Health problems and risks encountered among healthy and vulnerable Dutch travelers

Vlot, J.A.

7

Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) among travelers to Africa: destination-specific data pooled from three European prospective studies

Tinja Lääveri, Jessica A. Vlot, Alje P. van Dam, Hanni K. Häkkinen, Gerard J.B. Sonder, Leo G. Visser, Anu Kantele

BMC Infect Dis. 2018 jul 23;18(1):341

Abstract

Background One third of travelers to low- and middle-income regions of the tropics and subtropics become colonized by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE). The risk varies by destination and, for each traveler, may be substantially further increased by travelers' diarrhoea (TD) and antibiotic use. Despite the risk of TD in Africa, ESBL-PE acquisition rates in all studies are lower there than in Asia. Africa has become increasingly popular as a destination for international travelers, yet minimal data are available from the continent's subregions and countries.

Methods We analysed subregion- and country-specific data on carriage and risk factors for ESBL-PE colonization pooled from three prospective studies conducted between 2009 and 2013 among Finnish and Dutch travelers. The data were subjected to multivariable analysis of risk factors. In addition, we compared our data to two recent large investigations reporting data by subregion and country.

Results Our joint analysis comprised data on 396 travelers. The ESBL-PE colonization rate was highest in Northern Africa, followed by Middle and Eastern Africa, and lowest in Southern and Western Africa. Of individual countries with more than 15 visitors, the highest rates were seen for Egypt (12/17; 70.6%), Ghana (6/23; 26.1%), and Tanzania (14/81; 17.3%); the rates among travelers to Egypt were comparable to those reported in South and Southeast Asia. In a pooled multivariable analysis, travel destination, age, overnight hospitalisation abroad, TD, and use of fluoroquinolones were independently associated with increased ESBL-PE colonization rates.

Conclusions Even in areas with relatively low risk of colonization, antimicrobials clearly predispose to colonization with ESBL-PE. Travelers to Africa should be cautioned against unnecessary use of antibiotics.

Introduction

Every third traveler from industrialised countries that visits developing regions becomes colonized by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) [1-11]. While rates as high as 88% have been reported for travelers to South Asia [4-8,10,11] and 69% to Southeast Asia [4,6-8,10,11], considerably lower risks have been detected among travelers to the African continent, varying between 12% and 45% [3,4,6-8,10,11].

Data on colonization among visitors to various African countries or subregions remain scarce, as the vast majority of prospective studies report acquisition rates either for the whole continent [1,9] or only part of the subregions [3,4,6,8-10,12,13]; a few investigations provide data on a number of individual countries [7,11]. Travel destination, antibiotic use, age, and travelers' diarrhoea (TD) have been identified as major risk factors. Several other additional factors have been shown in single studies: type of travel, meal location and consumption of certain food products, such as ice cream and pastries [1,3-7,9-11,14]. While these factors all predispose to ESBL-PE colonization in general, studies presenting colonization risk factors by individual geographic areas are few [5,11], and none have focused exclusively on Africa. As the continent attracts increasing numbers of travelers [15], we decided to review the data published and pool subregion-derived findings of our three earlier investigations [4,6,10]. Combining these data with subregional carriage rates from two recent studies [7,11], our paper offers an insight into the subregion-related colonization risk of travelers to Africa.

Methods

Study design, volunteers and samples

To assess the colonization rates of ESBL-PE in Africa, we combined the data of travelers to Africa from three large studies:

(1) Finnish study by Kantele et al [6]. The volunteers travelled in 2009-2010; 196 of the 430 (45.6%) travelled in Africa. Faecal samples were used for analyses.

(2) Dutch study I by Paltansing et al [4]. The volunteers travelled in 2011; 103 of 338 (30.5%) travelled in Africa. Rectal swabs were used for analyses.

(3) Dutch study II by Reuland et al [10]. The volunteers travelled in 2012-2013 (of the travelers reviewed here, all but one travelled in 2012); 97 of 418 (23.2%) travelled in Africa; 63 (64.9%) faecal samples and 34 (35.1%) rectal swabs were analysed. In the original article, the authors report that the colonization rates were similar regardless of sample technique.

For all three prospective studies, the volunteers provided both pre- and post-travel stool samples / rectal swabs. Of the 14 (3.5%) travelers with pre-travel samples positive for ESBL-PE, three had the same strain detected in post-travel samples. In six volunteers, the post-travel sample was negative; these were included in the ESBL-PE(-) group. The five that contracted a different type of ESBL-PE during travel were included in the ESBL-PE(+) group. Travelers who contracted a new ESBL-PE strain during travel constituted the ESBL-PE(+) group, while all others belonged to the ESBL-PE(-) group. The following information was available from all three studies in comparable format: travel itinerary, travel duration, travel dates, age, sex, antimicrobial usage, occurrence of TD, and possible hospitalisation abroad (overnight stay or more).

In all studies, written informed consent was obtained from all participants and the Ethics Committees in the respective organisations approved the study protocols.

Collection of stool samples and identification of ESBL-PE strains

We have described earlier in detail the approaches to collection of samples (stools or swabs) and methods used for identification of ESBL-PE and carbapenemase-producing *Enterobacteriaceae* (CPE) [4,6,10].

Definition of TD and geographical subregions

For the purpose of the present study, TD was defined as three or more loose or liquid stools per day. Geographical subregions in Africa were defined according to the United Nations [16]: Southern Africa, Western Africa, Middle Africa, Eastern Africa, and Northern Africa. Travelers visiting more than one subregion in Africa were categorised on the basis of longest stay.

Statistical analyses

Statistical analyses were carried out with SPSS software version 24 (IBM Corp, Armonk, NY) and Stata version 15.1 (StataCorp. College Station, TX). Binomial regression model was used to obtain profile likelihood confidence intervals for the proportions of travelers with given risk factors and positive for ESBL-PE. The chi-square test, Fisher's exact test or binary logistic regression analysis were used to compare categorical variables when applicable. Binary logistic regression was used with continuous variables. Variables with a p-value <0.2 in the univariate analysis for ESBL-PE colonization were subjected to multivariable analysis together with doxycycline as antimalarial, gender and duration of travel in days. The shape of the form for travel duration and age were assessed by cubic splines and appeared log-linear. The interaction between variables of interest and studies was assessed. The final model was built using binary logistic regression analysis with a stepwise backward selection of variables by Akaike Information Criteria (AIC). Factors with 95% confidence intervals ranging only either above or below 1 were considered significant. The three studies pooled in the present paper [4,6,10] and the two others [7,11] used for comparisons were all brought together to produce a forest plot analysis. Heterogeneity between studies in forest plot was measured with I^2; values above 75% were considered high, 25%–75% moderate, and below 25%. For our pooled data, the interaction between studies and geographical subregions was analysed in the multivariable model.

Results

Demographic data, background characteristics, and occurrence of TD

Demographic data on travelers are presented in Table 1. Of the 396 travelers included in this study, 237 (59.8%) were women. The median age was 36 years (IQR 27-53) and the median duration of travel 19 days (IQR 14-25). One fourth of the travelers (n=105; 26.5%) had visited more than one country in Africa. The majority of the travelers visited either Western (27.8%) or Eastern (46.7%) Africa. Twenty-three (5.8%) had visited more than one subregion in Africa. In addition to Africa (or Europe *en route* to Africa), two volunteers (0.5%) had visited Jordania and two (0.5%) United Arab Emirates.

TD rates were lowest in Southern Africa (15/58; 25.9%); in other areas 37.8-46.7% of travelers contracted TD (Table 2). Of the 44 (11.1% of all travelers) courses of antibiotics, 30 (68.2%) were taken for TD. Eight (2.0% of all travelers) used beta-lactam antibiotics and 25 (6.3%) used fluoroquinolone antibiotics during travel.

ESBL-PE acquisition rates by subregion in the pooled data

In the pooled data (Table 2, Figure 1), 61 (15.4%) travelers became colonized by ESBL-PE; one Dutch traveler to Egypt became colonized by CPE. The highest ESBL-PE colonization rates were seen among travelers to Northern Africa (12/28; 42.9%), followed by Middle Africa (4/15; 26.7%) and Eastern Africa (30/185; 16.2%). Of travelers to Western and Southern Africa, 10.0% (11/110) and 6.9% (4/58), respectively, acquired ESBL-PE (Tables 1 and 2).

Of the nine countries with more than 15 visitors (Table 3), the highest ESBL-PE acquisition rates were seen among travelers to Egypt (12/17; 70.6%), Ghana (6/23; 26.1%), Tanzania (14/81; 17.3%), Uganda (4/26; 15.4%) and Kenya (12/82; 14.6%). As for the lowest colonization rates, of the 26 travelers to Senegal, three (11.5%) became colonized by ESBL-PE, in South Africa, 5/49 (10.2%) became colonized and in the Gambia the rate was only 3.4% (2/58); none of the 21 visitors to Namibia acquired ESBL-PE.

Results of the multivariable analysis for risk factors of ESBL-PE colonization in Africa

The initial univariate analysis (Table 1) detected the following factors with $p < 0.2$: age, original study, sampling technique, subregion in Africa, use of fluoroquinolones, beta-lactams or other AB / regimen not known, TD, and overnight hospitalisation abroad. When all of these factors, together with gender, duration of travel, and use of doxycycline as antimalarial were subjected to multivariable analysis, the following were found to be independently associated with increased risk: travel to Northern Africa, overnight hospitalisation abroad, age, TD and use of fluoroquinolones (Table 1).

Table 1 Demographics and risk factors of ESBL-PE acquisition in pooled data on 396 travelers from Finland and the Netherlands

				Univariate analysis			Multivariable analysis		
Characteristic	**total n (% of all)**	**ESBL-PE(+) n (%)**	**95% CI (%)[a]**	**P**	**OR**	**95% CI**	**P**	**AOR**	**95% CI**
Total	396 (100.0)	61 (15.4)							
Gender									
Male	159 (40.2)	24 (15.1)	10.1-21.2		1.0				
Female	237 (59.8)	37 (15.6)	11.4-20.6	0.889	1.0	0.6-1.8			
Age[b]									
Age, *median, years*	36 (IQR 27-53)	38.5 (IQR 25.5-55.5)		0.071	1.0	1.0-1-0	0.002	1.0	1.0-1.1
Study									
Kantele et al [6]	196 (49.5)	25 (12.8)	8.6-17.9		1.0			1.0	
Paltansing et al [4]	103 (26.0)	29 (28.2)	20.1-37.3	0.001	2.7	1.5-4.9	0.303	3.7	0.3-50.0
Reuland et al [10]	97 (24.5)	7 (7.2)	3.2-13.5	0.158	0.5	0.2-1.3	0.962	1.1	0.1-25.1
Sampling method									
Rectal swab	137 (34.6)	32 (23.4)	16.8-30.9	0.001	2.4	1.4-4.2	0.648	1.5	0.3-7.8
Stool sample	259 (65.4)	29 (11.2)	7.7-15.4		1.0				
Year of travel[b]									
(year of travel as a continuous variable)				0.909	1.0	0.8-1.2	0.609	0.8	0.3-2.1
2009	122 (30.8)	17 (13.9)	8.6-20.8						
2010	74 (18.7)	8 (10.8)	5.1-19.2						
2011	103 (26.0)	29 (28.2)	20.1-37.3						
2012-2013	97 (24.5)	7 (7.2)	3.2-13.5						
Destination subregion									
Southern Africa	58 (14.6)	4 (6.9)	2.2-15.3		1.0			1.0	
Northern Africa	28 (7.1)	12 (42.9)	25.8-61.2	<0.001	10.1	2.9-35.8	0.001	12.4	3.1-57.3
Middle Africa	15 (3.8)	4 (26.7)	9.2-51.5	0.042	4.9	1.1-22.7	0.056	5.6	0.9-33.6
Eastern Africa	185 (46.7)	30 (16.2)	11.4-22.0	0.084	2.6	0.9-7.8	0.058	3.1	1.1-11.2
Western Africa	110 (27.8)	11 (10.0)	5.3-16.5	0.505	1.5	0.5-4.9	0.528	1.5	0.4-6.2

				Univariate analysis			Multivariable analysis		
Characteristic	**total n (% of all)**	**ESBL-PE(+) n (%)**	**95% CI (%)[a]**	**P**	**OR**	**95% CI**	**P**	**AOR**	**95% CI**
Antibiotics									
no AB	352 (88.9)	44 (12.5)	9.3-16.2		1.0				
AB	44 (11.1)	17 (38.6)	25.2-53.4	<0.001	4.4	2.2-8.7			
AB: beta-lactams									
No	388 (98.0)	57 (14.7)	11.4-18.4		1.0			1.0	
Yes	8 (2.0)	4 (50.0)	19.1-80.9	0.022	5.8	1.4-23.9	0.118	3.4	0.5-21.9
AB: fluoroquinolones									
No	371 (93.7)	51 (13.7)	10.5-17.5		1.0			1.0	
Yes	25 (6.3)	10 (40.0)	22-5-59.5	0.002	4.2	1.8-9.8	0.005	4.7	1.5-13.9
AB others (other than beta-lactams or FQ) / unknown									
No	382 (96.5)	56 (14.7)	11.4-18.4		1.0			1.0	
Yes	14 (3.5)	5 (35.7)	14.6-61.7	0.048	3.2	1.0-10.0	0.059	3.8	0.9-14.6
Doxycycline as antimalarial									
No	362 (91.4)	56 (15.5)	12.0-19.4		1.0				
Yes	34 (8.6)	5 (14.7)	5.5-29.0	0.906	0.9	0.4-2.5			
Travelers' diarrhoea (TD)									
no TD	243 (61.4)	30 (12.3)	8.6-16.9		1.0				
TD	153 (38.6)	31 (20.3)	14.4-27.1	0.034	1.8	1.0-3.1	0.033	2.1	1.1-4.1
Overnight hospitalisation abroad (information missing n=1)									
No	389 (98.5)	57 (14.7)	11.4-18.4		1.0				
Yes	6 (1.5)	4 (66.7)	28.1-100	0.006	11.6	2.1-65.1	0.004	16.5	2.5-140.5
Duration of travel, (information missing n=1)[b]									
Median, days	19 (IQR 14-25)	18 (IQR 15-23)		0.828	1.0	1.0-1.0	0.276	1.0	1.0-1.0

[a] 95% confidence intervals are profile likelihood confidence intervals for proportion of ESBL(+) with given risk factor

[b] studied as a continuous variable in statistical analysis

Table 2 ESBL-PE colonization rates, occurrence of TD and antibiotic use in the pooled data on 396 travelers from Finland and the Netherlands in relation to geographical subregion visited

	All	Northern Africa	Middle Africa	Eastern Africa	Western Africa	Southern Africa
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Kantele et al (Finnish study) [6]						
total no. of travelers to subregion (% of all)	196	3 (1.5)	4 (2.0)	86 (43.9)	78 (39.8)	25 (12.8)
ESBL-PE (+)	25 (12.8)	2 (66.7)	1 (25.0)	14 (16.3)	5 (6.4)	3 (12.0)
AB	34 (17.3)	1 (33.3)	1 (25.0)	13 (15.1)	15 (19.2)	4 (16.2)
TD	71 (36.2)	1 (33.3)	1 (25.0)	34 (39.5)	29 (37.2)	6 (24.0)
Paltansing et al (Dutch study I) [4]						
total no. of travelers to subregion (% of all)	103	13 (12.6)	7 (6.8)	54 (52.4)	12 (11.7)	17 (16.5)
ESBL-PE (+)	29 (28.2)	7 (53.8)	3 (42.9)	14 (25.9)	4 (33.3)	1 (5.9)
AB	8 (7.8)	2 (15.4)	1 (14.3)	3 (5.6)	2 (16.7)	0 (0.0)
TD	39 (37.9)	7 (53.8)	4 (57.1)	19 (35.2)	5 (41.7)	4 (23.5)
Reuland et al (Dutch study II) [10]						
total no. of travelers to subregion (% of all)	97	12 (12.4)	4 (4.1)	45 (46.4)	20 (20.6)	16 (16.5)
ESBL-PE (+)	7 (7.2)	3 (25.0)	0 (0.0)	2 (4.4)	2 (10.0)	0 (0.0)
AB	2 (2.1)	0 (0.0)	0 (0.0)	2(4.4)	1 (16.7)	0 (0.0)
TD	43 (44.3)	5 (41.7)	2 (50.0)	17 (37.8)	14 (70.0)	5 (31.3)
Combined total of the three studies						
total no. of travelers to subregion (% of all)	396	28 (7.1)	15 (3.8)	185 (46.7)	110 (27.8)	58 (14.6)
ESBL-PE (+)	61 (15.4)	12 (42.9)	4 (26.7)	30 (16.2)	11 (10.0)	4 (6.9)
AB	45 (11.4)	3 (10.7)	2 (13.3)	18 (9.7)	18 (16.4)	4 (6.9)
TD	153 (38.6)	13 (46.4)	7 (46.7)	70 (37.8)	48 (43.6)	15 (25.9)

AB antibiotic use, *TD* travelers' diarrhoea

Table 3 ESBL-PE colonization rates from our pooled data of 396 travelers by country visited presented with the respective figures from studies by Ruppé et al [7] and Arcilla et al [11].

Country	Data pooled from three studies[a]: Total number of travelers (% of all visitors to Africa)	Data pooled from three studies[a]: ESBL-PE (+) cases / all visitors to country (%)	Data published by Ruppé et al[b] ESBL-PE (+) cases / all visitors to country (%)	Data published by Arcilla et al[c] ESBL-PE (+) cases / all visitors to country (%)
Northern Africa				
Egypt	17 (4.3)	12/17 (70.6)	-	24/30 (80.0)
Morocco	10 (2.5)	1/10 (10.0)	-	8/36 (22.2)
Tunisia	3 (0.8)	0/3 (0)	-	-
Middle Africa				
Cameroon	7 (1.8)	1/7 (14.3)	13/24 (54.2)	-
Central African Republic	-	-	0/1 (0.0)	-
Democratic Republic of Congo	8 (2.0)	3/8 (37.5)	-	-
Republic of Congo	6 (1.5)	2/6 (33.3)	8/13 (61.5)	-
Gabon	1 (0.3)	0/1 (0)	2/3 (66.7)	-
Sao Tome and Principe	-	-	0/1 (0.0)	-
Eastern Africa				
Djibouti	1 (0.3)	1/1 (100.0)	-	-
Ethiopia	14 (3.5)	2/14 (14.3)	2/4 (50.0)	-
Kenya	82 (20.7)	12/82 (14.6)	4/6 (66.7)	10/30 (33.3)
Madagascar	3 (0.8)	1/3 (33.3)	4/7 (57.1)	-
Malawi	14 (3.5)	2/14 (14.3)	-	-
Mauritius	1 (0.3)	1/1 (100.0)	-	-

Country	Data pooled from three studies[a]: Total number of travelers (% of all visitors to Africa)	Data pooled from three studies[a]: ESBL-PE (+) cases / all visitors to country (%)	Data published by Ruppé et al[b] ESBL-PE (+) cases / all visitors to country (%)	Data published by Arcilla et al[c] ESBL-PE (+) cases / all visitors to country (%)
Mozambique	8 (2.0)	1/8 (12.5)	0/1 (0.0)	-
Rwanda	5 (1.3)	0/5 (0)	-	-
Tanzania	81 (20.5)	14/81 (17.3)	7/11 (63.6)	14/57 (24.6)
Uganda	26 (6.6)	4/26 (15.4)	-	12/27 (44.4)
Western Africa				
Benin	13 (3.3)	1/13 (7.7)	4/11 (36.4)	-
Burkina Faso	2 (0.5)	0/2 (0)	4/8 (50.0)	-
Côte d'Ivoire	1 (0.3)	0/1 (0)	8/17 (47.1)	-
Gambia	58 (14.6)	2/58 (3.4)	-	8/49 (16.3)
Ghana	23 (5.8)	6/23 (26.1)	1/1 (100.0)	8/20 (40.0)
Guinea Bissau	1 (0.3)	0/1 (0)	0/3 (0.0)	-
Liberia	3 (0.8)	0/3 (0)	-	-
Mali	4 (1.0)	1/4 (25.0)	1/5 (20.0)	-
Nigeria	7 (1.8)	1/7 (14.3)	1/1 (100.0)	-
Senegal	26 (6.6)	3/26 (11.5)	17/45 (37.8)	-
Sierra Leone	3 (0.8)	1/3 (33.3)	-	-
Togo	6 (1.5)	2/6 (33.3)	9/12 (75.0)	-
Southern Africa				
Angola	1 (0.3)	0/1 (0)	1/3 (33.3)	-
Botswana	10 (2.5)	1/10 (10.0)	-	-
Lesotho	2 (0.5)	1/2 (50.0)	-	-
Namibia	21 (5.3)	0/21 (0)	-	-

Country	Data pooled from three studies[a]: Total number of travelers (% of all visitors to Africa)	Data pooled from three studies[a]: ESBL-PE (+) cases / all visitors to country (%)	Data published by Ruppé et al[b] ESBL-PE (+) cases / all visitors to country (%)	Data published by Arcilla et al[c] ESBL-PE (+) cases / all visitors to country (%)
South Africa	49 (12.4)	5/49 (10.2)	0/1 (0.0)	3/66 (4.5)
Swaziland	8 (2.0)	2/8 (25.0)	-	-
Zambia	13 (3.3)	1/13 (7.7)	-	-
Zimbabwe	7 (1.8)	1/7 (14.3)	-	-

There were no travelers to Burundi, Cape Verde, Chad, Equatorial Guinea, Eritrea, Guinea, Libya, Mauritania, Niger, Reunion, Seychelles, Somalia, South Sudan, and Sudan.

[a] The same traveler may have visited several countries.

[b] Only travelers that had visited only one country.

[c] The colonization rates of all individual countries visited were not published.

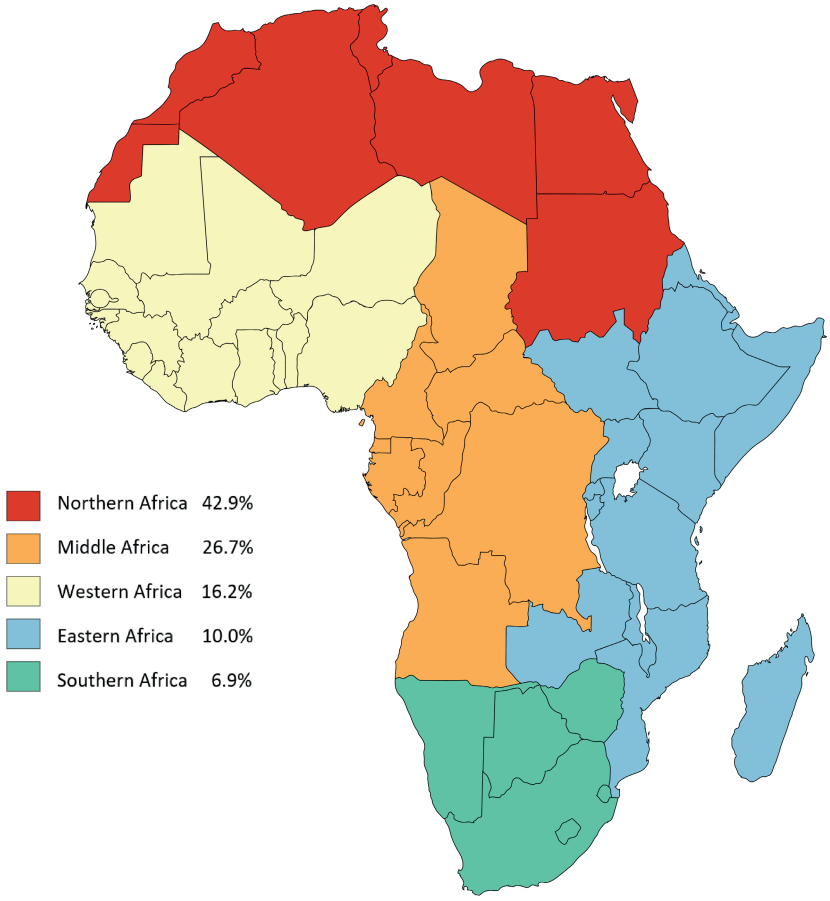


Figure 1 ESBL-PE acquisition rates in five African subregions; joint data on 396 travelers from Finland and the Netherlands (Created with Mapchart.net)

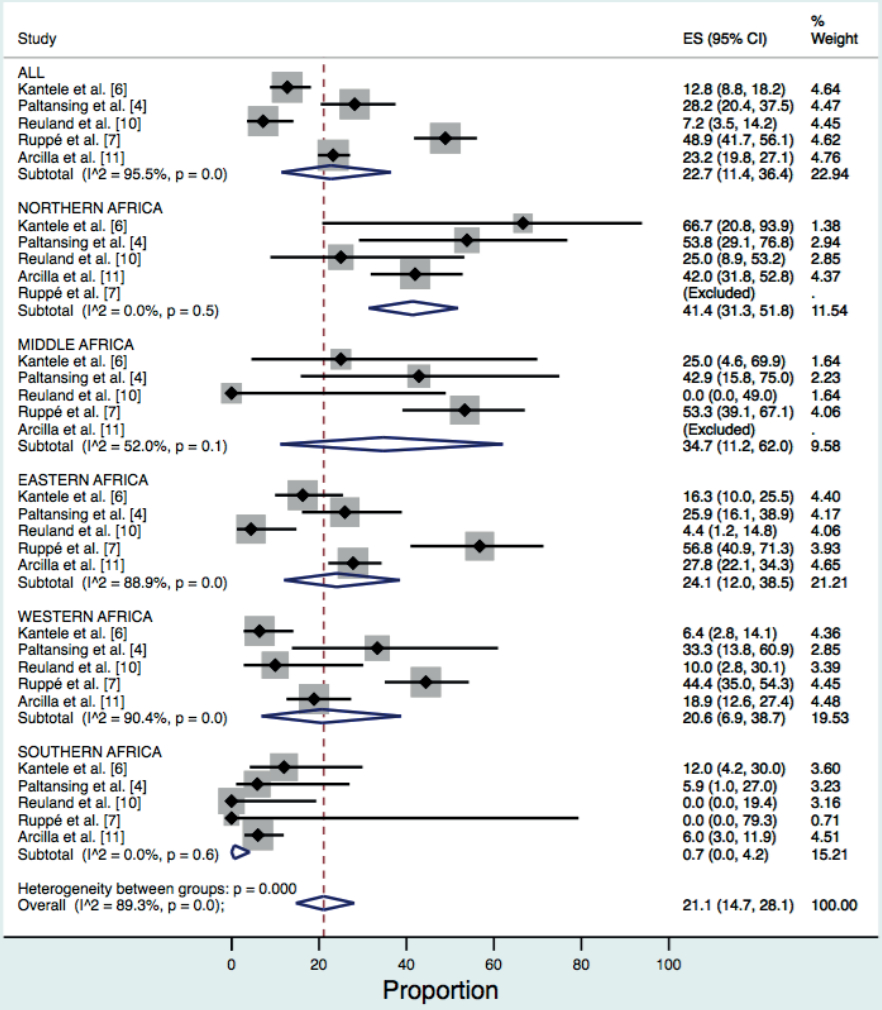
Results of meta-analysis of five studies

Table 4 and forest plot analysis (Figure 2) show the ESBL-PE colonization rates from the three studies pooled [4,6,10], together with investigations by Ruppé et al and Arcilla et al. [7,11] in relation to geographical subregion visited. For Southern and Northern Africa, heterogeneity between the five studies appeared low (I^2=0.0% and 0.0%, respectively), for Middle Africa moderate (I^2 52.0%), and Eastern and Western Africa high (I^2 88.9% and 90.4%, respectively). In the multivariable regression model of our pooled data, the interaction between subregions and the three studies was not found significant at 5% significance level.

Table 4 ESBL-PE colonization rates from the five studies [4,6,7,10,11] in relation to geographical subregion visited

	All	Northern Africa	Middle Africa	Eastern Africa	Western Africa	Southern Africa
Kantele et al [6] **(Finnish study) 2009-2010**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	25/196 (12.8)	2/3 (66.7)	1/4 (25.0)	14/86 (16.3)	5/78 (6.4)	3/25 (12.0)
Paltansing et al [4] **(Dutch study I) 2011**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	29/103 (28.2)	7/13 (53.8)	3/7 (42.9)	14/54 (25.9)	4/12 (33.3)	1/17 (5.9)
Reuland et al [10] **(Dutch study II) 2012-2013**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	7/97 (7.2)	3/12 (25.0)	0/4 (0.0)	2/45 (4.4)	2/20 (10.0)	0/16 (0.0)
Ruppé et al [7]**2012-2013 (**data on travelers visiting only one country)						
ESBL-PE (+) among travelers n (% of all v visitors to subregion)	89/182 (48.9)	N/A	24/45 (53.3)	21/37 (56.8)	44/99 (44.4)	0/1 (0)
Arcilla et al [11]**2012-2013**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	118/508 (23.2)	34/81 (42.0)	N/A	57/205 (27.8)	20/106 (18.9)	7/116 (6.0)
Combined total: ESBL-PE colonization rates	268/1086 (24.7)	46/109 (42.2)	28/60 (46.7)	108/427 (25.3)	75/315 (23.8)	11/175 (6.3)

Figure 2 Forest plots of ESBL-PE acquisition rates from five studies in relation to geographical subregions. Excluded = no travelers to subregion in study



Discussion

Africa is a continent with increasing numbers of travelers [15]. When pooling subregion- /country-specific data from three traveler studies [4,6,10], we found the risk of contracting ESBL-PE to vary significantly between the various parts of Africa. In addition, comparing our joint data with two recent large reports [7,11] providing subregion- and country-specific data enabled us to investigate the current subregion- and country-specific knowledge about ESBL-PE acquisition by travelers to Africa.

ESBL-PE colonization rates in Northern Africa

Our pooled data showed the highest acquisition rates (12/28; 42.9%) among visitors to Northern Africa, which accords with the results from the study by Arcilla et al (42.0%) [11]; Ruppé et al [7] did not report visitors to this subregion. Similar (43-44%) rates have been reported among Swedish travelers [3,12]. Visitors to Egypt appear to be at particularly high risk; 70.6% (12/17) of our subjects, 80.0% (23/40) of those in a study by Arcilla et al, and 50% (19/38) of those in another by Tham et al became colonized [11,14]. Moreover, all 12 travelers colonized by ESBL-PE in Northern Africa had visited Egypt. It is noteworthy that these proportions are as high as those among travelers to India/South Asia in various investigations [4-8,11]. Bassyouni et al reported carriage rates as low as 21% among healthcare workers in Egypt [17].

ESBL-PE colonization rates in Middle Africa

To our knowledge, only one previous study has reported ESBL-PE acquisition rates among visitors to Middle Africa; Ruppé et al [7] found 53.3% (24/45) of travelers to be colonized. In our pooled data, colonization rates in Middle Africa ranked second (4/15; 26.7%) among the subregions. In nonclinical samples obtained from local populations, carriage rates as high as 59% have been shown among healthy children in the Central African Republic [18], and 44-57% among inpatient carriers, hospital workers and their household members in Cameroon [19].

ESBL-PE rates in Eastern Africa

Colonization rates among travelers to Eastern Africa (30/185; 16.2%) were lower than those reported by Arcilla et al (57/205; 27.8%) [11], Lubbert et al (12/47; 25.5%)

[8], and Ruppé et al (17/29; 56.8%,) [7]. Our moderate colonization rates are supported by findings among local populations: ESBL-PE carriage rates between 11.6% and 16.5% have been reported for healthy community children in Tanzania, [20,21] and 5.3% for locals in Uganda, [22].

ESBL-PE colonization rates in Western Africa

ESBL-PE acquisition rates in Western Africa appear moderately low, but the results differ between studies: our pooled data showed proportions (11/110; 10.0%) close to those presented by Arcilla et al (20/106; 18.9%) [11], while higher rates have been found by Ruppé et al (44/99; 44.4%) [7] and Lubbert et al (5/12; 38.5%) [8] among German travelers to Western and Middle Africa. Moreover, in the research by Frickmann et al, 27.1% (13/48) of European military personnel with diarrhoea in Mali became colonized by ESBL-PE [23]. As for local populations, colonization rates of 22% have been reported for healthy volunteers in Burkina Faso [24] and 33% for healthy community children in Guinea-Bissau [25].

ESBL-PE colonization rates in southern Africa

Our low rates in Southern Africa (4/58; 6.8%) accord with those found by Arcilla et al (7/116; 6.0%)[11] and Lubbert et al (2/18; 11%) [8]. In our pooled data, the vast majority had visited South Africa or Namibia. Consistent with the low ESBL-PE acquisition rates, one study exploring local populations in South Africa reported maternal faecal carriage rates of 4.4% in South Africa [26].

Findings from multivariable analysis

Travelers' diarrhoea

ESBL-PE acquisition rates among those who contracted TD during travel (31/153; 20.3%) were higher than among those without TD (30/243; 12.3%) (AOR 2.1; 95% CI 1.1-4.1). This was expected, since TD was identified as a risk factor in two of the three original studies [6,10] and numerous others [1,3,7,8,11,12].

Antimicrobial medications

Forty-four (11.1%) travelers had taken antimicrobial medications during travel. Of the Finns, 17.3% (34/196) took antibiotics while this proportion was 5.0% (10/200) among the Dutch. In multivariable analyses, fluoroquinolone antibiotics were an

independent risk factor for ESBL-PE colonization (ESBL-PE(+) 40.0%; AOR 4.7; 95% CI 1.5-13.9). Other antibiotic groups did not reach statistical significance in the risk factor analysis, yet the numbers of travelers using each individual antibiotic type were small; eight had taken beta-lactams (ESBL-PE(+) 50.0%; AOR 3.4, CI 0.5-21.9) and 14 other antimicrobials (ESBL-PE(+) 35.7%; AOR 3.8 CI 0.9-14.6). Ruppé et al found beta-lactam usage to predispose to colonization by ESBL-PE (20/25; 80%)[7].

Even though taken by 34 (8.6%) travelers as an antimalarial, doxycycline was not associated with increased ESBL-PE rates (ESBL-PE(+) 5/34; 14.7%; AOR 0.9, 95% CI 0.4-2.5). This finding accords with other studies [7,11]. However, these data do not allow conclusions on the total impact of doxycycline on antimicrobial resistance, as these investigations only analysed the ESBL or CPE feature of the *Enterobacteriaceae*; the potential to select doxycycline-resistant strains in general or other types of multidrug-resistant bacteria was not explored. Indeed, we recently showed that fluoroquinolone intake predisposes selectively to colonization by fluoroquinolone-resistant bacteria [27]. Thus, the effect of doxycycline on other bacteria and travelers' microbiota deserves further research.

Increasing age as risk factor

Increasing age proved an independent risk factor for ESBL-PE colonization in Africa. Only two earlier reports [3,6] have described similar results, as opposed to several others [7,8,11]. Moreover, in one study conducted among returning travelers with diarrhoea, increasing age even appeared protective [28]. The role of age remains unclear. There may be other factors associated with increasing age, such as co-medications / comorbidities or altered immune response not covered in these studies that interfere with the analyses in either direction. As the risk of bacteraemic infections caused by resistant *Enterobacteriaceae* increases with age [29], the risk factors in the older age groups warrant further studies.

Overnight hospitalisation

In our joint data, overnight hospitalisation predisposed to colonization with ESBL-PE. Although numerous retrospective studies have shown high colonization rates by multiresistant bacteria among travelers hospitalized in high-prevalence countries [30-32], to our knowledge, this is the first study to actually show in a prospective setting hospitalisation abroad as a risk factor for ESBL-PE acquisition. In previous

prospective traveller studies, overnight hospitalisations has either not been analysed separately from other health care contacts in the risk factor analyses [7,11] or the proportion of travelers requiring a stay in hospital for treatment has been small or negligible (0-0.5%) [3,8]. In our data, six (1.5% of all subjects) needed overnight hospitalisation.

Travel destination

In multivariable analysis, when compared to Southern Africa, travel to Northern Africa was associated with higher colonization rates. The rates presumably vary between subregions and countries according to the background prevalence of the local populations [33]. They may also depend on several other factors, such as local culture-related food production and preparation habits and hygienic conditions and, of course, whether the traveler contracts TD and takes antibiotics (see above).

Other risk factors

Even though multiresistant *Enterobacteriaceae* have become increasingly prevalent globally [33], colonization rates were not found to increase during the study period (2009-2013). Neither individual studies nor sampling techniques were found statistically significant factors in the multivariable analysis. Travel duration was not seen to be associated with increased risk in univariate or multivariable analysis. This may be explained by a proportion of travelers becoming colonized already on arrival and the carriage resolving while abroad (Professor Kantele, unpublished observation).

Limitations of the study

As the data for the joint risk factor analysis were derived from three separate studies, some data had been collected in differing formats rendering the results incomparable. Moreover, although pooling served to increase the validity and precision of study results, the data remained insufficient in some occasions for analysis in any great detail: In Additional file 1: Table S1, we present the factors available from two out of three studies [4,6]: purpose of travel, diet (omnivore or vegetarian), type of accommodation, use of medications (antidiarrhoeals, proton-pump inhibitors, and antiemetics) and contact with local health care (other than hospitalisation). The five investigations appeared heterogeneous in the forest plot analysis, however, in the

multivariable analysis of the pooled data, the interaction between subregions and studies was not found statistically significant.

Information concerning mild gastrointestinal symptoms in the 'no TD' group was only available for the Finnish volunteers (48.8% of all 'no TD' cases). To pool the three studies, we had to define TD as three or more stools per 24 hours; milder diarrhoea cases were categorised as 'no TD', although even mild TD also may predispose to ESBL-PE acquisition.

Conclusion

ESBL-PE colonization rates in African subregions appear moderate, with the exception of Northern Africa, especially Egypt. Also on this continent, however, TD and antibiotic use increase the risk of individual travelers acquiring ESBL-PE.

Abbreviations

AB: antibiotic; ESBL: Extended-spectrum beta-lactamase; ESBL-PE: Extended-spectrum beta-lactamase-producing *Enterobacteriaceae;* TD: Travelers' diarrhoea

Ethics approval and consent to participate

In all studies, written informed consent was obtained from all participants and the Ethics Committees in the respective organisations approved the study protocols. (METc, NL29769.029.09) of the VU University Medical Centre (NTR Trial ID NTR2453); Ethics Committee of the Department of Medicine in Helsinki University Hospital (406/13/03/01/08); Medical Ethics Committee of the Leiden University Medical Center. (P11.036).

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to ongoing further analyses on the data but are available from the corresponding author on reasonable request.

Competing interests

TL, JV, APvD, HH, GS, LV, declare no competing interests. AK has received honorary for lectures (Pfizer, MSD, Valneva, Immuron) and membership in advisory board (Valneva), and an investigator-initiated grant (Pfizer), none of these relevant to the current manuscript.

Funding

The three original studies were funded by: Finnish government subsidy for health science research (grant numbers: TYH2012141, TYH 2013218 and TYH 2014216), the SSAC Foundation (grant number SLS-504141) and the Paulo Foundation; Research and Development fund GGD Amsterdam and ZonMw, the Netherlands Organisation for Health Research and Development (grant 125020011); the European Society of Clinical Microbiology and Infectious Diseases (ESCMID Study Group Research Grant) and by the Department of Medical Microbiology of the Leiden University Medical Center, the Netherlands. None of study sponsors were not involved in the study design, collection, analysis or interpretation of data.

Authors' contributions

Study concept and design TL, JV, GS, LV, AK; acquisition of data TL, JV, APvD, HH, GS, LV, AK; analysis and interpretation of results TL, JV, AK; drafting of manuscript TL, AK; statistical analysis TL; Critical comments of the manuscript JV, APvD, HH, GS, LV; final approval of version published TL, JV, APvD, HH, GS, LV, AK. All authors have read and approved the manuscript.

Acknowledgements

We thank Jukka Ollgren for expert advice in statistical analyses.

References

1. Tängden T, Cars O, Melhus A, Lowdin E. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. Antimicrob Agents Chemother 2010; 54: 3564-3568.
2. Tham J, Walder M, Melander E, Odenholt I. Duration of colonization with extended-spectrum beta-lactamase-producing *Escherichia coli* in patients with travellers' diarrhoea. Scand J Infect Dis 2012; 44: 573-577.
3. Östholm-Balkhed A, Tarnberg M, Nilsson M, Nilsson LE, Hanberger H, Hällgren A, Travel Study Group of Southeast Sweden. Travel-associated faecal colonization with ESBL-producing *Enterobacteriaceae*: incidence and risk factors. J Antimicrob Chemother 2013; 68: 2144-2153.
4. Paltansing S, Vlot JA, Kraakman ME, Mesman R, Bruijning ML, Bernards AT, et al. Extended-Spectrum beta-Lactamase-producing *Enterobacteriaceae* among Travelers from the Netherlands. Emerg Infect Dis 2013; 19: 1206-1213.
5. Kuenzli E, Jaeger VK, Frei R, Neumayr A, DeCrom S, Haller S, et al. High colonization rates of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in Swiss travellers to South Asia- a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors. BMC Infect Dis 2014; 14: 528-2334-14-528.
6. Kantele A, Lääveri T, Mero S, Vilkman K, Pakkanen SH, Ollgren J, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing *Enterobacteriaceae*. Clin Infect Dis 2015; 60: 837-846.
7. Ruppé E, Armand-Lefevre L, Estellat C, Consigny PH, El Mniai A, Boussadia Y, et al. High Rate of Acquisition but Short Duration of Carriage of Multidrug-Resistant *Enterobacteriaceae* After Travel to the Tropics. Clin Infect Dis 2015; 61: 593-600.
8. Lubbert C, Straube L, Stein C, Makarewicz O, Schubert S, Mossner Jet al. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing *Enterobacteriaceae* in international travelers returning to Germany. Int J Med Microbiol 2015; 305: 148-156.
9. Angelin M, Forsell J, Granlund M, Evengard B, Palmgren H, Johansson A. Risk factors for colonization with extended-spectrum beta-lactamase producing *Enterobacteriaceae* in healthcare students on clinical assignment abroad: A prospective study. Travel Med Infect Dis 2015; 13: 223-229.
10. Reuland EA, Sonder GJ, Stolte I, Al Naiemi N, Koek A, Linde GB, et al. Travel to Asia and traveller's diarrhoea with antibiotic treatment are independent risk factors for acquiring ciprofloxacin-resistant and extended spectrum beta-lactamase-producing *Enterobacteriaceae*-a prospective cohort study. Clin Microbiol Infect 2016; 22: 731.e1-731.e7.
11. Arcilla MS, van Hattem JM, Haverkate MR, Bootsma MC, van Genderen PJ, Goorhuis A, et al. Import and spread of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* by international travellers (COMBAT study): a prospective, multicentre cohort study. Lancet Infect Dis 2017; 17: 78-85.
12. Vading M, Kabir MH, Kalin M, Iversen A, Wiklund S, Naucler P, et al. Frequent acquisition of low-virulence strains of ESBL-producing *Escherichia coli* in travellers. J Antimicrob Chemother 2016; 71: 3548-3555.

13. Mizuno Y, Miura Y, Yamaguchi T, Matsumoto T. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* colonisation in long-term overseas business travellers. Travel Med Infect Dis 2016; 14: 561-567.

14. Tham J, Odenholt I, Walder M, Brolund A, Ahl J, Melander E. Extended-spectrum beta-lactamase-producing *Escherichia coli* in patients with travellers' diarrhoea. Scand J Infect Dis 2010; 42: 275-280.

15. United Nations World Tourism Organization (UNWTO), World Tourism Barometer. Available at: http://mkt.unwto.org/barometer. Accessed 15 October 2017.

16. United Nations, Department of Economic and Social Affairs. Definition of major areas and regions (World Population Prospects, Revision 2015). 2015.Available at: https://esa.un.org/unpd/wpp/General/Files/Definition_of_Regions.pdf. Accessed 15 October 2017

17. Bassyouni RH, Gaber SN, Wegdan AA. Fecal carriage of extended-spectrum beta-lactamase- and AmpC- producing *Escherichia coli* among healthcare workers. J Infect Dev Ctries 2015; 9: 304-308.

18. Farra A, Frank T, Tondeur L, Bata P, Gody JC, Onambele M, et al. High rate of faecal carriage of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in healthy children in Bangui, Central African Republic. Clin Microbiol Infect 2016; 22: 891.e1-891.e4.

19. Magoue CL, Melin P, Gangoue-Pieboji J, Okomo Assoumou MC, Boreux R, De Mol P. Prevalence and spread of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in Ngaoundere, Cameroon. Clin Microbiol Infect 2013; 19: E416-20.

20. Tellevik MG, Blomberg B, Kommedal O, Maselle SY, Langeland N, Moyo SJ. High Prevalence of Faecal Carriage of ESBL-Producing *Enterobacteriaceae* among Children in Dar es Salaam, Tanzania. PLoS One 2016; 11: e0168024.

21. Mshana SE, Falgenhauer L, Mirambo MM, Mushi MF, Moremi N, Julius R, et al. Predictors of blaCTX-M-15 in varieties of *Escherichia coli* genotypes from humans in community settings in Mwanza, Tanzania. BMC Infect Dis 2016; 16: 187-016-1527-x.

22. Najjuka CF, Kateete DP, Kajumbula HM, Joloba ML, Essack SY. Antimicrobial susceptibility profiles of *Escherichia coli* and *Klebsiella pneumoniae* isolated from outpatients in urban and rural districts of Uganda. BMC Res Notes 2016; 9: 235-016-2049-8.

23. Frickmann H, Warnke P, Frey C, Schmidt S, Janke C, Erkens K, et al. Surveillance of Food- and Smear-Transmitted Pathogens in European Soldiers with Diarrhea on Deployment in the Tropics: Experience from the European Union Training Mission (EUTM) Mali. Biomed Res Int 2015; 2015: 573904.

24. Ouedraogo AS, Sanou S, Kissou A, Poda A, Aberkane S, Bouzinbi Net al. Fecal Carriage of *Enterobacteriaceae* Producing Extended-Spectrum Beta-Lactamases in Hospitalized Patients and Healthy Community Volunteers in Burkina Faso. Microb Drug Resist 2017; 23: 63-70.

25. Isendahl J, Turlej-Rogacka A, Manjuba C, Rodrigues A, Giske CG, Naucler P. Fecal carriage of ESBL-producing *E. coli* and *K. pneumoniae* in children in Guinea-Bissau: a hospital-based cross-sectional study. PLoS One 2012; 7: e51981.

26. Kaba M, Manenzhe RI, Moodley C, Zar HJ, Nicol MP. Epidemiology of extended-spectrum beta-lactamase- and carbapenemase-producing bacteria in stool from apparently healthy children, South Africa. Int J Infect Dis 2016; 45: 95.

27. Kantele A, Mero S, Kirveskari J, Lääveri T. Fluoroquinolone antibiotic users select fluoroquinolone-resistant ESBL-producing *Enterobacteriaceae* (ESBL-PE) - Data of prospective traveller study. Travel Med Infect Dis 2017.

28. Barreto Miranda I, Ignatius R, Pfuller R, Friedrich-Janicke B, Steiner F, Paland M, et al. High carriage rate of ESBL-producing *Enterobacteriaceae* at presentation and follow-up among travellers with gastrointestinal complaints returning from India and Southeast Asia. J Travel Med 2016; 23: tav024.

29. Bou-Antoun S, Davies J, Guy R, Johnson AP, Sheridan EA, Hope RJ. Descriptive epidemiology of *Escherichia coli* bacteraemia in England, April 2012 to March 2014. Euro Surveill 2016; 21: 10.2807/1560-7917.ES.2016.21.35.30329.

30. Nemeth J, Ledergerber B, Preiswerk B, Nobile A, Karrer S, Ruef C, et al. Multidrug-resistant bacteria in travellers hospitalized abroad: prevalence, characteristics, and influence on clinical outcome. J Hosp Infect 2012; 82: 254-259.

31. Kaspar T, Schweiger A, Droz S, Marschall J. Colonization with resistant microorganisms in patients transferred from abroad: who needs to be screened? Antimicrob Resist Infect Control 2015; 4: 31-015-0071-6. eCollection 2015.

32. Khawaja T, Kirveskari J, Johansson S, Väisänen J, Djupsjobacka A, Nevalainen A, et al. Patients hospitalized abroad as importers of multiresistant bacteria-a cross-sectional study. Clin Microbiol Infect 2017.

33. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal Colonization With Extended-spectrum Beta-lactamase-Producing *Enterobacteriaceae* and Risk Factor Among Healthy Individuals: A Systematic Review and Metaanalysis. Clin Infect Dis 2016; 63: 310-318.

Supplementary data

Additional Table S1 Factors available in same format only from the studies of Kantele et al [6] and Paltansing et al [4] and not included in the pooled data of this report.

	Total n (% of all)	ESBL-PE (+) n (%)	ESBL-PE (-) n (%)	P-value	Univariate OR	95% CI
Antidiarrhoeal medication (information missing: 97; 24.5%)						
None	244 (81.6)	41 (16.8)	203 (83.2)		1.0	
Loperamide	52 (17.4)	12 (23.1)	40 (76.9)	0.286	1.5	0.7-3.1
Other	3 (1.0)	1 (33.3)	2 (66.7)	0.464	2.5	0.2-27.9
PPI/antacid (information missing: 98; 24.7%)						
No	277 (93.0)	50 (18.1)	227 (81.9)		1.0	
PPI	18 (6.0)	4 (22.2)	14 (77.8)	0.658	1.3	0.4-4.1
Other antacid	3 (1.0)	0 (0)	3 (100.0)	0.999	n/a	n/a
Purpose of travel (information missing: 99; 25.0%)						
Holiday	216 (72.7)	38 (17.6)	178 (82.4)		1.0	
Work/business	37 (12.5)	5 (13.5)	32 (86.5)	0.679	0.8	0.3-2.2
Living abroad	14 (4.7)	3 (21.4)	11 (78.6)	0.612	1.4	0.4-5.3
Studying/ volunteering	21 (7.1)	7 (33.3)	14 (66.6)	0.057	2.6	1.0-6.7
VFR	9 (3.0)	4 (44.4)	5 (55.6)	0.041	4.1	1.1-16.2
Antiemetics (information missing: 98; 24.7%)						
No	293 (98.3)	55 (18.8)	238 (81.2)		1.0	
Yes	5 (1.7)	2 (40.0)	3 (60.0)	0.244	2.9	0.5-17.7
Diet (information missing: 164; 41.4%)						
Omnivore	214 (92.2)	49 (22.9)	165 (77.1)		1.0	
Vegetarian	18 (7.8)	2 (11.1)	16 (88.9)	0.247	0.4	0.1-1.9
Health care contact (information missing: 97; 24.5%)						
No	274 (91.6)	50 (18.2)	224 (81.8)		1.0	
Yes	25 (8.4)	7 (28.0)	18 (72.0)	0.235	1.7	0.7-4.4
Accommodation (information missing: 105; 26.5%)						
Hotel	152 (52.2)	23 (15.1)	129 (84.9)		1.0	
Guesthouse / lodge	62 (21.3)	13 (21.0)	49 (79.0)	0.302	1.5	0.7-3.2
With locals / own home	56 (19.2)	10 (17.9)	46 (82.1)	0.634	1.2	0.5-2.8
Other	21 (7.2)	7 (33.3)	14 (66.7)	0.045	2.8	1.0-7.7