Prevalence and risk factors for carriage of ESBL-producing Enterobacteriaceae in a population of Dutch travellers: A cross-sectional study

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ABSTRACT

Background: We investigated prevalence and predictive factors for ESBL-E carriage in a population of mostly travellers prior to their travel (n = 2216). In addition, we examined ESBL genotype before travel and compared these to returning travellers.
Method: A questionnaire and faecal sample were collected before travel, and a second faecal sample was collected immediately after travel. Faecal samples were analysed for ESBL-E, with genotypic characterization by PCR and sequencing. Risk factors for ESBL-E carriage prior to travel were identified by logistic regression analyses.
Results: Before travel, 136 participants (6.1%) were colonized with ESBL-E. Antibiotic use in the past three months (OR$_{adjusted}$ 2.57; 95% CI 1.59–4.16) and travel outside of Europe in the past year (1.92, 1.28–2.87) were risk factors for ESBL-E colonisation prior to travel. Travel outside of Europe carried the largest attributable risk (39.8%). Prior to travel 31.3% (40/128) of participants carried *bla*CTX-M 15 and 21.9% (28/128) *bla*CTX-M 14/18. In returning travellers 633 acquired ESBL-E of who 53.4% (338/633) acquired *bla*CTX-M 15 and 17.7% (112/633) *bla*CTX-M 14/18.
Conclusion: In our population of Dutch travellers we found a pre-travel ESBL-E prevalence of 6.1%. Prior to travel, previous antibiotic use and travel outside of Europe were the strongest independent predictors for ESBL-E carriage, with travel outside of Europe carrying the largest attributable risk. Our molecular results suggest ESBL genes found in our study population prior to travel were in large part travel related.

1. Introduction

The prevalence of antimicrobial resistance in the community has increased to significant levels in many countries, even in those with historically prudent use of antibiotics [1,2]. Globally, ESBL-E prevalence varies from 2 to 46% between communities from different sub-

regions [3]. Every year ESBL-E carriage rates increase worldwide with more than 5% among healthy individuals [2,3]. Also in Europe, an increase in ESBL-E community carriage rates has been documented over the past years [4]. Three previous studies found an ESBL-E prevalence of 4.5–8.6% among healthy Dutch individuals [5–7]. Two of these identified travel to Asia or Africa in the previous 12 months and the use of proton pump inhibitors (PPI's) to be associated with a higher risk for ESBL-E carriage in the community. Other risk factors were the use of antimicrobials, travel to North and Latin America, keeping cows, living in the proximity of a mink farm, and owning or having contact with a horse [5–7]. In countries with similar ESBL-E community carriage rates as the Netherlands, previous antibiotic use was identified as a predictor in Japan, Germany and France [3,8–10]. Travel to Asia or Africa and travel to Africa or Greece were identified as predictors for ESBL-E carriage in Swedish and German communities, respectively [9,11].

Overall, studies found a variety of risk factors. Therefore, elucidation of risk factors is needed to identify definitive sources for ESBL-E carriage in the community and to foresee possible public health risks and interventions. In this paper, we report on the prevalence of and risk factors for ESBL-E carriage in a large convenience cohort of travellers living in the community in the Netherlands prior to their planned intercontinental travel. In addition, we compared genotypes and resistance profiles of ESBL-E isolated before and after intercontinental travel.

2. Methods

2.1. Study design and participants

To determine risk factors for ESBL-E carriage in the community we used a population of 2001 travellers and 215 household members of those travellers who were enrolled in the COMBAT-study, a multicenter longitudinal cohort study on the risk of ESBL-E acquisition during international travel [12]. Participants were included from November 2012 until November 2013. All participants had provided a faeces sample, collected by rectal swab (Fecal Swab with transport medium; Copan, Brescia, Italy), and a questionnaire 1–3 weeks before travel. Thus, the results of this baseline culture and the accompanying

metadata reflect, to some extent, the endemic level and potential determinants of ESBL-E carriage in the Dutch general population. Fig. 1 depicts a flowchart of the study design used to answer the research questions of this paper.

2.2. Procedures

Rectal swabs were incubated in tryptic soy broth supplemented with vancomycin (50 mg/L). After overnight culture, the broth was subcultured onto chromID ESBL agar plates (bioMerieux, Marcy l'Etoile, France). After overnight incubation, all morphologically distinct colonies were identified to the species level using a matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (Bruker Microflex LT, Bruker, London, UK). For all Enterobacteriaceae antibiotic minimum inhibitory concentrations were measured with the automated susceptibility testing system Vitek 2 (bioMerieux). Phenotypical confirmation of ESBL production was performed by combination disc diffusion tests, according to current national Dutch guidelines [13]. The presence of ESBL genes was confirmed by PCR using primers specific for CTX-M enzyme groups 1, 2, 8, 9, and 25. Sequence confirmation was performed to further characterize the most prevalent and largest CTX-M groups, 1 and 9 [12].

2.3. Statistical analysis

Predictors for ESBL-E carriage prior to travel were determined by multivariable logistic regression models that were constructed according the method proposed by Bursac and colleagues [14] and analysed with IBM SPSS Statistics (version 21.0). Data from pre-travel questionnaires were used to determine potential risk factors for ESBL-E carriage and included demographics, pre-existing morbidity and medication use, food consumption, travel history, hospital admissions and antibiotic use during the past three months. Results are presented as odds ratios (ORs) and 95% confidence intervals (CI_{95}). The ORs were used for calculating the population attributable risk (PAR), i.e. the proportion of participants that would not be ESBL carriers if the risk factor was eliminated.

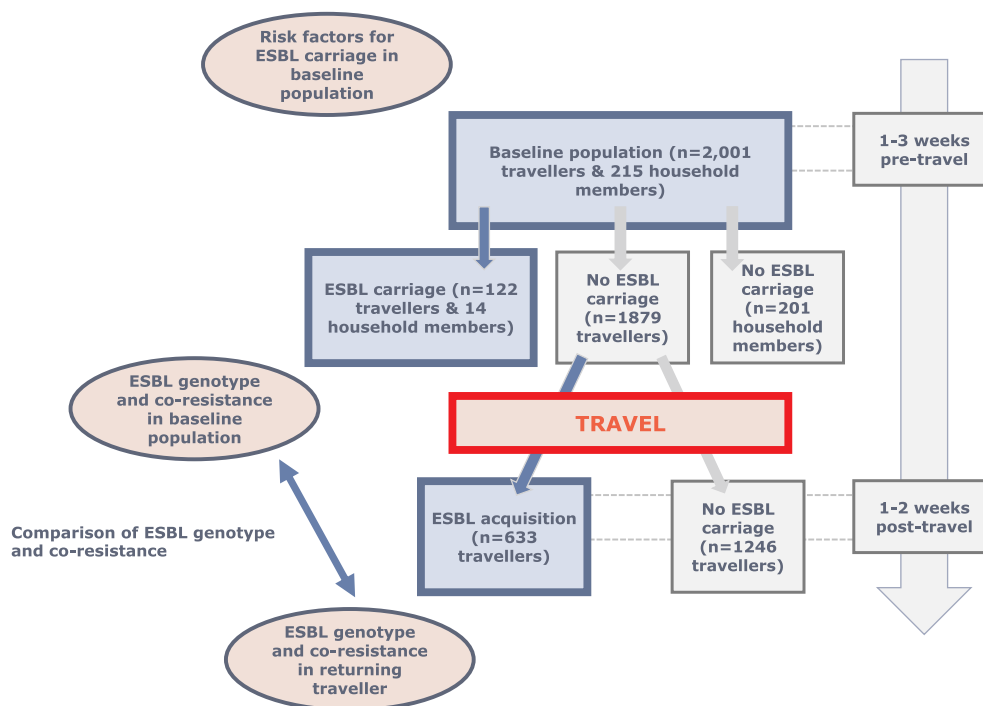Differences in co-resistance/multidrug resistance between ESBL-

Fig. 1. Flow chart of study design.

Table 1

Predictors for ESBL-E carriage for travellers and non-travelling household members prior to travel in the final adjusted logistic regression model.

	Number of travellers prior to travel	Number of travellers with ESBL colonisation prior to travel	Travellers with ESBL colonisation prior to travel (%)	OR adjusted (95% CI)	p
Type of participant					
Traveller	2001	122	6.1		
Non-travelling household member	215	14	6.5	1.11 (0.60–2.04)	0.75
Education level					
No education, elementary school or pre-vocational secondary education†	290	11	3.8		
Vocational secondary education	323	16	5.0	1.66 (0.68–4.01)	0.26
Senior general secondary education or pre-university education	249	22	8.8	3.14 (1.34–7.35)	0.01
Higher professional education	704	49	7.0	2.38 (1.09–5.19)	0.03
Academic education	642	37	5.8	1.76 (0.78–3.96)	0.17
Antibiotic use the past three months					
No†	1989	108	5.4		
Yes	222	27	12.2	2.57 (1.59–4.16)	< 0.001
Chronic disease					
No†	1700	111	6.5		
Yes	488	21	4.3	0.60 (0.36–1.01)	0.053
Daily patient contact					
(No) profession in healthcare without daily patient contact†	1819	102	5.6		
Medical or other profession in healthcare with daily patient contact	366	30	8.2	1.49 (0.95–2.33)	0.08
Frequency of travel in past twelve months					
No trip	207	14	6.8		
1 or 2 trip(s)	923	45	4.9	0.53 (0.27–1.03)	0.06
3 or 4 trips	671	50	7.5	0.69 (0.35–1.38)	0.29
5 or more trips	362	24	6.6	0.63 (0.29–1.37)	0.25
Travel to Asia					
No†	1753	93	5.3		
Yes	463	43	9.3	1.58 (1.04–2.39)	0.03
Travel to Africa					
No†	1960	109	5.6		
Yes	256	27	10.5	2.19 (1.36–3.52)	0.001
Travel to Oceania					
No†	2174	128	5.9		
Yes	42	8	19.0	3.63 (1.59–8.29)	0.002

† reference category

Table 2

Population-attributable risk (PAR) of predictors for ESBL-E carriage prior to travel.

predictor	PAR
Antibiotic use the past three months	14.9%
Travel outside of Europe	39.8%
Travel to Asia	13.2%
Travel to Africa	13.4%
Travel to Oceania	4.8%

E.coli isolated from participants prior to travel and acquired ESBL-*E. coli* isolates in returning travellers were determined using chi square tests. In case a traveller had more than one ESBL-producing *E. coli*, only the first isolate was included in the analysis. Multidrug resistance was defined as *E. coli* non-susceptible to one or more agent(s) in three or more antimicrobial classes [15]. To determine differences in genotype in ESBL-producing *E. coli* from travellers who acquired these during travel to different subregions according to the United Nations geoscheme [12], we used multivariable logistic regression models.

3. Results

3.1. Risk factors for ESBL-E colonisation prior to travel

2001 travellers and 215 non-travelling household members were included in the original COMBAT-study. From the complete study population 136 participants (122 travellers and 14 non-travelling household members) were found to carry ESBL-E prior to travel (Fig. 1).

Antibiotic use in the past three months was the strongest independent predictor for ESBL-E colonisation prior to travel (adjusted OR 2.57, CI$_{95}$ 1.59–4.16 (Table 1, Supplementary Table A1). To assess effects of different antibiotic classes in the model, we exchanged the variable antibiotic use during the past three months (no vs yes) for a variable indicating antibiotic class (no antibiotics; beta-lactam; quinolone; or other antibiotics). In this analysis, beta-lactam use was most strongly associated with ESBL-E colonisation (OR$_{adjusted}$ 4.07, CI$_{95}$ 2.00–8.28). Quinolone use (OR$_{adjusted}$ 1.88, 0.41–8.69) was not statistically significantly associated with ESBL-E colonisation (Supplementary Table A1). 14.9% of ESBL-E carriage prior to travel could be attributed to antibiotic use in the past three months (Table 2).

Travel outside of Europe in the past year was also associated with ESBL-E colonisation prior to travel (OR$_{adjusted}$ 1.92, CI$_{95}$ 1.28–2.87) (Supplementary Table A1). The PAR was 39.8% for travel outside of Europe. In more detail, we detected associations between ESBL-E colonisation prior to travel and previous travel to Africa (OR$_{adjusted}$ 2.19, CI$_{95}$ 1.36–3.52), Asia (OR$_{adjusted}$ 1.58, CI$_{95}$ 1.04–2.39) and Oceania (OR$_{adjusted}$ 3.63, CI$_{95}$ 1.59–8.29) in the past year (Table 1). To assess effects of different subregions in the model, we exchanged the variable indicating the continent (Africa, Asia or Oceania) with a variable indicating the different subregions according to the United Nations Geoscheme. By this classification, travel to Northern Africa (OR$_{adjusted}$ 3.76, CI$_{95}$ 2.15–6.55), Eastern Asia (OR$_{adjusted}$ 3.16, CI$_{95}$ 1.31–7.58), and Australia and New Zealand (OR$_{adjusted}$ 3.73, CI$_{95}$ 1.63–8.54) in the past year were associated with ESBL-E colonisation prior to travel (Supplementary Table A1). Participants working in healthcare with daily patient contact tended to be associated with an increased risk for
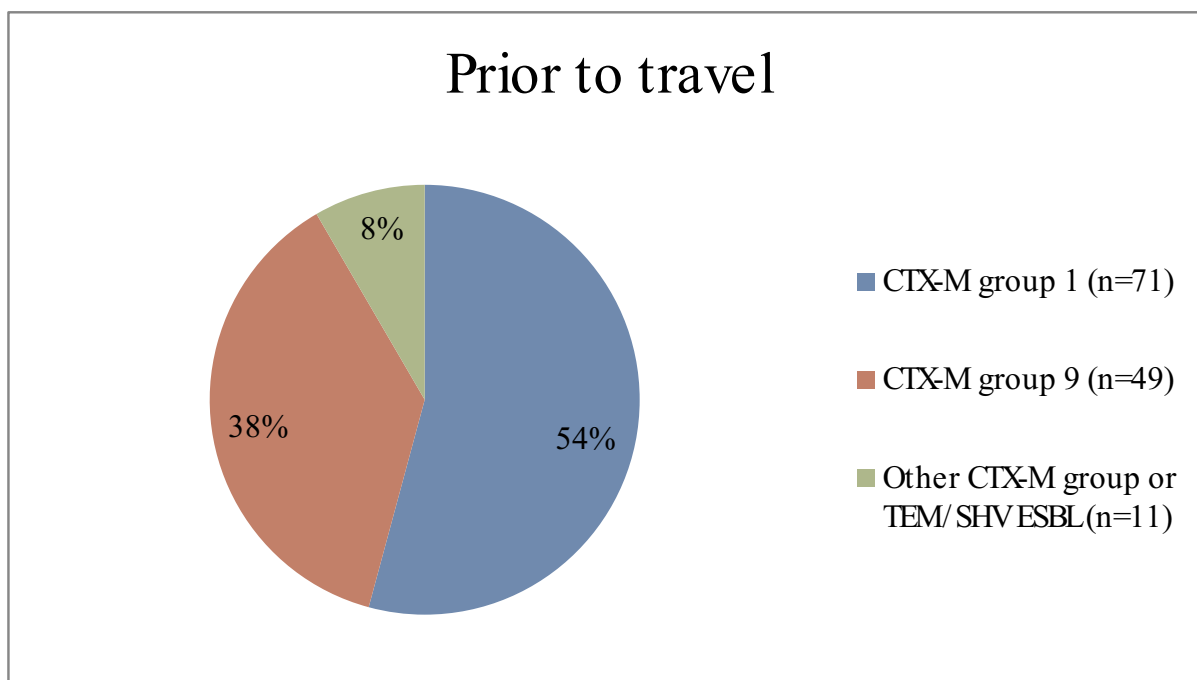
Fig. 2a. Distribution of ESBL groups prior to travel (T0) (n = 128 travellers and household members).
*Only unique ESBL genes per participant were included in the pie diagram. If a participant carried two of the same ESBL genes, the ESBL gene was only included once in this pie diagram.

ESBL-E carriage prior to travel ($OR_{adjusted}$ 1.49, CI_{95} 0.95–2.33). Other variables including pre-existent chronic bowel disease, diarrhoea, dietary variables, and use of antacids were not associated with ESBL-E colonisation prior to travel.

3.2. Comparison of ESBL-E genotypes in study population prior to travel to study population returning from travel

Before travel, 136 participants were colonized with ESBL-E, from which 164 morphologically different strains were isolated. Of travellers that were negative for ESBL-E prior to travel, 633 travellers acquired ESBL-E during travel, from which 859 morphologically different strains were isolated [12].

In both the study population prior to travel and the population returning from travel, CTX-M group 1 was the most prevalent ESBL group, being found in respectively 71/131 (54.2%) and 428/692 (61.8%) of isolates in ESBL-E colonized participants. The second most prevalent ESBL group was CTX-M group 9, that was detected in 49/131 (37.4%) and 209/692 (30.2%) of isolates in participants, respectively (Fig. 2a and b). Prior to travel, 40 of 128 participants carried *bla*CTX-M-15 (31.3%), 28 *bla*CTX-M-14/18 (21.9%), 14 *bla*CTX-M-1 (10.9%) and 11 *bla*CTX-M-27 (8.6%) (Fig. 3a). In the study population returning from travel 338 of 633 travellers (53.4%) acquired *bla*CTX-M-15, 112 *bla*CTX-M-14/18 (17.7%), 70 *bla*CTX-M-27 (11.1%) and 52 *bla*CTX-M-55/57 (8.2%) (Fig. 3b).

Among participants that acquired ESBL-E during travel, prevalence of ESBL groups and ESBL genes differed per subregion (Supplementary Figure A1 and A2). Multivariable logistic regression models showed travellers to Middle- and Eastern Africa ($OR_{adjusted}$ 2.6, CI_{95} 1.2–5.5), Northern Africa ($OR_{adjusted}$ 2.7, CI_{95} 1.1–6.9), Western Africa ($OR_{adjusted}$ 7.5, CI_{95} 1.6–35.0) and Southern Asia ($OR_{adjusted}$ 9.5, CI_{95} 4.3–20.7) were at increased risk for CTX-M group 1 acquisition when compared to travellers who did not visit these subregions. More specifically, travellers to Western Africa ($OR_{adjusted}$ 9.6, CI_{95} 2.1–44.5), Southern Asia ($OR_{adjusted}$ 9.3, CI_{95} 4.4–19.3) and Western Asia ($OR_{adjusted}$ 11.7, CI_{95} 1.4–95.8) were at increased risk for acquisition of ESBL gene CTX-M-15. Furthermore, travellers to Central- and Eastern Asia were at increased

risk for acquisition of CTX-M group 9 ($OR_{adjusted}$ 3.3, CI_{95} 1.4–7.5) and ESBL-gene CTX-M-14/18 ($OR_{adjusted}$ 3.5, CI_{95} 1.5–7.9) compared to travellers who did not visit this subregion (data not shown).

3.3. Comparison of co-resistance in study population prior to travel to study population returning from travel

Prior to travel 120 participants carried at least one ESBL-producing *E. coli*, with a total of 150 morphologically different *E. coli* strains. 585 returning travellers acquired at least one ESBL-producing *E. coli* with a total of 759 morphologically different *E. coli* strains. Co-resistance to gentamicin (p < 0.001), nitrofurantoin (p = 0.02), trimethoprim-sulfamethoxazole (p < 0.001) and multidrug resistance (p = 0.004) were significantly more prevalent among ESBL-E isolated from participants returning from travel compared to those isolated from participants before travel (Table 3).

4. Discussion

The ESBL-E carriage rate of 6.1% observed among this cohort of Dutch individuals prior to travel was slightly higher (versus 4.5% and 5.1%) and lower (versus 8.6%) compared to previous Dutch studies among healthy individuals [5–7] and is slightly higher than the overall carriage rate of 4% measured in healthy individuals in Northern Europe [3]. The two major determinants for ESBL-E carriage prior to travel, antibiotic use and travel outside of Europe, reinforce previous findings [5–7]. The most prevalent ESBL genes, both prior to travel and returning from travel, were *bla*CTX-M-15 and *bla*CTX-M-14/18.

Our large study population made it possible to study risk factors for pre-travel carriage in 136 participants. Although previous antibiotic use, in particular beta-lactam antibiotics, was the strongest independent predictor for ESBL-E carriage prior to travel, only 14.9% of ESBL-E carriage could be attributed to antibiotic use prior to travel. Quinolone use was the antibiotic class most strongly associated with ESBL-E acquisition during travel [12], but was not significantly associated with ESBL-E carriage prior to travel, possibly because of a lack of power. Kantele et al. demonstrated that the use of fluoroquinolones during
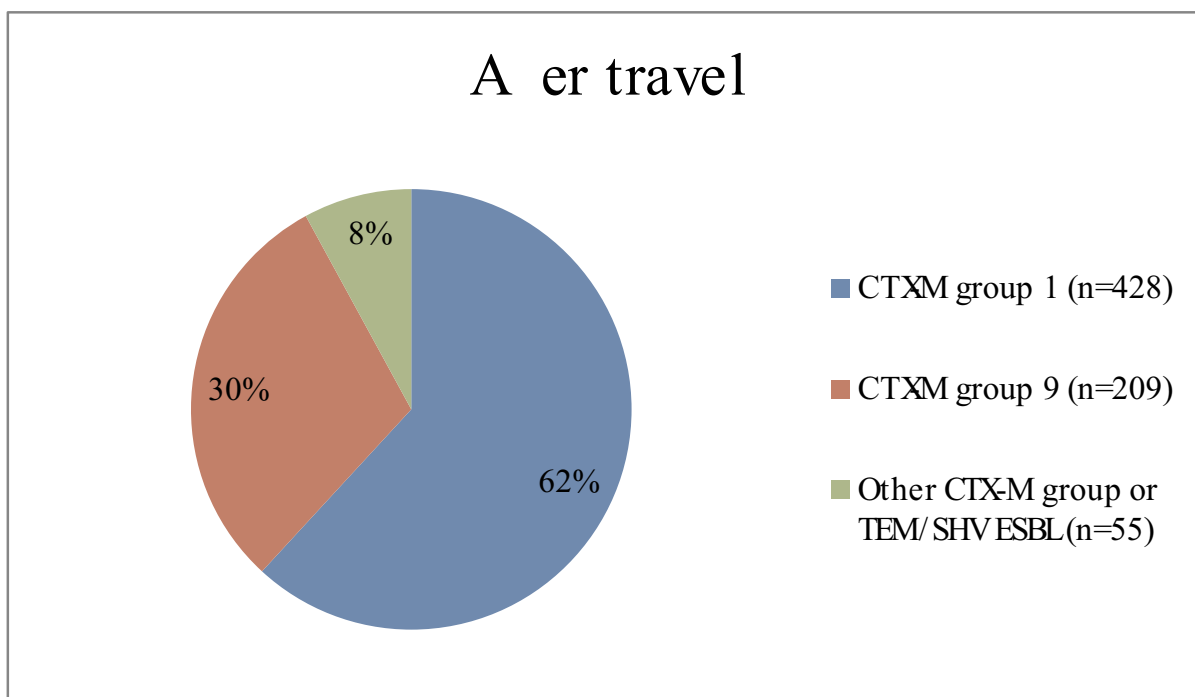
A er travel

- CTXM group 1 (n=428)
- CTXM group 9 (n=209)
- Other CTX-M group or TEM/SHV ESBL (n=55)

8%
30%
62%

Fig. 2b. Distribution of ESBL groups after travel (T1) (n = 633 travellers with ESBL acquisition).
*Only unique ESBL genes per participant were included in the pie diagram If a traveller acquired two of the same ESBL genes, the ESBL gene was only included once in this pie diagram.

travel selected for ESBL-E acquisition during travel [16].

Travel outside of Europe in the past 12 months was another strong independent predictor for ESBL-E carriage prior to travel, and carried the largest attributable risk (39.8% versus 14.9% for antibiotic use). Particularly, those who travelled to Eastern Asia, Northern Africa and Australia or New Zealand were at increased risk for ESBL-E carriage prior to travel. This is in line with other studies, which report travel to Asia or Africa as an important predictor for ESBL-E carriage in the community [6,7,9,11]. In addition to previous travel to Asia or Africa, Reuland et al. found travel to the United States of America to be a risk factor for ESBL-E carriage in the community [6], which was not confirmed in our study. Interestingly, in our study previous travel to

Australia and/or New Zealand was a newly discovered predictor for community ESBL-E carriage, even after correcting for travel duration (data not shown). There were 41 participants who had previously travelled to Australia and/or New Zealand, of which 8 (19.5%), who all had travelled to Australia, carried ESBL-E prior to travel. So far, no data has been published on the prevalence of ESBL-E carriage in Australian communities and traveller studies typically lack data on ESBL-E acquisition during travel in Australia. However, a high ESBL-E rate of 18% has been reported in long-term care facilities in Australia and an ESBL-E rate of 12% among *E. coli* hospital isolates [17,18]. The role of possible sources for ESBL-E carriage in the Australian community deserves clarification.
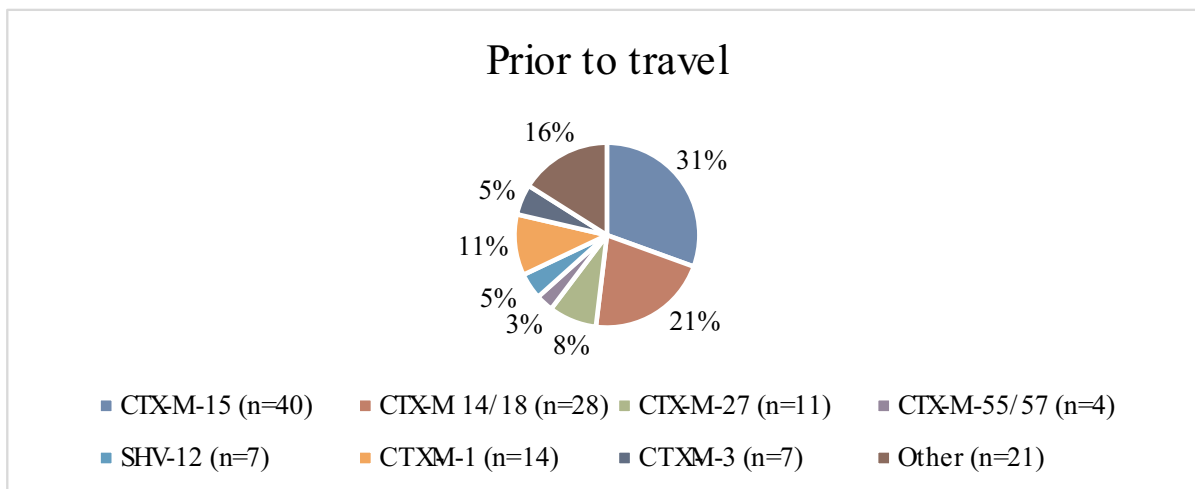

Prior to travel

16%
5%
11%
5%
3%
8%
21%
31%

- CTX-M-15 (n=40)
- CTX-M 14/18 (n=28)
- CTX-M-27 (n=11)
- CTX-M-55/57 (n=4)
- SHV-12 (n=7)
- CTXM-1 (n=14)
- CTXM-3 (n=7)
- Other (n=21)

Fig. 3a. Distribution of unique ESBL genes (n = 131) prior to travel (T0) (n = 128 travellers and household members).
*Other: CTX-M 32 (n = 2), CTX-M group 1 not specified (n = 4), CTX-M 24/65 (n = 2), CTX-M 9 (n = 1),CTX-M group 9 not specified (n = 7),TEM-52 (n = 3), SHV-2 (n = 2).
†ESBL-E isolates from 8 travellers were excluded from the pie diagram due to failure to determine the specific gene at baseline (T0).
‡ With the primers used no distinction could be made between CTX-M 15/28/94/167, CTX-M 14/17/18, CTX-M 1/61/138, CTX-M 3/22/162 and CTX-M 55/79/164.
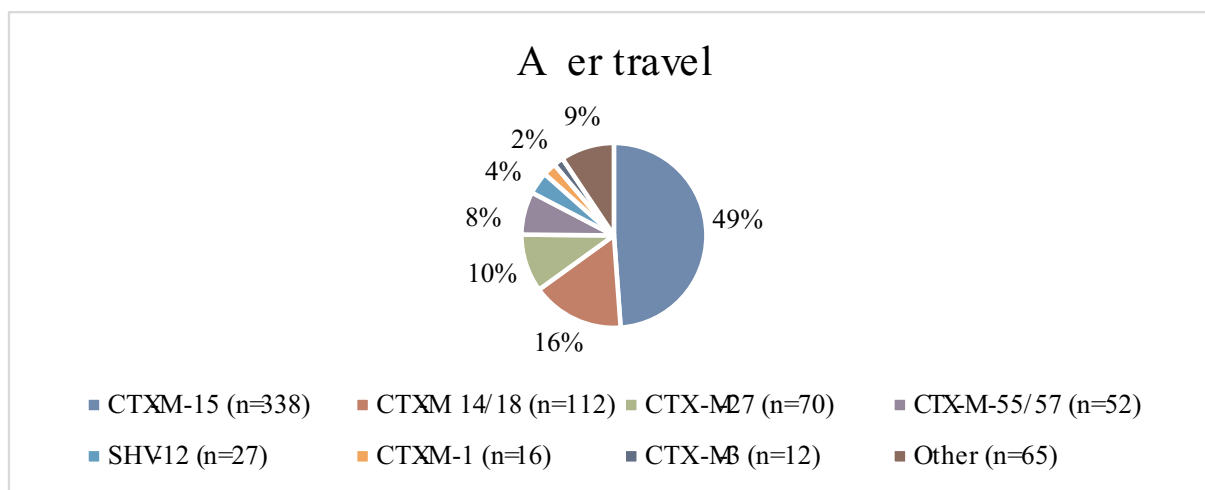
Fig. 3b. Distribution of unique ESBL genes (n = 692) after travel (T1) (n = 633 travellers with ESBL acquisition).
*Other: CTX-M-14-like (n = 10), CTX-M group 8 (n = 9), CTX-M-65 (n = 8), CTX-M-32 (n = 7), CTX-M group 2 (n = 7), CTX-M-24b (n = 6), TEM-52c (n = 4), SHV-2a (n = 3), CTX-M-24 (n = 2), TEM-176 (n = 2), CTX-M-15 like (n = 2), CTX-M-38 (n = 1), SHV-2 (n = 1), SHV-28 (n = 1), VEB (n = 1), CTX-M group 1 not specified (n = 1).

Table 3
Co-resistance rates among ESBL-*E. coli* strains isolated from study population prior to travel versus those isolated directly after travel.

antibiotic	Co-resistance prior to travel	Co-resistance returning from travel	p[c]
	(n = 120 participants[a])	(n = 585 participants[a])	
imipenem	0 (0.0%)	2 (0.3%)	0.521
meropenem	0 (0.0%)	1 (0.2%)	0.650
gentamicin	18 (15.0%)	180 (30.8%)	< 0.001
nitrofurantoin	1 (0.8%)	35 (6.0%)	0.020
trimethoprim- sulfamethoxazole	56 (46.7%)	377 (64.4%)	< 0.001
ciprofloxacin	43 (35.8%)	262 (44.8%)	0.071
colistin	0 (0.0%)	8 (1.4%)	0.198
multidrug resistance[b]	36 (30.0%)	259 (44.3%)	0.004

[a] Co-resistance was determined for participants with ESBL-positive *E. coli* isolates only. In case a participant carried/acquired more than one *E. coli* isolate, co-resistance was only determined for the first *E. coli* isolate.
[b] Multidrug resistance to gentamicin, trimethoprim-sulfamethoxazole, ciprofloxacin.
[c] p-value determined using chi-square tests.

In agreement with other studies, no association between consumption of food products including chicken meat and ESBL-E carriage prior to travel was found. There has been debate whether food items are an important source of ESBL-producing *E. coli* in humans. It has been suggested successful ESBL-carrying plasmids facilitate transmission between different reservoirs, however a recent study failed to demonstrate a close link between ESBL-carrying plasmid types from people in the general population and livestock or food-associated reservoirs [19,20]. We also did not find an association between use of antacids and ESBL-E carriage prior to travel. This conflicting finding with previous research may be explained by that we did not make a distinction between use of PPI's and neutralizing antacids. Therefore it could be that our participants were mostly using neutralizing antacids, which have not been associated with ESBL-E carriage yet, as opposed to PPI's [6,7,21].

In line with the worldwide epidemiology of ESBL genotypes, we found returning travellers from Western Africa, Southern Asia and Western Asia to be at increased risk for *bla*CTX-M-15 acquisition and returning travellers from Central- and Eastern Asia to be at increased

risk for *bla*CTX-M-14/18 acquisition [2,22]. Our study did not have the statistical power to test the association between pre-travel carriage of *bla*CTX-M-15 or *bla*CTX-M-14/18 and previous travel to *bla*CTX-M-15 or *bla*CTX-M-14 endemic regions. However, as *bla*CTX-M-14/18 is not prevalent in the Netherlands [6,7,23,24], these genes found prior to travel could very well be acquired during previous travels by our participants. The proportion of *bla*CTX-M-14/18 of 21% in ESBL genes in our population prior to travel is higher or comparable to other Dutch studies, which found a proportion of *bla*CTX-M-14 of 13–19% in the community [6,7,23].

Significantly more gentamicin, nitrofurantoin, trimethoprim-sulfamethoxazole and multidrug resistant *E. coli* isolates were carried by participants returning from travel than before travel. A possible explanation could be a relatively rapid loss of genes encoding for co-resistances in ESBL-E over time [25,26]. The persistence of carriage of ESBL-E seems not to be a random process as a recent study demonstrated certain strain/gene combinations were more prevalent in prolonged carriers in the community [27]. More studies are needed to identify whether strain, plasmid or gene related factors are responsible for persistence of ESBL-E carriage and to delineate the dynamics of resistance gene acquisition and loss.

A limitation of our study was that the PAR in our study cannot be fully extrapolated to the general adult population in the Netherlands, as participants were recruited from travel clinics, they were more likely to travel internationally and had the financial means to do so.

5. Conclusion

International travel is a major risk factor for ESBL-E carriage in the Dutch population and may - directly or indirectly - be a substantial if not dominant contributor to the endemic level of ESBL-E carriage in the Dutch general population. With current predictions of further growth in international travel, we envision that travel will constitute an important driving force for ESBL-E carriage in the community of countries like the Netherlands, that are otherwise relatively prudent regarding their antibiotic usage.

Contribution

MSA and JMvH did the study, collected the data, and contributed to the study design. PJJvG, CS, HAV, MDdJ, DCM, and JP designed the study and are members of the supervising board. MSA, JMvH, CS, HAV, DCM, and JP contributed to the data analysis and interpretation. MSA,

JMvH, PJJvG, HAV, JP and DCM drafted the Article with help from all authors. All authors read and approved the final version of the paper.

Declaration of competing interest

We declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2019.101547.

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