International travel is considered to be an important risk factor for acquisition of multidrug-resistant Enterobacteriaceae (MRE). The aim of this systematic review was to determine the effect of international travel on the risk of post-travel faecal carriage of MRE. Secondary outcomes were risk factors for acquisition of MRE. A systematic search for relevant literature in seven international databases was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Articles needed to report on (i) foreign travel, (ii) screening of asymptomatic participants, (iii) antimicrobial susceptibility data and (iv) faecal Enterobacteriaceae carriage. Two researchers independently screened the abstracts, assessed the full article texts for eligibility and selected or rejected them for inclusion in the systematic review. In case of disagreement, a third researcher decided on inclusion. Eleven studies were identified. In all studies, a high prevalence (> 20%) of carriage of MRE after international travel was found. The highest prevalence was observed in travellers returning from southern Asia. Foreign travel was associated with an increased risk of carriage of MRE. Further research is needed to assess if this leads to an increase in the number of infections with MRE. Systematic review registration number: PROSPERO CRD42015024973.

Introduction

Rationale

Worldwide, the number of international travellers has grown from 25 million in 1950 to 1,087 million in 2013 [1]. According to the World Tourism Organization, this number is expected to increase by an average of 3.3% a year [1]. Of the international travellers visiting developing countries, 22–64% have self-reported health problems and about 8% require medical care during or after travel [2,3]. Healthy travellers may be exposed to a broad range of microorganisms while travelling, including drug-resistant Enterobacteriaceae, which may subsequently be introduced into their home country [4,5].

Enterobacteriaceae are Gram-negative bacteria that are part of the human body’s normal commensal flora, called microbiota. Enterobacteriaceae, such as Escherichia coli and Klebsiella species, are capable of causing both healthcare-associated and community-acquired infections [6]. Multidrug-resistant Enterobacteriaceae (MRE), including extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-E) and plasmid-mediated Amp C-producing Enterobacteriaceae (pAmp C-E) are emerging worldwide [7]. Cases of carbapenemase-producing Enterobacteriaceae (CPE) are also reported more frequently [8].

Since 2003, community carriage rates of MRE have increased dramatically in various regions, such as South-East Asia, the Western Pacific and the Eastern Mediterranean [7]. During visits to such areas, travellers might acquire MRE and become asymptomatic carriers of MRE. In their home country, they may cause spread in the community and contribute to worldwide emerging antimicrobial resistance [6,9,10]. Acquired MRE in the digestive tract are considered apathogenic, however carriage of such Enterobacteriaceae have resulted in clinically relevant infections [8]. International travel has been reported as a risk factor for urinary tract infections caused by ESBL-E [11,12]. The question arises if these observations warrant clinicians being aware of MRE in recently returned otherwise healthy, international travellers who seek medical attention even for unrelated conditions.
Flowchart for literature search on the acquisition of multidrug-resistant *Enterobacteriaceae* in international travel (n = 4,989)

Articles identified in Embase, MEDLINE, Web of Science, Scopus, The Cochrane Library, PubMed and Google Scholar (n=5,189)

Articles identified by searching references in published articles (n=0)

Duplicates removed (n=2,791)

Articles screened (n=2,398)

Articles not eligible based on title and/or abstract (n=2,362)

Articles retrieved for further evaluation (n=36)

Studies excluded for the following reasons (n=25):
- Letter to the editor (n=2)
- Review (n=4)
- Study design (n=1)
- Oral or poster presentation (3)
- No ESBL-*Enterobacteriaceae* (n=6)
- Symptomatic patients (n=7)
- No travel (n=1)
- Results of a follow-up study (n=1)

Articles included in systematic review (n=11)

ESBL: extended-spectrum beta-lactamase.

The queries differed per database searched and were developed with help of a biomedical information specialist (Box). Articles written in English, German, French and Dutch were included.

For inclusion the article needed to fulfil the following criteria [1]: It needed to be related to foreign travel [2], report on screening in asymptomatic participants [3], present antimicrobial susceptibility data and [4] report on faecal Enterobacteriaceae carriage. We used the following exclusion criteria: case reports, reviews, meta-analyses, veterinary medicine, in vitro studies and studies regarding symptomatic patients. The reference lists of reviews were screened to identify studies possibly missed by the search.

Two researchers (R.H. and J.A.) independently performed the screening of the abstracts. Any discordant result was discussed in consensus meetings. After
screening the abstracts, the full text of the articles was assessed for eligibility by the same two researchers and selected or rejected for inclusion in the systematic review. In case of disagreement a third researcher (A.V.) decided on inclusion.

Data collection process
The following data (if available) were extracted from each article: year of publication, country of the study, study period, study design, microorganism studied, study population, study size, age, sex, sample time before and after travel, duration of travel, travelling in pairs or groups, symptoms during travel, countries visited, MRE prevalence before travel, MRE prevalence after travel, MRE resistance acquired during travel, resistance to other antibiotic drugs of acquired MRE, risk factors for acquisition (among which travel to predefined United Nations geographical regions: southern Asia, Asia except southern Asia, Africa, South and Central America, North America, Europe and Oceania [14]), method of MRE susceptibility determination, phenotypic approaches, genotypic characterisation of post-travel MRE isolates, molecular typing of post-travel MRE isolates, duration of MRE colonisation and MRE transmission to household contacts. To obtain missing data, authors of the articles were contacted.

Quality assessment
We assessed the methodological quality and the risk of bias in individual studies that may affect the cumulative evidence, using tools for assessing quality and susceptibility to bias in observational studies as recommended in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [15,16].

Data synthesis and analysis
As a result of the design of the studies (cohort studies) and the heterogeneity in patient populations (e.g. travellers, healthcare workers and healthcare students), a formal meta-analysis was not possible. Therefore, the study results were summarised to describe the main outcomes of interest. The principle summary measure was percentage of MRE acquisition during travel, defined as ESBL-E or pAmp C-E. Furthermore, risk factors for acquisition of drug resistance were assessed. If possible, percentages not presented in the articles were calculated from the available data.

Results

Study selection
A total of 2,398 studies were identified through database searching after duplicates had been removed (Figure). After screening of titles and summaries, 36 articles were selected for full-text assessment. Eleven articles were included in the qualitative synthesis of the systematic review (see Figure for reasons for exclusion) [17-27].

Study characteristics
Eleven prospective cohort studies, conducted in northern and western Europe, Australia and the United States (US) were included [17-27]. The characteristics of these studies are shown in Table 1. Nine studies investigated travellers visiting a travel or vaccination clinic, one study hospital staff and contacts, and one study healthcare students working or studying abroad. The number of study participants ranged from 28 to 574. The median age of travellers in the individual studies varied between 25 and 66 years, with the youngest group being healthcare students. In all studies, the majority of travellers were female (range: 55–78%). The proportion of participants who were lost to follow up varied from 3.8% (4/106) [18] to 30% (12/40) [21]. The mean duration of travel was similar in all studies (14–21 days). In the study by Angelin et al. on healthcare students, median length of stay was 45 days (range: 13–365 days) [22]. In four studies, follow-up samples of MRE carriers were collected at six months after returning from travel, and in one of these studies, samples were collected monthly in the first three months with further follow-up until 12 months after return [25]. Ten studies used a phenotypic method for susceptibility testing, with genotypic confirmation of ESBL positivity by PCR [17-22,24-27]. One study used a PCR-based approach [23]. In one study, only isolated E. coli were included, whereas other studies included all isolated Enterobacteriaceae, which mainly consisted of E. coli [17-27].

Acquisition of multidrug-resistant Enterobacteriaceae
Faecal carriage of MRE varied from 1 to 12% before travel and acquisition of MRE from 21% to 51% (Table 2 [17-21,23-27].

In the study by Kuenzli et al. on travellers to the Indian subcontinent only, a much higher MRE acquisition rate of 69% was demonstrated [26]. The risk of acquisition of MRE varied with the geographical region (Table 3 [17-21,23-27]. Travel to southern Asia posed the highest risk (range: 29–88%), followed by other Asian countries (18–67%) and Northern Africa (range: 31–57%). Acquisition of MRE after travelling to sub-Saharan Africa (range: 0–49%) or South and Central America (range: 0–33%) was less frequent, and three studies did not observe any acquisition of MRE after travel to South or Central America (Table 3). Acquisition of MRE after travel to North America, Europe and Oceania was rare. Results of the genotypic characterisation of MRE isolated after travel are presented in Table 2, the majority of the genes belonged to the CTX-M type.

Risk factors for acquisition of multidrug-resistant Enterobacteriaceae
Besides travel destinations, other risk factors for acquiring MRE were age, use of antibiotics during travel (beta-lactam use) and gastroenteritis or other gastrointestinal symptoms (Table 2). The study of Kantele et al., designed to study these risk factors as primary
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study period</th>
<th>Population characteristics</th>
<th>Study size</th>
<th>Median age in years (range or SD)</th>
<th>Proportion of women in %</th>
<th>Identification of MRE-positive organisms in post-travel isolates</th>
<th>Sample method used</th>
<th>Sample time (range) before/after travel</th>
<th>Mean duration of travel in days (range)</th>
<th>Total number of co-travellers participating in study</th>
<th>Follow-up of resistant isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tängdén [17]</td>
<td>Sweden</td>
<td>November 2007–31 January 2009</td>
<td>Travel clinic</td>
<td>100</td>
<td>43 (2–84)</td>
<td>55</td>
<td>Enterobacteriaceae 100% (24/24) E. coli</td>
<td>Stool sample</td>
<td>Unknown</td>
<td>16 (5–26)</td>
<td>23</td>
<td>6 months</td>
</tr>
<tr>
<td>Kennedy [18]</td>
<td>Australia</td>
<td>January 2008–April 2009</td>
<td>Hospital staff and contacts</td>
<td>102</td>
<td>45 (17–77)</td>
<td>62</td>
<td>E. coli</td>
<td>Rectal or perianal swab</td>
<td>Within 2 weeks before and after</td>
<td>21 (9–35)</td>
<td>Unknown</td>
<td>6 months</td>
</tr>
<tr>
<td>Östhlm-Balkhed [19]</td>
<td>Sweden</td>
<td>September 2008–April 2009</td>
<td>Vaccination clinic</td>
<td>231</td>
<td>54 (58–76)</td>
<td>59</td>
<td>Enterobacteriaceae 92% (224/245) E. coli</td>
<td>Stool sample</td>
<td>15 (5–114) days / 3 (0–91) days</td>
<td>16 (4–119)</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Kantele [20]</td>
<td>Finland</td>
<td>March 2009–February 2010</td>
<td>Travel clinic</td>
<td>430</td>
<td>49 (0–77)</td>
<td>61</td>
<td>Enterobacteriaceae 97% (94/97) E. coli</td>
<td>Stool sample</td>
<td>Before and first (or second) stool after</td>
<td>19 (4–73)</td>
<td>83</td>
<td>None</td>
</tr>
<tr>
<td>Weisenberg [21]</td>
<td>United States</td>
<td>July 2009–February 2010</td>
<td>Travel clinic</td>
<td>28</td>
<td>66 (41–83)</td>
<td>68</td>
<td>Enterobacteriaceae 100% (171) E. coli</td>
<td>Stool sample</td>
<td>1 week before/ 1 week after</td>
<td>16 (8–24)</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Angelin [22]</td>
<td>Sweden</td>
<td>April 2010–January 2014</td>
<td>Healthcare students</td>
<td>99</td>
<td>75 (15–20)</td>
<td>78</td>
<td>Enterobacteriaceae 100% (361/360) E. coli</td>
<td>Stool sample</td>
<td>Close to departure/ 1 to 2 weeks after returning</td>
<td>45 (33–365)</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>von Wintersdorff [23]</td>
<td>The Netherlands</td>
<td>November 2010–August 2012</td>
<td>Travel clinic</td>
<td>122</td>
<td>43 (18–72)</td>
<td>58</td>
<td>Not done</td>
<td>Stool sample</td>
<td>Before and immediately after</td>
<td>21 (5–240)</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Paltansing [24]</td>
<td>The Netherlands</td>
<td>March 2011–September 2011</td>
<td>Travel clinic</td>
<td>370</td>
<td>33 (29–82)</td>
<td>63</td>
<td>Enterobacteriaceae 92% (346/361) E. coli</td>
<td>Rectal swab</td>
<td>Immediately before and after</td>
<td>21 (6–90)</td>
<td>None</td>
<td>6 months</td>
</tr>
<tr>
<td>Ruppé [25]</td>
<td>France</td>
<td>February 2012–April 2013</td>
<td>Vaccination centres</td>
<td>574</td>
<td>36 (SD 13)</td>
<td>61</td>
<td>Enterobacteriaceae 93% (491/526) E. coli</td>
<td>Stool sample</td>
<td>Within 1 week before and after</td>
<td>20 (15–30)</td>
<td>None</td>
<td>12 months</td>
</tr>
<tr>
<td>Kuenzli [26]</td>
<td>Switzerland</td>
<td>December 2012–October 2013</td>
<td>Travel clinic</td>
<td>170</td>
<td>43 (30–53)</td>
<td>56</td>
<td>Enterobacteriaceae 98% (157/161) E. coli</td>
<td>Rectal swab</td>
<td>1 week before/ directly after</td>
<td>18 (5–35)</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Lübbert [27]</td>
<td>Germany</td>
<td>May 2013–April 2014</td>
<td>Travel clinic</td>
<td>205</td>
<td>34 (5–76)</td>
<td>57</td>
<td>Enterobacteriaceae 92% (58/63) E. coli</td>
<td>Stool sample</td>
<td>Before/within 1 week after</td>
<td>21 (3–218)</td>
<td>22</td>
<td>6 months</td>
</tr>
</tbody>
</table>

E. coli: *Escherichia coli*; MRE: multidrug-resistant Enterobacteriaceae; SD: standard deviation.

- **a** Number of travellers who provided pre- and post-travel swab.
- **b** Data of MRE-positive isolates newly acquired during travel.
- **c** Data of MRE-positive isolates post-travel.
- **d** Healthcare students, median duration of stay.
outcome, showed that travel diarrhoea (adjusted odds ratio (AOR) = 31.0; 95% confidence interval (CI): 2.7–358.1) and antibiotic therapy for travel diarrhoea (AOR = 3.0; 95% CI: 1.4–6.7) proved to be the most important risk factors for acquiring MRE [20]. In the study of Kuenzli et al. in which only travellers to southern Asia were included, risk factors for MRE acquisition were length of stay, visit to family or friend and consumption of ice cream or pastry (Table 2) [26]. Angelin et al. found a significant association for travel to the South-East Asia region (OR = 30; 95% CI: 6.3–147.2), and antibiotic treatment during travel (OR = 5; 95% CI: 1.1–26.2), but found no association with travellers’ diarrhoea or patient-related healthcare work [22].

Resistance of multidrug-resistant Enterobacteriaceae to other antibiotic drugs

Resistance of post-travel MRE isolates to various antibiotics was determined in nine studies (Table 4) [17-19,21-24,26,27]. In the study by Wintersdorff et al., a PCR-based approach was used, therefore it was not possible to determine which microorganism carried the resistance genes [23]. The resistance data to other antibiotic drugs in the study by Kennedy et al. were not part of the publication, but were provided on request [18]. Antimicrobial resistance was high for ciprofloxacin, varying from 31% to 57%, and for cotrimoxazole, varying from 49% to 86% [17-19,21-24,26,27]. Aminoglycoside resistance was high for gentamicin (range: 17–50%) and tobramycin (range: 18–59%) and low for amikacin (range: 2–5%) [17-19,21-24,26,27]. Carbapenemase-producing Enterobacteriaceae were observed in four travellers who had all visited India (in the study by Ruppé et al., two OXA-181 and one New Delhi metallo-beta-lactamase 1 (NDM-1), and in the study by Kuenzli et al., one NDM-1 but this strain was not included in the resistance results) [25,26]. Resistance to nitrofurantoin, colistin and fosfomycin was only analysed in some of the studies (Table 4) [18,19,21-23,26].

Duration of multidrug-resistant Enterobacteriaceae carriage after return, risk factors for a long duration and rate of infection after travel

Five studies analysed MRE carriage six months after travel, and the persistence rate of acquired MRE after six months was 6–24% of travellers (Table 2) [17,18,24,25,27]. Ruppé et al. analysed MRE carriage one, two, three, six and twelve months after travel, showing persistence of carriage of an acquired MRE in 34, 19, 10, 5 and 2%, respectively [25]. Travellers to Asia showed longer carriage of MRE compared with other travel destinations. Carriage of multidrug-resistant Escherichia coli had a lower risk for prolonged carriage than other multidrug-resistant species. No other risk factors were found for prolonged carriage of MRE. Eight travellers in this study reported an episode of urinary tract infection after their return, but no microbiological data were available [25]. In the study by Tängdén et al., five of 21 travellers remained carriers of MRE after six months. However, none of these participants reported clinical infections [17]. In the study of Kennedy et al., one person developed a urinary tract infection with a travel-related organism [18]. Kantele et al. performed a one-year laboratory-based follow-up and did not find any clinical samples with MRE [20].

Rate of transmission to household members

Only one study screened household contacts for MRE after return of the index traveller. Household contacts were defined as persons who shared the same household with a participant on a regular basis. Two of 11 contacts were found MRE-positive [24]. Both carried a different ESBL-producing E. coli based on multilocus sequence typing (MLST) than the associated traveller.

Limitations of the studies

The quality of the studies and the susceptibility of bias between the studies were assessed. In all but one study, participants constituted a non-random sample of the general travelling population [17-21,23-27]. However, Angelin et al. studied healthcare students working or studying abroad [22]. Studies were performed on three different continents. Travel destinations and travel behaviour may differ considerably between different nationalities and age groups. Including co-travellers, as done in all studies except Paltansing et al. and Ruppé et al., can result in similar travel behaviour and therefore, similar risk factors. Overall, the main outcome was not influenced by recall or interviewer bias. For other outcomes such as risk factors, the risk of recall bias or interviewer bias was low because of the use of self-administered questionnaires.

Every study had participants lost to follow-up for post-travel stool samples and follow-up stool samples. Asymptomatic faecal carriage of MRE is probably not related to loss to follow-up, therefore, the risk of information bias is small. Ruppé et al. calculated post-travel MRE carriage as those travellers with persisting MRE carriage divided by all travellers with MRE acquisition plus all travellers without MRE post-travel [25]. However, travellers without MRE were not included in the follow-up. As a result, local MRE acquisition was not included in the calculated post-travel MRE carriage prevalence. Therefore the true prevalence can be assumed to be higher.

In five studies, travellers visited multiple regions or even continents during their trip [17-20,27]. In these travellers, it was not possible to attribute MRE prevalence or MRE acquisition to a certain geographical region. However, travellers in these studies were included in the MRE prevalence or MRE acquisition rates of more than one geographical region, which may have introduced information bias.

Seven studies used stool samples for detection of MRE [17,19-21,23,25,27] and three studies used rectal or perianal swabs for detection of MRE [18,24,26]. This might have influenced detection of MRE carriage.
<table>
<thead>
<tr>
<th>Study</th>
<th>Method of MRE determination</th>
<th>Phenotypic approaches</th>
<th>Results genotypic characterisation post-travel MRE isolates</th>
<th>Results molecular typing of post-travel MRE isolates</th>
<th>MRE prevalence pre-travel % (ratio)</th>
<th>MRE prevalence post-travel % (ratio)</th>
<th>New MRE acquisition during travel % (ratio)</th>
<th>Persistent newly acquired MRE carriage 6 months after travel % (ratio)</th>
<th>Results univariate/multivariate risk factor analysis for MRE acquisition</th>
<th>MRE in non-travelling household contacts % (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tängdén [17]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Enrichment broth, selective media, AST: Etest, MRE confirmation: disc diffusion</td>
<td>TEM (n = 14), SHV (n = 3), CTX-M group 1 (n = 14) of which CTX-M-15 (n = 7), CTX-M-1 (n = 4), CTX-M group 4 (n = 2) of which CTX-M-9 (n = 1), CTX-M-14 (n = 2), CTX-M-27 (n = 6)</td>
<td>No data</td>
<td>1 (5/105)</td>
<td>No data</td>
<td>24 (24/100)</td>
<td>24 (5/21)</td>
<td>Gastroenteritis; travel to India</td>
<td>No data</td>
</tr>
<tr>
<td>Kennedy [18]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Enrichment broth, selective media, AST: Vitek2, MRE confirmation: disc diffusion</td>
<td>TEM or SHV (n = 4), CTX-M group 1 (n = 12), CTX-M group 9 (n = 6), and pAmpC genes (n = 6)</td>
<td>No data</td>
<td>2 (2/106)</td>
<td>22 (22/102)</td>
<td>21 (21/100)</td>
<td>6 (1/106)</td>
<td>Gastroenteritis; use of antibiotics; travelling to Asia, South America and/or Middle East/Africa</td>
<td>No data</td>
</tr>
<tr>
<td>Östholm-Balkhed [19]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Selective media, AST: Etest, MRE confirmation: Etest</td>
<td>TEM-19 (n = 1), SHV (n = 6), CTX-M-15-like (n = 36), CTX-M-14-like (n = 35), CTX-M-27-like (n = 3), CTX-M-53-like (n = 5), CTX-M-1/61-like (n = 3), CTX-M-2-like (n = 2), CTX-M-3-like (n = 1), pAmpC genes (n = 2)</td>
<td>No data</td>
<td>2 (6/251)</td>
<td>31 (23/725)</td>
<td>30 (60/206)</td>
<td>No data</td>
<td>Age; diarrhoea or other gastrointestinal symptoms; travel to Asia, Africa (north of equator), Indian subcontinent</td>
<td>No data</td>
</tr>
<tr>
<td>Kantele [20]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Selective media, AST: Vitek2, MRE confirmation: disc diffusion</td>
<td>79% CTX-M-type (CTX-M-1 and CTX-M-9 most prevalent), other common strains TEM and OXA (data not published)</td>
<td>No data</td>
<td>1 (5/430)</td>
<td>22 (99/430)</td>
<td>21 (90/430)</td>
<td>No data</td>
<td>Traveller’s diarrhoea; age; use of antibiotics for traveller’s diarrhoea</td>
<td>No data</td>
</tr>
<tr>
<td>Weisenberg [21]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Selective media, AST: Vitek2, MRE confirmation: disc diffusion</td>
<td>SHV-12 (n = 1), CTX-M-14 (n = 3), CTX-M-15 (n = 2), no gene detected (n = 17)</td>
<td>MLST typing 7 multidrug-resistant E. coli isolates: ST 39, 8 (n = 2), 37, 399, 437, 83</td>
<td>4 (2/28)</td>
<td>25 (7/28)</td>
<td>26 (7/27)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

**Table 2A**

Risk of multidrug-resistant *Enterobacteriaceae* in travellers (n = 11 studies)

---

**Abbriviations**


*a* Percentage of MRE-positive post-travel samples in those travellers whose pre-travel sample was MRE-negative.

*b* Acquired genes detected in post travel MRE isolates.

*c* Prevalent genes detected in post-travel MRE isolates.

*d* Risk factors for resistance to gentamicin, ciprofloxacin and/or third generation cephalosporins.

*e* Multivariable logistic regression analysis; participants ESBL-positive before travel were excluded.

*f* Binary regression analysis.

*g* Carbapenemase-positive isolates were included in the definition MRE.
### Table 2B
Risk of multidrug-resistant *Enterobacteriaceae* in travellers (n = 11 studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of MRE determination</th>
<th>Phenotypic approaches</th>
<th>Results genotypic characterisation post-travel MRE isolates</th>
<th>Results molecular typing of post-travel MRE isolates</th>
<th>MRE prevalence pre-travel % (ratio)</th>
<th>MRE prevalence post-travel % (ratio)</th>
<th>New MRE acquisition during travel % (ratio)</th>
<th>Persistent newly acquired MRE carriage 6 months after travel % (ratio)</th>
<th>Results univariate/multivariate risk factor analysis for MRE acquisition</th>
<th>MRE in non-travelling household contacts % (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelin [22]</td>
<td>Phenotypic approach for detection of ESBL, pAmp C and phenotypic approach with genotypic characterisation for detection of OXA-48/OXA-81</td>
<td>Selective media, AST; disc diffusion, MRE confirmation: Etest (ESBL), disc diffusion (pAmpC)</td>
<td>No data</td>
<td>No data</td>
<td>7 (7/99)</td>
<td>36 (36/99)</td>
<td>35 (35/99)</td>
<td>No data</td>
<td>Travel to the South-East Asia region (India, Nepal, Vietnam, Indonesia, Sri Lanka); antibiotic treatment during travel*</td>
<td>No data</td>
</tr>
<tr>
<td>von Wintersdorff [23]</td>
<td>Metagenomic approach (detection blaCTX-M)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>9 (11/122)</td>
<td>34 (41/122)</td>
<td>32 (39/111)</td>
<td>No data</td>
<td>Travel to Indian subcontinent†</td>
<td>No data</td>
</tr>
<tr>
<td>Paltansing [24]</td>
<td>Phenotypic approach with genotypic characterisation by microarray</td>
<td>Enrichment broth, selective media, AST; Vitek 2, MRE confirmation: disc diffusion</td>
<td>No data</td>
<td>No data</td>
<td>9 (32/370)</td>
<td>36 (133/370)</td>
<td>33 (113/338)</td>
<td>No data</td>
<td>Travel to South or East Asia†</td>
<td>18 (2/11)</td>
</tr>
<tr>
<td>Ruppe [25]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Enrichment broth, selective media, AST; disc diffusion</td>
<td>Predominant CTX-M-type (95.4%) among which CTX-M-group 1 predominated (85.7% of all CTX-M); OXA-81 (n = 2), ND-M-1 (n = 1)*</td>
<td>No data</td>
<td>12 (85/700)</td>
<td>No data</td>
<td>51 (292/574)</td>
<td>No data</td>
<td>Travel to Asia or sub-Saharan Africa; beta-lactam use during travel; diarrhea during travel†</td>
<td>No data</td>
</tr>
</tbody>
</table>


* Percentage of MRE-positive post-travel samples in those travellers whose pre-travel sample was MRE-negative.
† Acquired genes detected in post-travel MRE isolates.
‡ Univariate statistics.
§ Prevalent genes detected in post-travel MRE isolates.
‖ Risk factors for resistance to gentamicin, ciprofloxacin and/or third generation cephalosporins.
¶ Multivariable logistic regression analysis; participants ESBL-positive before travel were excluded.
‖ Binary regression analysis.
¶ Carbenapenemase-positive isolates were included in the definition MRE.
Table 2C

Risk of multidrug-resistant Enterobacteriaceae in travellers (n = 11 studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of MRE determination</th>
<th>Phenotypic approaches</th>
<th>Results genotypic characterisation post-travel MRE isolates</th>
<th>Results molecular typing of post-travel MRE isolates</th>
<th>MRE prevalence pre-travel % (ratio)</th>
<th>MRE prevalence post-travel % (ratio)</th>
<th>New MRE acquisition during travel % (ratio)</th>
<th>Persistent newly acquired MRE carriage 6 months after travel % (ratio)</th>
<th>Results univariate/multivariate risk factor analysis for MRE acquisition</th>
<th>MRE in non-travelling household contacts % (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuenzli [26]</td>
<td>Phenotypic approach with genotypic screening by microarray and confirmation by PCR/DNA sequence analysis</td>
<td>Enrichment broth, selective media, AST: Vitek2; MIC for meropenem and ertapenem: Etest, MRE confirmation: disc diffusion, modified Hodge test</td>
<td>TEM-1-like (n = 33), SHV-23RS/240K (n = 7), SHV-3 RS (n = 1), SHV-5/12-like (n = 1), SHV-2/3-like (n = 1)</td>
<td>CTX-M-15-like (n = 48), CTX-M group 9 (n = 1), CTX-M group 1 (n = 24), predominant ESBL gene was CTX-M-15 (80 representative E. coli isolates analysed)</td>
<td>80 representative E. coli isolates analysed by rep-PCR; not clonally related. MLST performed on 34 randomly selected E. coli isolates: only 3 pandemic strains found (ST131 n = 2; ST648 n = 1)</td>
<td>3 (5/173)</td>
<td>No data</td>
<td>70 (118/170)</td>
<td>No data</td>
<td>Travel to India, Bhutan or Nepal; visiting friends and relatives; consumption of ice cream and pastry; length of stay</td>
</tr>
<tr>
<td>Lübbert [27]</td>
<td>Phenotypic approach with genotypic confirmation by PCR</td>
<td>Selective media, AST: microbroth dilution method, MRE confirmation: Etest</td>
<td>SHV-12 (n = 1), CTX-M group 1 (n = 37) of which CTX-M-15 (n = 33), CTX-M-55 (n = 4), CTX-M group 9 (n = 19) of which CTX-M-14 (n = 9), CTX-M-27 (n = 1), CTX-M-65 (n = 1)</td>
<td>No data</td>
<td>No data</td>
<td>30 (58/199)</td>
<td>No data</td>
<td>31 (63/205)</td>
<td>No data</td>
<td>Travel to India or South-East Asia; gastroenteritis</td>
</tr>
</tbody>
</table>


* Percentage of MRE-positive post-travel samples in those travellers whose pre-travel sample was MRE-negative.

* Acquired genes detected in post-travel MRE isolates.

* Univariate statistics.

* Prevalent genes detected in post-travel MRE isolates.

* Risk factors for resistance to gentamicin, ciprofloxacin and/or third generation cephalosporins.

* Multivariable logistic regression analysis; participants ESBL-positive before travel were excluded.

* Binary regression analysis.

* Carbapenemase-positive isolates were included in the definition MRE.
### Table 3
Proportion of travellers who acquired multidrug-resistant Enterobacteriaceae, by travel destination (n = 11 studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Southern Asia % (ratio)</th>
<th>Asia except southern Asia % (ratio)</th>
<th>Northern Africa % (ratio)</th>
<th>Sub-Saharan Africa % (ratio)</th>
<th>South and Central America % (ratio)</th>
<th>North America % (ratio)</th>
<th>Europe % (ratio)</th>
<th>Oceania % (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tängdén [17]a,b</td>
<td>78 (7/9)</td>
<td>29 (10/34)</td>
<td>32 (4/12)</td>
<td>4 (1/23)</td>
<td>0 (0/7)</td>
<td>0 (0/2)</td>
<td>13 (2/16)</td>
<td>-</td>
</tr>
<tr>
<td>Kennedy [18]a,c</td>
<td>57 (38/14)</td>
<td>25 (21/85)</td>
<td>33 (1/3)</td>
<td>0 (0/2)</td>
<td>20 (1/5)</td>
<td>20 (2/10)</td>
<td>14 (3/21)</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>Östholm-Balkhed [19]a,b</td>
<td>71 (10/14)</td>
<td>43 (26/60)</td>
<td>57 (17/30)</td>
<td>21 (15/71)</td>
<td>16 (5/31)</td>
<td>0 (0/15)</td>
<td>0 (0/15)</td>
<td>No data</td>
</tr>
<tr>
<td>Kantele [20]b,d</td>
<td>46 (28/63)</td>
<td>32 (37/116)</td>
<td>67 (2/3)</td>
<td>12 (23/193)</td>
<td>0 (0/40)</td>
<td>0 (0/2)</td>
<td>0 (0/15)</td>
<td>No data</td>
</tr>
<tr>
<td>Weisenberg [21]b</td>
<td>29 (2/7)</td>
<td>25 (1/4)</td>
<td>33 (1/3)</td>
<td>13 (1/8)</td>
<td>33 (2/6)</td>
<td></td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Angelin [22]</td>
<td>63 (25/40)</td>
<td>67 (6/9)</td>
<td>No data</td>
<td>10 (4/40)</td>
<td>0 (0/5)</td>
<td>0 (0/4)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Paltansing [24]c,d</td>
<td>72 (18/25)</td>
<td>41 (60/146)</td>
<td>40 (4/10)</td>
<td>24 (20/82)</td>
<td>15 (9/60)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Ruppé [25]c</td>
<td>88 (53/60)</td>
<td>66 (61/93)</td>
<td>No data</td>
<td>49 (89/182)</td>
<td>31 (48/155)</td>
<td>No data</td>
<td>No data</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>Kuenzli [26]c</td>
<td>69</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Lübbert [27]a,b</td>
<td>72 (13/18)</td>
<td>33 (24/73)</td>
<td>No data</td>
<td>24 (19/78)</td>
<td>8 (6/78)</td>
<td>0 (0/2)</td>
<td>20 (2/10)</td>
<td>No data</td>
</tr>
</tbody>
</table>

MRE: multidrug-resistant Enterobacteriaceae.

a Travellers visiting more than one region are categorised in all the visited geographical regions.
b Study reports data on MRE acquisition in travellers.
c Study reports data on MRE prevalence in travellers.
d Travellers visiting more than one region are categorised in the geographical region with the longest stay for this study.
e One traveller who visited Iran is categorised in Asia instead of Southern Asia.
f 42 travellers visited more than one region in Asia and may be represented in more than one column in the Table; 28 of them acquired MRE.
g Exact numbers unpublished.

Southern Asia: Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, Sri Lanka.

Asia (without southern Asia): Armenia, Azerbaijan, Bahrain, Brunei, Cambodia, China, Cyprus, Georgia, Hong Kong, Indonesia, Iraq, Israel, Jordan, Japan, Kazakhstan, Kuwait, Kyrgyzstan, Laos, Lebanon, Mongolia, Malaysia, Myanmar, North Korea, Oman, Philippines, Qatar, Saudi Arabia, South Korea, Singapore, Palestine, Syria, Tajikistan, Thailand, Timor-Leste, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, Viet Nam, Yemen.

Northern Africa: Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, Western Sahara.


South and Central America: Anguilla, Antigua and Barbuda, Argentina, Aruba, Bahamas, Barbados, Belize, Bolivia, Bonaire, Sint Eustatius and Saba, Brazil, British Virgin Islands, Cayman Islands, Chile, Colombia, Costa Rica, Cuba, Curaçao, Dominican Republic, Ecuador, El Salvador, Falkland Islands, French Guiana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, Saint-Barthélemy, Sint Maarten, Suriname, Trinidad and Tobago, Turks and Caicos Islands, US Virgin Islands, Uruguay, Venezuela.

North America: Bermuda, Canada, Greenland, Saint Pierre and Miquelon, United States.

Europe: Åland Islands, Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Channel Islands, Croatia, Czech Republic, Denmark, Estonia, Faeroe Islands, Finland, the former Yugoslav Republic of Macedonia, France, Germany, Gibraltar, Greece, the Holy See, Hungary, Iceland, Ireland, Isle of Man, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Moldova, Romania, Russia, San Marino, Serbia, Slovenia, Spain, Svalbard and Jan Mayen, Sweden, Switzerland, Ukraine, United Kingdom.

Discussion

In this systematic review we found a high prevalence of faecal carriage of MRE after international travel. The highest prevalence of MRE was observed in isolates from travellers returning from southern Asia, with up to 88% acquisition of MRE. In addition to the antibiotics not effective against MRE, an alarmingly high prevalence of resistance to other commonly used antibiotics such as cotrimoxazole (49–86%), ciprofloxacin (31–57%) and aminoglycosides (gentamicin 17–71%) was observed in ESBL-positive isolates in travellers in all studies [17-27].

Returning international travellers with MRE may introduce these microorganisms in their home countries. This may cause community-onset infections with MRE in patients without obvious risk factors transmitted by healthy carriers through food or person-to-person contact [9]. Infections caused by MRE are associated with poorer outcome and a higher overall mortality rate than infections caused by susceptible bacteria [28]. In this review, all studies showed an increased prevalence of faecal carriage of ESBL after international travel. It is not possible to evaluate the proportion of travellers who will develop infection with these resistant bacteria. However, studies have demonstrated that international travel is a risk factor associated with developing an infection with an MRE [11,12,29].

Many countries have infection prevention and control guidelines to detect and treat multidrug-resistant organisms (MDROs) including MRE [30]. In countries with low prevalence of MRE, infection prevention and control guidelines mainly include strategies for early identification and isolation of patients recently hospitalised in foreign hospitals [30,31]. Patients with a recent history of travel to MRE-endemic areas but not admitted to healthcare facilities abroad are not normally considered at risk for carriage of MDROs. However, in hospitalised patients with a recent history of travel, increased rates of carriage of MRE have been observed [11,29,30]. Physicians should be aware of the risk that patients with recent travel to areas with high faecal carriage of MRE, as presented in this review, may introduce MRE to the hospital. Routine screening

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**Table 4**

Antibiotic drug resistance of newly acquired multidrug-resistant Enterobacteriaceae in travellers (n = 11 studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ciprofloxacin % (ratio)</th>
<th>Cotrimoxazole % (ratio)</th>
<th>Gentamicin % (ratio)</th>
<th>Amikacin % (ratio)</th>
<th>Tobramycin % (ratio)</th>
<th>Carabapenem % (ratio)</th>
<th>Nitrofurantoin % (ratio)</th>
<th>Colistin % (ratio)</th>
<th>Fosfomycin % (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tängdén [17]</td>
<td>50b</td>
<td>79 (59/24)</td>
<td>45b</td>
<td>No data</td>
<td>38b</td>
<td>o³</td>
<td>o³</td>
<td>No data</td>
<td>8.0b</td>
</tr>
<tr>
<td>Kennedy [18]</td>
<td>55 (12/22)</td>
<td>No data</td>
<td>50 (11/22)</td>
<td>No data</td>
<td>59 (13/22)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Kantele [20]</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Weisenberg [21]</td>
<td>43 (3/7)</td>
<td>86 (6/7)</td>
<td>43 (3/7)</td>
<td>No data</td>
<td>No data</td>
<td>0 (0/7)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Angelin [22]</td>
<td>57 (28/49)</td>
<td>75b</td>
<td>30b</td>
<td>No data</td>
<td>No data</td>
<td>0 (0/49)</td>
<td>2b</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>von Wintersdorff [23]</td>
<td>37 (45/122)</td>
<td>56 (68/122) qnr8</td>
<td>56 (68/122) qnr5</td>
<td>No data</td>
<td>71 (86/122) aac(6’)-aph(2’’-1)</td>
<td>71 (86/122) aac(6’)-aph(2’’-1)</td>
<td>71 (86/122) aac(6’)-aph(2’’-1)</td>
<td>0 (0/122) blaNDM</td>
<td>No data</td>
</tr>
<tr>
<td>Paltansing [24]</td>
<td>36</td>
<td>67</td>
<td>35</td>
<td>No data</td>
<td>37</td>
<td>0</td>
<td>29</td>
<td>0</td>
<td>No data</td>
</tr>
<tr>
<td>Ruppé [25]</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>0.6 (3/526)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Kuenzli [26]</td>
<td>41 (64/157)</td>
<td>49 (77/157)</td>
<td>5 (7/157)</td>
<td>18 (28/157)</td>
<td>0 (0/157)</td>
<td>2 (3/157)</td>
<td>0 (0/157)</td>
<td>0.6 (1/157)</td>
<td>No data</td>
</tr>
<tr>
<td>Lübbert [27]</td>
<td>43 (25/58)</td>
<td>83 (48/58)</td>
<td>17 (10/58)</td>
<td>2b</td>
<td>22b</td>
<td>0³</td>
<td>No data</td>
<td>0³</td>
<td>16³</td>
</tr>
</tbody>
</table>

bla: beta-lactamase; CPE: carbapenemase-producing Enterobacteriaceae; ESBL: extended-spectrum beta-lactamase.

Data extracted from bar chart, exact numbers unpublished.

Prevalent resistance genes in faecal samples post-travel.

Resistance among prevalent ESBL-positive isolates detected in pre- and post-travel samples.

Three acquired CPE detected in post-travel samples.
for MRE seems indicated in such patients. Furthermore, empiric antibiotic therapy may fail when an infection by MRE is not taken into account. Therefore, careful recording of travel history needs to be incorporated in each patient evaluation. As shown in this review, there is also an increased risk of resistance against other antibiotics in travellers with MRE carriage. It is likely that this is caused by multiple genes, each encoding resistance to different classes of antibiotics, which are often found on the same bacterial mobile genetic element (e.g. a plasmid) [32]. As a result, other antibiotics, such as aminoglycosides, will also fail in many MRE-positive patients.

Of all MDROs, emergence of CPE is most worrisome because of the limited treatment options for these infections. NDM-1-producing Enterobacteriaceae have been found in environmental samples in endemic regions [33]. CPE (NDM-1) in patients from the United Kingdom with a recent history of travelling or medical tourism to India are already an important public health problem [8]. Case reports have also demonstrated acquisition of CPE in travellers without contact with medical healthcare facilities [34,35]. In this review, four travellers from India were carrying a carbapenemase-producing E. coli [25,26]. Preliminary results of the Carriage Of Multiresistant Bacteria After Travel (COMBAT) study, a large-scale multicentre longitudinal cohort study conducted in the Netherlands among 2001 travellers, show acquisition of CPE in four travellers [36].

There are, besides the destination of travel, additional risk factors for acquiring MRE during travel. Antibiotic therapy was found to increase the risk [20,22]. In five studies, traveller’s diarrhoea or gastroenteritis were associated with an increased risk of MRE acquisition during travel [17-20,25]. Also, in one study, meticulous hand hygiene or strict consumption of bottled water did not lower the risk of acquiring MRE [22]. Therefore, it is not clear whether hygiene-related travel advice will decrease faecal carriage of MRE. Surprisingly, healthcare-related activities did not pose an increased risk of acquiring MRE in one study [22].

MRE and CPE could also be carried by food. International spread of these bacteria by food supply has been reported [37]. In this review, only one study showed that food consumption (ice cream and pastry) was associated with MRE carriage in travellers to southern Asia, whereas most of the studies did not focus on dietary patterns during travel.

One limitation of this review is the recruitment of travellers from travel clinics only, resulting in inclusion of very few travellers with European destinations. Some European countries such as Greece and Cyprus are also endemic for MRE and popular travel destinations [34]. In addition, travellers visiting their country of origin, especially Morocco and Turkey usually do not ask for a pre-travel consultation, although these countries are endemic for MRE and CPE [34]. It is not clear whether not including these patients may have led to an under- or overestimation of MRE acquisition.

Another limitation is the lack of sufficient data regarding the duration of carriage and the transmission among non-travelling household members. The study by Ruppé et al. suggests that three months after return, MRE carriage is comparable with the baseline prevalence before travelling. However, the study did not include baseline prevalence in the follow-up. The COMBAT study will address some of these questions [38].

**Conclusion**

International travel is a major risk factor for acquisition of MRE. This risk is particularly high after travelling to (southern) Asia and in persons with travel-related diarrhoea and antibiotic use. Carriage of MRE-positive isolates is also associated with a high risk of resistance to ciprofloxacin, cotrimoxazole and aminoglycosides. Further research is needed to assess duration of carriage, spread to household contacts and whether introduction of MRE results in an increase of MRE infections. Our results, combined with the worldwide emergence of CPE, further stress the importance of infection prevention and control guidelines.

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**Conflict of interest**

None declared.

**Authors’ contributions**

Robert-Jan Hassing: This author made substantial contributions to acquisition of data and analysis and interpretation of data; this author participated in drafting the article; this authors gave final approval of the version to be submitted and any revised version. Jelmer Alsma: This author made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data; this author participated in drafting the article; this authors gave final approval of the version to be submitted and any revised version. Bruno H. Stricker: This author made substantial contributions to conception and design, acquisition of data and analysis and interpretation of data; this author participated in revising the article critically for important intellectual content; this authors gave final approval of the version. Perry J. van Genderen: This author made substantial contributions to conception and design; this author participated in revising the article critically for important intellectual content; this authors gave final approval of the version.
to be submitted and any revised version. Annelies Verbon: This author made substantial contributions to conception and design and analysis and interpretation of data; this author participated in revising the article critically for important intellectual content; this author gave final approval of the version to be submitted and any revised version.

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