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Foreign Travel Is a Major Risk Factor for Colonization with *Escherichia coli* Producing CTX-M-Type Extended-Spectrum β-Lactamases: a Prospective Study with Swedish Volunteers▽

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Foreign travel has been suggested to be a risk factor for the acquisition of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*. To our knowledge, this has not previously been demonstrated in a prospective study. Healthy volunteers traveling outside Northern Europe were enrolled. Rectal swabs and data on potential travel-associated risk factors were collected before and after traveling. A total of 105 volunteers were enrolled. Four of them did not complete the study, and one participant carried ESBL-producing *Escherichia coli* before travel. Twenty-four of 100 participants with negative pretravel samples were colonized with ESBL-producing *Escherichia coli* after the trip. All strains produced CTX-M enzymes, mostly CTX-M-15, and some coproduced TEM or SHV enzymes. Coresistance to several antibiotic subclasses was common. Travel to India was associated with the highest risk for the acquisition of ESBLs (88%; $n = 7$). Gastroenteritis during the trip was an additional risk factor ($P = 0.003$). Five of 21 volunteers who completed the follow-up after 6 months had persistent colonization with ESBLs. This is the first prospective study demonstrating that international travel is a major risk factor for colonization with ESBL-producing *Enterobacteriaceae*. Considering the high acquisition rate of 24%, it is obvious that global efforts are needed to meet the emergence and spread of CTX-M enzymes and other antimicrobial resistances.

The prevalence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* is increasing globally, and community-onset infections with ESBL-producing *Escherichia coli* are a major clinical concern in many countries (5, 12, 16, 24). Known risk factors for infection with ESBL-producing bacteria include recent hospitalization or antibiotic use, urinary tract catheters, older age, and diabetes (5, 24, 25).

There are marked geographical differences in the proportions of ESBL production among clinical isolates of *Klebsiella pneumoniae* and *E. coli*. A high prevalence of ESBL production has been reported for South America (>40% of *K. pneumoniae* and 5 to 10% of *E. coli* isolates) and Asia (20 to 30% and 15 to 20%, respectively) (2, 11, 32). The highest rates so far were reported from a multicenter survey study in India (>55% and >60%, respectively) (18). Significantly lower prevalences of ESBL phenotypes have been reported for Europe (10 to 15% and 5 to 10%, respectively) and North America (5 to 10% and <5%, respectively) (2, 9, 20). In Europe, the highest rates of ESBL-producing clinical isolates have been reported for Southern and Eastern European countries (15 to 30%) (7). In contrast, the rate of infections by ESBL-producing *K. pneumoniae* and *E. coli* is still very low in Sweden (<3%) (27).

Data on fecal carriage with ESBLs in healthy individuals are lacking for most countries, including Sweden, but the rate of fecal carriage has been estimated to be 10% in Asia and was reported to be 5.5% and 13.2% in Spain and Saudi Arabia, respectively (10, 14, 30). Most likely, however, the geographical differences in prevalences of ESBL phenotypes in clinical cultures covary with the proportion of healthy individuals colonized with isolates producing ESBLs.

Based on these geographical differences and a few retrospective studies of patients infected with bacteria producing ESBLs, foreign travel to countries with higher prevalences of ESBL-producing *Enterobacteriaceae* was suggested to be a risk factor for the acquisition of ESBLs (8, 15). A recent Swedish study of patients with traveler's diarrhea reported an increased prevalence of fecal colonization with ESBL-producing bacteria for patients who had traveled outside Europe compared with the prevalence for those returning from European countries (29). However, no prospective study confirming this finding has previously been reported. The primary objective of our study was to prospectively study the fecal acquisition of ESBL-producing *Enterobacteriaceae* during foreign travel and the persistence rate of acquired ESBL-producing isolates after 6 months. Our secondary objective was to assess potential travel-associated risk factors for the acquisition of ESBL-producing bacteria, such as destination, gastroenteritis, and antibiotic use during travel.

(The results of this study were in part presented at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2008.)

MATERIALS AND METHODS

Study design. Starting in November 2007, healthy Swedish travelers planning a trip outside Northern Europe were included in the study. Information and necessary materials to participate in the study were available at travel consultation clinics in Uppsala. After written consent, the participants were asked to collect a pretravel fecal sample and to fill out a questionnaire, including personal data, information on cotravelers, previous medical history, and details of the planned trip. Travelers who suffered from a severe chronic disease or needed

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daily medication were not included. Samples and questionnaires were sent to the Department of Clinical Microbiology and the Department of Infectious Diseases, Uppsala University Hospital. Upon return, the procedure was repeated. The second questionnaire included data on gastroenteritis and antibiotic use during the trip. Participants who did not provide the second sample and questionnaire, carried an ESBL-producing *Enterobacteriaceae* isolate before travel, or returned to Sweden later than 31 January 2009 were excluded at this point. The participants could choose to be informed about their microbiology findings or not.

Travelers who acquired bacteria producing ESBLs and who chose to be informed about their results were asked to fill out a third questionnaire after 6 months. This questionnaire contained questions regarding clinical infections and antibiotic treatment during the follow-up period. In addition, the travelers were asked to deliver a third fecal sample. This study was approved by the Regional Ethics Review Board in Uppsala.

Bacteria and media. All fecal samples were collected with the Copan transport system (Copan Diagnostics, Corona, CA). The samples were inoculated in Luria-Bertani broth (Becton Dickinson, Sparks, MD) supplemented with cefotaxime (2.5 μg/ml) to select for cephalosporin-resistant strains. The broth was thereafter inoculated onto MacConkey agar (Acumedia Manufacturers, Inc., Lansing, MI) with cefotaxime (5-μg) and ceftazidime (10-μg) discs (Oxoid Ltd., Basingstoke, United Kingdom). Colonies growing within the expected zones of cefotaxime and ceftazidime or just cefotaxime (inhibition zones of <24 mm) were characterized to the species level by conventional methods or by use of a Vitek 2 instrument (bioMérieux, Lyon, France). Phenotypic confirmation of ESBL production was performed by a disc diffusion synergy test, as described previously by Jarlier and coworkers (13). All broths and plates were incubated overnight at 35°C in a room atmosphere.

ESBL typing. Isolates with phenotypic ESBL production were screened for $bla_{\text{CTX-M}}$, bla_{TEM}, and bla_{SHV} with PCR, as described previously (17, 22). PCR products from isolates carrying genes encoding CTX-M-type ESBLs were sequenced after using modified primers. The nucleotide sequences of both strands were determined by using a BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA) and an ABI 3130 instrument (Applied Biosystems) according to the manufacturers' instructions. The gene sequences were analyzed with SeqScape v2.5 and BioEdit v7.0 sequence alignment editors (Ibis Therapeutics, Carlsbad, CA) and compared with sequences in the NCBI database (http://blast.ncbi.nlm.nih.gov/Blast.cgi).

Antibiotic susceptibility. The MICs of the following antibiotics were determined for all ESBL-producing isolates by the Etest method (AB Biodisk, Solna, Sweden): amdinocillin, ciprofloxacin, ertapenem, fosfomycin, gentamicin, imipenem, meropenem, nitrofurantoin, piperacillin-tazobactam, tobramycin, and trimethoprim-sulfamethoxazole. The susceptibility testing was carried out according to the manufacturer's instructions, and the results were interpreted by the MIC breakpoints recommended by EUCAST (the European Committee on Antimicrobial Susceptibility Testing) (www.eucast.org). The quality control strain included was *E. coli* ATCC 25922.

Identification of diarrheagenic *Escherichia coli*. Due to the frequent episodes of gastroenteritis among travelers who acquired ESBL-producing *E. coli* strains, six specific virulence genes associated with enteropathogenic, enterohemorrhagic, enterotoxigenic, enteroinvasive (33), and enteroaggregative *E. coli* (28) were explored. The methods were modified to fit the GeneAmp PCR 9700 system (Applied Biosystems, Inc., Foster City, CA). In brief, DNA was prepared by boiling a single colony from a culture grown overnight in 100 μl sterile H_2O at 95°C for 10 min. A *Taq* PCR Master Mix kit (Qiagen, Solna, Sweden) was used for the PCR. Forward and reverse primers (0.2 μM; Eurogentech S.A., Seraing, Belgium) and 2 μl of the DNA preparation were added to the mixture. The final reaction mixture volume was 25 μl. The following program was used: 94°C for 10 min followed by 35 cycles of 94°C for 45 s; 50°C (*lt* and *st*), 55°C (stx_1, stx_2, and *ipaH*), or 58°C (pCVD432 fragment) for 45 s; and 72°C for 1 min. The last cycle was followed by a final extension step at 72°C for 10 min. Positive and negative controls were added for each run. The amplified products were visualized on a 1% agarose gel stained with ethidium bromide. The sizes of the products were compared with an O'GeneRulerExpress DNA ladder (Fermentas Sweden, Helsingborg, Sweden). The positive-control strains were kindly provided by the Swedish National Food Administration, Uppsala, Sweden. Before the control strains were used, the amplified DNA fragments in the target genes were sequenced.

Statistical analysis. McNemar's test, generalized previously by Durkalski et al. for clustered data, was used for comparison of ESBL colonization rates before traveling to colonization rates after traveling (6). For the risk factor analysis, the Pearson test was used for categorical data and the Wilcoxon test was used for continuous data. For all comparisons, a P value of <0.05 was considered to represent statistical significance. All statistical analyses were performed by using R software, version 2.8.0 (available at http://www.r-project.org).

TABLE 1. Countries and continents visited by travelers who completed the study[a]

Continent	Country	No. of travelers
Africa	Ethiopia	2
	Gambia	1
	Ghana	2
	Kenya	9
	Malawi	1
	Morocco	1
	Mozambique	4
	Rwanda	5
	Senegal	1
	South Africa	11
	Tanzania	2
	Tunisia	1
Asia	Bhutan	1
	China	4
	India	8
	Cambodia	3
	Tajikistan	1
	Thailand	25
	Vietnam	3
Central America	Mexico	4
	West Indies	1
	Not specified	1
Middle East	Egypt	8
	Jordan	4
North America	United States	2
South America	Ecuador	1
Southern Europe	Albany	2
	Croatia	2
	France	2
	Greece	4
	Italy	5
	Slovenia	1
	Spain	6
	Turkey	1

[a] Note that some participants visited several countries and that the sum of travelers in this table exceeds the actual number of 100.

RESULTS

Study population. During the 15-month study period, 105 volunteers provided written consent, questionnaires, and rectal swabs and were enrolled in the study. Four of them did not complete the study, and one participant carried an ESBL-producing *E. coli* strain before leaving Sweden.

One hundred travelers (55 women and 45 men) with a median age of 43 years (range, 2 to 84 years) were included in the analysis. The median length of stay abroad was 2 weeks (range, 1 to 26 weeks), and the most common reason for the trip was vacation (n = 89). Fifteen travelers visited more than one country during their trip, and three visited more than one continent. In total, 35 different countries were visited (for continental distribution, see Table 1). In some cases cotravelers participated in groups of two (n = 13), three (n = 4), four (n = 4), five (n = 1), or six (n = 1).

TABLE 2. Distribution of CTX-M genes detected in 24 strains of *Escherichia coli* isolated from rectal swabs after foreign travel[a]

Continent or region	No. of isolates				
	Group I		Group IV		
	CTX-M-1	CTX-M-15	CTX-M-9	CTX-M-14	CTX-M-27
Africa		1			
Asia (India excluded)		2	1	5	2
India		7			
Southern Europe	1	1			
Middle East		2	2		
Total	1	13	3	5	2

[a] PCR amplification with subtype-specific primers was used.

ESBL-producing *Enterobacteriaceae*. For 24 of 100 travelers with initially negative samples, ESBL-producing *E. coli* strains were detected in posttravel rectal swabs. No other ESBL-producing *Enterobacteriaceae* strains were found. The difference in the colonization rate before the trip compared to that after the trip was statistically significant ($P < 0.001$). CTX-M enzymes were identified in all 24 ESBL-producing strains. Of the CTX-M enzymes detected, 14 belonged to CTX-M group I (CTX-M-1 and -15) and 10 belonged to group IV (CTX-M-9, -14, and -27) according to the classification reported previously by Pitout et al. (21). Some isolates coproduced the SHV ($n = 3$) and TEM ($n = 11$) enzymes. The distribution of the CTX-M, SHV, and TEM enzymes is displayed in Table 2. Overall, CTX-M-15 was predominant (13/24 strains). All travelers who acquired ESBL-producing strains after travel to India carried CTX-M-15 (7/7 strains), whereas CTX-M-14 was more common after travel to other Asian countries (5/9 strains).

The *in vitro* antibiotic susceptibilities of the 24 ESBL-producing *E. coli* strains are shown in Fig. 1. Coresistance to antibiotics other than cephalosporins was common: 19 of 24 ESBL-producing *E. coli* strains displayed resistance to trimethoprim-sulfamethoxazole, and half of the isolates were resistant to fluoroquinolones and aminoglycosides, respectively. Nine strains displayed resistance to more than two antibiotic subclasses. High susceptibility rates were demonstrated for nitrofurantoin, amdinocillin, and the carbapenems.

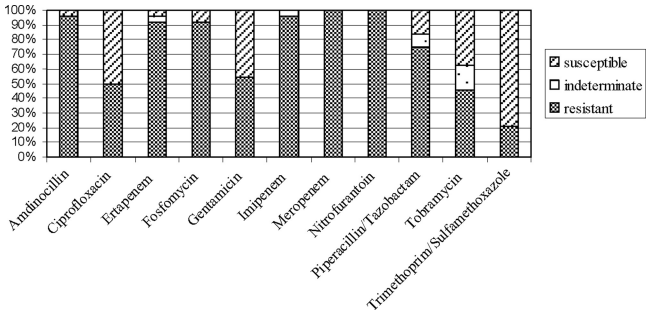

FIG. 1. *In vitro* antibiotic susceptibilities of 24 ESBL-producing *Escherichia coli* strains acquired after foreign travel. Susceptibilities were determined by the Etest method, and the results were interpreted according to EUCAST guidelines.

TABLE 3. Travel destinations of travelers who were negative for ESBL-producing strains before the trip and rate of fecal colonization with ESBL-producing *E. coli* strains upon return[a]

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

[a] The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$). Three participants visited more than one continent, and therefore, the sum of travelers in this table exceeds the actual number of 100.

Travel-associated risk factors. The rate of acquisition of an ESBL-producing strain was highest for travelers visiting India (7/8 isolates; $P < 0.001$) (Table 3). Travel to other destinations was associated with the following rates of posttravel ESBL colonization: 32% for Asia (India excluded), 29% for the Middle East, 13% for Southern Europe, and 0 to 4% for other parts of the world.

Participants who acquired ESBL-producing *E. coli* strains were more likely to have had gastroenteritis during the trip than others ($P = 0.003$). An analysis of six specific virulence genes associated with diarrheagenic *E. coli* revealed only one case of enteropathogenic *E. coli* (EPEC) infection, and this participant did not suffer from gastroenteritis. No other travel-associated risk factors were found (Table 4).

In total, 10 participants were treated with antibiotics during travel. Seven travelers treated for respiratory tract infections with cephalosporins ($n = 3$), penicillins ($n = 2$), tetracyclines

TABLE 4. Descriptive statistics on 100 Swedish travelers with negative pretravel rectal swabs for ESBL-producing *Enterobacteriaceae*[a]

Parameter	Value for group	
	ESBL negative ($n = 76$)	ESBL positive ($n = 24$)
No. (%) of male travelers	35 (46)	10 (42)
Median age (yr)	42	47
No. (%) of vegetarians	2 (3)	0 (0)
Median length of stay (wk) (%)	2.0	2.0
No. (%) of travelers on vacation	67 (88)	22 (92)
No. (%) of business travelers	10 (13)	2 (8)
No. (%) of travelers visiting friends or relatives	10 (13)	1 (4)
No. (%) of travelers staying at a hotel	61 (80)	20 (83)
No. (%) of backpacking travelers	6 (8)	4 (17)
No. (%) of travelers staying with friends or relatives	9 (12)	5 (21)
No. (%) of travelers with gastroenteritis	17 (22)	13 (54)
No. (%) of travelers on antibiotic treatment	7 (9)	3 (12)

[a] Seventy-six travelers were negative for ESBL-producing strains after their trip, whereas 24 carried ESBL-producing *Escherichia coli*. The only statistically significant difference between the groups was gastroenteritis during travel ($P = 0.003$).

($n = 1$), or erythromycin ($n = 1$) were ESBL negative upon their return. In contrast, all three travelers treated with ciprofloxacin for gastroenteritis acquired ESBL-producing *E. coli* strains.

Persistence of colonization with ESBL-producing strains after 6 months. Two of 24 travelers who acquired ESBL-producing strains had chosen not to be informed about their laboratory results and were therefore excluded from the 6-month follow-up, and one person did not provide the follow-up sample and questionnaire. Three participants had been treated for upper respiratory tract infections with penicillin, penicillin plus azithromycin, and doxycycline, respectively. Five of 21 participants who completed the follow-up had persistent colonization with ESBL-producing *E. coli* strains. None of these participants reported a clinical infection or antibiotic use during the follow-up period.

DISCUSSION

This is the first prospective study of foreign travel as a risk factor for colonization with ESBL-producing *Enterobacteriaceae*. Our results clearly demonstrate that travel to areas with a higher prevalence of strains producing ESBLs is a risk factor for the acquisition of ESBL-producing bacteria. Even when using a modified statistical model adjusting for participants in groups, the difference in colonization rates with ESBL-producing bacteria before travel versus those after travel was highly significant. The acquisition of ESBL-producing *E. coli* during foreign travel may be a significant source for increasing rates of colonization by bacteria producing ESBLs in Sweden and other countries with a low prevalence of ESBLs and a comparably low rate of consumption of antibiotics.

CTX-M genes were detected in all ESBL-producing strains in our study, which is consistent with the fact that these enzymes increasingly dominate the ESBL pandemic (26). However, some strains producing ESBLs other than the CTX-M type may have been lost, since cefotaxime was used as a selecting agent in the inoculation broth. The high prevalence of CTX-M-15 genes detected in our material reflects the worldwide spread of these enzymes (3, 4, 10, 17, 31). Although the number of isolates in our study was too small for statistical analysis, there seems to be some correlation between the CTX-M types acquired and travel destinations. All Indian ESBL-producing isolates carried CTX-M-15 genes, which is the only CTX-M type reported from India so far, and the majority of ESBL-producing isolates from other Asian countries carried CTX-M-14 genes, which is the dominating CTX-M type in this area (10, 19). These results support that the ESBL-producing isolates detected in our study were in fact acquired at the travel destinations. Similar findings were also reported by previous retrospective studies of travelers infected or colonized with ESBL-producing *E. coli* strains (21, 29).

A high rate of coresistance to potentially active drugs is a common feature of ESBL-producing *E. coli* strains (26) and was also seen in our material. Overall, nine strains were resistant to more than two antibiotic subclasses tested, which seriously limits therapeutic options in cases of a clinical infection. Although the level of carbapenem resistance among ESBL-producing *E. coli* and *K. pneumoniae* strains is still very low in most countries, it is worrisome that two isolates in our material displayed reduced susceptibility to these antibiotics. High susceptibility rates were demonstrated for nitrofurantoin and amdinocillin, which are currently recommended for lower urinary tract infections in Sweden, suggesting that these antibiotics can be used empirically even when infection with an imported ESBL-producing *E. coli* strain is suspected.

Participants visiting India were most likely to acquire ESBL-producing strains. Despite the small number of travelers to India, this was highly statistically significant, and previous studies also pointed out that visits to India in particular appear to be a risk factor for infection with ESBL-producing *E. coli* (8, 15). Although not statistically significant, travel to other countries in Asia and the Middle East was also associated with a higher risk of colonization by ESBL-producing strains (32 and 29%, respectively) in our study, which might well reflect the rates of ESBL production and fecal colonization in the countries visited (9, 11, 18, 32).

The risk of acquisition of ESBL-producing strains was strongly associated with gastroenteritis during travel. However, analyses of specific virulence genes associated with diarrheagenic *E. coli* revealed only one case of enteropathogenic *E. coli* (EPEC). These results suggest that the acquired ESBL-producing *E. coli* strains themselves did not cause gastroenteritis. Rather, we believe that participants suffering from gastroenteritis were exposed to contaminated food or water containing both diarrheagenic and ESBL-producing *E. coli* strains. However, person-to-person transmission of ESBL-producing strains is a known fact and might also have occurred, even within travel groups or families included in the study (23). Antibiotic treatment during travel was not a significant risk factor in this study, but notably, all three participants treated for gastroenteritis with ciprofloxacin acquired ESBL-producing strains.

We expected a far lower rate of acquisition of ESBL-producing strains than the 24% found, and our study was therefore not designed to enable a detailed analysis of the duration of colonization. However, the 6-month persistence rate of 24% is consistent with previous results for hospitalized patients (1). More prospective studies are needed in this area to assess the importance of foreign travel as a source of increasing rates of colonization with ESBL-producing *Enterobacteriaceae* and spread in the community.

The simple, prospective design of our study was a feasible means of evaluating foreign travel as a risk factor for the acquisition of ESBL-producing *Enterobacteriaceae*. By providing pretravel fecal samples, the participants constituted their own control group, thus adjusting for possible confounding factors in the traveling part of the population. The risk for statistical errors associated with retrospective studies and multivariate analysis, such as selection or recall bias and type 1 error, was reduced. Also, the prospective design enabled a detailed analysis of travel-associated risk factors that has not been possible to assess in previous retrospective studies (8, 15, 29).

In conclusion, considering the high rate of acquisition of ESBL-producing isolates and the extent of international travel in many countries, it is obvious that global efforts are needed to meet the emergence and spread of CTX-M enzymes and other antimicrobial resistances. Further international cooperation on rational antibiotic use and control is urgently needed.

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