Review

Travel-acquired ESBL-producing Enterobacteriaceae: impact of colonization at individual and community level

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Editorial decision 20 December 2016; accepted 20 December 2016

Abstract

Background: Antibiotic resistance is a rapidly increasing global emergency that calls for action from all of society. Intestinal multidrug-resistant (MDR) bacteria have spread worldwide with extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-PE) as the most prevalent type. The millions of travelers annually visiting regions with poor hygiene contribute substantially to this spread. Our review explores the underlying data and discusses the consequences of the colonization.

Methods: PubMed was searched for relevant literature between January 2010 and August 2016. We focused on articles reporting (1) the rate of ESBL-PE acquisition in a group of travelers recruited before/after international travel, (2) fecal carriage of ESBL-PE as explored by culture and, for part of the studies, (3) analysis of factors predisposing to colonization.

Results: We reviewed a total of 16 studies focusing on travel-acquired ESBL-PE. The acquisition rates reveal that 20-70% of visitors to (sub)tropical regions get colonized by ESBL-PE. The main risk factors predisposing to colonization during travel are destination, travelers diarrhea, and antibiotic use.

Conclusions: While most of those colonized remain asymptomatic, acquisition of ESBL-PE may have consequences both at individual and community level. We discuss current efforts to restrict the spread.

Key words: Extended-spectrum beta-lactamase, ESBL, Escherichia coli, ESBL-PE, multi-drug resistant bacteria, MDR, travel, traveller, colonization, antibiotics, travellers’ diarrhea, TD

Introduction

The multi-drugresistant (MDR) bacteria constitute a global emergency,¹ with factors such as international travel and trade contributing to its widespread spread. The MDR bacteria, of which extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-PE) has become the most common type, are highly prevalent in developing regions of the (sub)tropics. A substantial proportion of visitors to these destinations get colonized by ESBL-PE. Back home, they may spread the bacteria to their close contacts and local hospitals—and contribute to further dissemination of MDR bacteria worldwide.

ESBL-PE in Outline

ESBL are plasmid-borne beta-lactamases belonging to the Ambler class A.² These enzymes confer to the strain an ability to hydrolyze the most commonly used beta-lactam antibiotics including penicillins and oxyimino-beta-lactams (e.g. cefotaxime, ceftazidime, aztreonam). The only beta-lactam families that ESBL-PE remain fully susceptible to are cephamycins and carbapenems. Combinations with beta-lactam inhibitors partly restore the activity of several beta-lactams. However, severe ESBL-PE infections often require treatment with carbapenems, highly effective drugs¹ which should be used very prudently.
The spread of ESBL-PE has occurred as two successive waves. The first included dissemination of strains producing TEM and SHV-derived β-lactamases. These ESBL-PE mostly belonged to the *Klebsiella* and *Enterobacter* genus and spread almost exclusively within hospitals. During the 1980s and 1990s, they caused small outbreaks relatively easily contained by infection control measures. This first ESBL-PE wave declined after the turn of the century, only to be replaced during the last decennium by the second wave involving CTX-M-type ESBL-PE, which mainly differ by two features. First, CTX-M ESBL are mostly seen in the *Escherichia coli* species, probably because of the remarkable fit between this species and the type of plasmid. Second, the spread was not restricted to hospitals but occurred also in community settings.

As a result, the proportions of ESBL-PE infections have increased everywhere, consistent with the well-known parallel between colonization and infection. Increasing rates have been seen in both community-acquired and nosocomial infections. According to a recent meta-analysis, colonization rates in American and European communities range from 2 to 4%, whereas those in the eastern Mediterranean, Southeast Asia and Africa reach 15, 22 and 22%, respectively, and exceed even that in the West Pacific region, with an estimated 46% carriage. These regional differences are clearly seen in hospitals, especially in areas with the highest carriage rates, as shown by recent studies carried out in India and Cambodia, where approximately half of the bacteria isolated from blood cultures at hospitals were identified as ESBL-PE.

### Risk Factors for ESBL-PE Acquisition Among Travellers

Numerous studies conducted more than a decade ago have shown that, in addition to classic risk factors, overseas travel is associated with the acquisition of infections caused by ESBL-PE. At the same time, a series of community patients with CTX-M- *E. coli* urinary tract infections (UTI) was published. Although the classic risk factors for ESBL-PE were lacking, all had a recent history of travelling to the Indian subcontinent. In 2010, Tham *et al.* published an investigation among 242 travellers with travellers’ diarrhea (TD), 24% of whom were found colonized by ESBL-PE. In the first prospective study undertaken to quantify the rate of ESBL-PE acquisition, which was reported in 2010 by Tängden *et al.*, ESBL-PE were found in 24% of the cohort of 105 travellers. The highest risk destination was India (88%), followed by Asia (32%) and the Middle East (29%). These findings were confirmed by later investigations (Table 1), many of which also looked at risk factors predisposing travellers to ESBL-PE acquisition. Although the accumulated data are somewhat heterogeneous regarding study designs, risk factors tested or traveller populations, certain conclusions are evident: ESBL-PE acquisition is driven at least by three independent factors: (i) country visited, (ii) occurrence of TD and (iii) use of antibiotics during travel.

Travel to tropical regions like South Asia and Southeast Asia are one of the most frequently identified risk factors. Acquisition rates as high as 93 and 91% have been found among subjects visiting Vietnam and India, respectively. The main factors accounting such rates in high-risk regions include massive uncontrolled use of antibiotics to treat both humans and animals, high percentage of ESBL-PE carriage among the population, inadequate hygiene, and vast contamination of local environment, drink and food.

Association with TD is also clearly shown in risk factor studies (Table 1). It appears reasonable to think that uncontrolled conditions in TD lead to intestinal dysbiosis that decreases resistance to colonization by exogenous bacteria, among these MDR in the surroundings. The finding of antibiotic exposure as a risk factor accords with reports on antibiotics predisposing to ESBL-PE carriage within community and at hospitals. Individual antibiotic classes have not been explored separately among travellers due to inadequate numbers of cases, but data exist both for fluoroquinolones and β-lactams as factors predisposing to ESBL-PE acquisition. By altering the intestinal microbiota, antibiotics disrupt its ability to resist colonization by new intruders, a phenomenon well known as colonization resistance. The substantial impact of TD and antibiotics is well exemplified by a recent study: among travellers to Indian subcontinent, ESBL-PE was contracted by 23% of those staying healthy, 47% of those with TD but not using antibiotics, and 80% of those with TD who took antibiotics.

Other predisposing factors (Table 1) are reported more frequently, either because they are only rarely tested or the specifics varying among the study populations, such as age, type of travel and consumption of ice cream and pastries. Data on the duration of exposure are not consistent. Malaria prophylaxis appears not to have an impact, yet further studies are needed. Only one report has addressed loperamide intake, finding no association with increased risk of ESBL-PE acquisition unless combined with antibiotics.

### Consequences for Travellers, Contacts and Community

In a vast majority of cases, ESBL-PE colonization remains asymptomatic and does not lead to infection. The consequences, even at the individual level, can be substantial if the bacteria succeed in causing an infection, since MDR infections have a higher risk of treatment failures, longer hospitalization stays and greater mortality. Data on the actual risk of a colonized traveller developing an infection are scarce. Even though international travel is considered as a risk factor for contracting ESBL-PE UTI, the actual risk appears only low. In a recent study drawing on a survey of laboratory databases, none of 90 colonized travellers had laboratory-verified pyelonephritis or any other severe ESBL-PE infections in a 1-year follow-up; still, the most common *E. coli* infection, lower UTI, was not addressed since urine cultures are not taken from patients with cystitis symptoms. Another study explored ESBL-PE prevalence rates among patients attending an Infectious Diseases ward and found an increased risk of ESBL-PE carriage and symptomatic ESBL-PE infection among patients with a history of international travel during the past 12 months: 23/191 (23%) patients with travel history were colonized and out of these, 4/23 (17%) had UTI and one had bacteremia (4%) with a culture-verified ESBL-PE. The low risk among healthy travellers concurs with a recent study showing the vast majority of travel-acquired ESBL-PE to lack virulence factors of uropathogenic strains.
On the other hand, in other investigations, a pandemic spread of the uropathogenic ST131 ESBL _E. coli_ has been reported.\(^45\)

Travel-acquired ESBL-PE tends to disappear fairly quickly after returning home: only 5–35% of those with travel-acquired ESBL-PE were carriers 6 months later.\(^17,23,26,28\) In one study, a cohort of 245 travellers with travel-acquired ESBL-PE were subjected to monthly monitoring. The strain was found in one-third of the cohort (33.9%, 83/245) after 4 weeks, but only 5% at 6 months data collected.\(^28\) Thus, the risk of ESBL-PE transmission or infection of the cohort may not be a concern beyond a few months post return.\(^28\)

In a study among ESBL-PE positive travellers, 18% (2/11) of close contacts acquired the same ESBL-PE—\(^23\)—and possibly ran the risk of an ESBL-PE infection comparable to that of the initially colonized traveller. Such transmission may not only affect household contacts; eventually, the bacteria can reach local hospitals. Travellers’ role in bacterial transmission to new hosts in the home country. Travellers who have recently returned from high-risk regions may not be flagged upon admission into a home country hospital.

### Efforts to Decrease ESBL-PE Transmission by Travellers

While there is no single way of halting the worldwide emergence of antibiotic resistance, all reasonably possible means should be used

| First author (year) | Origin of travellers; prospective (P), retrospective (R) | Number of subjects, years data collected | Pre-travel ESBL-PE cases/all (%) | Post-travel ESBL-PE cases/all (%) | Risk factors in univariate/multivariable analysis |
|---------------------|--------------------------------------------------------|----------------------------------------|-------------------------------|---------------------------------|-----------------------------------------------|
| Tham et al., 2010\(^6\) | Sweden (R)                                             | 242 with TD, 2007–08                   | NA                            | 58/242 (28)                     | NA                                            |
| Tängden et al., 2010\(^7\) | Sweden (P)                                             | 100, 2007–10                          | 1/105 (1)                     | 24/100 (24)                     | India, TD                                    |
| Kennedy et al., 2010\(^8\) | Australia (P)                                          | 102 2008–09                           | 2/106 (2)                     | 22/102 (22)                     | Asia, South America, Middle-East, Africa, TD, AB use\(^8\) |
| Peirano et al., 2011\(^9\) | Canada (R)                                             | 113 with TD, 2009                     | NA                            | 26/113 (23)                     | NA                                            |
| Weissenberg et al., 2012\(^10\) | USA (P)                                                | 28, 2009–10                           | 1/28 (4)                      | 7/28 (25)                       | NA                                            |
| Ostholm-Balkhed et al., 2013\(^11\) | Sweden (P)                                             | 231, 2008–09                          | 6/251 (2)                     | 68/226 (30)                     | Asia, Africa, Indian subcontinent, TD, Age    |
| Lausch et al., 2013\(^12\) | Denmark (R)                                            | 88, 2011                               | NA                            | 11/88 (13)                      | TD, duration of travel                        |
| Paltansing et al., 2013\(^13\) | The Netherlands (P)                                    | 370, 2011                              | 32/370 (9)                    | 113/338 (33)                     | South and East Asia                          |
| Kuenzli et al., 2014\(^14\) | Switzerland (P)                                        | 175, 2012–13                          | 5/175 (3)                     | 118/170 (69)                     | Duration of travel, type of travel, ice cream and pastry |
| Kantele et al., 2015\(^15\) | Finland (P)                                            | 430, 2009–10                          | 5/430 (1)                     | 90/430 (21)                      | Destination, TD, AB use, age                  |
| Lubbert et al., 2015\(^16\) | Germany (P)                                            | 205, 2013                              | 14/205 (7)                    | 58/191 (30)                      | India, South-East Asia, TD                    |
| Epelboin et al., 2015\(^17\) | France (R)                                             | 191 admitted to ID ward\(^*\), NA    | 2012–13                      | 23/191 (12)                      | Asia, visiting friends and relatives or migrants |
| Ruppé et al., 2015\(^18\) | France (P)                                             | 574, 2012–13                          | 81/700 (12)                   | 292/574 (51)                     | Asia, Sub-Saharan Africa, TD, AB use, type of travel |
| Angelin et al., 2015\(^19\) | Sweden (P)                                             | 107, 2010–14                          | 7/99 (7)                      | 35/99 (35)                       | South-East Asia, AB use                       |
| Reuland et al., 2016\(^20\) | The Netherlands (P)                                    | 445, 2012–13                          | 27/445 (6)                    | 98/418 (23)                      | Combination of TD and AB use                  |
| Barreto Miranda et al., 2016\(^21\) | Germany (R)                                            | 211 with TD, 2013–14                  | NA                            | 107/211 (51)                     | South-East Asia, Indian subcontinent, age    |

*Cases with newly acquired ESBL-PE.

Risk factors analyzed for a variety of resistant _Enterobacteriaceae_ (not only ESBL-PE).

Infectious Diseases ward.
to combat it. Preventing colonization offers one logical approach to restricting travel-related spread and, therefore, current travel advice should focus on identified risk factors (Table 1). Avoiding travel to high risk regions is not within the scope of this paper. Those heading there should be actively advised by travel medicine practitioners about two main risk factors, TD and antibiotic use. While prevention of TD by taking hygiene and food precautions has proved unsuccessful, antibiotic use during travel can be restricted. After all, these drugs are for the most part used against TD, a disease with mainly spontaneous recovery.

Accordingly, apart from specific groups, a UK guideline advises about antibiotic use for self-treatment as follows: ‘If diarrhoea is severe or associated with blood and mucous in the stool, medical attention must be sought. If no medical treatment is readily available antibiotic self-treatment may be used.’ Similarly, a Finnish guideline only recommends antibiotics for treating patients with a high fever, bloody stools, an exceptionally severe illness or deteriorating condition, and for specific groups with an underlying disease which might deteriorate because of TD or lead to particularly serious symptoms. Antibiotics are not recommended for the prevention of TD at all or only in special circumstances. Instead of antibiotics, medications with impact on gastrointestinal functions have been recommended for mild/moderate TD. Interestingly, a recent review on loperamide found only meager data comparing the efficacy of loperamide with that of antibiotics, and reported a lack of studies that would adequately show the superiority of one of these over the other. In a recent analysis, antibiotics, both when taken alone and together with loperamide, were found to predispose to ESBL-colonization (40 vs. 70%), while loperamide used singly showed rates similar to a group taking both when taken alone and together with loperamide, were found to predispose to ESBL-colonization (40 vs. 70%), while loperamide used singly showed rates similar to a group taking no medications (20 vs. 21%).

It is not possible to screen all travellers upon return. However, when admitted to hospitals, a risk evaluation is needed, and to prevent secondary cases, contact precautions should be taken to contain the spread of MDR bacteria. Special emphasis should be put on patients with the highest probability to spread the bacteria (i.e. those treated abroad at ICU, those with urinary catheter, wounds or a history of antibiotic intake). Currently, hospitals do not have risk-based guidelines, but many use contact precautions for travellers hospitalized abroad, and screen them for colonization by various MDR bacteria. Since these guidelines vary considerably between hospitals and countries, consensual guidelines would be valuable.

**Conclusion**

As ESBL-PE have become highly prevalent in developing (sub)tropics regions, a substantial proportion of visitors to these destinations get colonized—and remain carriers for several months. Major risk factors for colonization include destination, TD and antibiotic use. ESBL-PE carriage mostly remains asymptomatic. The risk of clinical ESBL-PE infection is small, but the disease tends to entail treatment failures and even increased mortality. Travellers may spread the bacteria to their household contacts and, eventually, hospitals in their home countries. Further studies of travellers are needed to address the impact of various antibiotic classes and the risks at individual and community levels. The bottom line is that hundreds of millions of people visit tropical regions annually—and a substantial proportion of them do contribute to the transport of ESBL-PE worldwide.

**Funding**

The work was supported by the Finnish Governmental Subsidy for Health Science Research, the SSAC Foundation and the Paulo Foundation.

**Acknowledgements**

The authors thank Dr Tinja Lääräri for valuable comments on the manuscript.

**Conflict of interest:** A.K. reports honorary from membership of advisory group (Valneva 2016), honorary from lectures (Baxter, Crucell, GSK, Pfizer, PaxVax, MSD, Valneva), and an investigator-initiated grant (Pfizer). None are relevant for the present study. P.L.W. and A.A. declare no conflicts of interest.

**References**

1. O’Neill J. Tackling drug-resistant infections globally: Final report and recommendations. http://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf (15 August 2016, date last accessed).

2. Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci 1980; 289: 321–31.

3. Nicolau DP. Carbapenems: a potent class of antibiotics. Expert Opin Pharmacother 2008; 9: 23–37.

4. Kliebe C, Nies BA, Meyer JF et al. Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. Antimicrob Agents Chemother 1985; 28: 302–7.

5. Petit A, Gerbaud G, Sriot D et al. Molecular epidemiology of tem-3 (ctx-M) beta-lactamase. Antimicrob Agents Chemother 1990; 34: 219–24.

6. Marcade G, Deschamps C, Boyd A et al. Replicon typing of plasmids in *Escherichia coli* producing extended-spectrum beta-lactamases. J Antimicrob Chemother 2009; 63: 67–71.

7. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev 2013; 26: 744–58.

8. Reddy P, Malczynski M, Oebas A et al. Screening for extended-spectrum beta-lactamase-producing enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. Clin Infect Dis 2007; 45: 846–52.

9. Karanika S, Karantanos T, Arvanitis M et al. Fecal colonization with extended-spectrum beta-lactamase-producing enterobacteriaceae and risk factors among healthy individuals: a systematic review and meta-analysis. Clin Infect Dis 2016; 63: 310–8.

10. Alagesan M, Gopolakrishnan R, Panchatcharam SN et al. A decade of change in susceptibility patterns of Gram-negative blood culture isolates: a single center study. Germs 2015; 5: 63–77.

11. Vliegher ER, Huang TD, Phe T et al. Prevalence and distribution of beta-lactamase coding genes in third-generation cephalosporin-resistant Enterobacteriaceae from bloodstream infections in Cambodia. Eur J Clin Microbiol Infect Dis 2015; 34: 1223–9.

12. Rodriguez-Bano J, Lopez-Cerero L, Navarro MD et al. Faecal carriage of extended-spectrum beta-lactamase-producing *Escherichia coli*; Prevalence, risk factors and molecular epidemiology. J Antimicrob Chemother 2008; 62: 1142–9.
13. Rodriguez-Bano J, Navarro MD, Romero L et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in nonhospitalized patients. J Clin Microbiol 2004; 42: 1089–94.

14. Laupland KB, Church DL, Vidakovich J et al. Community-onset extended-spectrum beta-lactamase ESBL producing Escherichia coli: Importance of international travel. J Infect 2008; 57: 441–8.

15. Freeman JT, McBride SJ, Heffernan H et al. Community-onset genitourinary tract infection due to CTX-M-15-producing Escherichia coli among travelers to the Indian subcontinent in New Zealand. Clin Infect Dis 2008; 47: 689–92.

16. Tham J, Odenholt I, Walder M et al. Extended-spectrum beta-lactamase-producing Escherichia coli in patients with travellers’ diarrhoea. Scand J Infect Dis 2010; 42: 273–80.

17. 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: 3564–8.

18. Kennedy K, Collignon P. Colonisation with Escherichia coli resistant to “critically important antibiotics”: a high risk for international travellers. Eur J Clin Microbiol Infect Dis 2010; 29: 1501–6.

19. Perano G, Laupland KB, Gregson DB, Pitout JD. Colonization of returning travelers with CTX-M-producing Escherichia coli. J Travel Med 2011; 18: 299–303.

20. Weisenberg SA, Mediavilla JR, Chen L et al. Extended spectrum beta-lactamase-producing Enterobacteriaceae in international travellers and non-travelers in New York city. PLoS One 2012; 7: e45141.

21. Ostholm-Balkhed A, Tarnberg M, Nilsson M et al. Travel-associated faecal colonization with ESBL-producing Enterobacteriaceae: incidence and risk factors. J Antimicrob Chemother 2013; 68: 2144–53.

22. Lausch KR, Fuursted K, Larsen CS, Storgaard M. Colonisation with multi-resistant Enterobacteriaceae in hospitalised Danish patients with a history of recent travel: a cross-sectional study. Travel Med Infect Dis 2013; 11: 320–3.

23. Paltansing S, Vlot JA, Kraakman ME et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae among travelers from the Netherlands. Emerg Infect Dis 2013; 19: 1206–13.

24. Kuenzl E, Jaeger VK, Frei R 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: 528–37.

25. Kantele A, Lääveri T. Increased risk of colonization by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Clin Infect Dis 2015; 60: 837–46.

26. Lubbert C, Straube L, Stein C et al. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. Int J Med Microbiol 2015; 305: 149–56.

27. Epelboin L, Robert J, Tsyrina-Kouyoumdjian E et al. High rate of multidrug-resistant gram-negative bacilli carriage and infection in hospitalized returning travelers: a cross-sectional cohort study. J Travel Med 2015; 22: 292–9.

28. Rappe E, Armand-Lefèvre L, Estellar C 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.

29. Angelin M, Forsell J, Granlund M et al. 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: 223–9.

30. Reuland EA, Al Naiemi N, Kaiser AM et al. Prevalence and risk factors for carriage of ESBL-producing Enterobacteriaceae in Amsterdam. J Antimicrob Chemother 2016; 71: 1076–82.

31. Barreto Miranda I, Ignatius R, Pflüger R 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: 1–7.

32. Adegjii AT, Ogunjobi AA. Detection of extended spectrum beta-lactamases resistance genes among bacteria isolated from selected drinking water distribution channels in southwestern Nigeria. Biomed Res Int 2016; 2016: 7149295.

33. Talukdar PK, Rahman M, Nabi A et al. Antimicrobial resistance, virulence factors and genetic diversity of Escherichia coli isolates from household water supply in Dhaka, Bangladesh. PLoS One 2013; 8: e61090.

34. Zhang H, Zhou Y, Guo S, Chang W. Prevalence and characteristics of extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae isolated from rural well water in Taian, China. 2014. Environ Sci Pollut Res Int 2015; 22: 11488–92.

35. Zurfluh K, Nuesch-Inderbinen M, Morach M et al. Extended-spectrum-beta-lactamase-producing Enterobacteriaceae—a case-control study in a low prevalence country. Emerg Infect Dis 2015; 21: 1971; 69: 405–11.

36. Kantele A. A call to restrict prescribing antibiotics for travellers’ diarrhoea—travel medicine practitioners can play an active role in preventing the spread of antimicrobial resistance. Travel Med Infect Dis 2015; 13: 213–4.

37. Kantele A, Mero S, Kirveskari J, Lääveri T. Increased risk for ESBL-producing bacteria from co-administration of loperamide and antimicrobial drugs for travelers’ diarrhea. Emerg Infect Dis 2016; 22: 117–20.

38. Schwabe MJ, Navon-Venezia S, Kaye KS et al. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2006; 50: 1257–62.

39. Osthoff M, McGuinness SI, Wagen AZ, Eisen DP. Urinary tract infections due to extended-spectrum beta-lactamase-producing Gram-negative bacteria: identification of risk factors and outcome predictors in an Australian tertiary referral hospital. Int J Infect Dis 2015; 34: 79–83.

40. Søraas A, Sundsfjord A, Sandven I et al. Risk factors for community-acquired urinary tract infections caused by ESBL-producing Enterobacteriaceae—a case-control study in a low prevalence country. PLoS One 2013; 8: e69581.

41. Vading M, Kabir MH, Kalin M et al. Frequent acquisition of low-virulence strains of ESBL-producing Escherichia coli in travellers. J Antimicrob Chemother 2016; 71: 3548–55.

42. Nicolas-Chanoine MH, Bertrand X, Madec JY. Escherichia coli ST131, an intriguing clonal group. Clin Microbiol Rev 2014; 27: 543–74.

43. Rogers BA, Kennedy KJ, Sidjabat HE et al. Prolonged carriage of resistant E. coli by returned travellers: clonality, risk factors and bacterial characteristics. Eur J Clin Microbiol Infect Dis 2012; 31: 2413–20.
47. Hilty M, Betsch BY, Bogli-Stuber K et al. Transmission dynamics of extended-spectrum beta-lactamase-producing Enterobacteriaceae in the tertiary care hospital and the household setting. *Clin Infect Dis* 2012; 55: 967–75.

48. Valverde A, Grill F, Coque TM et al. High rate of intestinal colonization with extended-spectrum-beta-lactamase-producing organisms in household contacts of infected community patients. *J Clin Microbiol* 2008; 46: 2796–9.

49. UNWTO. Annual report. http://cf.cdn.untwo.org/sites/all/files/pdf/annual_report_2015_lr.pdf (15 August 2016, date last accessed).

50. Reinheimer C, Kempf VA, Gottig S et al. Multidrug-resistant organisms detected in refugee patients admitted to a university hospital, Germany June-December 2015. *Euro Surveill* 2016; 21(2): pii=30110.

51. 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.

52. Nemeth J, Ledergerber B, Preiswerk B et al. Multidrug-resistant bacteria in travellers hospitalized abroad: prevalence, characteristics, and influence on clinical outcome. *J Hosp Infect* 2012; 82: 254–9.

53. Birgand G, Armand-Lefevre L, Lepainteur M et al. Introduction of highly resistant bacteria into a hospital via patients repatriated or recently hospitalized in a foreign country. *Clin Microbiol Infect* 2014; 20: O887–90.

54. Shlim DR. Looking for evidence that personal hygiene precautions prevent traveler’s diarrhea. *Clin Infect Dis* 2005; 41(Suppl 8): S531–5.

55. Mattila L, Sironen A, Kyrönseppä H et al. Risk behavior for travelers’ diarrhea among Finnish travelers. *J Travel Med* 1995; 2: 77–84.

56. Fitfortravel. Traveller’s diarrhoea. http://www.fitfortravel.nhs.uk/advice/disease-prevention-advice/travellers-diarrhoea.aspx (15 August 2015, date last accessed).

57. Finnish Institute of Health and Welfare. Traveler’s health guide: Travelers’ diarrhea. http://www.terveyskirjasto.fi/terveyskirjasto/ktl.mat?pselaus=107937 (16 December 2016, date last accessed).

58. Lääveri T, Sterne J, Rombo L, Kantele A. Systematic review of loperamide: no proof of antibiotics being superior to loperamide in treatment of mild/moderate travellers’ diarrhoea. *Travel Med Infect Dis* 2016; 14: 299–312.