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Original Article

Prevalence and household risk factors for fecal carriage of ESBL-producing, sequence type 131, and extraintestinal pathogenic *Escherichia coli* among children in southern Taiwan

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Fecal carriage;
Children;
Risk factor;
Household density

Abstract *Background:* The rapidly increasing prevalence of antimicrobial-resistant *Escherichia coli* (*E. coli*) is a global concern. This study determined the prevalence and risk factors for the fecal carriage of drug-resistant *E. coli* and extraintestinal pathogenic *E. coli* (ExPEC) among children.
Materials and methods: In this prospective study, stool samples from children aged 0—18 years were obtained within three days of hospitalization between April 2016 and March 2019. *E. coli* were selected and tested for extended-spectrum β-lactamase (ESBL)-production and antimicrobial susceptibility. Multilocus sequence typing, *bla*CTX-M gene groups and ExPEC were determined using polymerase chain reactions. Questionnaires were recorded for risk factor analysis.

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Results: Among 179 *E. coli* isolates, 44.1% were multi-drug resistant, 20.7% produced ESBL, and 50.3% were ExPEC. Children carrying ESBL-producing *E. coli* were younger than those carrying non-ESBL strains. Several anthropogenic factors, including drinking water process, pork consumption, pets and household density might be associated with ESBL-producing *E. coli*, sequence type (ST) 131 *E. coli*, or ExPEC fecal carriage. Compared with families who live in less crowded houses, participants with pets had a similar trend of higher risks of ESBL-producing *E. coli*, ST131 *E. coli*, and *ExPEC* fecal carriage among those living in houses accommodating relatively more people.
Conclusions: Children accounted for a large proportion of instances of feces carrying ESBL *E. coli*. In addition to antimicrobial control for people and livestocks, avenues of exposure, such as drinking water, food, pets, household density, and socioeconomic deprivation might present potentially novel opportunities to reduce the burden of nonsusceptible *E. coli* and ExPEC.

Background

The global prevalence of community-acquired antimicrobial-resistant *Escherichia coli* (*E. coli*) is increasing. Traditionally, β-lactam antibiotics have been the treatment of choice for children. However, within the past two decades, extended-spectrum β-lactamase (ESBL)-producing and multidrug-resistant (MDR) *E. coli* have posed a serious threat to global health.[1–5] In 2008, two research groups studying *bla*CTX-M-15 ESBL-producing *E. coli* described the occurrence of sequence type (ST) 131 in multiple countries in three continents.[6] In our previous investigation, the majority of clinical infections in Taiwan caused by ESBL-producing *E. coli* belonged to *bla*CTX-M-14 and *bla*CTX-M-15 strains.[5,7,8] Additionally, the prevalence of non-susceptible *E. coli* in children's feces was high in 2013 and 2014, of which 37% were instances of MDR, 8.3% were instances of ESBL-producing *E. coli*, and ST131 was the most common ESBL-producing *E. coli* clonal group present in the feces of children.[2] Extraintestinal pathogenic *E. coli* (ExPEC) is another variant of concern; it possesses specific virulence factors and can potentially cause illness in healthy individuals, resulting in extraintestinal infections.[9,10] In addition, we would like to figure out their association with antimicrobial resistance. Thus, in the present study, we investigate the prevalence, molecular epidemiology, and risk factors for fecal carriage of ESBL, CTX-M, ST131, MDR *E. coli*, and ExPEC among children.

Materials and methods

Participants and collection of fecal samples

A cross-sectional study for which ethical approval was obtained from the ethics committee of Kaohsiung Veterans General Hospital (KVGH) (approval No. VGHKS16-CT2-04) was conducted between April 2016 and March 2019 in KVGH. In this prospective study, children aged 0—18 years who were admitted to the Department of Pediatrics at KVGH were approached by the investigator who provided information about the study. After the parents or legal guardians (and participants aged >7 years) agreed to participate, they provided freshly passed (within 1 h) fecal samples in the provided sterile container within 3 days of admission. With the study assistant's aid, they also completed a questionnaire in which they provided clinical, demographic, and household information. Antimicrobial prescriptions were checked against the National Health Insurance-PharmaCloud database of antimicrobials to ascertain whether the participants had taken antimicrobials within 3 months prior to providing the feces sample. Household density was calculated as the number of people living in the dwelling divided by the number of rooms, bathrooms, and toilets in the same house. Children with history of underlying chronic disease or without complete consent, questionnaires, or fecal samples were excluded from this study. Underlying chronic disease was defined as a preexisting chronic disease that required regular follow-up in clinics, such as congenital heart disease, autoimmune diseases, chronic kidney disease, diabetes, or psychiatric disorders.

Questionnaire design

All questions in the questionnaire were standardized so that all respondents receive the same questions with identical wording. Those clinical and demographic characteristics that can't be ranked, such as sex or race, were recorded as nominal variables. Those categories that can be ranked, such as household population and room numbers were recorded as ordinal variables. Estimation for food consumption was collected from Likert-type questions by rating scales with consumption days per week.

Microbiological analysis and antimicrobial susceptibility testing

Before being placed in incubation at 37 °C for 24 h, each participant's fecal sample was spread on a CHROMagar ECC plate (CHROMagar, Paris, France), on which *E. coli* colonies appeared as blue and were selected for further serial dilution.[2,11] One colony was selected for further analysis.

A Vitek 2 automated system (Vitek AMS; bioMerieux Vitek Systems, Hazelwood, MO, USA) with ID-GN and AST-N320 cards (Durham, NC, USA) was applied to the selected *E. coli* colony to test for antimicrobial susceptibility. In addition to using the AST-N320 card to investigate ESBL production, ESBLs were also detected through double-disk synergy and confirmed using agar strip gradient methods.[2] The breakpoints of antimicrobial agents and the ESBL-producer tests for the duration of the study period were determined according to the M100-S26 (2016) of the Clinical and Laboratory Standards Institute standards.[12] Isolates that were not susceptible to three or more categories of antimicrobials were defined as being MDR.[13]

Detection of ST131, multi-locus sequence typing (MLST), and blaCTX-M gene groups

A multiplex polymerase chain reaction assay was used for sequence typing of ST 69, 73, and 95 in addition to ST 131 for the 179 *E. coli* isolates.[5,14] These 4 lineages are the most common ST associated with urinary tract infections and bloodstream infections was determined.[14] The positive and negative control used isolates confirmed by MLST described in our previous work.[8] The primers for PCR amplification and sequencing of the housekeeping genes (*adk*, *fumC*, *gyrB*, *icd*, *mdh*, *purA*, and *recA*) were synthesized from a commercial company (Genomics Biotech Corp. New Taipei City Taipei, Taiwan) according to the primer sequences given for MLST.[15] Multiplex PCR and additional specific PCR were performed by using specific primers to detect CTX-M groups 1, 2, 8, and 9 and the common group 1 (*bla*CTX-M-3,15) and group 9 (*bla*CTX-M-14) variants for the 179 *E. coli* isolates.[2,16,17]

Detection of ExPEC

Multiplex PCR was applied to identify ExPECs, which were defined as harboring more than two of the following five genes: aerobactin system (*iutA*), S and F1C fimbriae (*sfaS* and *focG*), group 2 polysaccharide capsule (*kpsM II*), P fimbriae (*papA*), and Dr-binding adhesins (*afa*).[18]

Statistical analysis

Statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA) ver.18.0. Comparisons between categorical variables were performed using Fisher's exact or chi-square tests to determine the risk associated with having positive cultures for certain microbial phenotype(s) or genotype(s). The risk levels were expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Continuous variables were analyzed through a *t* test or Mann—Whitney *U* test.

A stratified *t* test or Mann—Whitney *U* test was used to determine the subgroup differences for the relationship between pets and household density. Statistical significance was indicated by two-sided *P* values < 0.05.

Results

Participants

We analyzed the data of 241 children who gave their written informed consent and who provided fecal samples and a completed questionnaire. Samples from 62 (25.7%) children exhibited no *E. coli* growth on the culture media and were therefore excluded from the study. The remaining 179 (74.3%) children were eligible for further analysis and comprised 101 (56.4%) boys and 78 (43.6%) girls. The clinical and demographic characteristics of the participants are presented in Table 1.

Antimicrobial susceptibility testing

Among the 179 *E. coli* isolates, 25.7% (N = 46) were susceptible to all tested antimicrobials. No strain exhibited reduced susceptibility to ertapenem or imipenem. As illustrated in Fig. 1A, the nonsusceptible rates were 66.5%, 47.5%, 36.3%, 30.2%, 20.1%, 19.0%, and 4.5% in the categories of β-lactam/β-lactamase inhibitors, TMP/SMZ, cephalosporins, tetracyclines, aminoglycosides, ciprofloxacin, and colistin, respectively. Among the 179 isolates, 20.7% (N = 37) belonged to ESBL-producing strains, and 44.1% of the *E. coli* strains were MDR. The nonsusceptible rate among the accumulated categories is presented in Fig. 1B. Among the 34 *E. coli* isolates not susceptible to ciprofloxacin, 85% (N = 29) were MDR, 38.2% (N = 13) produced ESBLs, and 5.9% (N = 2) were not susceptible to colistin.

Prevalence of fecal carriage of ESBL-producing *E. coli* and blaCTX-M gene characterization

Among the 37 ESBL-producing *E. coli* isolates, the presence of the *bla*CTX-M gene was confirmed in the majority (56.8%, N = 21) of strains, and comprised mainly of the CTX-M-1 (N = 13, all were $bla_{\text{CTX-M-3,15}}$) and CTX-M-9 (N = 6, all were $bla_{\text{CTX-M-14}}$) groups. As illustrated in Fig. 2A, among the 21 *bla*CTX-M clones, seven were ST131, and 16 were confirmed as MDR. Among the 13 CTX-M-1 group and 6 CTX-M-9 group strains, three and four were confirmed as ST131, respectively. Coresistance to other antibiotics was common in the isolates containing the blaCTX-M gene, of which 76.2% (N = 16) were MDR. The distribution of ST131, non-ST131, MDR, non-MDR, and blaCTX-M typing *E. coli* isolates among the 37 children carrying ESBL-producing *E. coli* are recorded in Supplementary Table 1.

MLST

Among the four sequence types (ST)s in the MLST, ST131 (23 isolates; 12.8%) was most prevalent, followed by ST95 (12 isolates; 6.7%), ST69 (8 isolates; 4.5%), and ST73 (7 isolates, 3.9%). ST131 was primarily associated with $bla_{\text{CTX-M-14}}$ (5/23, 21.7%) and $bla_{\text{CTX-M-3,15}}$ (3/23, 13%).

Table 1 Clinical and demographic characteristics of 179 participating children.

Characteristics	Number	Percentage
Age (ave±sd, days)	1095.49 ± 1161.61	
<6 months	20	11.2%
6–12 months	26	14.5%
1–3 years	78	43.6%
3–6 years	44	24.6%
6–12 years	11	6.1%
Race		
Minnan Taiwanese	111	62.0%
Mainland Taiwanese	50	27.9%
Hakka Taiwanese	11	6.1%
Aboriginal Taiwanese	6	3.4%
Others	1	0.6%
Gender		
Male	101	56.4%
Female	78	43.6%
School attendance	52	29.1%
Overseas travel within 1 year	30	16.8%
Travel to south Asia or China within 1 year	10	5.6%
Hospitalization within 3 months	20	11.2%
Antimicrobial use within 3 months	97	54.2%
Probiotics use within 3 months	84	46.9%

ave±sd, average ± standard deviation

The proportions of the ESBL, MDR, and ciprofloxacin-nonsusceptible, and ST131/O25b among the 179 *E coli* isolates are displayed in Fig. 2B. O25b-positive isolates were found in 16 *E. coli* isolates, of which 10 were ESBL producers and 11 were MDR. Compared with the non-ESBL (2/142) and ciprofloxacin-susceptible (3/145) groups, the ESBL (7/37) and ciprofloxacin-nonsusceptible (6/34) groups had considerably higher rates of O25b–ST131 positivity (1.4% versus 18.9% and 2.1% versus 17.6%, respectively).

ExPEC

Among the 179 isolates, 50.3% (N = 90) of the isolates were identified as ExPEC, accounting for 86.7%, 56.7%, 74.4%, 65.6%, and 51.1% of instances of positivity of *iutA*, *sfaS*/*focG*, *kpsM II*, *papA*, and *afa*, respectively. The distributions of MDR, and ciprofloxacin-nonsusceptible *E. coli*, 025b, STs, CTX-M group, *bla*CTX-M, and ExPEC among the 179 isolates are illustrated in Fig. 3. As presented in Supplementary Table 2, compared to non-ExPEC, the ExPEC had higher proportions of ESBL, ST131, MDR, and ciprofloxacin-nonsusceptibility (19.1% versus 22.2% (p value = 0.606), 5.6% versus 20% (p value = 0.004), 33.7% versus 54.4% (p value = 0.005), and 7.9% versus 30% (p value < 0.001), respectively).

Risk factors

We further analyzed the risk factors and characteristics associated with the participants. In this subgroup analysis, we included the 179 participants who had completed the consent form and questionnaire and whose stool sample contained a positive *E. coli* culture. The associations

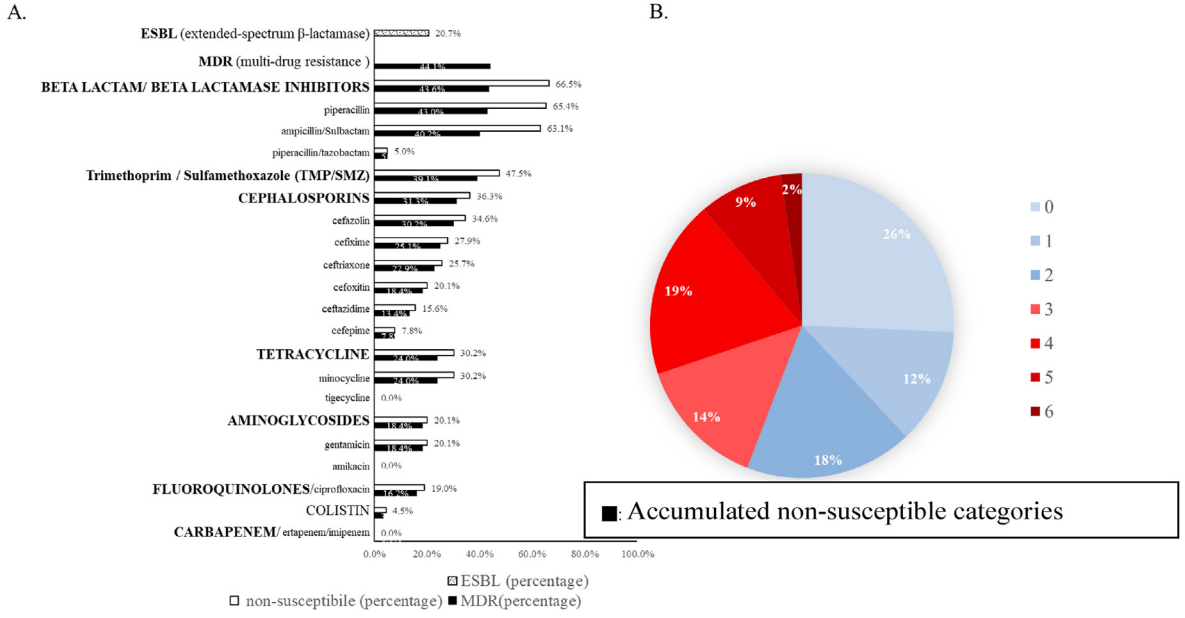

Figure 1. A. Proportion of nonsusceptibility to categories of antimicrobials among 179 *E. coli* isolates. B. Nonsusceptible rate among accumulated categories among 179 *E. coli* isolates.
E. coli: Escherichia coli
ESBL: extended-spectrum β-lactamase
MDR: multidrug-resistant.

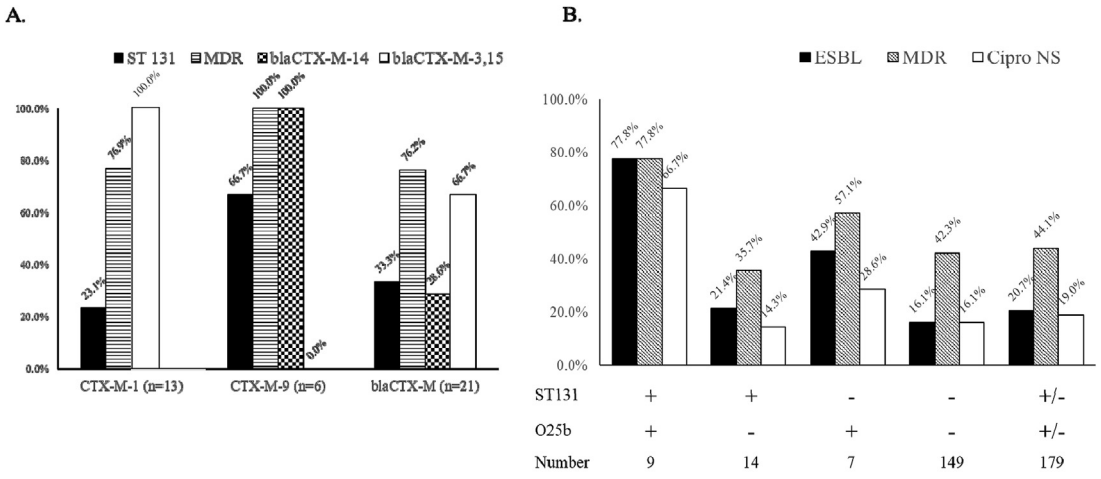

Figure 2. A. Proportion of CTX-M group and *bla*CTX-M among 37 ESBL-producing *E. coli* isolates. B. Proportion of ESBL, MDR, and ciprofloxacin-nonsusceptibility and ST131/O25b among 179 *E. coli* isolates.
ESBL: extended-spectrum β-lactamase
E. coli: Escherichia coli
MDR: multidrug-resistant E. coli
ST: sequence type
Cipro NS: Ciprofloxacin non-susceptible
+: positive;
-: negative.

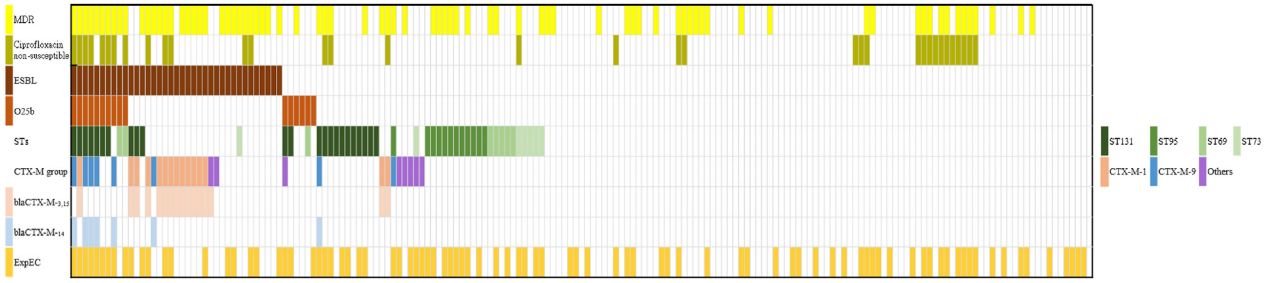

Figure 3. Distribution of MDR, and ciprofloxacin-nonsusceptible, 025b, STs, CTX-M group, and *bla*CTX-M *E. coli*, and ExPEC strains among the 179 *E. coli* isolates.
MDR: multidrug-resistant
ST: sequence type
E. coli: Escherichia coli
ESBL: extended-spectrum β-lactamase
ExPEC: extraintestinal pathogenic E. col.

between multiple individual factors and fecal carriage of ESBL, ST131 *E. coli*, and ExPEC were assessed. Compared with the children carrying non-ESBL-producing *E. coli*, the children whose feces carried ESBL-producing *E. coli* were much younger; on average, aged 3.23 and 1.92 years, respectively ($P = 0.012$). The prevalences of ESBL-producing *E. coli*, ST131 *E. coli*, and *ExPEC* colonization were not significantly correlated with sex, race, overseas travel within the past year, prior hospitalization, or use of antimicrobials or probiotics within the previous 3 months. The full list of factors with their univariate odd-ratios (ORs) and 95% confidence intervals (CIs) are displayed in Table 2. Data on drinking water, food, type of housing, pets, and housing density and their association with the fecal carriage of ESBL-producing *E. coli*, ST131 *E. coli*, or ExPEC are described as below.

Drinking water

Children who drank water after it had been purified through portable water filter jug had lower risks of ESBL-producing *E. coli* ($P = 0.041$) in their feces. The OR associated with tap water, spring water, bottled water, or reverse osmosis (RO) system were not statistically significant in the analysis of the relationship between the source of drinking water and carriage of ESBL-producing *E. coli*, ST131 *E. coli*, or ExPEC (Table 3).

Food

Compared with children who did not, children who consumed pork more than three days a week had a higher

Table 2 Characteristics of the 179 children and the proportion of ESBL, ST131, and ExPEC of their 179 *E. coli* isolates.

	ESBL (n = 37)	Non-ESBL (n = 142)	*p* value	OR (95% CI)	ST131 (n = 23)	non-ST131 (n = 156)	*p* value	OR (95% CI)	ExpEC (n = 90)	non-ExpEC (n = 89)	*p* value	OR (95% CI)
Age (ave±sd, days)	700.0 ± 122.8	1180.3 ± 103.7	0.012*		913.1 ± 172.6	1122.4 ± 96.3	0.296		1121.6 ± 131.9	1069.1 ± 113.4	0.763	
Gender												
Female	16	62	1.000	1.00	9	69	0.822	1.00	36	42	0.368	1.00
Male	21	82		1.02 (0.49–2.11)	14	87		1.23 (0.50–3.02)	54	47		1.34 (0.74–2.42)
School attendance												
No	28	99	0.546	1.00	17	110	0.811	1.00	64	63	1.000	1.00
Yes	9	43		0.74 (0.32–1.70)	6	46		0.84 (0.31–2.28)	26	26		0.98 (0.52–1.88)
Overseas travel within 1 year												
No	29	120	0.458	1.00	19	130	1.000	1.00	72	77	0.317	1.00
Yes	8	22		1.51 (0.61–3.72)	4	26		1.05 (0.33–3.35)	18	12		1.60 (0.72–3.56)
Travel to south Asia or China within 1 year												
No	34	135	0.433	1.00	21	148	0.619	1.00	84	85	0.747	1.00
Yes	3	7		1.70 (0.42–6.93)	2	8		1.76 (0.35–8.86)	6	4		1.52 (0.41–5.57)
Hospitalization within 3 months												
No	30	129	0.138	1.00	20	139	0.726	1.00	80	79	1.000	1.00
Yes	7	13		2.32 (0.85–6.30)	3	17		1.23 (0.33–4.56)	10	10		0.99 (0.39–2.50)
Antimicrobials use within 3 months												
No	13	69	0.194	1.00	11	71	1.000	1.00	39	43	0.550	1.00
Yes	24	73		1.75 (0.82–3.70)	12	85		0.91 (0.38–2.19)	51	46		1.22 (0.68–2.20)
Probiotic use within 3 months												
No	20	75	1.000	1.00	11	84	0.658	1.00	44	51	0.296	1.00
Yes	17	67		0.95 (0.46–1.97)	12	72		1.27 (0.53–3.06)	46	38		1.40 (0.78–2.53)

ave±sd, average ± standard deviation
*p value from t test.
ESBL: extended-spectrum β-lactamase
ST: sequence type
ExPEC: extraintestinal pathogenic *E. coli*
E. coli: *Escherichia coli*
OR: odd ratio
CI: confidence interval.

Table 3 Risk factors for drinking water and food for fecal carriage of ESBL, ST131, and ExPEC *E. coli* isolates.

	ESBL (n = 37)	Non-ESBL (n = 142)	*p* value	OR (95% CI)	ST131 (n = 23)	non-ST131 (n = 156)	*p* value	OR (95% CI)	ExpEC (n = 90)	non-ExpEC (n = 89)	*p* value	OR (95% CI)
Tap water												
No	33	134	0.274	1.00	21	146	0.655	1.00	85	82	0.566	1.00
Yes	4	8		2.03 (0.58–7.15)	2	10		1.39 (0.29–6.79)	5	7		0.69 (0.21–2.26)
Spring water												
No	24	95	0.846	1.00	16	103	0.817	1.00	57	62	0.429	1.00
Yes	13	47		1.10 (0.51–2.34)	7	53		0.85 (0.33–2.19)	33	27		1.33 (0.71–2.48)
Bottled												
No	35	135	1.000	1.00	21	149	0.325	1.00	86	84	0.747	1.00
Yes	2	7		1.10 (0.22–5.54)	2	7		2.027 (0.40–10.41)	4	5		0.78 (0.20–3.01)
Reverse Osmosis												
No	19	86	0.351	1.00	14	91	1.000	1.00	53	52	1.000	1.00
Yes	18	56		1.46 (0.70–3.01)	9	65		0.90 (0.37–2.20)	37	37		0.98 (0.54–1.78)
Portable water filter jug												
No	34	109	0.041	1.00	19	124	1.000	1.00	75	68	0.268	1.00
Yes	3	33		0.29 (0.08–1.01)	4	32		0.82 (0.26–2.57)	15	21		0.65 (0.31–1.36)
Food												
Vegetarian	5	26	0.629	1.00	4	27	1.000	1.00	18	13	0.430	1.00
Non-vegetarian	32	116		1.43 (0.51–4.03)	19	129		0.99 (0.31–3.16)	72	76		0.68 (0.31–1.50)
Pork (intake days per week)												
≦3	29	111	0.978	1.00	14	126	0.031	1.00	71	69	0.825	1.00
> 3	8	31		0.99 (0.41–2.38)	9	30		2.70 (1.07–6.82)	19	20		0.92 (0.45–1.88)
Egg (intake days per week)												
≦3	22	93	0.495	1.00	16	99	0.569	1.00	57	58	0.798	1.00
> 3	15	49		1.29 (0.62–2.72)	7	57		0.76 (0.30–1.96)	33	31		1.08 (0.59–2.00)
Chicken (intake days per week)												
≦2	28	104	0.764	1.00	16	116	0.626	1.00	66	66	0.900	1.00
> 2	9	38		0.88 (0.38–2.03)	7	40		1.27 (0.49–3.31)	24	23		1.04 (0.54–2.03)
Fish (intake days per week)												
≦2	23	81	0.574	1.00	15	89	0.459	1.00	51	53	0.696	1.00
> 2	14	61		0.81 (0.39–1.70)	8	67		0.71 (0.28–1.77)	39	36		1.13 (0.62–2.04)
Beef (intake days per week)												
≦1	31	123	0.658	1.00	20	134	1.000	1.00	73	81	0.056	1.00
> 1	6	19		1.25 (0.46–3.40)	3	22		0.91 (0.25–3.33)	17	8		2.36 (0.96–5.79)
Duck (intake days per week)												
≦0	34	121	0.418	1.00	18	137	0.209	1.00	75	80	0.198	1.00
> 0	3	21		0.51 (0.14–1.81)	5	19		2.00 (0.67–6.02)	15	9		1.78 (0.73–4.31)

ESBL: extended-spectrum β-lactamase
ST: sequence type
ExPEC: extraintestinal pathogenic *E. coli*
E. coli: *Escherichia coli*
OR: odd ratio
CI: confidence interval.

Table 4 Univariate and multiple logistic regression analysis for the relationship between food consumption and fecal carriage of ST131 *E. coli* isolates.

	Univariate Regression Analysis		Multiple Regression Analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Pork (intake days per week)				
≦3	1.00	0.036	1.00	0.012
> 3	2.70 (1.07–6.82)		4.81 (1.42–16.29)	
Egg (intake days per week)				
≦3	1.00	0.569	1.00	0.350
> 3	0.76 (0.30–1.96)		0.60 (0.21–1.75)	
Chicken (intake days per week)				
≦2	1.00	0.626	1.00	0.818
> 2	1.27 (0.49–3.31)		0.87 (0.27–2.80)	
Fish (intake days per week)				
≦2	1.00	0.460	1.00	0.087
> 2	0.71 (0.28–1.77)		0.37 (0.12–1.16)	
Beef (intake days per week)				
≦1	1.00	0.891	1.00	0.537
> 1	0.91 (0.25–3.33)		0.64 (0.15–2.66)	
Duck (intake days per week)				
≦0	1.00	0.216	1.00	0.156
> 0	2.00 (0.67–6.02)		2.54 (0.70–9.19)	

ST: sequence type
E. coli: *Escherichia coli*
OR: odd ratio
CI: confidence interval.

risk carrying ST131 *E. coli* ($P = 0.031$). However, no significant relationship was detected between ESBL-producing *E. coli*, ST131, and ExPEC fecal carriage and the consumption of other food, such as eggs, children, fish, beef, duck, or vegetables (Table 3). In addition, as shown in Table 4, the effect of all variants on independent variable and odd ratios in multiple logistic regression, pork intake might be an independent risk factor ($p = 0.012$). Compared to those children with lower pork consumption, the children with higher pork consumption had a higher risk of ST131 *E. coli* carriage, without being affected by other meat consumption.

Housing

Participants whose residence contained ≤2 rooms had a higher risk of carrying ST131 *E. coli* ($P = 0.047$) compared with those living in a house with >2 rooms. Household population numbers, type of housing, and numbers of bathrooms or toilets had no relationship with ESBL-producing *E. coli*, ST131 *E. coli*, or *ExPEC* carriage (Table 5).

Pets

As illustrated in Table 5, those who kept pets in the house generally had a lower risk of carrying ESBL-producing *E. coli* ($P = 0.044$) in their feces. Those who had pet rabbits, however, had a higher risk of ST131 *E. coli* fecal carriage ($P = 0.044$).

Household density

Participants who had higher ratios of household population to bathroom number had higher risks of carrying ST131 *E. coli* ($P = 0.045$) than participants with a lower ratio. The ratios of household population to room number, household population to bathroom number, and household population to toilet number were not related to the risk of ESBL-producing *E. coli* or ExPEC (Table 6).

Stratified analysis for the relation between pets and crowdedness

As presented in Table 6, participants who had pets and did not have ESBL-producing *E. coli* in their feces lived in residences in which fewer people shared a bathroom and toilet (on average, 2.48 and 2.33 people, respectively) than those who carried ESBL-producing *E. coli* (on average, 4.75 and 3.46 people, respectively). This trend was also similar among those who carried ST131 *E. coli* and ExPEC. A stratified analysis of the subgroups suggests a possible trend between raising pets and household density. Risks of carrying ESBL-producing *E. coli*, ST131 *E. coli*, and ExPEC among participants who owned pets might be present only among those who lived in houses containing more people.

Discussion

Reported rates of ESBL-producing *E. coli* community carriage were almost always less than 10% in all areas before 2008 but often higher afterwards. In 2008, the carriage rate in Thailand increased considerably for the first time and reached more than 60%.[1,19] Our previous study conducted between October 2013 and September 2014 noted that among strains of nonsusceptible *E. coli* in children, 36.9% were MDR, 18.5% were nonsusceptible to ciprofloaxin, and 8.3% produced ESBL.[2] This study conducted from April 2016 to March 2019 in the same hospital determined that the proportions of MDR, ciprofloaxin-nonsusceptible, and ESBL-producing *E. coli* were much higher, at 44.1%, 19%, and 20.7% respectively.

CTX-M-type ESBL-producing *E. coli* has rapidly spread among the global community.[20] In the present study, ST131 was mainly associated with $bla_{\text{CTX-M-14}}$-producing *E. coli*, and $bla_{\text{CTX-M-3,15}}$ comprised the majority of resistant mechanisms in strains other than ST131 (Fig. 3). A total of 56.8% of ESBL-producing *E. coli* contained the *bla*CTX-M gene. This rate is similar to those reported in China (50.5%)[20] and much higher than those reported in France (6%)[21] and the United Kingdom (11.3%).[22] The causes of higher carriage rates in developing countries than in industrialized countries are uncertain.[1] In this study,

Table 5 Risk factors for household condition and pets for fecal carriage of ESBL, ST131, and ExPEC *E. coli* isolates.

	ESBL (n = 37)	Non-ESBL (n = 142)	*p* value	OR	ST131 (n = 23)	non-ST131 (n = 156)	*p* value	OR	ExpEC (n = 90)	non-ExpEC (n = 89)	*p* value	OR
Household population												
N > 4	13	72	0.100	1.00	9	76	0.503	1.00	44	41	0.765	1.00
N ≦ 4	24	70		1.90 (0.90–4.02)	14	80		1.48 (0.60–3.61)	46	48		0.89 (0.50–1.61)
Type of housing												
Appartment	14	62	0.523	1.00	9	67	0.823	1.00	42	34	0.291	1.00
House	23	80		1.27 (0.61–2.68)	14	89		1.17 (0.48–2.87)	48	55		0.71 (0.39–1.28)
Room numbers												
N > 2	17	73	0.584	1.00	7	83	0.047	1.00	43	47	0.551	1.00
≦2	20	69		1.25 (0.60–2.57)	16	73		2.60 (1.01–6.67)	47	42		1.22 (0.68–2.20)
Bathroom numbers												
N > 1	27	113	0.380	1.00	14	126	0.054	1.00	65	75	0.070	1.00
N ≦ 1	10	29		1.44 (0.63–3.32)	9	30		2.70 (1.07–6.82)	25	14		2.06 (0.99–4.29)
Toilet numbers												
N > 1	32	119	0.804	1.00	17	134	0.213	1.00	73	78	0.304	1.00
N ≦ 1	5	23		0.81 (0.29–2.29)	6	22		2.15 (0.76–6.05)	17	11		1.65 (0.73–3.76)
Pet raising												
No	31	94	0.044	1.00	14	111	0.336	1.00	64	61	0.746	1.00
Yes	6	48		0.38 (0.15–0.97)	9	45		1.59 (0.64–3.92)	26	28		0.89 (0.47–1.68)
Dog												
No	32	108	0.171	1.00	16	124	0.282	1.00	68	72	0.387	1.00
Yes	5	34		0.50 (0.18–1.37)	7	32		1.70 (0.64–4.47)	22	17		1.37 (0.67–2.80)
Cat												
No	36	133	0.690	1.00	23	146	0.365	1.00	86	83	0.536	1.00
Yes	1	9		0.41 (0.05–3.35)	0	10		0.86 (0.81–0.92)	4	6		0.64 (0.18–2.36)
Fish												
No	37	137	0.585	1.00	23	151	1.000	1.00	90	84	0.029	1.00
Yes	0	5		0.79 (0.73–0.85)	0	5		0.87 (0.82–0.92)	0	5		0.48 (0.41–0.56)
Bird												
No	37	138	0.582	1.00	22	153	0.426	1.00	88	87	1.000	1.00
Yes	0	4		0.79 (0.73–0.85)	1	3		2.32 (0.23–23.28)	2	2		0.99 (0.14–7.18)
Rabbit												
No	37	139	1.000	1.00	21	155	0.044	1.00	89	87	0.621	1.00
Yes	0	3		0.79 (0.73–0.85)	2	1		14.76 (1.28–169.93)	1	2		0.49 (0.04–5.49)

ESBL: extended-spectrum β-lactamase
ST: sequence type
ExPEC: extraintestinal pathogenic *E. coli*
E. coli: *Escherichia coli*
OR: odd ratio.

Table 6 Stratified analysis for risk factors of household density and pets for fecal carriage of ESBL, ST131, and ExPEC *E. coli* isolates.

		ESBL (n = 31)	Non-ESBL (n = 94)	T test	ST131 (n = 14)		Non-ST131 (n = 111)	T test	ExpEC (n = 64)	Non-ExpEC (n = 61)	T test
		ave±se	ave±se	*p* value	ave±se		ave±se	*p* value	ave±se	ave±se	*p* value
Household population/room number	Without pet	2.21 ± 0.16	2.31 ± 0.11	0.592	2.49 ± 0.27		2.26 ± 1.03	0.423	2.15 ± 0.10	2.43 ± 0.15	0.130
	With pet	1.89 ± 0.19	1.99 ± 0.11	0.672	2.42 ± 0.23		1.89 ± 0.11	0.059	1.96 ± 0.12	1.99 ± 0.17	0.912
	Total	2.16 ± 0.13	2.20 ± 0.08	0.778	2.46 ± 0.18		2.15 ± 0.08	0.128	2.09 ± 0.08	2.29 ± 0.12	0.176
Household population/bathroom number	Without pet	2.82 ± 0.21	2.72 ± 0.15	0.674	2.99 ± 0.33		2.71 ± 1.36	0.450	2.78 ± 0.18	2.71 ± 0.17	0.778
	With pet	4.75 ± 1.24	2.48 ± 0.16	0.126	4.31 ± 0.86		2.41 ± 0.16	0.059	3.29 ± 0.38	2.21 ± 0.16	0.014
	Total	3.14 ± 0.28	2.64 ± 0.11	0.103	3.51 ± 0.41		2.63 ± 0.10	0.045	2.55 ± 0.13	2.92 ± 0.17	0.078
Household population/toilet number	Without pet	2.35 ± 0.17	2.45 ± 0.13	0.659	2.49 ± 0.28		2.42 ± 1.24	0.825	2.34 ± 0.15	2.52 ± 0.16	0.404
	With pet	3.46 ± 0.94	2.29 ± 0.14	0.272	3.47 ± 0.68		2.21 ± 0.12	0.101	2.86 ± 0.30	2.04 ± 0.13	0.016
	Total	2.53 ± 0.21	2.40 ± 0.10	0.569	2.87 ± 0.32		2.37 ± 0.09	0.137	2.48 ± 0.14	2.37 ± 0.12	0.528

ave±se, average ± standard error.
ESBL: extended-spectrum β-lactamase
ST: sequence type
ExPEC: extraintestinal pathogenic *E. coli*
E. coli: *Escherichia coli*.

children carrying ESBL-producing *E. coli* in their feces were much younger than those who did not, which is consistent with our previous report that the proportion of *E. coli* infections caused by ESBL-producing strains is higher in pediatric patients than in adult patients.[7] Data on the risk factors for ESBL-producing *E. coli* carriage within the community is scarce in Taiwan. In this study, we determined factors that may contribute to the fecal carriage of ESBL-producing *E. coli*, ST131, MDR *E. coli*, and pathogenic *E. coli* among children.

In the present study, the distribution of proportions of ESBL, ST131, MDR, and ciprofloxacin-nonsusceptibility among the ExPEC were higher than non- ExPEC. The transmission of pathogenic *E. coli* through the water supply is a key public health concern, especially in areas with a high prevalence of antimicrobial resistance.[23] Drinking boiled water might decrease the prevalence of fecal carriage of ExPEC. In addition, pretreating the water appropriately with a filter prior to drinking might decrease the risk of carrying ESBL-producing *E. coli* in our study. However, the consumption of tap water, spring water, RO water, mineral water, or unboiled water was not significantly correlated with any decrease in ESBL-producing *E. coli*, ST131, or ExPEC carriage. Hence, instead of presence in the water, ESBL-producing *E. coli* and ST131 might be transferred from the household environment to the water container.

Intrafamilial spread between in-house contacts has been suggested as the cause of the increase in community-acquired infections caused by ESBL-producing bacteria.[24,25] In our study, a higher household population is not related to the status of ESBL-producing *E. coli*, ST131, or ExPEC fecal carriage. However, higher ratios of household population to room number and household population to bathroom number were significantly associated with the fecal carriage rate of ST131 *E. coli*, indicating intrafamilial spread of ST131 *E. coli* is more closely related to household density than population.

Studies increasingly report the isolation of MDR *E. coli* from livestock, such as chickens, ducks, pigs, and cattle in Asia (China, South Korea and Lebanon) and Europe (the United Kindom and the Netherlands), as well as meat and the environment.[26–28] In our series, children with a higher pork intake had higher risk of carrying ST131 *E. coli* in their feces than children who consumed less pork. However, we could not determine a significant relationship between having a vegetarian and versus nonvegetarian diet and the fecal carriage of ESBL-producing *E. coli*, ST131, and ExpEC. Our results are similar to a study that observed similar rates of colonization among vegetarians and those who were not vegetarians.[29] Cooking processes and various environmental conditions might also have impacts in the presence of *E. coli* in consumed food.

Some reports have maintained that keeping pets has caused up to a sevenfold increase in *E. coli* carriage rates[30]; others studies, however, have reported no significant carriage rate increases among those who have contact with animals or keep pets.[31,32] In our series of pet keeping, the risk of resistant strain carriage in ESBL-producing *E. coli* and ST131 *E. coli* were not consistent before stratified analysis for the relationship between pets and household density. For example, as illustrated in Table 5, those who kept pets

in the house generally had a lower risk of carrying ESBL-producing *E. coli* (P = 0.044) in their feces; by contrast, those who had pet rabbits had a higher risk of ST131 *E. coli* fecal carriage (P = 0.044). In addition, those who kept pets had a lower risk ESBL-producing *E. coli* fecal carriage. However, as presented in Table 6, the proportion of ESBL-producing or ST131 *E. coli*, and ExPEC fecal carriage among participants with pets consistently increased after household density (ratios of population to bathroom or toilet number) was analyzed, implying that raising pets does not protect people from contracting ESBL-producing *E. coli* in a single disguised analysis. As indicated in the findings from a stratified analysis for the relationship between pets and household density presented in Table 6, participants with pets had a higher risk of carrying ESBL-producing or ST131 *E. coli* or ExPEC in their feces among those whose family had a higher ratio of household population to bathroom or to toilet number. This might suggest that compared with having pets, household density had a greater effect on the fecal carriage of ESBL-producing *E. coli*, O25b-ST131, and ExPEC. This also implies that the possible association of ST131 *E. coli* fecal carriage with higher ratios of household population to bathrooms is intensified by having pets in the house.

The carriage rate is higher among families of a lower socioeconomic bracket, and poverty is the main factor determining carriage rates.[33] Because poor health and sanitation conditions increase the spread of fecal-oral ESBL, compliance with hygienic regulations is a worthy topic of investigation.[33] In our study, the risk factors for resistant or pathogenic *E. coli* colonization were significantly associated with possible socioeconomic status—related consumption, such as those relating to portable water filter jug, pet ownership, and spacious household facilities, highlighting the necessity of socioeconomic analysis and larger samples in future studies.

This study, therefore, raises a number of critical public health concerns. First, a more widespread nationwide prospective multi-center longitudinal study that analyzes the relationship between children, family carriage, and environmental exposure from multiple geographical areas is required to determine prevalence and risk factors for resistant or pathogenic *E. coli* carriage. Second, effective prevention strategies are required to limit the widespread circulation of ESBL-producing *E. coli*, ST131 *E. coli*, and ExPEC among the community and to contain the threat of emerging drug resistance among various enteric bacterial pathogens. Third, we should strengthen antimicrobial stewardship during treatment and might have to discourage the nontherapeutic use of antimicrobials in human, pets and food animals to reduce antimicrobial resistance. Lastly, amelioration for the household environment and individuals of a lower socioeconomic bracket should be taken into consideration to reduce the burden of drug resistant and pathogenic *E. coli* fecal carriage among Taiwanese children.

This study has several limitations. The sources of household drinking water were very diverse; in addition, some families used multiple sources. These two causes might dilute the detection of risk association with each source. The insignificance in the evaluation of risks for drinking water sources might be resulted in an insufficient numbers in each subgroup. In addition, the degree of doneness for cooking was not recorded and the participants' socioeconomic profile was not determined based on data on their family's annual income. However, these limitations were mitigated by the use of data on family history, weekly food intake consumption, and the ratio of household population to facility numbers as a means to minimize these biases. Nonetheless, findings based on a determination of the participant's socioeconomic status based on household density and facility should be interpreted with caution. Besides, we did not provide internal checks between different questions in the questionnaire to get higher reliability of the answers, although we had emphasized the importance of data accuracy to the respondents before presenting questionnaires. Additionally, we did not detect antimicrobial activity in the fecal samples. Despite our use of history taking for medication and data from the National Health Insurance-PharmaCloud database to screen for antimicrobial prescriptions minimized this bias, there might still be cases where the use of antimicrobial agents was unknown or records were not uploaded. Therefore, the analysis and interpretation of the results still need to be cautious. In addition, to improve the limitation due to too small numbers of cases in each subgroup, larger-scale studies are warranted in the future.

Conclusion

In conclusion, a total of 20.7% of children in this study carried ESBL-producing *E. coli*, with the predominant β-lactamase enzyme type being *bla*CTX-M of which ST131 was mostly $bla_{\text{CTX-M-14}}$. Positive correlations were present between the drinking water processing and the carriage of ESBL-producing *E. coli*. Both amounts of pork consumption and household density were likely correlated with the carriage of ST131 *E. coli*. Additionally, children with pets in dense households had a possible trend for higher carriage rates of ESBL-producing *E. coli*, ST131 *E. coli*, and ExPEC. This study reports possible connections between household drinking water, food, pets, environment and fecal carriage of nonsusceptible *E. coli* and ExPEC, and the findings elucidate the potential contribution of population-level exposure to nonsusceptible *E. coli* and ExPEC infections in Taiwan. Therefore, policies to confront antimicrobial resistance might not be enough to focus only on human antibiotic stewardship but also need be broadened to the strategy of pets and food animal antimicrobial control, as well as human behavior, such as hygiene of drinking supply, food processing, pets contact, household environmental improvement and even socioeconomic science.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.04.001.