, was approved by the New Zealand Health and Disability Ethics Committee (HDEC) - central committee (reference 15/CEN/47).

Acknowledgments

We thank Tracey Whaanga for her role in case follow-up and questionnaire delivery. The laboratory work was assisted by Maggie Chan, Jacinda Aplin, Lynn Rogers, Rukhshana Akhter, Harry Cookson, and Ahmed Fayaz from ^{m}Epilab at Massey; Matilda Germanov at Labtests Auckland, and Tina Littlejohn at Medlab Central. Ji Zhang, David Wilkinson, and Samuel Bloomfield provided additional bioinformatics support. We wish to acknowledge the use of New Zealand eScience Infrastructure (NeSI) high-performance computing facilities, as part of this research.

Author contributions

LTR: Methodology, data collection, statistical and genomic analyses, investigation, writing – original draft. JCM: Methodology, statistical analysis, investigation, supervision, writing - review and editing. JB Conceptualization, methodology, investigation, supervision, writing - review & editing. DD: Conceptualization, data collection, methodology, investigation, writing - review & editing. ACM: Methodology, investigation, supervision, writing - review & editing. PJB: Methodology, genomic analysis, investigation, supervision, writing - review & editing. ZG: Data collection, methodology, investigation, writing - review & editing. MGB: Conceptualization, investigation, writing - review & editing. JD: Conceptualization, investigation, data collection, writing – review & editing. MGR: Conceptualization, investigation, writing - review & editing NPF: Conceptualization, funding acquisition, investigation, formal analysis, visualization, writing - review & editing. SAB: Methodology, genomic analysis, supervision, investigation, writing – original draft & editing.

Data availability

Sequence reads generated from this study have been deposited in the NCBI Sequence Read Archive under the BioProject numbers **PRJNA656363** and **PRJNA600954**.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.12.013.

References

[1] Heffernan H, Woodhouse R, Draper J, Ren X. 2016 survey of extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Wellington: Institute of Environmental Science and Research* 2018:1–17.

[2] Torres E, López-Cerero L, Morales I, Navarro MD, Rodríguez-Baño J, Pascual A. Prevalence and transmission dynamics of *Escherichia coli* ST131 among contacts of infected community and hospitalized patients. *Clin Microbiol Infect* 2018;**24**:618–23. doi:10.1016/j.cmi.2017.09.007.

[3] Freeman JT, McBride SJ, Heffernan H, Bathgate T, Pope C, Ellis-Pegler RB. Community-onset genitourinary tract infection due to CTX-M-15–Producing *Escherichia coli* among travelers to the Indian subcontinent in New Zealand. *Clin Infect Dis* 2008;**47**:689–92. doi:10.1086/590941.

[4] Heffernan HM, Woodhouse RE, Pope CE, Blackmore TK. Prevalence and types of extended-spectrum β-lactamases among urinary *Escherichia coli* and *Klebsiella spp*. in New Zealand. *Int J Antimicrob Agents* 2009;**34**:544–9. doi:10.1016/j.ijantimicag.2009.07.014.

[5] Rogers BA, Ingram PR, Runnegar N, Pitman MC, Freeman JT, Athan E, et al. Sequence type 131 fimH30 and fimH41 subclones amongst *Escherichia coli* isolates in Australia and New Zealand. *Int J Antimicrob Agents* 2015;**45**:351–8. doi:10.1016/j.ijantimicag.2014.11.015.

[6] Kantele A, Lääveri T. Extended-spectrum beta-lactamase-producing strains among diarrhoeagenic *Escherichia coli*-prospective traveller study with literature review. *J Travel Med* 2022;**29** taab042. doi:10.1093/jtm/taab042.

[7] Kaper JB, Nataro JP, Mobley HLT. Pathogenic *Escherichia coli*. *Nat Rev Microbiol* 2004;**2**:123–40. doi:10.1038/nrmicro818.

[8] Nicolas-Chanoine MH, Bertrand X, Madec JY. *Escherichia coli* ST131, an intriguing clonal group. *Clin Microbiol Rev* 2014;**27**:543–74. doi:10.1128/CMR.00125-13.

[9] Wyres KL, Nguyen TNT, Lam MMC, Judd LM, van Vinh Chau N, Dance DAB, et al. Genomic surveillance for hypervirulence and multi-drug resistance in invasive *Klebsiella pneumoniae* from South and Southeast Asia. *Genome Med* 2020;**12**:11. doi:10.1186/s13073-019-0706-y.

[10] Freitag C, Michael GB, Kadlec K, Hassel M, Schwarz S. Detection of plasmid-borne extended-spectrum β-lactamase (ESBL) genes in *Escherichia coli* isolates from bovine mastitis. *Vet Microbiol* 2017;**200**:151–6. doi:10.1016/j.vetmic.2016.08.010.

[11] Michael GB, Kaspar H, Siqueira AK, de Freitas Costa E, Corbellini LG, Kadlec K, et al. Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* isolates collected from diseased food-producing animals in the GERM-Vet monitoring program 2008–2014. *Vet Microbiol* 2017;**200**:142–50. doi:10.1016/j.vetmic.2016.08.023.

[12] Salgado-Caxito M, Benavides JA, Adell AD, Paes AC, Moreno-Switt AI. Global prevalence and molecular characterization of extended-spectrum β-lactamase producing-*Escherichia coli* in dogs and cats – a scoping review and meta-analysis. *One Health* 2021;**12**:100236. doi:10.1016/j.onehlt.2021.100236.

[13] Trongjit S, Assavacheep P, Samngamnim S, My TH, An VTT, Simjee S, et al. Plasmid-mediated colistin resistance and ESBL production in *Escherichia coli* from clinically healthy and sick pigs. *Sci Rep* 2022;**12**:2466. doi:10.1038/s41598-022-06415-0.

[14] Karkaba A, Grinberg A, Benschop J, Pleydell E. Characterisation of extended-spectrum β-lactamase and AmpC β-lactamase-producing Enterobacteriaceae isolated from companion animals in New Zealand. *N Z Vet J* 2017;**65**:105–12. doi:10.1080/00480169.2016.1271730.

[15] Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. *Lancet Infect Dis* 2018;**18**:e368–78. doi:10.1016/S1473-3099(18)30296-2.

[16] Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase–producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. *Clin Infect Dis* 2016;**63**:310–18. doi:10.1093/cid/ciw283.

[17] Damborg P, Olsen KEP, Møller Nielsen EM, Guardabassi L. Occurrence of *Campylobacter jejuni* in pets living with human patients infected with *C. jejuni*. *J Clin Microbiol* 2004;**42**:1363–4. doi:10.1128/JCM.42.3.1363-1364.2004.

[18] Ferreira JP, Anderson KL, Correa MT, Lyman R, Ruffin F, Reller LB, et al. Transmission of MRSA between companion animals and infected human patients presenting to outpatient medical care facilities. *PLoS One* 2011;**6**:e26978. doi:10.1371/journal.pone.0026978.

[19] Pomba C, Rantala M, Greko C, Baptiste KE, Catry B, van Duijkeren E, et al. Public health risk of antimicrobial resistance transfer from companion animals. *J Antimicrob Chemother* 2017;**72**:957–68. doi:10.1093/jac/dkw481.

[20] Sato Y, Mori T, Koyama T, Nagase H. *Salmonella* Virchow infection in an infant transmitted by household dogs. *J Vet Med Sci* 2000;**62**:767–9. doi:10.1292/jvms.62.767.

[21] Cozma AP, Rimbu CM, Zendri F, Maciuca IE, Timofte D. Clonal dissemination of extended-spectrum cephalosporin-resistant Enterobacterales between dogs and humans in households and animal shelters of Romania. *Antibiotics (Basel)* 2022;**11**. doi:10.3390/antibiotics11091242.

[22] Johnson JR, Davis G, Clabots C, Johnston BD, Porter S, DebRoy C, et al. Household clustering of *Escherichia coli* sequence type 131 clinical and fecal isolates according to whole genome sequence analysis. *Open Forum Infect Dis* 2016;**3**:ofw129. doi:10.1093/ofid/ofw129.

[23] Toombs-Ruane LJ, Benschop J, French NP, Biggs PJ, Midwinter AC, Marshall JC, et al. Carriage of extended-spectrum-beta-lactamase- and Ampc beta-lactamase-producing *Escherichia coli* strains from humans and pets in the same households. *Appl Environ Microbiol* 2020;**86**:e01613–20. doi:10.1128/AEM.01613-20.

[24] Karkaba A, Benschop J, Hill KE, Grinberg A. Characterisation of methicillin-resistant *Staphylococcus aureus* clinical isolates from animals in New Zealand, 2012–2013, and subclinical colonisation in dogs and cats in Auckland. *N Z Vet J* 2017;**65**:78–83. doi:10.1080/00480169.2016.1222919.

[25] Belas A, Marques C, Menezes J, da Gama LT, Cavaco-Silva P, Pomba C. ESBL/pAmpC-producing *Escherichia coli* causing urinary tract infections in non-related companion animals and humans. *Antibiotics (Basel)* 2022;**11**:559. doi:10.3390/antibiotics11050559.

[26] Schmiedel J, Falgenhauer L, Domann E, Bauerfeind R, Prenger-Berninghoff E, Imirzalioglu C, et al. Multiresistant extended-spectrum beta-lactamase-producing Enterobacteriaceae from humans, companion animals and horses in central Hesse, Germany. *BMC Microbiol* 2014;**14**:187. doi:10.1186/1471-2180-14-187.

[27] Yasugi M, Hatoya S, Motooka D, Matsumoto Y, Shimamura S, Tani H, et al. Whole-genome analyses of extended-spectrum or AmpC beta-lactamase-producing *Escherichia coli* isolates from companion dogs in Japan. *PLoS One* 2021;**16**:e0246482. doi:10.1371/journal.pone.0246482.

[28] Rogers BA, Ingram PR, Runnegar N, Pitman MC, Freeman JT, Athan E, et al. Community-onset *Escherichia coli* infection resistant to expanded-spectrum cephalosporins in low-prevalence countries. *Antimicrob Agents Chemother* 2014;**58**:2126–34. doi:10.1128/AAC.02052-13.

[29] The New Zealand Companion Animal Council Companion animals in New Zealand *2016*. Auckland: The New Zealand Companion Animal Council; 2016.

[30] Ejaz H, Younas S, Abosalif KOA, Junaid K, Alzahrani B, Alsrhani A, et al. Molecular analysis of bla_{SHV}, bla_{TEM}, and bla_{CTX-M} in extended-spectrum β-lactamase producing Enterobacteriaceae recovered from fecal specimens of animals. *PLoS One* 2021;**16**:e0245126. doi:10.1371/journal.pone.0245126.

[31] Meyer E, Gastmeier P, Kola A, Schwab F. Pet animals and foreign travel are risk factors for colonisation with extended-spectrum β-lactamase-producing *Escherichia coli*. *Infection* 2012;**40**:685–7. doi:10.1007/s15010-012-0324-8.

[32] Miller ME, Hui SL, Tierney WM. Validation techniques for logistic regression models. *Stat Med* 1991;**10**:1213–26. doi:10.1002/sim.4780100805.

[33] Tibshirani R. Regression shrinkage and selection via the lasso. *J R Stat Soc B* 1996;**58**:267–88. doi:10.1111/j.2517-6161.1996.tb02080.x.

[34] Friedman JH, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010;**33**:1–22. doi:10.18637/jss.v033.i01.

[35] Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 1966;**45**:493–6. doi:10.1093/ajcp/45.4_ts.493.

[36] European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints - breakpoints and guidance version 8.1, http://www.eucast.org/clinical_breakpoints/; 2018 [accessed 04 June 2018].

[37] Seemann T, Goncalves da Silva A, Bulach D, Schultz M, Kwong J, Howden B. Nullarbor, Github, https://github.com/tseemann/nullarbor; 2017. [accessed 28 August 2017].

[38] Burgess SA, Aplin J, Biggs PJ, Breckell G, Benschop J, Fayaz A, et al. Characterisation of AmpC and extended-spectrum beta-lactamase producing *E. coli* from New Zealand dairy farms. *Int Dairy J* 2021;**117**:104998. doi:10.1016/j.idairyj.2021.104998.

[39] Zhang J, Xiong Y, Rogers L, Carter GP, French N. Genome-by-genome approach for fast bacterial genealogical relationship evaluation. *Bioinformatics* 2018;**34**:3025–7. doi:10.1093/bioinformatics/bty195.

[40] Huson DH. SplitsTree: analyzing and visualizing evolutionary data. *Bioinformatics* 1998;**14**:68–73. doi:10.1093/bioinformatics/14.1.68.

[41] Letunic I, Bork P. Interactive Tree Of Life (iTOL) v5: an online tool for phylogenetic tree display and annotation. *Nucleic Acids Res* 2021;**49**:W293–6. doi:10.1093/nar/gkab301.

[42] Abricate ST. Github, https://github.com/tseemann/abricate; 2017 [accessed 28 August 2017].

[43] Feldgarden M, Brover V, Haft DH, Prasad AB, Slotta DJ, Tolstoy I, Tyson GH, Zhao S, Hsu CH, McDermott PF, Tadesse DA, Morales C, Simmons M, Tillman G, Wasilenko J, Folster JP, Klimke W. Validating the AMRFinder tool and resistance gene database by using antimicrobial resistance genotype-phenotype correlations in a collection of isolates. *Antimicrob Agents Chemother* 2019;**63**:e00483 -19.. doi:10.1128/AAC.00483-19.

[44] Seemann T. Snippy: fast bacterial variant calling from NGS reads, https://github.com/tseemann/snippy; 2015 [accessed 28 August 2017].

[45] Marques C, Belas A, Aboim C, Cavaco-Silva P, Trigueiro G, Gama LT, et al. Evidence of sharing of *Klebsiella pneumoniae* strains between healthy companion animals and cohabiting humans. *J Clin Microbiol* 2019;**57**:e01537 -18. doi:10.1128/JCM.01537-18.

[46] Butcher CR, Rubin J, Mussio K, Riley LW. Risk factors associated with community-acquired urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*: a systematic review. *Curr Epidemiol Rep* 2019;**6**:300–9. doi:10.1007/s40471-019-00206-4.

[47] Søraas A, Sundsfjord A, Sandven I, Brunborg C, Jenum PA. Risk factors for community-acquired urinary tract infections caused by ESBL-producing

Enterobacteriaceae–a case–control study in a low prevalence country. *PLoS One* 2013;**8**:e69581. doi:10.1371/journal.pone.0069581.
[48] Chervet D, Lortholary O, Zahar JR, Dufougeray A, Pilmis B, Partouche H. Antimicrobial resistance in community-acquired urinary tract infections in Paris in 2015. *Med Mal Infect* 2018;**48**:188–92. doi:10.1016/j.medmal.2017.09.013.
[49] Goyal D, Dean N, Neill S, Jones P, Dascomb K. Risk factors for community-acquired extended-spectrum beta-lactamase-producing Enterobacteriaceae infections-a retrospective study of symptomatic urinary tract infections. *Open Forum Infect Dis* 2019;**6**:ofy357. doi:10.1093/ofid/ofy357.
[50] Hertz FB, Schønning K, Rasmussen SC, Littauer P, Knudsen JD, Løbner-Olesen A, et al. Epidemiological factors associated with ESBL- and non ESBL-producing *E. coli* causing urinary tract infection in general practice. *Infect Dis (Lond)* 2016;**48**:241–5. doi:10.3109/23744235.2015.1103895.
[51] Søgaard M, Heide-Jørgensen U, Vandenbroucke JP, Schønheyder HC, Vandenbroucke-Grauls CMJE. Risk factors for extended-spectrum β-lactamase-producing *Escherichia coli* urinary tract infection in the community in Denmark: a case–control study. *Clin Microbiol Infect* 2017;**23**:952–60. doi:10.1016/j.cmi.2017.03.026.
[52] Arcilla MS, van Hattem JM, Haverkate MR, Bootsma MCJ, van Genderen PJJ, Goorhuis A, et al. Import and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis* 2017;**17**:78–85. doi:10.1016/S1473-3099(16)30319-X.
[53] Kantele A, Kuenzli E, Dunn SJ, Dance DAB, Newton PN, Davong V, et al. Dynamics of intestinal multidrug-resistant bacteria colonisation contracted by visitors to a high-endemic setting: a prospective, daily, real-time sampling study. *Lancet Microbe* 2021;**2**:e151–8. doi:10.1016/S2666-5247(20)30224-X.
[54] Kennedy K, Collignon P. Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers. *Eur J Clin Microbiol Infect Dis* 2010;**29**:1501–6. doi:10.1007/s10096-010-1031-y.
[55] West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol* 1995;**142**:1103–12. doi:10.1093/oxfordjournals.aje.a117563.
[56] Mieth L, Mayer MM, Hoffmann A, Buchner A, Bell R. Do they really wash their hands? Prevalence estimates for personal hygiene behaviour during the COVID-19 pandemic based on indirect questions. *BMC Public Health* 2021;**21**:12. doi:10.1186/s12889-020-10109-5.
[57] Hapuarachchi IU, Hannaway RF, Roman T, Biswas A, Dyet K, Morgan X, et al. Genetic evaluation of ESBL-producing *Escherichia coli* urinary isolates in Otago, New Zealand. *JAC Antimicrob Resist* 2021;**3**:dlab147. doi:10.1093/jacamr/dlab147.
[58] Drinkovic D, Morris AJ, Dyet K, Bakker S, Heffernan H. Plasmid-mediated AmpC beta-lactamase-producing *Escherichia coli* causing urinary tract infection in the Auckland community likely to be resistant to commonly prescribed antimicrobials. *N Z Med J* 2015;**128**:50–9.
[59] Dyet K, Woodhouse R, Heffernan H. Annual survey of extended-spectrum b-lactamase (ESBL)-producing Enterobacteriaceae. *Wellington: Institute of Environmental Science and Research* 2014:NZ2014.
[60] Madrazo M, Esparcia A, López-Cruz I, Alberola J, Piles L, Viana A, et al. Clinical impact of multidrug-resistant bacteria in older hospitalized patients with community-acquired urinary tract infection. *BMC Infect Dis* 2021;**21**:1232. doi:10.1186/s12879-021-06939-2.
[61] Richelsen R, Smit J, Schønheyder HC, Laxsen Anru P, Gutiérrez-Gutiérrez B, Rodríguez-Bãno J, et al. Outcome of community-onset ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia and urinary tract infection: a population-based cohort study in Denmark. *J Antimicrob Chemother* 2020;**75**:3656–64. doi:10.1093/jac/dkaa361.
[62] Shamsrizi P, Gladstone BP, Carrara E, Luise D, Cona A, Bovo C, et al. Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria-producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. *BMJ, (Open)* 2020;**10**:e030266. doi:10.1136/bmjopen-2019-030266.
[63] Carvalho I, Safia Chenouf NS, Cunha R, Martins C, Pimenta P, Pereira AR, et al. Antimicrobial resistance genes and diversity of clones among ESBL- and acquired AmpC-producing *Escherichia coli* isolated from fecal samples of healthy and sick cats in Portugal. *Antibiotics (Basel)* 2021;**10**:1536. doi:10.3390/antibiotics10030262.
[64] Liu FL, Kuan NL, Yeh KS. Presence of the extended-spectrum-β-lactamase and plasmid-mediated AmpC-encoding genes in *Escherichia coli* from companion animals-a study from a university-based veterinary hospital in Taipei. *Taiwan. Antibiotics (Basel)* 2021;**10**. doi:10.3390/antibiotics10121536.
[65] Sealey JE, Hammond A, Mounsey O, Gould VC, Reyher KK, Avison MB. Molecular ecology and risk factors for third-generation cephalosporin-resistant *Escherichia coli* carriage by dogs living in urban and nearby rural settings. *J Antimicrob Chemother* 2022;**77**:2399–405. doi:10.1093/jac/dkac208.
[66] Karkaba A, Hill K, Benschop J, Pleydell E, Grinberg A. Carriage and population genetics of extended spectrum beta-lactamase-producing *Escherichia coli* in cats and dogs in New Zealand. *Vet Microbiol* 2019;**233**:61–7. doi:10.1016/j.vetmic.2019.04.015.
[67] Garcia-Fierro R, Drapeau A, Dazas M, Saras E, Rodrigues C, Brisse S, et al. Comparative phylogenomics of ESBL-, AmpC- and carbapenemase-producing *Klebsiella pneumoniae* originating from companion animals and humans. *J Antimicrob Chemother* 2022;**77**:1263–71. doi:10.1093/jac/dkac041.
[68] Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the Globalization of CTX-M. *Clin Microbiol Rev* 2013;**26**:744–58. doi:10.1128/CMR.00023-13.
[69] Clermont O, Christenson JK, Denamur E, Gordon DM. The Clermont Escherichia coli phylo-typing method revisited: improvement of specificity and detection of new phylo-groups. *Environmental Microbiology Reports* 2013;**5**:58–65.