Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study

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SUMMARY

Background

International travel contributes to the dissemination of antimicrobial resistance. We investigated the acquisition of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) during international travel, with a focus on predictive factors for acquisition, duration of colonisation, and probability of onward transmission.

Methods

Within the prospective, multicentre COMBAT study, 2001 Dutch travellers and 215 non-travelling household members were enrolled. Faecal samples and questionnaires on demographics, illnesses, and behaviour were collected before travel and immediately and 1, 3, 6, and 12 months after return. Samples were screened for the presence of ESBL-E. In post-travel samples, ESBL genes were sequenced and PCR with specific primers for plasmid-encoded β-lactamase enzymes TEM, SHV, and CTX-M group 1, 2, 8, 9, and 25 was used to confirm the presence of ESBL genes in follow-up samples. Multivariable regression analyses and mathematical modelling were used to identify predictors for acquisition and sustained carriage, and to determine household transmission rates. This study is registered with ClinicalTrials.gov, number NCT01676974.

Findings

633 (34·3%) of 1847 travellers who were ESBL negative before travel and had available samples after return had acquired ESBL-E during international travel (95% CI 32·1–36·5), with the highest number of acquisitions being among those who travelled to southern Asia in 136 of 181 (75·1%, 95% CI 68·4–80·9). Important predictors for acquisition of ESBL-E were antibiotic use during travel (adjusted odds ratio 2·69, 95% CI 1·79–4·05), traveller's diarrhoea that persisted after return (2·31, 1·42–3·76), and pre-existing chronic bowel disease (2·10, 1·13–3·90). The median duration of colonisation after travel was 30 days (95% CI 29–33). 65 (11·3%) of 577 remained colonised at 12 months. CTX-M enzyme group 9 ESBLs were associated with a significantly increased risk of sustained carriage (median duration 75 days, 95% CI 48–102, p=0·0001). Onward transmission was found in 13 (7·7%) of 168 household members. The probability of transmitting ESBL-E to another household member was 12% (95% CI 5–18).

Interpretation

Acquisition and spread of ESBL-E during and after international travel was substantial and worrisome. Travellers to areas with a high risk of ESBL-E acquisition should be viewed as potential carriers of ESBL-E for up to 12 months after return.

Funding

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INTRODUCTION

Antimicrobial resistance constitutes an increasingly important human health hazard worldwide.[1] The use of antibiotics in human beings and food animals is a well established driving force behind increasing resistance.[2] Given the enormous growth of international tourism, from 25 million travellers in 1950 to 1·133 billion in 2014,[3] international travel might also contribute substantially to the rise in resistance because resistant bacteria or bacterial mobile genetic elements carrying resistance genes (eg, plasmids) may be rapidly transported between regions.[4] An important part of antimicrobial resistance genes is found on plasmids and codes for extended-spectrum β lactamase enzymes ([ESBLs] eg, TEM, SHV, and CTX-M) and carbapenemases that confer resistance to most β-lactam antibiotics.[2,4] Additionally, ESBL-producing Enterobacteriaceae (ESBL-E) and carbapenemase-producing Enterobacteriaceae (CPE) are typically resistant to multiple other antibiotic classes, which leaves few to no effective antimicrobial agents for prevention and treatment of infections.[4,5]

Previous studies have reported frequent acquisition of ESBL-E associated with various predictors and sporadic acquisition of CPE among international travellers.[6–10] However, data on ESBL-E colonisation after travel and assessment of associated predictors for sustained carriage and onward transmission within households are very limited. Such data are needed to establish the public health risk of the introduction and spread of antimicrobial resistance by travellers, and the potential needs and measures to monitor or manage these risks. Identifying individuals at risk of ESBL-E carriage enables appropriate measures to be taken to prevent introduction and spread of ESBL-E or CPE and for empirical adjustment of antibiotic treatment in individuals to optimise clinical care. We investigated the acquisition of ESBL-E during international travel, the associated predictive factors for acquisition, duration of colonisation, and onward transmission to household members.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed on Aug 17, 2015, with the search terms "Gram negative bacteria", "Enterobacteriaceae", "Escherichia", "Klebsiella", "Salmonella", "Shigella", "Yersinia", "travel", "tourist", "tourism", "turista", "aviation", "air transport", "airport", "resistance", "colonisation", "antibiotic", "susceptibility", "carriage", and "carrier". We did a systematic review and identified 11 eligible studies. We updated this search on April 14, 2016, and found no new prospective studies. The results of the 11 prospective cohort studies showed high acquisition rates of extended-spectrum β-lactamase-producing Enterobacteriaceae

(ESBL-E) among travellers who had returned from southern Asia and northern Africa. Four travellers who visited India acquired carbapenemase-producing Enterobacteriaceae (CPE). However, whether antibiotic use and traveller's diarrhoea are predictors for ESBL-E acquisition was unclear. Moreover, these studies did not sufficiently address duration of ESBL-E carriage among travellers or onward transmission within households. One study asked travellers to provide stool samples up to 12 months after return, but duration of carriage was defined by ESBL phenotype. One other study looked at household transmission, but because only 11 household contacts were included, no reliable conclusion could be inferred about the risk of household transmission.

Added value of this study

In this large-scale, longitudinal cohort study, we followed up travellers and their non-travelling household members for up to 12 months after travel. The large sample size meant that we could investigate ESBL-E acquisition among travellers who had returned from a large number of countries across the world, including those such as Uganda, for which community carriage rates of ESBL-E were previously unknown. We identified several predictors (some new) for ESBL-E acquisition, including factors specific to subregions. Moreover, we were able to ascertain duration of ESBL-E carriage and associated resistance genes, identify predictors for sustained colonisation, and to model transmission rates mathematically within households.

Implications of all the available evidence

High frequencies of ESBL-E acquisition during travel, subsequent sustained carriage, and evidence of onward transmission within households show that travellers contribute to the emergence and spread of ESBL-E on a global scale. Active screening for ESBL-E and CPE and adjustment of empirical antimicrobial therapy should be considered for returning travellers at increased risk of ESBL-E carriage. However, implications for infection prevention and antibiotic treatment policies will differ locally because the degree of consequence of acquisition and spread of ESBL-E by travellers is highly dependent on local ESBL-E prevalence in the country of origin.

METHODS

Study design and participants

The study design and methods have been described in detail elsewhere.[11] Briefly, we did a multicentre, longitudinal, prospective cohort study involving travellers who were followed up from 1–3 weeks before travel departure until 12 months after return. To

study household transmission, we also assessed non-travelling household members in the same period.

Eligible participants were adults (age ≥18 years) planning to travel for at least 1 week and up to 3 months. They were recruited at three outpatient travel clinics across the Netherlands from November, 2012, to November, 2013. The study was approved by the Medical Research Ethics Committee, Maastricht University Medical Centre (METC 12-4-093). All participants provided written informed consent.

Procedures

Participants were provided with faeces collection kits and instructed to self-collect faecal swabs (appendix) before and immediately and 1 month after travel. If any of these samples contained ESBL-E, the traveller and his or her household members were asked to provide further samples at 3, 6, and 12 months after travel. If no samples were positive for ESBL-E, no additional samples were collected. Questionnaires were also collected at all timepoints to obtain information on potential risk factors for ESBL-E acquisition, including demographics, illnesses, and behaviour before, during, and after travel.

Samples were processed immediately after receipt. They were inoculated in tryptic soy broth supplemented with vancomycin (50 mg/L) to select for Enterobacteriaceae. The broth was then subcultured on chromID ESBL (bioMérieux, Marcy l'Etoile, France). All morphologically distinct colonies were characterised to the species level with matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (Bruker Microflex LT, Bruker, London, UK). Antibiotic minimum inhibitory concentrations were measured with the automated susceptibility testing system Vitek 2 (bioMérieux) for all Enterobacteriaceae. ESBL production was phenotypically confirmed by the combination disc diffusion test, according to current national Dutch guidelines.[12]

All phenotypically confirmed ESBL-E isolates acquired during travel were screened for the presence of ESBL genes with microarray, as described previously (appendix). The presence of ESBL genes was confirmed by PCR with primers specific for CTX-M enzyme groups 1, 2, 8, 9, and 25 and in-house primer sets. Further characterisation by sequencing was done for the most prevalent and largest CTX-M groups, 1 and 9. PCR confirmation and sequencing of genes for TEM and SHV ESBLs were limited to isolates that had negative microarray results for all CTX-M genes. A generic CTX-M PCR was done if no ESBL genes were detected by microarray, and, if positive, was followed by specific PCR and sequence confirmation for the different CTX-M groups (appendix). Sequences were compared with those in the NCBI GenBank and Lahey databases.

Acquisition was defined as the absence of ESBL-E in faecal samples before travel and the presence of ESBL-E in those obtained immediately after travel, as identified by phenotypic tests. Duration of carriage was defined by the last positive sample harbouring an ESBL of the same group (TEM, SHV, or CTX-M group 1, 2, 8, 9, or 25, or a combination)

as detected immediately after travel. Participants with consecutive samples positive for ESBL-E were classified as being persistent carriers and those with ESBL-E-positive samples interspersed with at least one negative sample were classified as being intermittent carriers.

Statistical analysis

Incidence proportions and incidence per 100 person-days of travel and accompanying 95% CIs for ESBL-E acquisition were calculated for each subregion (appendix) and country of destination. Incidence per 100 person-days of travel was calculated with a maximum likelihood method that was based on a constant acquisition rate with right-censored and interval-censored data.

Predictors for ESBL-E acquisition were determined by logistic regression models that were based on the method proposed by Bursac and colleagues[13] (appendix) and analysed with IBM SPSS Statistics (version 21.0). Results are presented as odds ratios (ORs) and 95% CIs. We did separate analyses for the subregions of southeast Asia, southern Asia, and eastern Africa, as several dietary variables (eg, consumption of chicken, barbecue meat, or pork) interacted with specific travel destination subregions.

Time to decolonisation was assessed with Kaplan-Meier survival analyses with right censoring for participants whose last provided sample was ESBL-E positive. Univariable and multivariable Cox's regression analyses were done to identify predictors associated with decolonisation (appendix). Results are presented as hazard ratios (HRs) and 95% CIs (HRs <1·00 indicate decreased risk of decolonisation and, therefore, increased duration of carriage).

A Markov model was used to calculate the probability of transmission within households. For computational reasons, this model was based on ESBL-E as defined by phenotypic confirmation, and only data from households consisting of at most five people were included, but these accounted for 98% of households. The model took into account false-negative results, missing culture results, and unobserved colonisation times. The method of calculation was as follows. ESBL-E-positive people (travellers or non-travelling household members) transmit ESBL-E to household members with rate β. Transmission from other sources was incorporated by the background transmission parameter α. Decolonisation of ESBL-E occurred with rate γ. Negative cultures could be false negative and affect the estimate of the sensitivity (ϕ). The specificity of culture was assumed to be 100%. Thus, the probability of transmission from an ESBL-E-positive to an ESBL-E-negative person, given that the ESBL-E-negative household member did not acquire ESBL-E via another route, could be calculated as $\beta/(\beta+\gamma)$. Model parameters were simultaneously estimated with a maximum likelihood method in Mathematica version 9.0. This study is registered with ClinicalTrials.gov, number NCT01676974.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

2737 travellers were screened for eligibility, of whom 2001 were included in the study (appendix), with median age 50·5 years (IQR 32·8–60·7) and good health before travelling in most (table 1). 49 travellers were lost to follow-up.

The main purpose for travel was tourism (1655 [84·2%] of 1965 travellers) and the median travel duration was 20 days (IQR 15·0–25·0; table 1). The subregions most frequently visited were southeast Asia (n=650), eastern Africa (n=287), South America (n=228), and southern Asia (n=217). 122 (6·1%) of 2001 travellers were carrying ESBL-E before travel, leaving 1879 at risk of ESBL-E acquisition. 1847 (98·3%) of these submitted faecal samples after travel, among whom 633 had acquired at least one ESBL-E during travel (table 2), giving an acquisition rate of 34·3% (95% CI 32·1–36·5). From these 633 travellers, 859 morphologically different ESBL-E strains were isolated (759 Escherichia coli, 67 Klebsiella pneumoniae, and 33 other species). CTX-M-15 was the most frequently acquired ESBL gene, being found in 338 (53·4%) of 633 travellers (appendix).

ESBL-E were most frequently acquired in southern Asia (75·1%, 95% CI 68·4–80·9), followed by central and eastern Asia (48·8%, 38·4–59·3; table 2, figure 1), but the frequency of acquisition varied widely between countries. Among the 22 most frequently visited countries, acquisition was highest in India (88·6%, 95% CI 79·8–93·9) and lowest in Suriname (3·6%, 1·0–12·1; appendix). Acquisition was also common after travel to eastern African countries, such as Uganda (44·4%, 27·6–62·7, appendix).

In the multivariable logistic regression, antibiotic use during travel was the strongest independent predictor for ESBL-E acquisition (table 3). To assess the effects of different antibiotic classes in the model, we exchanged the variable antibiotic use during travel (no *vs* yes) for a variable indicating antibiotic class (no antibiotics *vs* β-lactam, or quinolone, or other). Quinolone use was most strongly associated with ESBL acquisition (adjusted OR 6·0, 95% CI 2·9–12·4), whereas associations were non-significant for use of β-lactam (2·2, 0·95–5·14) or other antibiotics (1·7, 0·59–2·35). We also detected strong associations between ESBL-E acquisition and diarrhoea during travel and, particularly, traveller's diarrhoea that persisted on return (table 3). Travellers who had occasionally consumed food from street vendors were at increased risk of acquiring ESBL-E compared with those who had avoided street food vendors, and the risk increased further in travellers who consumed food from street vendors daily (table 3). Self-reported pre-existing chronic bowel disease was another notable risk factor for ESBL-E acquisition (table 3).

Table 1. Baseline characteristics of travellers and non-travelling household members

	Travellers (n=2001)*	Non-travelling household members (n=215)†
Sex		
Male	920 (46·0%)	80 (37·2%)
Female	1081 (54·0%)	135 (62·8%)
Age (years)	50·5(32·8–60·7)	46·9(25·7–55·8)
Education level		
No education, elementary school, or prevocational secondary education	243 (12·4%)	78 (36·4%)
Vocational secondary education	280 (14·2%)	37 (17·3%)
Senior general secondary education or education up to university	200 (10·2%)	45 (21·0%)
Higher professional education	642 (32·7%)	53 (24·7%)
Academic (university) education	595 (30·3%)	38 (17·8%)
Antibiotic use in previous 3 months		
No	1760 (90·1%)	189 (88·3%)
Yes	194 (9·9%)	25 (11·7%)
Travel in past year		
None	185 (9·5%)	27 (12·6%)
In Europe	915 (46·9%)	124 (57·7%)
Outside Europe	852 (43·6%)	64 (29·8%)
Chronic disease‡		
No	1500 (77·2%)	173 (82·0%)
Yes	443 (22·8%)	38 (18·0%)
Chronic bowel disease‡		
No	1912 (97·4%)	212 (99·1%)
Yes	51 (2·6%)	2 (0·9%)
Continent visited during travel§		
Asia	1016 (50·8%)	NA
Africa	633 (31·6%)	NA
America	326 (16·3%)	NA
Europe	21 (1·0%)	NA
Oceania	5 (0·2%)	NA
Duration of index travel (days)	20 (15·0–25·0)	NA
Purpose of index travel		
Holiday	1655 (84·2%)	NA
Work or internship	161 (8·2%)	NA
Visiting family or relatives	82 (4·2%)	NA
Other reason	66 (3·4%)	NA

Data are number (%) or median (IQR). NA=not applicable. *Some numbers do not add up to 2001 because of missing data. †Some numbers do not add up to 215 because of missing data. ‡Self-reported by traveller or household member. §If travellers visited multiple continents, only the main continent visited is presented in this table.

Table 2. Incidence proportion and incidence per 100 person-days of travel for ESBL-E acquisition in Dutch travellers, by subregion

	Number of travellers (n=1847)*	Number of travellers who acquired ESBL-E (n=633)†	ESBL-E incidence proportion (95% CI)‡	Number of travel-days	Mean (SD) duration of travel (days)	ESBL-E incidence per 100 person-days of travel (95% CI)§
Southern Asia	181 (9·8%)	136 (21·5%)	75·1 (68·4–80·9)	3727	20·6 (11·0)	7·2 (5·9–8·6)
Central and eastern Asia	84 (4·5%)	41 (6·5%)	48·8 (38·4–59·3)	1712	20·4 (10·8)	3·5 (2·5–4·7)
Western Asia	28 (1·5%)	12 (1·9%)	42·9 (26·5–60·9)	305	10·9 (7·5)	5·8 (3·0–9·9)
Northern Africa	81 (4·4%)	34 (5·4%)	42·0 (31·8–52·9)	981	12·1 (5·7)	4·5 (3·1–6·2)
Southeastern Asia	540 (29·2%)	200 (31.6%)	37·0 (33·1–41·2)	12 493	23·1 (11·6)	2·1 (1·8–2·4)
Caribbean and Central America	86 (4·7%)	24 (3·8%)	27·9 (19·5–38·2)	1653	19·2 (12·4)	1·7 (1·1–2·5)
Middle and eastern Africa	205 (11·1%)	57 (9·0%)	27·8 (22·1–34·3)	4060	19·8 (14·3)	1·6 (1·2–2·1)
Western Africa	106 (5·7%)	20 (3·2%)	18·9 (12·6–27·4)	1638	15·5 (11·1)	1·4 (0·8–2·0)
South America	180 (9·7%)	33 (5·2%)	18·3 (13·4–24·6)	4778	26·5 (14·7)	0·8 (0·5–1·1)
Southern Africa	116 (6.3%)	7 (1·1%)	6·0 (2·5–12·0)	2522	21·7 (8·6)	0·3 (0·1–0·6)
Northern America, Europe, and Oceania	17 (1·0%)	1 (<1·0%)	5·9 (1·1–27·0)	292	17·2 (11·3)	0·4 (0–1·6)

ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae. *Numbers do not add up to 1847 because 221 travellers visited more than one subregion (66 with ESBL-E acquisition) and destination information was missing for two. †Numbers do not add up to 633 because 66 travellers visited multiple subregions and destination information was missing for two. ‡Based on binomial distribution (Wilson's score interval). §Calculated with the maximum likelihood estimation method based on a constant acquisition rate with right-censored and interval-censored data.

In the multivariable logistic regression, antibiotic use during travel was the strongest independent predictor for ESBL-E acquisition (table 3). To assess the effects of different antibiotic classes in the model, we exchanged the variable antibiotic use during travel (no *vs* yes) for a variable indicating antibiotic class (no antibiotics *vs* β-lactam, or quinolone, or other). Quinolone use was most strongly associated with ESBL acquisition (adjusted OR 6·0, 95% CI 2·9–12·4), whereas associations were non-significant for use of β-lactam (2·2, 0·95–5·14) or other antibiotics (1·7, 0·59–2·35). We also detected strong associations between ESBL-E acquisition and diarrhoea during travel and, particularly, traveller's diarrhoea that persisted on return (table 3). Travellers who had occasionally consumed food from street vendors were at increased risk of acquiring ESBL-E compared with those who had avoided street food vendors, and the risk increased further in travellers who consumed food from street vendors daily (table 3). Self-reported pre-existing chronic bowel disease was another notable risk factor for ESBL-E acquisition (table 3).

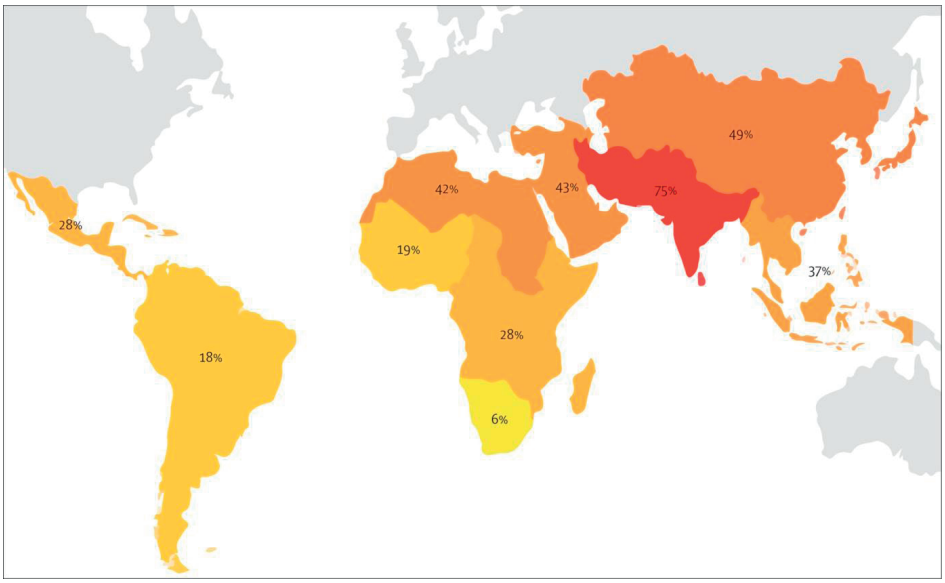

Figure 1. Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

In the separate analyses for three of the visited subregions, the consumption of raw vegetables and antibiotic use were predictors of ESBL-E acquisition in southeastern Asia. In southern Asia, the strongest predictors were contact with orphan children and daily food consumption at a hostel or guesthouse. In eastern Africa, the strongest associations were daily visits to the local markets and staying in rural areas (appendix).

Sustained ESBL-E carriage (persistent and intermittent) after acquisition was seen in 42·9%, 25·1%, 14·3%, and 11·3% of travellers at 1, 3, 6, and 12 months after return, respectively. Most of these participants were continuously colonised (appendix). The median duration of post-travel colonisation was 30·0 days (95% CI 28·9–33·1, figure 2). ESBL-producing *K pneumoniae* and travel to western Asia were associated with the shortest times to decolonisation. Travellers who acquired a CTX-M group 9 ESBL had a significantly increased risk of sustained carriage compared with travellers who acquired a CTX-M group 1 ESBL (appendix).

Of 215 non-travelling household members included in the study, 63 were ESBL-E negative at baseline and shared households with people who acquired ESBL-E while travelling. Additionally, 105 co-travellers who were ESBL-E negative immediately after return shared households with travellers who acquired ESBL-E. Thus, 168 household members (in 152 households) were at risk of ESBL-E transmission. Evidence of onward transmission within households was found in 13 (7·7%) of these 168 household members (ten co-travellers and three non-travelling household members, appendix), who

Table 3. Predictors for ESBL-E acquisition among travellers in the final adjusted logistic regression model

	Number of travellers at risk (n=1847)*	Number of travellers who acquired ESBL-E (n=633)†	Odds ratio (95% CI)‡	p value	Adjusted odds ratio (95% CI)§	p value
Pre-existing bowel disease						
No	1793 (97·3%)	606 (33·8%)	1·00	..	1·00	..
Yes	50 (2·7%)	24 (48·0%)	2·34 (1·26–4·34)	0·007	2·10 (1·13–3·90)	0·019
Beach holiday						
No	1404 (76·1%)	504 (35·9%)	1·00	..	1·00	..
Yes	441 (23·9%)	127 (28·8%)	0·72 (0·55–0·93)	0·010	0·73 (0·56–0·95)	0·021
Traveller's diarrhoea¶						
No	1085 (60·1%)	329 (30·3%)	1·00	..	1·00	..
During travel	593 (32·8%)	235 (39·6%)	1·56 (1·24–1·96)	<0·001	1·42 (1·12–1·80)	0·003
Immediately after travel	41 (2·3%)	14 (34·1%)	1·19 (0·58–2·44)	0·640	1·3 (0·63–2·68)	0·477
During travel and immediately after travel	87 (4·8%)	44 (50·6%)	2·42 (1·50–3·91)	<0·001	2·31 (1·42–3·76)	0·001
Antibiotic use during travel‖						
No	1697 (92·8%)	553(32·6%)	1·00	..	1·00	..
Yes	132 (7·2%)	73 (55·3%)	2·65 (1·80–3·91)	<0·001	2·69 (1·79–4·05)	<0·001
Attendance of large (religious) gathering						
No	1744 (94·6%)	595 (34·1%)	1·00	..	1·00	..
Yes	100 (5·4%)	36 (36·0%)	0·56 (0·34–0·92)	0·020	0·57 (0·34–0·94)	0·028
Daily hand hygiene before meals						
None	782 (42·4%)	265 (33·9%)	1·00	..	1·00	..
Clean with alcohol	161 (8·7%)	69 (42·9%)	1·03 (0·71–1·51)	0·870	0·97 (0·66–1·44)	0·885
Clean with soap	666 (36·1%)	200 (30·0%)	0·82 (0·64–1·04)	0·100	0·77 (0·60–0·99)	0·044
Clean with alcohol and soap	235 (12·7%)	97 (41·3%)	1·03 (0·74–1·44)	0·860	1·12 (0·79–1·59)	0·518
Meal at street food stalls during travel						
Never	1248 (67·7%)	386 (30·9%)	1·00	..	1·00	..
Occasionally	513 (27·8%)	205 (40·0%)	1·37 (1·08–1·73)	0·010	1·33 (1·04–1·71)	0·022
Daily	83 (4·5%)	40 (48·2%)	2·09 (1·30–3·38)	0·003	1·78 (1·07–2·95)	0·025

ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae. *Numbers do not add up to 1847 because of missing values. Valid percentages are reported after removal of missing values, which were assumed to be random. †Numbers do not add up to 633 because of missing values. The demoninators for percentages are the numbers of travellers at risk given in the previous column. ‡Only adjusted for travel destination subregion, defined according to the United Nations geoscheme: Caribbean and Central America, middle and eastern Africa, central and eastern Asia, North America, Europe, and Oceania, southern Asia, southeastern Asia, western Asia, northern Africa, southern Africa, western Africa, and South America. §Adjusted for travel destination and travel variables shown in table. ¶Defined as ≥3 unformed stools within 24 h, with or without accompanying symptoms. ‖Most frequently used to treat gastroenteritis (41 [31·1%] of 132 travellers), of whom 17 (41·5%) took them without consulting a doctor.

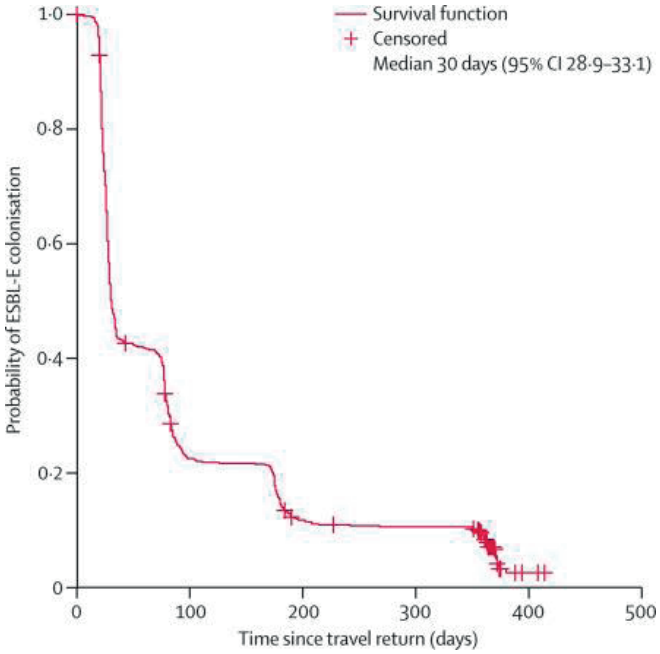

Figure 2. Kaplan-Meier estimate of time to decolonisation of ESBL-E in travellers
ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae.

had one or more follow-up isolates with the same ESBL group (TEM, SHV, CTX-M group 1, 2, 8, 9, or 25) as had been acquired by the index traveller.

We subsequently used a Markov model to estimate the transmission rate of ESBL-E after introduction into a household. We included 3330 people from 1542 households in the estimation of probability of transmission of ESBL-E after introduction. 381 households consisted of one person, 774 of two people, 187 of three, 160 of four, and 40 of five. Person-to-person transmission was estimated to occur at a rate of 0·0013 (95% CI 0·0005–0·0024) per colonised person per day, with background transmission occurring at a rate of 0·00073 (0·00054–0·0009) per day. The decolonisation rate was 0·010 (0·0092–0·011) per day. The sensitivity of the screening process was 90% (86–93). Thus, the probability of transmission from an ESBL-E-positive to an ESBL-E-negative person in the household was 12% (5–18).

DISCUSSION

Results from this large cohort study of travellers indicated that the risk of ESBL-E acquisition during travel is high, especially during travel to Asia and northern Africa. 11·3% of travellers who acquired EBSL-E remained colonised at 12 months after return, and

the estimated probability of onward transmission within households was 12%. Other important predictors for ESBL-E acquisition during travel were antibiotic use, traveller's diarrhoea that persisted after return, and pre-existing chronic bowel disease.

The frequency with which ESBL-E was imported by travellers is worrisome. 75·1% of travellers to southern Asia and 40–50% of those to central or eastern Asia, western Asia, and northern Africa acquired ESBL-E while travelling. Additionally, in central and eastern Africa, frequency of ESBL-E acquisition was substantial in some countries, particularly Uganda (44·4%). So far, data on acquisition among travellers to countries in central and eastern Africa have been very limited. Additionally, we have previously shown acquisition of carbapenemases and plasmid-mediated *mcr-1* colistin-resistance genes in, respectively, five and six travellers in this study cohort.[14,15]

Only two of six studies that previously did multivariable risk factor analysis identified antibiotic use and traveller's diarrhoea as significant travel-associated predictors for ESBL-E acquisition,[6–8] which probably reflects limited power to do extensive risk factor analysis. Self-reported pre-existing chronic bowel disease (mainly inflammatory bowel disease, irritable bowel syndrome, and coeliac disease) was a new predictor for ESBL-E acquisition in this study. Antibiotic use, traveller's diarrhoea, and chronic bowel disease have well established associations with dysbiosis of the gut microbiota.[16–18] A dysbiosis-induced reduction in colonisation resistance being the underlying biological mechanism through which these factors predispose to ESBL-E acquisition is, therefore, conceivable. Antimicrobial agents have substantial effects on the gut microbiota, which mainly manifest as decreased colonisation resistance resulting in consequent emergence of pathogenic or antibiotic-resistant strains.[19] In this study we found that, second to travel destination, antibiotic use was the strongest predictor for ESBL-E acquisition, particularly quinolone use during travel. Pervasive disturbance in the human microbiota has been reported after ciprofloxacin treatment.[16,20] For amoxicillin, although the effect on the human microbiota is moderate, an increase in the abundance of resistant Enterobacteriaceae has been reported after its use.[16,19] Similar to other studies,[21] antibiotics were mostly used to treat gastroenteritis. Counselling before travel to refrain from the use of antibiotics to treat self-limiting infections could reduce the import of ESBL-E by travellers. Kantele and colleagues,[22] for example, showed that use of loperamide alone to treat mild traveller's diarrhoea was not associated with an increased risk of ESBL-E colonisation.

The significantly higher frequency of ESBL-E acquisition among travellers to Asia than other regions is probably due to the widespread dissemination of ESBL-E in these regions and high risk of food contamination. Diet-associated predictors, therefore, might differ by travel destination, and might have been missed in previous studies that did not stratify data by destination. In the overall analysis, food consumption from street vendors was associated with an increased risk of ESBL-E acquisition, but in the strati-

fied analysis in southern Asia daily food consumption at a hostel or guesthouse and in southeastern Asia consumption of raw vegetables were predictive factors.

While the frequency of acquisition of ESBL-E by travellers is fairly consistent across studies, duration of carriage has varied from 5% to 24% at 6 months after return.[6] In our study, we found that 65 (11·3%) of 577 travellers who acquired ESBL-E during travel had sustained colonisation (persistent or intermittent) 12 months after return. Although our study focused on asymptomatic carriage of ESBL-E, international travel has also been associated with ESBL-E infection among patients in the community and in hospital.[23,24] Depending on the local policies, therefore, empirical adjustment of antimicrobial therapy should be considered in patients recently returned from international travel.

Our findings suggest that strains or plasmids carrying CTX-M group 9 ESBL genes have a colonisation advantage that results in sustained carriage. This finding agrees with those from other studies showing sustained carriage associated with these genes in travellers returningfrom Asia, in the community and in hospital.[25,26] Moreover, colonisation in this study was longer in travellers who acquired ESBL-producing *E coli* than in those with ESBL-producing *K pneumoniae*. These observations might be explained by accessory colonisation factors, such as P-fimbriae or aerobactin, or differences in fitness costs and plasmid stability between *E coli* and *K pneumoniae*.[27,28]

Our mathematical model of onward transmission of ESBL-E in households of travellers, which took into account factors such as total number of household members, estimated 12% probability of transmission. In households of recently discharged patients, Hilty and colleagues[29] reported transmission of ESBL-E to 20 (22·7%) of 88 household contacts. This higher risk might be due to more frequent and longer exposure times of caregiving household members to discharged patients. Practising hand hygiene at home might lessen the risk of household transmission of ESBL-E.[30]

Our study has some potential limitations. First, as in most epidemiological studies, our study population was probably more affluent and healthy than the average for the general population, which could have led to selection that affected the frequency of ESBL-E acquisition and the statistical power and generalisability of the results. However, for bias to occur, selection would have to affect both the exposure and the outcome, which is unlikely in prospective cohort studies. Inferences drawn from our study are also unlikely to be affected by (selective) attrition, since loss to follow-up was minimal and 12-month follow-up was achieved in 92·2% of participants after travellers returned. Second, faecal cross-contamination during collection of stool samples could theoretically have affected the estimations of colonisation and transmission. We aimed to keep the risk of cross-contamination to a minimum by providing participants with clear instructions for sample collection, including graphics. Lastly, although our results showed very low background transmission rates, in the absence of molecular typing of strains or mobile genetic elements harbouring ESBL genes, some overestimation of the duration of

colonisation and household transmission due to novel ESBL-E acquisition from outside the household cannot be completely excluded.

320 million people visit Asia, northern Africa, and the Middle East per year[3] and, therefore, international travel is expected to contribute substantially to the emergence and spread of ESBL-E in travellers' countries of origin. Taking into account the total number of Dutch travellers visiting these regions annually, we estimate that each year between 3·0% and 7·1% of the Dutch population acquires an ESBL-E during travel to destinations outside Europe, northern America, and Oceania (appendix). Overall, with acquisition of 34·3% and sustained carriage after acquisition seen in 11·3% of travellers 12 months after return, plus a 12% probability of household transmissions, our findings support the substantial contribution of international travel to the spread of ESBL-E and antimicrobial resistance worldwide. The degree of consequence of the emergence and spread of antimicrobial resistance by travellers, however, differs by region, and is highly dependent on local prevalence of antimicrobial resistance in the country of origin.

CONTRIBUTORS

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. MRH, MCJB, AG, MPG, AMOL, NM, and EES contributed to the study design, data collection, or both. MSA, JMvH, MRH, MCJB, PJJvG, CS, HAV, MDdJ, DCM, and JP contributed to the data analysis and interpretation. MSA, JMvH, MRH, and JP drafted the Article with help from all authors. MSA, JMvH, MRH, MCJB, PJJvG, AG, MPG, CS, EES, HAV, MDdJ, DCM, and JP contributed to the critical revision of the drafts for important intellectual content. All authors read and approved the final version of the paper.

DECLARATION OF INTERESTS

We declare no competing interests.

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SUPPLEMENTARY APPENDIX

MATERIALS AND METHODS

Collection of fecal samples
Genotypic characterization of ESBL-E
Classification of travel destinations into subregions according to according to United Nations geoscheme
Logistic regression analyses
Cox regression analyses

SUPPLEMENTARY TABLES

Table E1: Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847).

Table E2: Incidence proportion and incidence rates (per 100 person-days of travel) for ESBL-E acquisition in Dutch travellers according to the most visited countries (n=1047).

Table E3: Predictors for ESBL-E acquisition among at risk travellers to South-Eastern Asia (n = 540) in the final adjusted logistic regression model after manual stepwise elimination.

Table E4: Predictors for ESBL-E acquisition among at risk travellers to Southern Asia (n = 181) in the final adjusted logistic regression model after manual stepwise elimination.

Table E5: Predictors for ESBL-E acquisition among at risk travellers to Eastern Africa (n = 190) in the final adjusted logistic regression model after manual stepwise elimination.

Table E6: Univariable and multivariable Cox regression analyses on potential predictors for prolonged ESBL-E carriage upon acquisition during travel (n = 633).

Table E7: Predictors for prolonged ESBL-E carriage upon acquisition (n = 633) during travel in the final adjusted Cox regression model.

Table E8: Estimation of annual travel-related ESBL-E acquisition in Dutch population in 2013 (excluding North America, Europe & Oceania).

SUPPLEMENTARY FIGURES

Figure E1. Flowchart of study.

Figure E2. Acquisition of unique ESBL genes (n = 692) by travellers (n = 633) with ESBL-E acquisition.

Figure E3. Duration of ESBL-E carriage among travellers with ESBL-E acquisition (n = 633).

Figure E4. Stratified Cox regression plots time to decolonization of ESBL-E in travellers according to travel destination Western Asia (A), ESBL genotype (B) and ESBL-producing species (C).

Figure E5. Flow chart of non-travelling and co-travelling household members at risk for acquisition of ESBL-E through onward transmission from household members that acquired ESBL-E during travel.

Figure E6. Model to estimate the transmission rate within households with 2 household members.

Figure E7. Model to estimate the transmission rate within households with 3 household members.

MATERIALS AND METHODS

Collection of fecal samples

Travellers and if applicable their participating non-travelling household members were instructed to self-collect fecal samples using the provided sample collection and shipment kits. The sample collection and shipment kit consisted of an instruction form, a safety bag, a bibulous tissue, a postage paid airbag envelope and a feces collection swab with modified Cary Blair transport medium (Fecal Swab®; Copan, Brescia, Italy).

In order to avoid potential cross-contamination and to ensure collection of sufficient fecal matter, participants were provided the following instructions on how to sample their stools: i. place plenty of toilet paper in the toilet before defecation to avoid stools to slide into the water; ii after defecation, stick the entire tip of the fecal swab in the stool to ensure that the entire tip is covered with fecal matter, and; iii. prevent at any cost that the fecal swab comes into contact with anything else that the stool itself (e.g. the toilet or toilet water). Subsequently, participants were instructed to package the sample according to the instructions and send to the laboratory immediately.

Genotypic characterization of ESBL-E

All phenotypically confirmed ESBL-E isolates acquired during travel were screened for the presence of ESBL genes using microarray as described previously.[1-3]

In short, bacterial DNA was extracted after overnight cultivation, followed by biotin labelling and amplification in a linear multiplex reaction using 184 primer and probe sets targeted at 124 resistance genes, and microarray hybridization in duplicate or triplicate of the resulting labelled mix (Identibac® AMR08; Alere Technologies GmbH, Jena, Germany). Mean signal intensities, as measured by calculating the quantitative staining value using IconoClust software installed on the Alere ArrayMate Reader, of the replicate spots per probe were used for analysis. Intensities of ≥0.4 were considered positive as established previously.[3]

The presence of ESBL genes was confirmed by PCR using primers specific for CTX-M groups 1, 2, 8, 9 and 25[1,4-6] and in-house primer sets. Further characterization by sequencing was performed for CTX-M groups 1 and 9. PCR confirmation and sequencing of detected TEM and SHV genes was limited to isolates with negative microarray results for all CTX-M group genes. A generic CTX-M PCR[7] was performed in case no ESBL genes were detected by microarray, and if positive, followed by specific PCR and sequence confirmation for the different CTX-M groups. Sequences were analysed using the NCBI GenBank (www.ncbi.nlm.nih.gov/) and Lahey (www.lahey.org/studies/web/html) databases.

Continent	UN subregion	countries
Africa	Eastern Africa	Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mayotte, Mozambique, Réunion, Rwanda, Seychelles, Somalia, Uganda United Republic of Tanzania, Zambia, Zimbabwe
	Middle Africa	Angola, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Sao Tome and Principe
	Northern Africa	Algeria, Egypt, Libya, Morocco, South Sudan, Sudan, Tunisia Western Sahara
	Southern Africa	Botswana, Lesotho, Namibia, South Africa, Swaziland
	Western Africa	Benin, Burkina Faso, Cape Verde, Cote d'Ivoire, Gambia Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria Saint Helena, Senegal, Sierra Leone, Togo
Americas	Carribean	Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Bonaire, Saint Eustatius and Saba, British Virgin Islands, Cayman Islands, Cuba, Curaçao, Dominica, Dominican Republic, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Montserrat, Puerto Rico, Saint-Barthélemy, Saint Kitts and Nevis, Saint Lucia, Saint Martin (French part), Saint Vincent and the Grenadines, Sint Maarten (Dutch part), Trinidad and Tobago, Turks and Caicos Islands, United States Virgin Islands
	Central America	Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama
	South America	Argentina, Bolivia (Plurinational State of), Brazil, Chile, Colombia, Ecuador, Falkland Islands (Malvinas), French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela (Bolivarian Republic of)
	Northern America	Bermuda, Canada, Greenland, Saint Pierre and Miquelon, United States
Asia	Central Asia	Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan
	Eastern Asia	China, China, Hong Kong Special Administrative Region China, Macao Special Administrative Region, Democratic People's Republic of, Korea, Japan, Mongolia, Republic of Korea
	Southern Asia	Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Maldives, Nepal, Pakistan, Sri Lanka
	South-Eastern Asia	Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Viet Nam
	Western Asia	Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, Yemen

Europe	Eastern Europe	Bulgaria, Czech Republic, Hungary, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, Ukraine
	Northern Europe	Åland Islands, Channel Islands, Denmark, Estonia, Faeroe Islands, Finland, Guernsey, Iceland, Ireland, Isle of Man, Jersey, Latvia, Lithuania, Norway, Sark, Svalbard and Jan Mayen Islands, Sweden, United Kingdom of Great Britain and Northern Ireland
	Southern Europe	Andorra, Bosnia and Herzegovina, Croatia, Gibraltar, Greece, Holy See, Italy, Malta, Montenegro, Portugal, San Marino, Serbia, Slovenia, Spain, The former Yugoslav Republic of Macedonia
	Western Europe	Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, Netherlands, Switzerland
Oceania	Australia & New Zealand	Australia, New Zealand, Norfolk Island
	Melanesia	Fiji, New Caledonia, Papua New Guinea, Solomon Islands Vanuatu
	Micronesia	Guam, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Northern Mariana Islands, Palau
	Polynesia	American Samoa, Cook Islands, French Polynesia, Niue Pitcairn, Samoa, Tokelau, Tonga, Tuvalu, Wallis and Futuna Islands

Classification of travel destinations into subregions according to United Nations geoscheme

Logistic regression analyses

To identify predictors associated with ESBL-acquisition during travel we used the purposeful selection method as proposed by Hosmer and Lemeshow. The selection process began by a bivariable logistic regression analysis for each individual predictor as independent variable and ESBL-E acquisition as dependent variable, while adjusting for travel destination. As travel destination appeared a strong confounder, this approach was used instead of a univariable regression as originally proposed by Hosmer and Lemeshow. Before starting the multivariable analysis, variables were tested for multicollinearity and for interaction with travel destination (subregion). Variables that showed interaction with travel destination were removed. Subsequently, all potential predictors with $p<0.25$ in the bivariable regression were entered together in a multivariable logistic regression model. This multivariable model was reduced by removing variables one at the time if they were neither statistically significant ($p< 0.05$, starting with the variable with the highest p-value) nor a confounder (change in one of the remaining parameter estimates greater than 20% compared to the full model). At the end of this step the model contained only significant variables and confounders. Thereafter all potential predictors that were initially not selected for the multivariable regression model (i.e. those with $p>0.25$ in the bivariable regression models) were added separately to the model with significant variables and confounders retained earlier. This step can be helpful in identifying predictors that, by themselves, are not significantly related to the outcome but make an important contribution in the presence of other variables. All variables that appear significant at $p<0.15$ were put in the model and the model is iteratively reduced as before. The final model only included significant variables ($p<0.05$) and confounders, presented with odds ratio's and accompanying 95% confidence intervals. Because several dietary variables (consumption chicken, BBQ meat, pork) interacted with travel destination in association to ESBL-E acquisition (effect modification), we decided to perform separate bivariable and multivariable analyses for the subregions South-Eastern Asia, Southern Asia and Eastern Africa. The logistic regression analyses per subregion were conducted following the same approach, with the exception that analyses were now adjusted for country of travel destination instead of subregion. See online supplementary material table E1 for all the potential predictors considered.

Cox regression analyses

Univariable Cox regression analyses were conducted to identify predictors associated with decolonization. Variables associated with $p< 0.05$ were subsequently entered into a multivariable Cox regression model. See the online supplementary material table E5 for all the potential predictors considered.

SUPPLEMENTARY TABLES

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847).

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Median age in years [IQR]						
	50·76 [33·04:60·73]	50·52 [32·33:59·95]	1·00 (0·99-1·00)	0·220		
Gender						
Male	847 (46·03%)	295/847 (34·83%)	1·00			
Female	993 (54·97%)	336/993 (33·84%)	0·97 (0·78-1·19)	0·748		
Median weight in kg [IQR]						
	75·00 [66·00:85·00]	76·00 [66·00:85·00]	1·00 (1·00-1·01)	0·521		
Country of birth						
Netherlands†	1719 (93·37%)	590/1719 (34·32%)	1·00			
Other country	122 (6·63%)	40/122 (32·79%)	0·83 (0·54-1·27)	0·391		
Education level						
No education, elementary school or pre-vocational secondary education †	234 (12·72%)	78/234 (33·33%)	1·00			
Vocational secondary education	266 (14·46%)	91/266 (34·21%)	1·08 (0·72-1·61)	0·707		
Senior general secondary education or pre-university education	181 (9·84%)	62/181 (34·25%)	0·90 (0·58-1·42)	0·657		
Higher professional education	599 (32·55%)	204/599 (34·06%)	1·04 (0·73-1·47)	0·846		
Academic education	560 (30·43%)	195/560 (34·82%)	1·04 (0·73-1·49)	0·817		
Housing						
Flat or apartment†	659 (35·82%)	223/659 (33·84%)	1·00			
Terraced house	621 (33·75%)	207/621 (33·33%)	1·00 (0·78-1·28)	0·985		
Semi-detached house	207 (11·25%)	74/207 (35·75%)	1·25 (0·88-1·78)	0·220		
Detached house	271 (14·73%)	93/271 (34·32%)	0·99 (0·71-1·37)	0·944		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Other	82 (4·46%)	32/82 (39·02%)	1·04 (0·62-1·76)	0·886		
Cigarette smoking						
No†	1329 (77·09%)	473/1329 (35·59%)	1·00			
Yes	395 (22·91%)	115/395 (29·11%)	0·75 (0·575-0·979)	0·034		
Alcohol use (median, number of glasses per week [IQR]						
	5·00 [2·00:10·00]	5·00 [2·00-10·00]	1·01 (0·99-1·02)	0·381		
Diarrhoea before travel§						
No diarrhoea	1447 (78·73%)	482/1447 (33·31%)	1·00			
Diarrhoea in the past three months	349 (18·99%)	130/349 (37·25%)	1·19 (0·92-1·56)	0·192		
Diarrhoea at this moment only	0 (0·00%)	0 (0·00%)				
Diarrhoea in the past three months and at this moment	42 (2·29%)	16/42 (38·10%)	1·03 (0·52-2·06)	0·926		
Fever within three months prior to travel						
No†	1637 (88·82%)	561/1637 (34·27%)	1·00			
Yes	206 (11·18%)	69/206 (33·50%)	0·92 (0·66-1·28)	0·611		
Antibiotic use within three months prior to travel						
No†	1662 (90·62%)	568/1662 (34·18%)	1·00			
Yes	172 (9·38%)	59/172 (34·30%)	1·11 (0·78-1·57)	0·578		
Chronic disease‖						
No†	1404 (76·89%)	480/1404 (34·19%)				
Yes	422 (23·11%)	142/422 (33·65%)	1·03 (0·80-1·33)	0·802		
Chronic bowel disease‖						
No†	1793 (97·29%)	606/1793 (33·80%)	1·00		1·00	

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Yes	50 (2·71%)	24/50 (48·00%)	2·34 (1·26-4·34)	0·007	2·10 (1·13-3·90)	0·019
Antacid use						
No†	1607 (87·38%)	545/1607 (33·91%)	1·00			
Yes	232 (12·62%)	84/232 (36·21%)	1·17 (0·85-1·60)	0·344		
Corticosteroid use						
No†	1706 (93·17%)	594/1706 (34·82%)	1·00			
Topical use	78 (4·26%)	19/78 (·24·36%)	0·62 (0·35-1·10)	0·100		
Oral use	47 (2·57%)	10/47 (21·28%)	0·60 (0·28-1·27)	0·178		
Immunosuppressant use						
No†	1812 (99·3%)	618/1812 (34·11%)	1·00			
Yes	13 (0·7%)	6/13 (46·15%)	2·31 (0·68-7·89)	0·181		
Diet						
No diet†	1669 (90·56%)	563/1669 (33·73%)	1·00			
Vegetarian or vegan diet	93 (5·05%)	44/93 (47·31%)	1·54 (0·98-2·44)	0·063		
Other diet (Islamic, Jewish, other)	81 (4·40%)	23/81 (28·40%)	0·63 (0·36-1·08)	0·093		
Probiotics use						
Never†	1059 (57·93%)	357/1059 (33·71%)	1·00			
Rare	321 (17·56%)	126/321 (39·25%)	1·20 (0·91-1·58)	0·205		
Occasionally	233 (12·75%)	73/233 (31·33%)	0·93 (0·67-1·30)	0·673		
Frequent	102 (5·58%)	31/102 (30·39%)	0·80 (0·49-1·29)	0·357		
Daily	113 (6·18%)	36/113 (31·86%)	0·93 (0·59-1·46)	0·739		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Daily patient contact						
No profession in healthcare†	1421 (77·95%)	482/1421 (33·92%)	1·00			
Profession in healthcare without daily patient contact	99 (5·43%)	30/99 (30·30%)	0·88 (0·55-1·41)	0·583		
Medical profession in healthcare with daily patient contact	160 (8·78%)	67/160 (41·88%)	1·43 (0·99-2·06)	0·055		
Other profession in healthcare with daily patient contact	143 (7·84%)	44/143 (30·77%)	0·95 (0·64-1·43)	0·814		
Accommodation during travel‖						
Luxury†	396 (21·46%)	136/396 (34·34%)	1·00			
Hotel or apartment	457 (24·77%)	169/457 (36·98%)	1·20 (0·88-1·63)	0·240		
Low budget	205 (11·11%)	77/205 (37·56%)	1·29 (0·88-1·90)	0·200		
Tent	51 (2·76%)	10/51 (19·61%)	0·79 (0·35-1·81)	0·580		
Family or local people	91 (4·93%)	27/91 (29·67%)	1·03 (0·60-1·77)	0·920		
Ship	31 (1·68%)	8/31 (25·81%)	0·93 (0·38-2·26)	0·870		
Other	72 (3·90%)	17/72 (23·61%)	0·96 (0·50-1·84)	0·910		
Several	542 (29·38%)	187/542 (34·50%)	1·14 (0·85-1·54)	0·380		
Purpose of travel						
Holiday†	1553 (84·17%)	540/1553 (34·77%)	1·00			
Work/internship	154 (8·35%)	47/154 (30·52%)	0·84 (0·56-1·25)	0·390		
Visit to family or friends	77 (4·17%)	24/77 (31·17%)	0·98 (0·58-1·66)	0·950		
Other	61 (3·31%)	20/61 (32·79%)	0·82 (0·45-1·51)	0·530		
Type of holiday						
Luxury						
No†	1698 (92·03%)	580/1698 (34·16%)	1·00			

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Yes	147 (7·97%)	51/147 (34·69%)	1·01 (0·69-1·48)	0·950		
Beach						
No†	1404 (76·10%)	504/1404 (35·90%)	1·00		1·00	
Yes	441 (23·90%)	127/441 (28·80%)	0·72 (0·55-0·93)	0·010	0·73 (0·56-0·95)	0·021
Active in nature						
No†	1172 (63·52%)	416/1172 (35·49%)	1·00			
Yes	673 (36·48%)	215/673 (31·95%)	0·90 (0·72-1·13)	0·370		
Backpacking						
No†	1442 (78·16%)	453/1442 (31·41%)	1·00			
Yes	403 (21·84%)	178/403 (44·17%)	1·55 (1·20-1·99)	<0·001		
Safari						
No†	1522 (82·49%)	554/1522 (36·40%)	1·00			
Yes	323 (17·51%)	77/323 (23·84%)	1·01 (0·67-1·52)	0·960		
Citytrip						
No†	1446 (78·37%)	481/1446 (33·26%)	1·00			
Yes	399 (21·63%)	150/399 (37·59%)	1·06 (0·82-1·38)	0·640		
Spiritual						
No†	1821 (98·70%)	620/1821 (34·05%)	1·00			
Yes	24 (1·30%)	11/24 (45·83%)	0·91 (0·36-2·30)	0·840		
Other						
No†	1489 (80·70%)	493/1489 (33·11%)	1·00			
Yes	356 (19·30%)	138/356 (38·76%)	1·09 (0·84-1·42)	0·510		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Median duration of travel in days [IQR]						
	20·00 [15·00:25·00]	20·00 [15·00:24·00]	1·00 (0·99-1·01)	0·790		
Traveller's diarrhoea§						
No traveller's diarrhoea†	1085 (60·08%)	329/1085 (30·32%)	1·00		1·00	
Diarrhoea during travel	593 (32·83%)	235/593 (39·63%)	1·56 (1·24-1·96)	<0·001	1·42 (1·12-1·80)	0·003
Diarrhoea immediately after travel	41 (2·27%)	14/41 (34·15%)	1·19 (0·58-2·44)	0·640	1·30 (0·63-2·68)	0·477
Diarrhoea during and immediately after travel	87 (4·82%)	44/87 (50·57%)	2·42 (1·50-3·91)	<0·001	2·31 (1·42-3·76)	0·001
Fever during travel						
No†	1728 (93·76%)	575/1728 (33·28%)	1·00			
Yes	115 (6·24%)	55/115 (47·83%)	1·57 (1·04-2·39)	0·030		
Medical care during travel						
None†	1767 (95·93%)	591/1767 (33·45%)	1·00			
Visit to doctor or hospital	75 (4·07%)	39/75 (52·00%)	2·10 (1·27-3·47)	<0·001		
Antibiotic use during travel						
No†	1697 (92·78%)	553/1697 (32·59%)	1·00		1·00	
Yes	132 (7·22%)	73/132 (55·30%)	2·65 (1·80-3·91)	<0·001	2·69 (1·79-4·05)	<0·001
Use anti-diarrhoeal drugs during travel						
No†	1460 (79·13%)	475/1460 (32·53%)				
Yes	385 (20·87%)	156/385 (40·52%)	1·36 (1·06-1·74)	0·020		
Use analgesics during travel						
No†	1510 (81·84%)	511/1510 (33·84%)	1·00			
Yes	335 (18·16%)	120/335 (35·82%)	1·02 (0·78-1·33)	0·900		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Use antacids during travel						
No†	1752 (94·96%)	598/1752 (34·13%)	1·00			
Yes	93 (5·04%)	33/93 (35·48%)	1·11 (0·69-1·80)	0·670		
Use other medication without prescription during travel						
No†	1631 (88·40%)	556/1631 (34·09%)	1·00			
Yes	214 (11·60%)	75/214 (35·05%)	1·14 (0·82-1·58)	0·440		
Activities during travel						
Attendance large (religious) gathering						
No†	1744 (94·58%)	595/1744 (34·12%)	1·00		1·00	
Yes	100 (5·42%)	36/100 (36·00%)	0·56 (0·34-0·92)	0·020	0·57 (0·34-0·94)	0·028
Visit to local market						
Never†	234 (12·69%)	65/234 (27·78%)	1·00			
Occasionally	1406 (76·25%)	462/1406 (32·86%)	1·00 (0·71-1·41)	0·990		
Daily	204 (11·06%)	104/204 (50·98%)	2·04 (1·32-3·15)	<0·001		
Visit to local population daily						
No†	1488 (80·69%)	499/1488 (33·53%)	1·00			
Yes	356 (19·31%)	132/356 (37·08%)	1·12 (0·86-1·46)	0·390		
Contact with orphan children						
No†	1566 (84·92%)	532/1566 (33·97%)	1·00			
Yes	278 (15·08%)	99/278 (35·61%)	1·15 (0·84-1·56)	0·380		
Contact with patients						
No†	1773 (96·15%)	609/1773 (34·35%)	1·00			

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Yes	71 (3·85%)	22/71 (30·99%)	1·07 (0·60-1·89)	0·830		
Daily contact with animals						
No†	1743 (94·52%)	601/1743 (34·48%)	1·00			
Yes	101 (5·48%)	30/101 (29·70%)	0·97 (0·60-1·56)	0·890		
Stay in rural area daily						
No†	1376 (74·62%)	496/1376 (36·05%)	1·00			
Yes	468 (25·38%)	135/468 (28·85%)	0·88 (0·68-1·15)	0·350		
Trek through jungle						
No†	1026 (55·64%)	370/1026 (36·06%)	1·00			
Yes	818 (44·36%)	261/818 (31·91%)	0·95 (0·76-1·18)	0·620		
Swim in sea daily						
No†	1689 (91·59%)	581/1689 (34·40%)	1·00			
Yes	155 (8·41%)	50/155 (32·26%)	0·90 (0·62-1·30)	0·570		
Swim in swimming pool daily						
No†	1622 (87·96%)	565/1622 (34·83%)	1·00			
Yes	222 (12·04%)	66/222 (29·73%)	0·81 (0·58-1·12)	0·200		
Swim in other waters						
No†	1313 (71·20%)	463/1313 (35·26%)	1·00			
Yes	531 (28·80%)	168/531 (31·64%)	1·01 (0·79-1·28)	0·950		
Daily hand hygiene before meals during travel						
No daily hand hygiene before meals†	782 (42·41%)	265/782 (33·89%)	1·00		1·00	
Daily hand washing before meals with alcohol	161 (8·73%)	69/161 (42·86%)	1·03 (0·71-1·51)	0·870	0·97 (0·66-1·44)	0·885

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Daily hand washing before meals with soap	666 (36·12%)	200/666 (30·03%)	0·82 (0·64-1·04)	0·100	0·77 (0·60-0·99)	0·044
Daily hand washing before meals with alcohol and soap	235 (12·74%)	97/235 (41·28%)	1·03 (0·74-1·44)	0·860	1·12 (0·79-1·59)	0·518
Daily hand hygiene after toilet use during travel						
No daily hand hygiene after toilet use†	372 (20·17%)	128/372 (34·41%)	1·00			
Daily hand washing after toilet use with alcohol	115 (6·24%)	49/115 (42·61%)	1·02 (0·64-1·63)	0·930		
Daily hand washing after toilet use with soap	1085 (58·84%)	341/1085 (31·43%)	0·91 (0·69-1·19)	0·470		
Daily hand washing after toilet use with alcohol and soap	272 (14·75%)	113/272 (41·54%)	1·05 (0·74-1·50)	0·790		
Location of meals during travel						
Daily meal at hotel						
No†	1244 (67·46%)	420/1244 (33·76%)	1·00			
Yes	600 (32·54%)	211/600 (35·17%)	0·90 (0·71-1·13)	0·370		
Daily meal at hostel/guesthouse						
No†	1708 (92·62%)	585/1708 (34·25%)	1·00			
Yes	136 (7·38%)	46/136 (33·82%)	1·03 (0·68-1·56)	0·900		
Daily meal at luxurious/ star restaurant						
No†	1725 (93·55%)	587/1725 (34·03%)	1·00			
Yes	119 (6·45%)	44/119 (36·97%)	1·16 (0·76-1·77)	0·490		
Daily meal at local restaurant						
No†	1211 (65·67%)	389/1211 (32·12%)	1·00			
Yes	633 (34·33%)	242/633 (38·23%)	1·28 (1·02-1·60)	0·030		
Meal at food stalls along the road						
Never†	1248 (67·68%)	386/1248 (30·93%)	1·00		1·00	

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Occasionally	513 (27·82%)	205/513 (39·96%)	1·37 (1·08-1·73)	0·010	1·33 (1·04-1·71)	0·022
Daily	83 (4·50%)	40/83 (48·19%)	2·09 (1·30-3·38)	0·003	1·78 (1·07-2·95)	0·025
Daily meal at home with family or local population during travel						
No†	1719 (93·22%)	596/1719 (34·67%)	1·00			
Yes	125 (6·78%)	35/125 (28·00%)	0·87 (0·56-1·35)	0·530		
Food consumption during travel						
Tap water¶						
Hardly ever†	1631 (88·55%)	597/1631 (36·60%)	1·00			
Occasionally	86 (4·67%)	17/86 (19·77%)	0·69 (0·38-1·24)	0·220		
Often	125 (6·79%)	17/125 (13·60%)	0·54 (0·31-0·95)	0·030		
Ice in soda¶						
Hardly ever†	967 (52·50%)	363/967 (37·54%)	1·00			
Occasionally	454 (24·65%)	136/454 (29·96%)	0·88 (0·67-1·15)	0·340		
Often	421 (22·86%)	132/421 (31·35%)	1·03 (0·78-1·37)	0·830		
Beef¶						
Hardly ever†	581 (31·54%)	247/581 (42·51%)	1·00			
Occasionally	803 (43·59%)	234/803 (29·14%)	0·80 (0·62-1·02)	0·080		
Often	458 (24·86%)	150/458 (32·75%)	1·04 (0·78-1·39)	0·780		
Pork¶						
Hardly ever†	967 (52·50%)	352/967 (36·40%)	1·00			
Occasionally	637 (34·58%)	179/637 (28·10%)	0·89 (0·69-1·13)	0·330		
Often	238 (12·92%)	100/238 (42·02%)	1·42 (1·03-1·96)	0·030		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Chicken¶						
Hardly ever†	290 (15·74%)	125/290 (43·10%)	1·00			
Occasionally	643 (34·91%)	198/643 (30·79%)	0·67 (0·49-0·92)	0·010		
Often	909 (49·35%)	308/909 (33·88%)	0·67 (0·49-0·90)	0·010		
Other meat¶						
Hardly ever†	1235 (67·05%)	453/1235 (36·68%)	1·00			
Occasionally	480 (26·06%)	146/480 (30·42%)	0·96 (0·75-1·23)	0·770		
Often	127 (6·89%)	32/127 (25·20%)	0·74 (0·47-1·16)	0·190		
BBQ meat¶						
Hardly ever†	1224 (66·45%)	453/1224 (37·01%)	1·00			
Occasionally	499 (27·09%)	153/499 (30·66%)	1·00 (0·78-1·27)	0·980		
Often	119 (6·46%)	25/119 (21·01%)	0·73 (0·45-1·18)	0·200		
Undercooked meat¶						
Hardly ever†	1712 (92·94%)	597/1712 (34·87%)	1·00			
Occasionally or often	130 (7·06%)	34/130 (26·15%)	1·21 (0·78-1·87)	0·400		
Raw meat[						
Never†	1766 (95·87%)	608/1766 (34·43%)	1·00			
Ever	76 (4·13%)	23/76 (30·26%)	1·11 (0·64-1·92)	0·720		
Eggs¶						
Hardly ever†	222 (12·05%)	71/222 (31·98%)	1·00			
Occasionally	593 (32·19%)	183/593 (·30·86%)	1·08 (0·75-1·55)	0·680		
Often	1027 (55·75%)	377/1027 (36·71%)	1·20 (0·86-1·68)	0·290		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Raw vegetables¶						
Hardly ever†	478 (25·95%)	169/478 (35·36%)	1·00			
Occasionally	665 (36·10%)	247/665 (37·14%)	1·32 (1·01-1·73)	0·040		
Often	699 (37·95%)	215/699 (30·76%)	1·21 (0·92-1·59)	0·180		
Salad prepared by others¶						
Hardly ever†	639 (34·69%)	243/639 (38·03%)	1·00			
Occasionally	659 (35·78%)	217/659 (32·93%)	1·00 (0·78-1·28)	1·000		
Often	544 (29·53%)	171/544 (31·43%)	1·11 (0·84-1·45)	0·470		
Unpeeled fruit¶						
Hardly ever†	1238 (67·21%)	436/1238 (35·22%)	1·00			
Occasionally	373 (20·25%)	119/373 (31·90%)	0·96 (0·73-1·26)	0·760		
Often	231 (12·54%)	76/231 (32·90%)	0·93 (0·68-1·29)	0·680		
Fruit prepared by others¶						
Hardly ever†	553 (30·02%)	181/553 (32·73%)	1·00			
Occasionally	598 (32·46%)	215/598 (35·95%)	1·22 (0·93-1·60)	0·150		
Often	691 (37·51%)	235/691 (34·01%)	1·28 (0·98-1·68)	0·070		
Shellfish¶						
Hardly ever†	1536 (83·39%)	525/1536 (34·18%)	1·00			
Occasionally or often	306 (16·61%)	106/306 (34·64%)	1·27 (0·96-1·69)	0·100		
Raw fish¶						
Hardly ever†	1683 (91·37%)	575/1683 (34·17%)	1·00			
Occasionally or often	159 (8·63%)	56/159 (35·22%)	1·30 (0·90-1·88)	0·160		

Table E1. Bivariable and multivariable logistic regression analyses on potential predictors for ESBL-E acquisition among at risk travellers (n = 1847). (continued)

	All travellers n (%)	Travellers with ESBL acquisition n/N (%)	Odds ratio (95%CI)*	p-value	Adjusted Odds ratio (95% CI)‡	p-value
Unpasteurized milk/cheese¶						
Hardly ever†	1690 (91·75%)	570/1690 (33·73%)	1·00			
Occasionally or often	152 (8·25%)	61/152 (40·13%)	1·50 (1·03-2·18)	0·040		
Fresh milk from bovine, sheep or goat[						
Never†	1781 (96·69%)	609/1781 (34·19%)	1·00			
Ever	61 (3·31%)	22/61 (36·07%)	0·83 (0·45-1·51)	0·540		

†reference category

*Only adjusted for travel destination defined as UN subregions: Caribbean/Central America, Middle/Eastern Africa, Central/Eastern Asia, Northern America/Europe/Oceania, Southern Asia, South-Eastern Asia, Western Asia, Northern Africa, Southern Africa, Western Africa, South America

‡Adjusted for travel destination as well as age, gender, weight, country of birth, education level, housing, alcohol use, diarrhoea, fever, antibiotic use, chronic disease, bowel disease, antacid/corticosteroid/immunosuppressant use, diet, probiotics use, daily patient contact, accommodation, purpose of travel, type of holiday, duration of travel (in days), traveller's diarrhoea, fever, medical care during travel, antibiotic use, use of medication without prescription (anti-diarrhoeal drugs;analgesics;antacids), activities during travel (attendance large (religious) gathering; visiting local markets, population; contact with orphan children/patients/animals, stay in rural area, trek through jungle, swim in sea/swimming pool/other waters, daily washing hands before eating/after toilet use, daily meal at hotel/ hostel, guesthouse/luxurious restaurant/local restaurant/, meal at food stalls along the road, daily meal at home with family or local population, consumption of tap water, ice in soda, beef, pork, chicken, other meat, BBQ meat, undercooked meat, raw meat, eggs, raw vegetables, salad prepared by others, unpeeled fruit, fruit prepared by others, shellfish, raw fish, unpasteurized milk/cheese, fresh milk from bovine, sheep or goat

§(Traveller's) diarrhoea was defined as three or more unformed stools per 24 hour period with or without accompanying symptoms

[Chronic disease and chronic bowel disease was considered to be present when self-reported to be present by traveller

||Luxury=all inclusive resort/4 or 5 star hotel, hotel or apartment= no star, 1,2, or 3 star hotel or apartment, low budget=low budget, sleep in, guesthouse, (youth) hostel

¶Hardly ever= never or less than once a week, occasionally= on average once a week, often= several times a week or daily

[Never=never, ever=less than once a week, on average once a week, several times a week or daily

Table E2. Incidence proportion and incidence rates (per 100 person-days of travel) for extended-spectrum beta-lactamase producing Enterobacteriaceae acquisition in Dutch travellers according to the most visited countries (n=1047).

Destination†	Travellers (n)	Travellers (n) with ESBL acquisition	ESBL incidence proportion		Travel-days all travellers	Mean duration of travel (SD)	ESBL incidence rate/100 pdt	
			%	95% CI‡			IR§	95% CI§
India	79	70	88·61	79·75-93·89	1647	20·85 (14·31)	12·18	9·05-16·25
Egypt	30	24	80·00	62·69-90·50	355	11·83 (3·70)	13·98	8·73-21·54
Nepal	29	23	79·31	61·61-90·15	623	21·48 (10·83)	7·49	4·64-11·57
Vietnam	36	26	72·22	56·01-84·15	833	23·14 (10·94)	6·10	3·91-9·14
Peru	20	12	60·00	38·66-78·12	430	21·50 (5·30)	4·28	2·26-7·37
China	67	36	53·73	41·92-65·14	1333	19·90 (11·28)	4·19	2·93-5·81
Myanmar	15	8	53·33	30·12-75·19	288	19·20 (3·95)	3·91	1·76-7·42
Thailand	89	46	51·69	41·45-61·78	1715	19·27 (5·77)	3·78	2·77-5·02
Sri Lanka	43	22	51·16	36·75-65·38	850	19·77 (6·34)	3·66	2·31-5·47
Uganda	27	12	44·44	27·59-62·69	586	21·70 (20·45)	2·65	1·41-4·49
Turkey	16	7	43·75	23·10-66·82	150	9·38 (2·85)	6·03	2·57-11·81
Ghana	20	8	40·00	21·88-61·34	372	18·60 (12·14)	2·65	1·20-4·97
Kenya	30	10	33·33	19·23-51·22	581	19·37 (16·47)	1·95	0·97-3·42
Malaysia	28	7	25·00	12·68-43·36	543	19·39 (6·18)	1·50	0·64-2·91
Tanzania	57	14	24·56	15·23-37·10	1010	17·72 (11·49)	1·73	0·99-2·76
Morocco	36	8	22·22	11·72-38·09	494	13·72 (7·21)	1·81	0·83-3·38
Mexico	18	4	22·22	9·00-45·22	271	15·06 (5·77)	1·73	0·53-4·03
Indonesia	211	40	18·96	14·24-24·78	4823	22·86 (8·95)	0·92	0·66-1·24
Gambia	49	8	16·33	8·51-29·04	669	13·65 (8·70)	1·30	0·59-2·43
Brazil	25	2	8·00	2·22-24·97	500	20·00 (7·64)	0·42	0·07-1·30
South Africa	66	3	4·55	1·56-12·53	1409	21·35 (8·31)	0·22	0·05-0·56
Suriname	56	2	3·57	0·99-12·12	1498	26·75 (15·54)	0·14	0·02-0·42

*ESBL, extended spectrum beta-lactamase; SD, standard deviation; 95% CI, 95% confidence interval; IR, incidence rate; pdt, person-days of travel

†data are shown for 22 countries with 15 or more visitors

‡based on binomial distribution (Wilson Score interval)

§calculated with maximum likelihood estimation method based on a constant acquisition rate with right-censored and interval-censored data

Table E3. Predictors for ESBL acquisition among at risk travellers to South-Eastern Asia (n = 540) in the final adjusted logistic regression model after manual stepwise elimination.

	Travellers at risk (%)‡	Travellers with ESBL acquisition n/N (%)	Adjusted odds ratio (95% CI)*	p-value
Antibiotic use during travel				
No†	485 (90·65%)	166/485 (34·23%)		
Yes	50 (9·35%)	32/50 (64·00%)	3·90 (1·90-7·98)	<0·001
Activities during travel				
Attendance large (religious) gathering				
No†	511 (94·81%)	193/511 (37·77%)		
Yes	28 (5·20%)	7/28 (25·00%)	0·29 (0·09-0·89)	0·031
Food consumption during travel				
Raw vegetables				
Hardly ever†	168 (31·17%)	43/168 (25·60%)		0·008
Occasionally	201 (37·29%)	79/201 (39·30%)	2·18 (1·29-3·68)	0·004
Often	170 (31·54%)	78/170 (45·88%)	1·97 (1·15-3·40)	0·014
Diet				
No diet†	490 (90·74%)	188/490 (38·37%)		0·007
Vegetarian or vegan diet	28 (5·19%)	10/28 (35·71%)	0·84 (0·28-2·53)	0·762
Other diet (Islamic, Jewish, other)	22 (4·07%)	2/22 (9·09%)	0·08 (0·02-0·38)	0·002

*Adjusted for travel destination and variables shown in bold
‡Numbers do not add up to 540 travellers because of missing data

Table E4. Predictors for ESBL acquisition among at risk travellers to Southern Asia (n = 181) in the final adjusted logistic regression model after manual stepwise elimination.

	Travellers at risk n (%)‡	Travellers with ESBL acquisition n/N (%)	Adjusted odds ratio (95% CI)*	p-value
Accommodation				
Luxury†	34 (18·78%)	28/34 (82·35%)		
Hotel or apartment	51 (28·18%)	39/51 (76·47%)	0·23 (0·05-0·96)	0·044
Low budget	26 (14·36%)	17/26 (65·38%)	0·09 (0·02-0·55)	0·008
Other	70 (38·67%)	52/70 (74·29%)	0·24 (0·06-1·00)	0·05
Contact with orphan children				
No†	141 (77·90%)	101/141 (71·63%)		
Yes	40 (22·10%)	35/40 (87·50%)	7·26 (1·74-30·26)	0·007
Daily meal at hostel/guesthouse daily during travel				
No†	159 (87·85%)	117/159 (73·58%)		
Yes	22 (12·15%)	19/22 (86·36%)	15·40 (2·62-90·56)	0·002
Daily meal at home with family or local population				
No†	171 (94·48%)	130/171 (76·02%)		
Yes	10 (5·52%)	6/10 (60·00%)	0·06 (0·01-0·42)	0·004
Frequency of consumption food				
Raw vegetables				
Hardly ever†	67 (37·02%)	57/67 (85·07%)		
Occasionally	73 (40·33%)	50/73 (68·49%)	0·34 (0·12-0·93)	0·036
Often	41 (22·65%)	29/41 (70·73%)	0·26 (0·08-0·87)	0·028
Shellfish				
Hardly ever†	171 (94·48%)	131/171 (76·61%)		
Occasionally or often	10 (5·52%)	5/10 (50·00%)	0·15 (0·03-0·78)	0·024

*Adjusted for travel destination and variables shown in bold
‡Numbers do not add up to 181 travellers because of missing data

Table E5. Predictors for ESBL acquisition among at risk travellers to Eastern Africa (n = 190) in the final adjusted logistic regression model after manual stepwise elimination.

	Travellers at risk n (%)‡	Travellers with ESBL acquisition n/N (%)	Adjusted odds ratio (95% CI)*	p-value
Accommodation				
Luxury†	32 (16·84%)	11/32 (34·38%)		
Hotel or apartment	35 (18·42%)	10/35 (28·57%)	0·63 (0·18-2·18)	0·466
Low budget	24 (12·63%)	6/24 (25·00%)	0·46 (0·11-2·01)	0·304
Other	99 (52·11%)	27/99 (27·27%)	0·54 (0·20-1·49)	0·235
Reason travel				
Holiday†	129 (67·89%)	37/129 (28·68%)		
Work/internship	31 (16·32%)	9/31 (29·03%)	0·76 (0·27-2·16)	0·607
Visit to family or friends	11 (5·79%)	5/11 (45·45%)	1·58 (0·36-6·86)	0·546
Other	19 (10·00%)	3/19 (15·79%)	0·38 (0·08-1·77)	0·215
Duration stay abroad (in days)	190	54	0·98 (0·94-1·02)	0·215
Visit to local market				
Never†	36 (18·95%)	12/36 (33·33%)		
Occasionally	132 (69·47%)	31/132 (23·48%)	0·62 (0·24-1·56)	0·307
Daily	22 (11·58%)	11/22 (50·00%)	4·89 (1·15-20·81)	0·032
Stay in rural area daily				
No†	87 (45·79%)	20/87 (22·99%)		
Yes	103 (54·21%)	34/103 (33·01%)	2·63 (1·20-5·79)	0·016
Swim in waters other than sea or swimming pool				
No†	159 (83·68%)	49/159 (30·82%)		
Yes	31 (16·32%)	5/31 (16·13%)	0·27 (0·07-1·02)	0·054
Location of meals during travel				
Meal at food stalls along the road during travel				
No†	187 (98·42%)	52/187 (27·81%)		
Yes	3 (1·58%)	2/3 (66·67%)	5·53 (0·26-119·66)	0·276
Gender				
Male	88 (46·56%)	29/88 (32·95%)		
Female	101 (53·44%)	25/101 (24·75%)	0·49 (0·23-1·06)	0·070

*Adjusted for travel destination and variables shown in bold
‡Numbers do not add up to 190 travellers because of missing data

Table E6. Univariable and multivariable Cox regression analyses on potential predictors for prolonged ESBL-E carriage upon acquisition during travel (n = 633).

	Travellers with ESBL acquisition n* (%)	Hazard ratio (95% CI)†	p-value	Adjusted Hazard ratio (95% CI)†‡	p-value
Genotype group					
CTX-M group 1 ESBL	399 (64·04%)				
CTX-M group 9 ESBL	175 (28·09%)	0·67 (0·56-0·81)	0·000	0·66 (0·53-0·81)	<0·001
CTX-M group 1 and CTX-M group 9 ESBL	10 (1·61%)	0·89 (0·44-1·79)	0·740	0·96 (0·47-1·94)	0·900
Other ESBL group	39 (6·26%)	1·12 (0·79-1·58)	0·532	0·95 (0·67-1·37)	0·797
ESBL species					
E. coli	537 (86·20%)				
K. pneumoniae	27 (4·33%)	2·23 (1·51-3·30)	0·000	2·17 (1·45-3·26)	<0·001
E. coli and *K. pneumoniae*	38 (6·10%)	1·28 (0·91-1·78)	0·155	1·27 (0·90-1·78)	0·176
Other species	21 (3·37%)	1·19 (0·75-1·89)	0·455	1·14 (0·71-1·82)	0·595
Age	617	1 (1·00-1·00)	0·234		
Gender					
Male	292 (47·02%)				
Female	329 (53·32%)	1·04 (0·88-1·23)	0·641		
Duration stay abroad (in days)	617	0·992 (0·986-0·999)	0·021	1·00 (0·99-1·00)	0·180
Bowel disease					
No†	596 (96·13%)				
Yes	24 (3·87%)	0·93 (0·62-1·42)	0·748		
Travel destination					
Central/Eastern Asia					
No†	580 (93·40%)				
Yes	41 (6·60%)	0·78 (0·56-1·11)	0·165	1·04 (0·68-1·59)	0·864
South-Eastern Asia					
No†	426 (68·60%)				
Yes	195 (31·40%)	0·90 (0·75-1·07)	0·222	1·07 (0·79-1·44)	0·671
Southern Asia					
No†	485 (78·10%)				
Yes	136 (21·90%)	0·87 (0·72-1·06)	0·171	0·87 (0·63-1·19)	0·376
Western Asia					
No†	609 (98·07%)				
Yes	12 (1·93%)	2·25 (1·27-4·00)	0·006	2·25 (1·20-4·22)	0·011
Northern Africa					
No†	587 (94·52%)				

Table E6. Univariable and multivariable Cox regression analyses on potential predictors for prolonged ESBL-E carriage upon acquisition during travel (n = 633). (continued)

	Travellers with ESBL acquisition n* (%)	Hazard ratio (95% CI)†	p-value	Adjusted Hazard ratio (95% CI)†‡	p-value
Yes	34 (5·48%)	1·35 (0·94-1·93)	0·101	1·29 (0·83-2·00)	0·264
Middle/Eastern Africa					
No†	564 (90·82%)				
Yes	57 (9·18%)	1·53 (1·16-2·02)	0·003	1·42 (0·98-2·07)	0·066
Southern Africa					
No†	616 (99·19%)				
Yes	5 (0·81%)	1·60 (0·66-3·86)	0·297	2·10 (0·84-5·26)	0·115
Western Africa					
No†	602 (96·94%)				
Yes	19 (3·06%)	1·09 (0·68-1·75)	0·712	0·90 (0·53-1·54)	0·707
Central America/ Caribbean					
No†	597 (96·14%)				
Yes	24 (3·86%)	1·14 (0·75-1·74)	0·537	1·21 (0·74-1·97)	0·449
South America					
No†	588 (94·69%)				
Yes	33 (5·31%)	1·06 (0·74-1·53)	0·743	1·04 (0·67-1·62)	0·846
Northern America/Europe/Oceania					
No†	620 (99·84%)				
Yes	1 (0·16%)	1·01 (0·14-7·19)	0·992	1·06 (0·15-7·66)	0·957
Traveller's diarrhoea					
No traveller's diarrhoea†	327 (53·34%)				
Diarrhoea during travel	229 (37·36%)	0·86 (0·72-1·02)	0·087		
Diarrhoea immediately after travel	14 (2·28%)	1·68 (0·98-2·87)	0·060		
Diarrhoea during travel and immediately after travel	43 (7·01%)	1·00 (0·73-1·37)	0·988		
Antibiotic use during travel					
No†	543 (88·15%)				
Yes	73 (11·85%)	0·82 (0·63-1·06)	0·124		
Antibiotic use in period since return (up to 1 month after return)					
No†	572 (94·70%)				
Yes	32 (5·30%)	1·01 (0·70-1·47)	0·941		

*Number of travellers with ESBL acquisition do not add up to 633 because of missing data
†Hazard ratio <1 indicated a decreased risk for decolonization
‡Adjusted for travel destination, ESBL genotype, ESBL-E species, age, gender, chronic disease, bowel disease, duration stay abroad
(in days), traveller's diarrhoea (yes/no), antibiotic use (yes/no), antibiotic use in period since return (up to 1 month after return)

Table E7. Predictors for prolonged ESBL-E carriage upon acquisition (n = 633) during travel in the final adjusted Cox regression model.

	Travellers with ESBL acquisition n*	Hazard ratio (95%CI)	p-value
Genotype group			
CTX-M group 1 ESBL	399 (64·04%)		
CTX-M group 9 ESBL	175 (28·09%)	0·66 (0·53-0·81)	<0·001
CTX-M group 1 and CTX-M group 9 ESBL	10 (1·61%)	0·96 (0·47-1·94)	0·900
Other ESBL genotype	39 (6·26%)	0·95 (0·67-1·37)	0·797
ESBL species			
E. coli	537 (86·20%)		
K. pneumoniae	27 (4·33%)	2·17 (1·45-3·26)	<0·001
E. coli and *K. pneumoniae*	38 (6·10%)	1·27 (0·90-1·78)	0·176
Other species	21 (3·37%)	1·14 (0·71-1·82)	0·595
Travel destination			
Central/Eastern Asia			
No†	580 (93·40%)		
Yes	41 (6·60%)	1·04 (0·68-1·59)	0·864
South-Eastern Asia			
No†	426 (68·60%)		
Yes	195 (31·40%)	1·07 (0,79-1,44)	0·671
Southern Asia			
No†	485 (78·10%)		
Yes	136 (21·90%)	0·87 (0,63-1,19)	0·376
Western Asia			
No†	609 (98·07%)		
Yes	12 (1·93%)	2·25 (1·20-4·22)	0·011
Northern Africa			
No†	587 (94·52%)		
Yes	34 (5·48%)	1·29 (0·83-2·00)	0·264
Middle/Eastern Africa			
No†	564 (90·82%)		
Yes	57 (9·18%)	1·42 (0·98-2·07)	0·066
Southern Africa			
No†	616 (99·19%)		
Yes	5 (0·81%)	2·10 (0·84-5·26)	0·115
Western Africa			
No†	602 (96·94%)		
Yes	19 (3·06%)	0·90 (0·53-1·54)	0·707
Central America/ Caribbean			

Table E7. Predictors for prolonged ESBL-E carriage upon acquisition (n = 633) during travel in the final adjusted Cox regression model. (continued)

	Travellers with ESBL acquisition n*	Hazard ratio (95%CI)	p-value
No†	597 (96·14%)		
Yes	24 (3·86%)	1·21 (0·74-1·97)	0·449
South America			
No†	588 (94·69%)		
Yes	33 (5·31%)	1·04 (0·67-1·62)	0·846
Northern America/Europe/Oceania			
No†	620 (99·84%)		
Yes	1 (0·16%)	1·06 (0·15-7·66)	0·957
Duration stay abroad (in days)	617	0·996 (0·989-1·002)	0·180

*Number of travellers with ESBL acquisition do not add up to 633 because of missing data
†Hazard ratio <1 indicated a decreased risk for decolonization

Table E8. Estimation of annual travel-related ESBL-E acquisition in Dutch population in 2013 (excluding Northern America, Europe & Oceania).

Region	acquisition rate		Dutch travellers per year¶	% of Dutch population		
	%	95% CI		(n = 16.781.000)§	Risk*	95% CI Risk*
Southern Asia	75·14	63·51-88·89	48·000	0·29	0·00214929	0·00181663-0·00254259
Central and Eastern Asia	48·81	35·94-66·29	78·000	0·46	0·00226874	0·00167053-0·00308123
Western Asia	42·86	24·34-75·46	895·000	5·33	0·02285901	0·01298153-0·04024593
Northern Africa	41·98	29·99-58·75	338·000	2·01	0·00845554	0·00604053-0·01183332
South-Eastern Asia	37·04	32·24-42·54	203·000	1·21	0·00448073	0·00390008-0·00514607
Caribbean and Central America	27·91	18·71-41·64	186·000	1·11	0·00309353	0·00207381-0·00461536
Middle and Eastern Africa	27·80	21·45-36·05	51·000	0·30	0·00084488	0·00065190-0·00109561
Western Africa	18·87	12·17-29·25	67·000	0·40	0·00075341	0·00048590-0·00116784
South America	18·33	13·03-25·79	61·000	0·36	0·00066631	0·00047365-0·00093748
Southern Africa	6·03	2·88-12·66	45·000	0·27	0·00016170	0·00007723-0·00033949
Yearly risk					**0·04573314**	**0·03017178-0·07100494**
Daily Risk					**0·00012530**	**0·00008266-0·00019453**

¶Based on Centraal Bureau voor de Statistiek (CBS): Long holidays per country and continent 2002-2013[8] Travellers visiting the same regions multiple times or visiting multiple regions will be counted multiple times

§ Number of travellers visiting a region divided by the size of the total Dutch population according to the Centraal Bureau voor de Statistiek at 1 January 2013

*Acquisition proportion multiplied by proportion of Dutch population annually visiting this region

SUPPLEMENTARY FIGURES

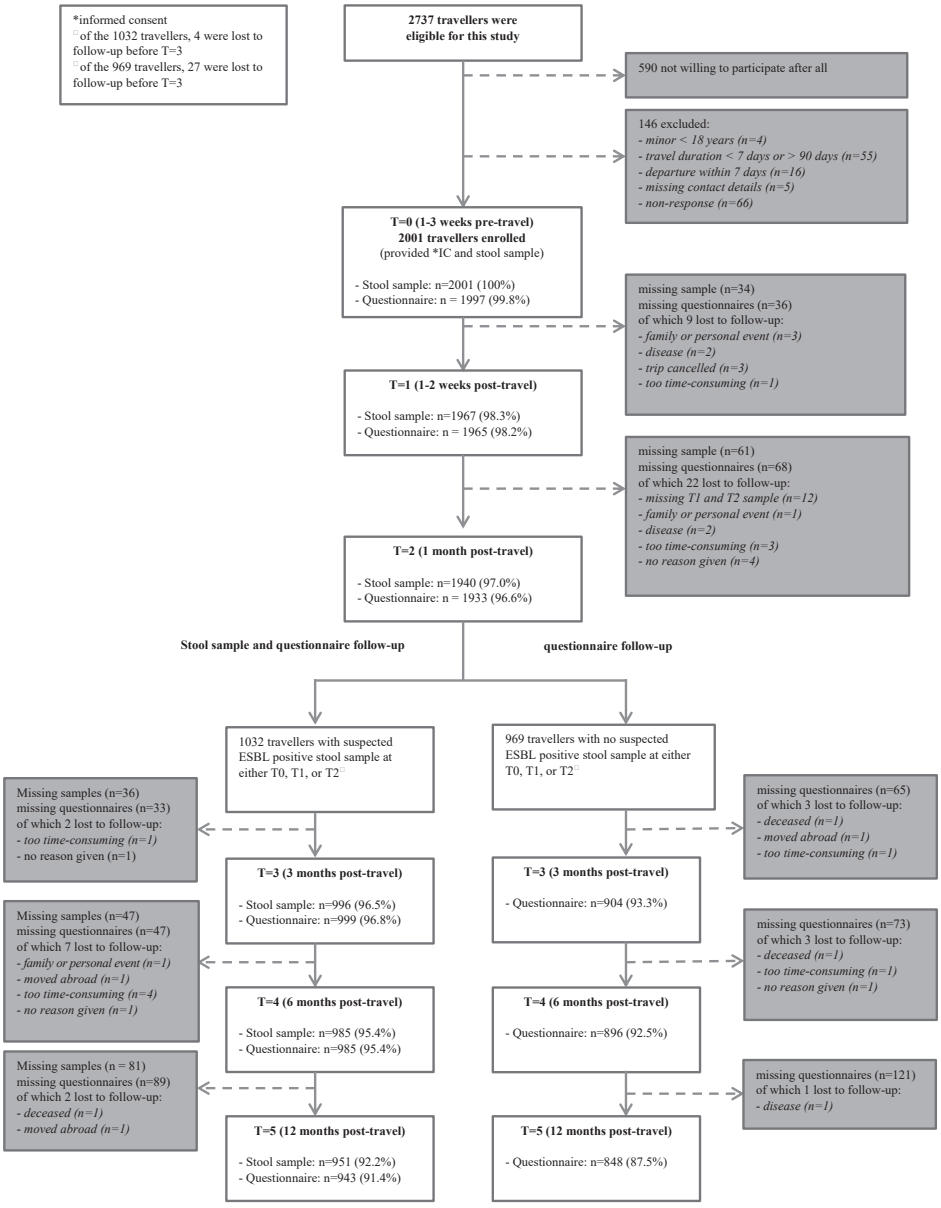


Figure E1. Flowchart of study.

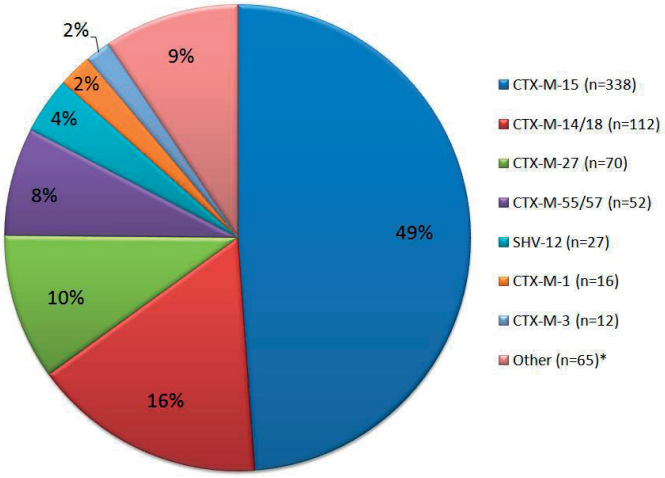
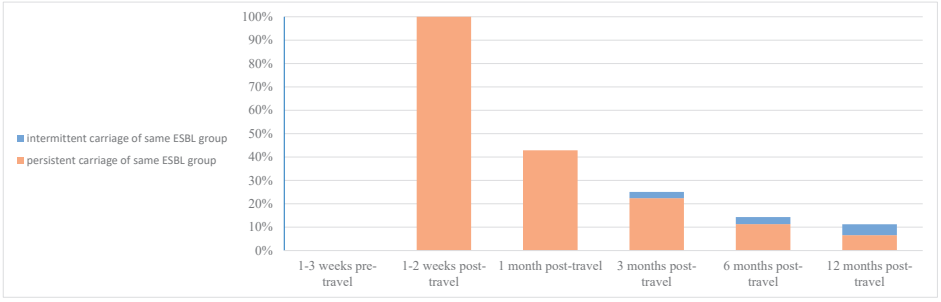


Figure E2. Acquisition of unique ESBL genes (n = 692) by travellers (n = 633) with ESBL-E acquisition. *Other: CTX-M-14-like (n=10), CTX-M group 8 (n=9), CTX-M-65 (n=8), CTX-M-32 (n=7), CTX-M group 2 (n=7), CTX-M-24b (n=6), TEM-52c (n=4), SHV-2a (n=3), CTX-M-24 (n=2), TEM-176 (n=2), CTX-M-15 like (n=2), CTX-M-38 (n=1), SHV-2 (n=1), SHV-28 (n=1),VEB (n=1), CTX-M group 1 not specified(n=1)



persistent carriage of same ESBL group	0% (0/633)	100% (623/623)	42.9% (263/613)	22.4% (136/606)	11.3% (68/601)	6.6% (38/577)
intermittent carriage of same ESBL group				2.6% (16/606)	3.0% (18/601)	4.7% (27/577)

Figure E3. Duration of ESBL-E carriage among travellers with ESBL-E acquisition (n = 633).

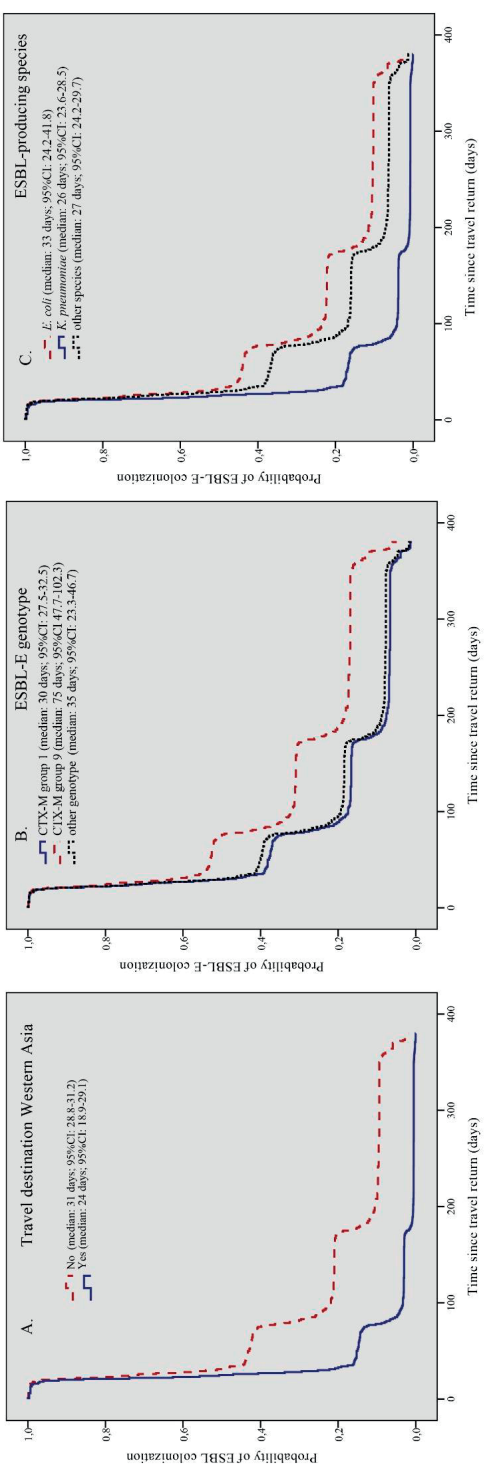


Figure E4. Stratified Cox regression plots time to decolonization of ESBL-E in travellers according to travel destination Western Asia (A), ESBL genotype (B) and ESBL-producing species (C).

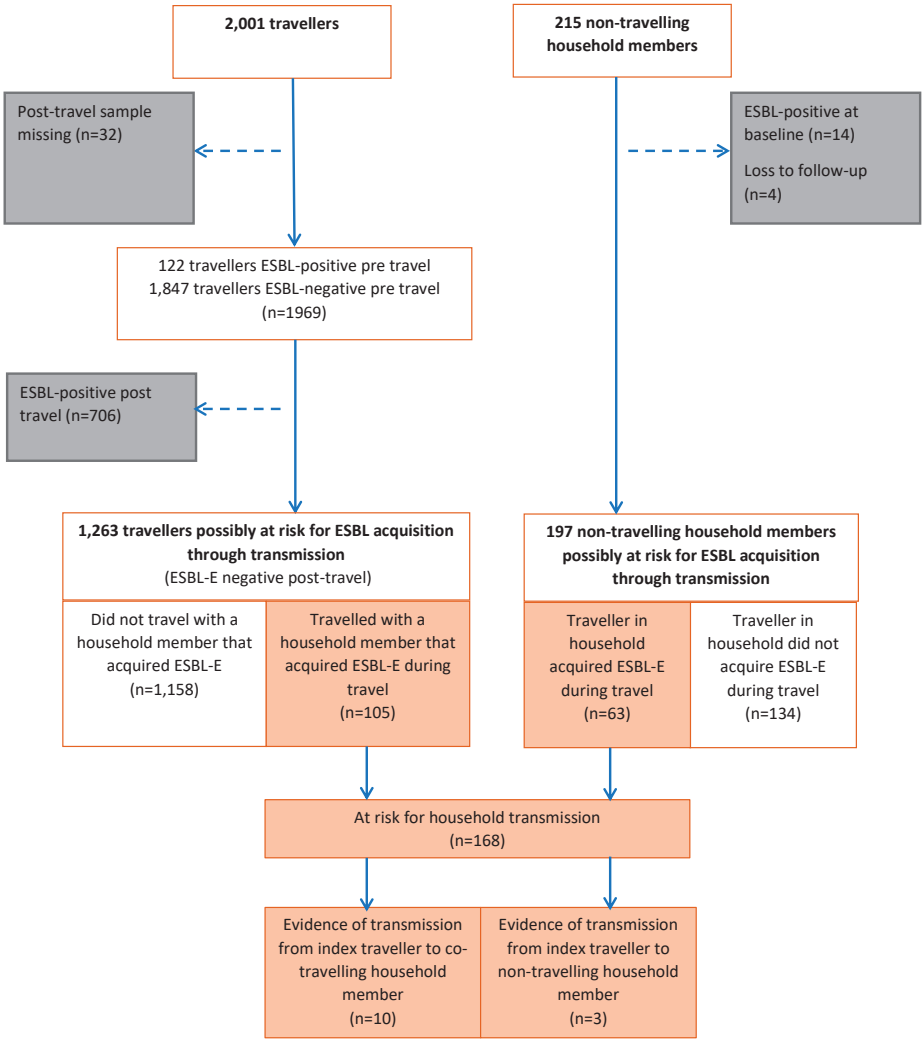


Figure E5. Flow chart of non-travelling and co-travelling household members at risk for acquisition of ESBL-E through transmission from household members that acquired ESBL-E during travel.

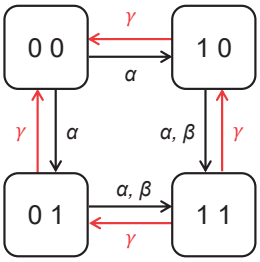


Figure E6. Model to estimate the transmission rate within households with 2 household members. Every square is a household, with an ESBL-negative (0) and/or positive (1) household member. Rates in red correspond to decolonization of an individual, rates in black correspond to acquisition. Alpha (α) = background acquisition rate. Beta (β) = within-household transmission rate. Gamma (γ) = decolonization rate.

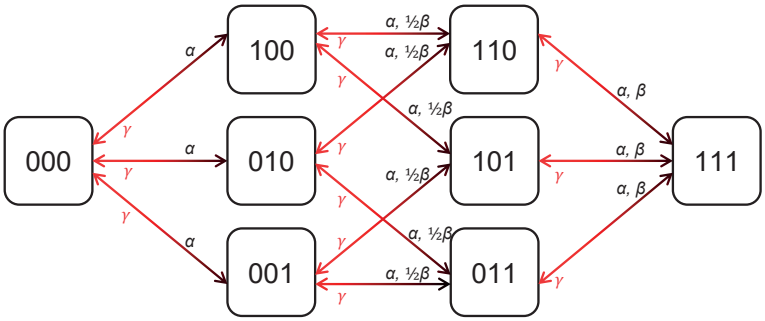


Figure E7. Model to estimate the transmission rate within households with 3 household members. Every square is a household, with ESBL-negative (0) and/or positive (1) household members. Rates in red (below the arrow) correspond to decolonization of an individual (from right to left), rates in black (above the arrow) correspond to acquisition (from left to right). Alpha (α) = background acquisition rate. Beta (β) = within-household transmission rate. Gamma (γ) = decolonization rate.

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