MAJOR ARTICLE

Antimicrobials Increase Travelers' Risk of Colonization by Extended-Spectrum Betalactamase-Producing *Enterobacteriaceae*

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(See the Editorial Commentary by Connor and Keystone on pages 847–8.)

Background. More than 300 million travelers visit regions with poor hygiene annually. A significant percentage of them become colonized by resistant intestinal bacteria such as extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) and may transmit the strains to others and to medical care settings when they return home. Despite the threats to global healthcare caused by an upsurge in antimicrobial resistance, no effort has been centered on prevention of colonization while traveling.

Methods. Stool samples were collected from 430 Finns before and after traveling outside Scandinavia. All specimens were analyzed for ESBL- and carbapenemase-producing *Enterobacteriaceae* (CPE). Questionnaires were used to survey volunteers about use of antimicrobials as well as other potential risk factors. The results were subjected to multivariable analysis.

Results. Twenty-one percent (90/430) of the travelers became colonized by ESBL-PE and none by CPE. Geographic region, occurrence of travelers' diarrhea (TD), age, and use of antimicrobial (AB) for TD were identified as independent risk factors predisposing to contracting ESBL-PE. Eleven percent of those in subgroup TD−AB−, 21% in TD+AB−, and 37% in TD+AB+ acquired ESBL-PE. The risk proved to be highest in South Asia (46%); 23% became colonized in subgroup TD−AB−, 47% in TD+AB−, and 80% in TD+AB+. In Southeast Asia, the rates were 14%, 37%, and 69%, respectively.

Conclusions. TD and antimicrobials for TD proved to be independent risk factors, with up to 80% of TD+AB+ travelers contracting ESBL-PE. In modern pre-travel counseling for those visiting high-risk regions, travelers should be advised against taking antibiotics for mild or moderate TD.

Keywords. ESBL; colonization; travel; antimicrobials; travelers' diarrhea.

Antimicrobial resistance is surging in regions where hygiene is poor and antimicrobial policy weakly implemented. The spread of resistant bacteria menaces healthcare worldwide, with strains being carried across the globe by international travelers and food and animal trade. Of the more than 1 billion annual travelers, about 300 million visit the riskiest regions and more than 20% return home colonized by resistant intestinal bacteria [1–11]. The task of improving hygiene and establishing reasonable antimicrobial policy in high-risk areas cannot be accomplished swiftly. In low-prevalence countries, the battle against the spread of resistant microbes currently focuses on precautions such as surveillance of resistance among bacteria and, in some countries, contact isolation of patients transferred from or hospitalized abroad [11]. Paradoxically, little attention is given to how initial colonization could be prevented while traveling.

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Broad resistance to antimicrobials in the *Enterobacteriaceae* family has emerged [11, 12]. Extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) have become particularly prominent, not only in nosocomial but also in community-onset *Enterobacteriaceae* infections worldwide [12]. There are many reports on the import of ESBL-PE by travelers [2–10]. Likewise, highly resistant strains that produce New Delhi metallo-beta-lactamase 1 (NDM-1) enzymes or other carbapenemases have already been introduced into many countries [11, 13–15]. A major cause for concern is the spread of multiresistant strains to healthcare settings. This has several consequences including treatment failures, increased mortality, and dramatic increases in the costs of public health [16].

Travelers often contract resistant intestinal bacteria unknowingly and may pass them on to close contacts [17]. For colonization to take place, the intruding, resistant bacteria must become incorporated into the mini-ecosystem of the gut microbiota [18]. When in balance, this microbiota acts as a barrier against potential pathogens and resistant microbes (colonization resistance) [18, 19]. While antibiotics have been reported to increase the risk of becoming colonized by resistant bacteria in healthcare settings [12, 20, 21], none of the studies conducted among healthy travelers have been large enough to allow accurate multivariable analysis of antimicrobial use.

In the global battle against multiresistant strains, the early steps of the transmission cascade should be targeted first. In a search for tools to prevent initial colonization, here, we investigate risk factors for contracting resistant intestinal bacteria, in particular, by scrutinizing the effect of antimicrobial use against travelers' diarrhea (TD).

MATERIALS AND METHODS

Study Design, Volunteers, and Samples

A total of 526 volunteers were enrolled at the Travel Clinic of Aava Medical Centre, which serves travelers who seek pre-travel advice, primarily those who intend to visit tropical/subtropical regions. Volunteers were recruited among consecutive travelers who consulted the same doctor while planning a trip outside the Nordic countries for more than 4 nights (Figure 1). They were

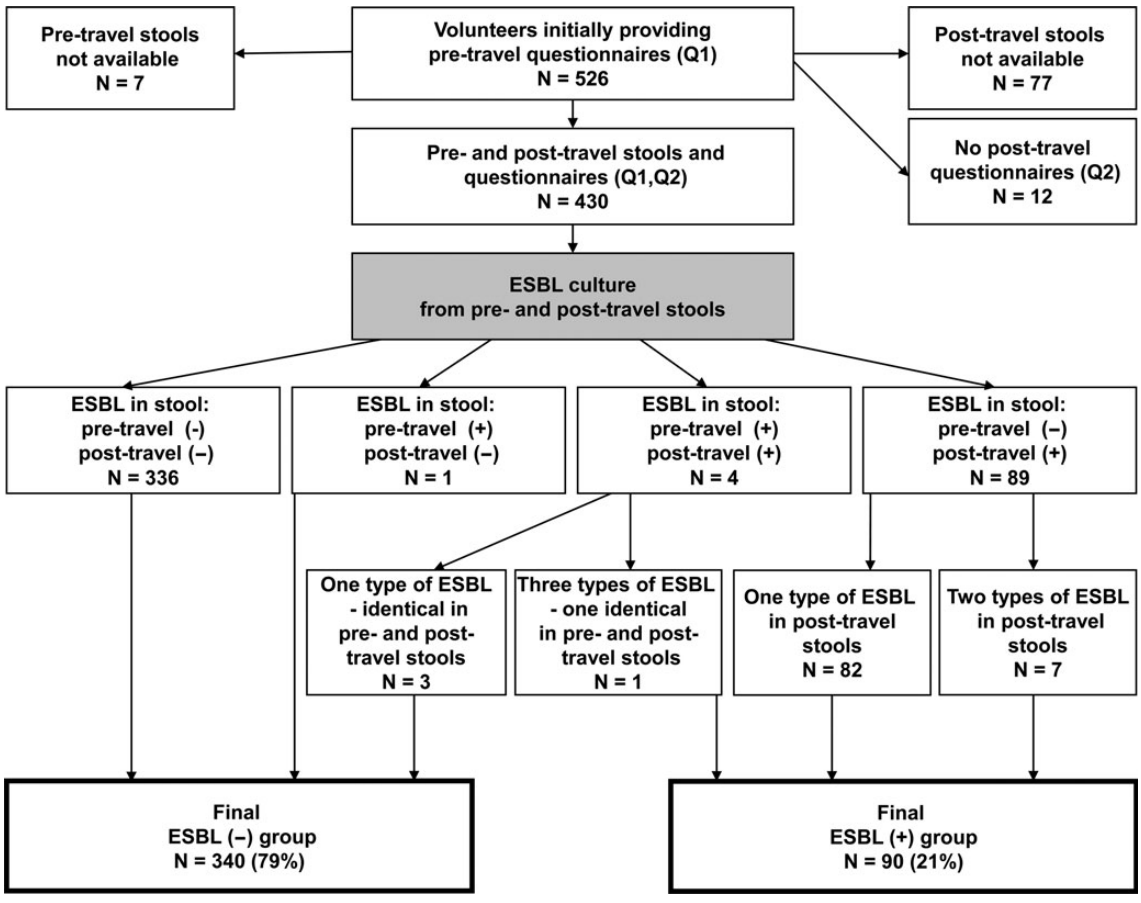

Figure 1. Study protocol for investigating risk factors associated with extended-spectrum beta-lactamase (ESBL)–producing *Enterobacteriaceae* colonization of Finnish travelers.

asked to provide pre-travel stool samples and to complete a questionnaire (Q1) and, on return home, to provide samples of the first (or second) stool and to complete a post-travel questionnaire (Q2). Those who provided both specimens and both questionnaires were included in the final analyses. For risk factor analysis, the participants were divided into 2 groups: ESBL (+) and ESBL(−). The ESBL(+) group included those who had contracted the strain during travel. The ESBL(+) group was recorded for laboratory-verified ESBL-PE in clinical samples over the following year.

The Ethics Committee of the Helsinki University Central Hospital approved the study protocol. Volunteers for this prospective cohort study were recruited over a 12-month period (1 March 2009 through 28 February 2010). All participants provided written informed consent.

Questionnaires

Q1 covered personal information, medical history, specifics regarding possible cotravelers, and an itinerary. Q2 collected travel-related information including a personal account of the course of the trip, symptoms, and medication.

Travel Destinations

The countries visited were grouped into the following 7 regions: South Asia, Southeast Asia, East Asia, North Africa and the Middle East, sub-Saharan Africa, South and Central America and the Caribbean, and Europe, Australia, and North America. The 29 travelers visiting more than 1 region were categorized by longest stay.

Definition of Travelers' Diarrhea

TD was defined according to the following World Health Organization criteria: passing 3 or more loose/liquid stools per 24 hours, or more frequently than normal for an individual [22].

Handling of Specimens

Stools were collected as swabs in Copan M40 Transystem tubes (Copan Diagnostics, Italy), sealed in special boxes, and sent by post (1–3 days) to the laboratory. Once delivered, they were frozen at −80°C and stored for analysis.

Identification of Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae*–Positive Strains

The swabs were cultured for 24 hours at 35°C on ESBL and *Klebsiella pneumoniae* carbapenemase (KPC) agars (CHROMagar, bioMérieux, Marcy l'Etoile, France). No growth of *Enterobactericeae* was detected on KPC agar. The putative ESBL-producing strains were identified using the automated VITEK GN system (bioMérieux), and genotypes were determined as described elsewhere [23]. The susceptibilities were tested with the VITEK 2 AST-N153 or AST-N184 card (bioMérieux) using the broth microdilution method and following Clinical and Laboratory Standards Institute (CLSI) guidelines. In addition, disc susceptibility tests were performed according to the criteria of the CLSI M100-S17, using Mueller Hinton agar (Oxoid, Thermo Fisher Scientific, Cambridge, United Kingdom); the double-disk synergy (Oxoid) test was used for cefotaxime (30 μg), ceftazidime (30 μg), and cefpodoxime (30 μg) alone or with clavulanic acid (10 μg) combinations.

Follow-up of Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae* in Clinical Samples

To spot laboratory-confirmed clinical ESBL-PE infections, a survey was conducted for the ESBL(+) group using the Helsinki University Hospital Laboratory (HUSLAB) database. This database covers approximately 90% of all ESBL-PE findings in clinical samples in the district (personal communication, Martti Vaara, HUSLAB).

Statistics

Univariate analyses were conducted using SPSS 19.0.0.1 software (SPSS Inc., Chicago, Illinois). For categorical variables, χ^2 test, Fisher exact test, or binary logistic regression analysis was used; for continuous variables, binary logistic regression analysis was used. Risk factors with a P value < .2 in the univariable model were chosen for further analysis by the multivariable model with binary logistic regression; of the strongly correlating risk factors, only 1 was picked. When the variables were selected for the final model, the Akaike information criteria were used. Values missing in the risk factors were taken into account by multiple imputations, reducing possible biases and efficiency loss. This involved assuming "missingness at random." Multivariable analyses were carried out with SPSS 21.0.0.1 (SPSS Inc.).

RESULTS

A total of 526 individuals returned Q1; 430 who fulfilled the inclusion criteria formed the final study population (Figure 1; background data and itineraries presented in Table 1). Twenty-one percent (90/430) of the individuals acquired ESBL-PE while traveling; no one carried carbapenemase-producing *Enterobacteriaceae*.

Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae* in Pre- and Post-Travel Specimens

A total of 5/430 pre-travel and 93/430 post-travel stools were positive for ESBL-PE (Figure 1). Of the 5 cases with a positive pre-travel sample, 4 were placed in the ESBL(−) group: 3 with an identical post-travel strain and 1 negative after the journey. The fifth was put in the ESBL(+) group, as 2 of his 3 post-travel ESBL-PE types was different from his pre-travel strain. Twenty-one percent (90/430) of all travelers constituted the ESBL(+) and 79% (340/430) constituted the ESBL(−) groups. Eight

Table 1. Results of Follow-up Study of Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae* Colonization During Travel: Characteristics of 430 Travelers and Results of an Unadjusted (Univariate) Risk Factor Analysis

Risk Factor	Travelers (n = 430) n (%)	ESBL(+) (n = 90) n [% of All Travelers With ESBL(+)]	ESBL(–) (n = 340) n [% of All Travelers With ESBL (–)]	Odds Ratio (95% Confidence Interval)	*P* value in Univariate Analysis
Sex					
Female	263 (61)	49 (54)	214 (63)	0.7 (.4–1.1)	.14
Male	167 (39)	41 (46)	126 (37)	1.0	N/A
Age, years (mean)	40 (range: 0–77) (SD 17.2)	41 (range:0–76) (SD 16.1)	39 (range:11–77) (SD 17.5)		.52
Age group (years)					.01
0–17	34 (8)	2 (2)	32 (9)	1.0	N/A
18–30	119 (28)	27 (30)	92 (27)	4.7 (1.1–20.9)[a]	.04[a]
31–50	146 (34)	33 (37)	113 (33)	4.7 (1.1–20.6)[a]	.04[a]
51–64	90 (21)	21 (23)	69 (20)	4.9 (1.1–22.0)[a]	.04[a]
≥65	41 (10)	7 (8)	34 (10)	3.3 (.6–17.0)[a]	.16[a]
Geographic region					.00
South Asia	61 (14)	28 (31)	33 (10)	1.0	N/A
Southeast Asia	101 (24)	33 (37)	68 (20)	0.8 (.4–1.7)[b]	.52[b]
East Asia	6 (1)	2 (2)	4 (1)	0.7 (.1–8.1)[b]	.76[b]
North Africa and the Middle East	12 (3)	4 (4)	8 (2)	1.5 (.3–7.7)[b]	.61[b]
Sub-Saharan Africa	193 (45)	23 (26)	170 (50)	0.2 (.1–0.4)[b]	.00[b]
South America, Central America, and the Caribbean	40 (9)	0 (0)	40 (12)	N/A	1.00[b]
North America, Europe, Australia	17 (4)	0 (0)	17 (5)	N/A	1.00[b]
Length of journey, days (mean; information missing for 93)	19 (SD 18.0) (range: 4–133)	27 (SD 28.3) (range 5–133)	17.5 (SD 13.9) (range:4–100)		.01
Length of journey (information missing for 93)					.21
7 d or less	50 (15)	8 (9)	42 (10)	1.0	N/A
8–15 d	162 (47)	21 (23)	141 (41)	0.8 (.3–1.9)[c]	.59[c]
16–30 d	96 (28)	25 (28)	71 (21)	1.8 (.8–4.5)[c]	.17[c]
Longer than 30 d	35 (8)	12 (13)	23 (7)	2.7 (1.0–7.7)[c]	.06[c]
TD	288 (67)	75 (83)	213 (63)	3.0 (1.6–5.4)	.00
Use of antimicrobial medications					.00
None	364 (85)	62 (69)	302 (89)	1.0	N/A
Antimicrobial for TD	52 (12)	24 (27)	28 (8)	4.2 (2.3–7.7)	.00
Antimicrobial for indications other than TD	14 (3)	4 (4)	10 (3)	2.0 (.6–6.4)	.27
Use of alcohol (information missing for 66)					
0–2 units/day	262 (72)	66 (81)	196 (70)	1.9 (1.1–3.6)	.03
≥3 units/day	102 (28)	16 (16)	86 (31)	1.0	N/A
Meals with locals (information missing for 24)	73 (18)	7 (8)	66 (21)	0.3 (.2–.8)	.01
Site of meals (>50% at restaurants vs mainly at own household) (information missing for 14)	345 (83)	82 (92)	263 (80)	0.4 (.2–.8)	.01
Contact with local healthcare	40 (9)	15 (17)	25 (7)	2.5 (1.3–5.0)	.01
Accommodation with locals/own household vs hotel/guesthouse (information missing 15)	65 (16)	7 (8)	58 (18)	0.4 (.2–.9)	.03
Use of probiotics	227 (53)	51 (57)	176 (52)	1.2 (.8–1.9)	.41
Use of bottled water	405 (96)	86 (96)	319 (95)	1.1 (.4–3.3)	.90
Consumed uncooked meat or fish	56 (13)	12 (13)	44 (13)	1.0 (.5–2.1)	.92
Neglected hand-washing (information missing 12)	53 (13)	10 (11)	43 (13)	0.8 (.4–1.8)	.65

Table 1 continued.

Risk Factor	Travelers (n = 430) n (%)	ESBL(+) (n = 90) n [% of All Travelers With ESBL(+)]	ESBL(−) (n = 340) n [% of All Travelers With ESBL (−)]	Odds Ratio (95% Confidence Interval)	*P* value in Univariate Analysis
Consumed salads (information missing for 24)	317 (78)	64 (75)	253 (79)	0.8 (.5–1.4)	.49
Chronic illness	93 (22)	22 (24)	71 (21)	1.2 (.7–2.1)	.47
Antimalarial chemoprophylaxis	238 (55)	48 (53)	190 (56)	0.9 (.6–1.49)	.67

Risk factors or risk factor groups included in the multivariable analysis are shown in bold.

Abbreviations: ESBL, extended-spectrum beta-lactamase; N/A, not applicable; SD, standard deviation; TD, travelers' diarrhea.

[a] Compared with the youngest age group.

[b] Compared with South Asia.

[c] Compared with shortest length of journey.

percent (7/90) had acquired 2 ESBL-PE strains, as judged by the results of a molecular analysis (data not shown; Figure 1). Seventy-nine percent of the strains belonged to CTX-M-type, CTX-M-1 and CTX-M-9 constituting the most prevalent types. Other common strains included TEM (56%) and OXA (25%).

Identification of Risk Factors Exposing to Colonization by Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae*

The results of the univariate analysis are shown in Table 1. Factors included in the final multivariable model are presented in Table 2.

Geographic Region as a Risk Factor

The risk of contracting ESBL-PE was highest in South Asia (46%), followed by Southeast Asia, East Asia, the region of North Africa together with the Middle East (33% in each of the 3 regions), and sub-Saharan Africa (12%). No cases were identified among visitors to Europe, Australia, or the Americas (Table 2).

Travelers' Diarrhea as a Risk Factor

Of all travelers, 67% (288/430) had TD; 26% (75/288) of the TD (+) and 11% (15/142) of the TD(−) subgroups became colonized by ESBL-PE (Table 2). Conversely, TD was contracted by 83% in the ESBL(+) and 63% in the ESBL(−) groups.

Use of Antimicrobials Against Travelers' Diarrhea as a Risk Factor

Antimicrobials were taken by 15% (66/430) of all travelers (doxycycline started as antimalarial prophylaxis not included) during their journeys. In 79% (52/66) of the cases, the drug was taken for TD (Table 2).

Antimicrobials taken to treat TD proved to be an independent risk factor (46% ESBL+) compared with those who did not take an antimicrobial (17% ESBL+; Table 2). In the study as a whole, the proportion of ESBL(+) cases was 11% in the subgroup TD−AB−, 21% in TD+AB−, and 37% in TD+AB+ (Figure 2). There were only 7 TD-AB+ travelers; none of them contracted ESBL-PE.

Age as a Risk Factor

In the TD(−) subgroup, the risk of ESBL-PE increased with increasing age (Table 2 and Supplementary Table 1). While no cases were seen in children, those aged 18–30, 31–50, 51–64, and 65+ years had 5%, 9%, 16%, and 25% cases of ESBL-PE, respectively. In the TD(+) subgroups, such increase with age was not seen.

Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae Among Travel Companions

Person-to-person transmission between co-travelers appeared not to be a significant route for contracting ESBL-PE (Supplementary Table 2). Fifty-one percent (218/430) of all travelers and 57% (51/90) of those colonized by ESBL-PE had traveled with 1 or more persons; some of these travelers also participated in this study. For each pair/group, the first to be ESBL-PE positive was marked as the index case (n = 35) and the other(s) as companion(s) (n = 48). The risk of ESBL-PE colonization among these pairs/groups was similar to the risk prevailing in the region visited (Table 2; Supplementary Table 2).

Antimalarials and Risk of Acquiring Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae

Antimalarials by themselves in univariate analysis were not found to be a risk factor (Table 1). No statistically significant differences were detected ($P = .72$) in ESBL-PE rates between the subgroups for mefloquine, atovaquone–proguanil, and doxycycline (Table 3). The proportion of participants with TD or taking antibiotics was similar in all subgroups.

Travelers With Concomitant Risk Factors

Those who had several risk factors also were most predisposed to contracting ESBL-PE. Accordingly, the highest risk was in South Asia, where the proportion of travelers with ESBL-PE was 46%; 23% in the TD-AB− group; 47% in the TD+AB− group; and 80% in the TD+AB+ group (Figure 2).

Table 2. Risk Factors of Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae* Colonization in the Final Multivariable Model After Backward Selection of Factors by Akaike Information Criteria.[a] Values are Given for Proportions With a Given Risk Factor, Adjusted Odds Ratios and *P*-values in Multivariable Analysis

Risk Factor	Proportion of Those Contracting ESBL-PE Among Travelers With the Given Risk Factor (%)	AOR (95% Confidence Interval) for Contracting ESBL-PE Among Travelers With the Given Risk Factor in Multivariable Analysis	*P* values in Multivariable Analysis
Sex			
Female	49/263 (19)	0.7 (.4–1.1)	.13
Male	41/167 (25)	1.0	N/A
Age group[b]	(see Table 1 and Supplementary Table 3)	2.5 (1.4–4.6)	.00
Age group/No TD	N/A	0.5 (.2–.9)	.02
Age group/TD	N/A	1.0	N/A
Geographic region			
South Asia	28/61 (46)	1.0	N/A
Southeast Asia	33/101 (33)	0.6 (.3–1.3)	.24
East Asia	2/6 (33)	0.6 (.1–5.1)	.67
North Africa and the Middle East	4/12 (33)	1.0 (.2–4.2)	.95
Sub-Saharan Africa	23/193 (12)	0.1 (.1–.3)	.00
South America, Central America, and the Caribbean	0/40 (0)	N/A	N/A
Europe, Australia, United States, and Canada	0/17 (0)	N/A	N/A
TD			
No TD	15/142 (11)	1.0	N/A
TD	75/288 (26)	31.0 (2.7–358.1)	.01
Use of antibiotics			
None	62/364 (17)	1.0	N/A
Antimicrobial for TD[c]	24/52 (46)	3.0 (1.4–6.7)	.01
Antimicrobial for indications other than TD[d]	4/14 (29)	3.6 (.8–16.0)	.10
Meals with locals[e] (information missing for 24)			
No	79/333 (24)	1.0	N/A
Yes	7/73 (10)	0.3 (.1–0.8)	.01
Contact with local healthcare[f]			
No	75/390 (19)	1.0	N/A
Yes	15/40 (38)	2.1 (.8–5.6)	.12

Abbreviations: AOR, adjusted odds ratios; ESBL-PE, extended-spectrum beta-lactamase–producing *Enterobacteriaceae*; N/A, not applicable; TD, travelers' diarrhea.

[a] Backward selection eliminated the following factors: length of journey,[e] use of alcohol,[e] type of accomodation,[e] site of meals.[e]

[b] Analyzed as continuous variables.

[c] 41/52 (79%) used fluoroquinolones, and 7/52 (13%) used macrolides.

[d] 5/14 (36%) used fluoroquinolones, and 2/14 (14%) used macrolides.

[e] Multiple imputation.

[f] Three patients were hospitalized while abroad, 2 of these ESBL-positive after travel.

Laboratory-based Follow-up

The 1-year laboratory-based follow-up showed no clinical samples with ESBL-PE in the ESBL-PE(+) group.

DISCUSSION

Serious action is needed to combat resistant intestinal microbes that are sweeping across the globe. In addition to current approaches, that is, surveillance and screening of returning travelers, efforts should be decisively directed toward preventing colonization en route and abroad. Here, we identified factors that predispose to contracting resistant gut microbes. In addition, we confirmed and expanded on several prospective [3, 4, 7, 8, 10] and retrospective [2, 5, 6, 9] investigations that showed that a significant proportion of those who traveled to tropical and subtropical areas became colonized by ESBL-PE. Despite the low number of participants described in earlier reports, the rates discovered (13%–33%; Table 4) do not differ much from our findings (21%). While geographic location is consistently recognized as a risk factor, many investigations either suffer from missing risk

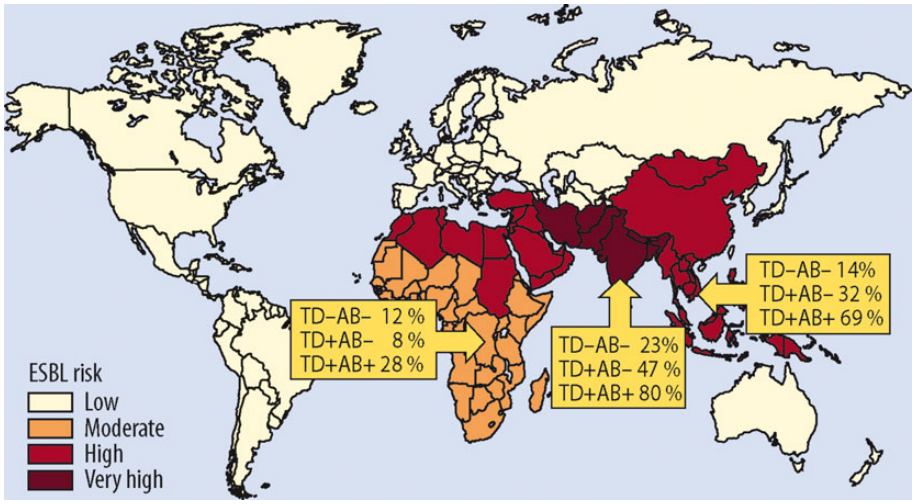

Figure 2. World map indicating the risk levels of contracting extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) in different geographic regions as established in the present investigation. In the entire study population, 21% of the travelers contracted ESBL-PE; 11% in subgroup TD−AB− (travelers' diarrhea/antimicrobials), 21% in TD+AB−, and 37% in TD+AB+ contracted ESBL-PE. The respective subgroup analyses for the regions with highest risk (Africa, South Asia, and Southeast Asia) are given in the boxes with arrows. The ESBL-PE strains contracted were all *Escherichia coli*, except for 2 *Klebsiella oxytoca* and 1 *Escherichia hermannii*.

data or their limited study population does not allow accurate analysis of factors potentially predisposing to ESBL-PE colonization.

The risk of contracting a resistant strain has been shown to vary considerably by geographic region (Table 4) [2–4, 6–10]. Our study verifies the general perception of a low ESBL-PE prevalence in Finland where only 1.2% of the pre-travel specimens were found positive. In concurrence with previous reports [2–4, 6–10], the risk of acquisition was highest for travelers to South Asia, followed by Southeast Asia, East Asia, and North Africa and the Middle East together. The risk appears to be relatively small in Latin America [2–4, 6–10].

The other factors that potentially predispose to colonization can be scrutinized in view of their ability to disrupt the balance of the mini-ecosystem of intestinal microbiota. According to our data, factors expected by themselves to cause a major disturbance in the intestinal microbial balance, that is, TD and antimicrobials, proved in multivariable analysis to be independent risk factors of colonization. The third risk factor was increasing age; this correlates with results from research both among travelers [8] and nontravelers [24]. Here, we showed the factor of age to be outweighed by the effect of TD (age was a risk factor only in the TD(−) group). Interestingly, meals with locals appeared to protect from colonization. The causes can only be speculated upon; travelers who are in close contact with locals might be frequent visitors and might have previously developed intestinal immunity, or perhaps food is served steaming hot without previous chilling.

TD has been suggested as a risk factor of contracting ESBL-PE during travel [2,4,7,8]. Of these studies, confounding factors have only been included in 1 study conducted by Östholm-Balkhed et al [8]; they reported ESBL-PE in 38% (36/95) of TD(+) and in 24% (32/131) of TD(−) travelers. These rates

Table 3. Antimalarial Prophylaxis as Risk Factor of Contracting Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae* Among Those Who Took Atovaquone/Proguanil, Mefloquine, or Doxycycline

Antimalarial	ESBL-PE (+) n = 48 (20%)	ESBL-PE (–) n = 190 (80%)	Odds Ratio (95% Confidence Interval)	*P* Value	Travelers' Diarrhea n = 171 (72%) *P* = .58	Other Antimicrobial n = 40 (17%) *P* = .16	Total n = 238
Atovaquone /proguanil	23 (18)	102 (82)	1.0		88 (70)	16 (13)	125 (53)
Mefloquine	14 (21)	53 (79)	1.2 (.6–2.5)	.68	51 (76)	10 (22)	67 (28)
Doxycycline	11 (24)	35 (76)	1.4 (.6–3.1)	.46	32 (70)	14 (21)	46 (19)

Abbreviation: ESBL-PE, extended-spectrum beta-lactamase–producing *Enterobacteriaceae*.

Table 4. Previous Studies of Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae* Acquired by Travelers

Author (Year)	Post-travel ESBL (+)/All (%)	Pre-travel ESBL (+)/all (%)	South Asia ESBL (+)/All (%)	Asia Other ESBL (+)/All (%)	Africa ESBL(+)/All (%)	Latin America ESBL (+)/All (%)	ESBL(+)/Travelers' Diarrhea (%) $^{*}P < .05$	ESBL(+)/Users of Antimicrobials (%) $^{*}P < .05$
Tham et al (2010; [2])	58/242 (28)	Not taken	11/14 (79)[a]	5/13 (38)[b]	2/17 (12)	1/10 (10)	58/242 (28)	Not reported
Tängden et al (2010; [3])	24/100 (24)	1/101	7/8 (88)[a]	10/31 (32)	1/25 (4)	0/7 (0)	13/30 (43)*	3/10 (30)
Kennedy (2010; [4])	50/102 (49)[c] ESBL: 22/102 (22)	2/106 (2)[c]	11/14 (79)[c]	29/56 (52)[c,d]	6/8 (75)[c,e]	3/5 (60)[c]	26/ 38 (68)*	19/ 28 (68)*[c]
Peirano et al (2011; [7])	26/113 (23)	Not taken	7/13 (54)[a]	6/20 (30)	9/17 (53)	1/8 (13)	26/113 (23)	Not reported
Weisenberg (2012; [6])	7/28 (25)	0/28	2/7 (29)	1/4 (25)	1/8 (13)	2/6 (33)	Not reported	Not reported
Östholm-Balkhed et al (2013; [8])	72/231 (31)	6/251 (2)	10/14 (71)[a]	24/58 (44)	15/71 (21)	5/29 (17)	36/95 (38)*	5/20 (25)
Lausch et al (2013; [9])	11/88 (13)	Not taken	3/8 (38)[a]	3/20 (15)	2/18 (11)	0/6 (0)	5/18 (28)*	3/14 (21)
Paltansing et al (2013; [10])	113/338 (33)	32/370 (9)	18/25 (72)	37/110 (34)[b]	20/82 (24)[f]	9/60 (15)	45/128 (35)	9/19 (47)
Present study (2014)	90/430 (21)	5/430 (1.2)	28/61 (46)	33/101 (33)[b]	23/193 (12)[f]	0/40 (0)	75/288 (26)*	28/66 (42)*

Abbreviation: ESBL, extended-spectrum beta-lactamase.

[a] India.

[b] Southeast Asia.

[c] Resistant *Escherichia coli*, not only ESBL.

[d] Southeast Asia and the Pacific.

[e] The Middle East and Africa.

[f] Sub-Saharan Africa.

are in agreement with those from our investigation, that is, 26% (75/288) and 11% (15/142), respectively.

Antimicrobial agents are among the most powerful factors affecting the barrier function of intestinal microbiota [18, 19]. Even a brief course of antibiotics can disrupt the balance for a long time; the effects on intestinal microbiota have been shown to persist even after 2 years [18]. Our study is the first to show that antimicrobials are indeed an independent risk factor that predisposes travelers to contracting ESBL-PE strains. Although Östholm-Balkhed et al [8] found no impact on colonization risk, they evaluated a smaller study population and a scant number of travelers who took antimicrobials. Kennedy and Collignon [4] reported that antibiotics increased travelers' risk of contracting various types of resistant *Escherichia coli*; however, TD and geographic area, 2 significant confounding factors, were not excluded. Nevertheless, their results support the present findings. The effect of antibiotics is aptly exemplified by the association between antimicrobial use and salmonellosis; the inoculum size necessary to cause disease is reduced 10 000-fold in mice pretreated with antibiotics [25]. In contrast to the niches opened by TD, those brought about by antimicrobials are not presumed to tempt all bacteria alike but, instead, favor those resistant to the drug used [18]. Creation of such a niche is obviously best to be avoided when visiting destinations with poor hygiene and high indigenous prevalence of resistant strains.

The colonization incidence was highest in participants who had several concomitant risk factors. In the region with greatest risk, South Asia, 23% of travelers in subgroup TD-AB–, 47% in TD+AB–, and 80% in the TD+AB+ contracted ESBL-PE. In Southeast Asia, the values were 14%, 32%, and 69%, respectively. The data suggest that most, if not all, travelers to these regions are exposed to ESBL-PE; in the best case, however, an intact barrier of intestinal microbiota will inhibit colonization.

Our research had some limitations. Although the size of our study population was the largest on this subject to date, conclusions based on results from regions with small numbers of travelers (East Asia, North Africa and Middle East, Europe, the Americas, and Australia) should be made with caution. Another limitation is that while our laboratory analysis focused on the clinically and epidemiologically important ESBL strains, we did not cover the typical low-level ampC resistance.

Therefore, to avoid colonization, the valid strategies are prevention of TD and restriction of antimicrobial use for TD while traveling. However, the current advice on how to protect oneself from TD has been insufficient [26]. Indeed, the only effective means of combating resistant microbes would be to refrain from use of unnecessary antimicrobials for TD. In our study, antibiotics were generally taken for the treatment of TD, the disease most commonly encountered abroad. While TD with severe symptoms undoubtedly requires antimicrobial treatment,

antibiotics are usually not needed for moderate and mild cases, as these usually resolve spontaneously [27]. In reality, however, a substantial proportion of travelers with mild diarrhea do take antibiotics [28]. Of our volunteers, 62% used antimicrobials for TD that they reported to be mild or moderate (data not shown). If travelers were instructed to be more cautious in their use of antimicrobials, the number of colonized individuals could decrease dramatically.

Probiotics (either for treating or preventing TD) failed to influence the risk of contracting ESBL-PE. Their protective efficacy against TD has also been modest [29]. When doxycycline was compared with other antimalarials, no difference was seen, possibly due to a significant number of intestinal bacteria having already become resistant to doxycycline [30].

Urinary tract infection (UTI) is considered the most common clinical infection caused by *E. coli*, and international travel has been reported as a risk factor for UTI by ESBP-PE [24, 31]. Among sexually active young females, the annual incidence of UTI has been estimated at 0.7% [32]. This is in agreement with our results, that is, no clinically verified ESBL-PE infections were revealed in our follow-up of the ESBL(+) group of 90 individuals. However, among the small proportion of those who contracted ESBL-PE and developed a clinical infection, the disease may be associated with treatment failures and increased mortality [16]. Furthermore, it should be pointed out that the consequences of colonization not only relate to a traveler's risk of getting infected with the resistant strain (individual sequela) but potentially also affect the overall resistance in his/her home country (community aspect) and the spread of resistant strains across the world (global aspect). With 20% of all travelers being colonized, 17%–24% of them at 6 months and 10% at 3 years after returning home [3, 10, 33], preventing the spread of resistant intestinal bacteria is a highly challenging task. Even in low-prevalence countries, infection control in healthcare settings mainly focuses on patients hospitalized while abroad. The present data suggest that measures should also embrace those with other significant risk factors such as a history of TD and use of antimicrobials when visiting high-risk areas. While the present study provides data on ESBL-PE, the results should also be applicable to any other type of resistant intestinal bacteria including carbapenemase-producing strains such as NDM-1.

CONCLUSION

There are 2 major tools for avoiding colonization by resistant intestinal bacteria while traveling: prevention of TD and restriction of the use of antimicrobials against TD. As the means to prevent TD have not been very successful, greater attention should be aimed at educating travelers to be more cautious in their use of antibiotics. We propose the following principles: antimicrobials should not be prescribed as prophylaxis against TD, and mild and moderate disease should, in general, not be treated with antimicrobials. In addition to guidelines on prevention of colonization, infection control measures applied to returning travelers at hospitals in low-prevalence countries should also be revised to adopt a risk-based approach.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. A. K., T. L., S. M., K. V., S. H. P., J. O., J. A., and J. K. declare no conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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