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Risk factors for acquisition of multidrug-resistant Enterobacterales among international travellers: A synthesis of cumulative evidence

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Systematic review and meta-analysis

Risk factors for acquisition of multidrug-resistant *Enterobacterales* among international travellers: A synthesis of cumulative evidence

Running title: Multidrug-resistant *Enterobacterales*and travellers

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Abstract

Background: Recent studies have shown that over 50% of people travelling to South East Asia return colonised with multidrug-resistant *Enterobacterales* (MRE) including carbapenemase-producing *Enterobacterales*. Importation of MRE by travellers and subsequent spread to family members, communities, and healthcare facilities poses real risks that have not yet been adequately assessed. This systematic review and meta-analysis aims to quantify the risk factors and interventions for reducing the risk of MRE acquisition among international travellers.

Methods: A systematic search was conducted in PubMed, Web of Science, and Scopus for analytical epidemiological studies containing data post-2000 that assessed the risk factors to acquire and/or interventions to reduce the risk of MRE acquisition in travellers. Two researchers independently screened all the studies and extracted the information, and disagreements were resolved through consensus. The proportions of MRE acquisition by the region of destination and the odds ratio (OR) for the different risk factors and/or interventions were pooled using the inverse variance heterogeneity model.

Results: Twenty studies (5253 travellers from high-income countries) were included in the meta-analysis. South Asia (58.7%, 95%CI:44.5-72.5%) and Northern Africa (43.9%; 95%CI:37.6-50.3%) were the travel destinations with the highest proportion of MRE acquisition. Inflammatory bowel disease (OR 2.1; 95%CI:1.2-3.8), use of antibiotics (OR 2.4; 95%CI:1.9-3.0), traveller's diarrhoea (OR 1.7; 95%CI:1.3-2.3), and contact with the healthcare system overseas (OR 1.5; 95%CI:1.1-2.2) were associated with MRE colonisation. Vegetarians (OR 1.4; 95%CI:1.0-2.0) and backpackers (OR 1.5; 95%CI:1.2-1.8) were also at increased odds of MRE colonisation. Few studies (n=6) investigated preventive measures and found that consuming only bottled water/beverages, meticulous hand hygiene, and probiotics had no protective effect on MRE colonisation.

Conclusions: International travel is an important driver for MRE spread worldwide. Future research needs to identify effective interventions to reduce the risk of MRE acquisition as well as design strategies to reduce local transmission on return.

Registration: PROSPERO CRD42018076853.

Keywords: antibiotic; antimicrobial; resistance; transmission; carriage; meta-analysis

Introduction

There is a large clinical and public health burden associated with antimicrobial resistance (AMR) in bacteria causing human infections. This burden is increasing over time and urgent action is required.[1,2] In a report commissioned by the UK Prime Minister, it was estimated that globally AMR could lead to 10 million excess deaths per year, and a cumulative cost of US$100 trillion by 2050.[3] The problem of AMR is much more pronounced in low-income countries with poor water quality and sanitation, uncontrolled use of antibiotics, inadequate infrastructure, and poor governance (i.e. corruption) all being important contributers.[4,5]

Although carriage of multidrug-resistant *Enterobacterales* (MRE) is much more prevalent in communities in low-income countries (mainly in South East Asia, Western Pacific, and Eastern Mediterranean regions),[6] high-income countries are not immune to this problem[7] (particularly in hospitals and long-term care facilities where there is high prevalence of MRE), and multi-resistant bacteria may also spread from country to country.[8] Global trade of food (including live animals) and international travel play major roles in the spread and transmission of resistant organisms.[9] The number of persons crossing international borders has continued to increase over many decades, which has provided an important opportunity for dissemination of MRE to other countries. Asymptomatic carriers can transport MRE between countries in their gut at alarming rates e.g., studies have found that 89% of travellers returning from India and Sri Lanka to the United Kingdom were MRE carriers.[10] These travellers, including medical tourists,[11] can transmit organisms to household contacts,[12,13] and may introduce the organism into the community,[14] healthcare facilities,[15] and the environment. Once established, these resistant organisms are extremely expensive and difficult to control.

In addition to the public health perspective of the risk of introduction of multidrug resistant pathogens, special clinical considerations should be taken with returning travellers

that are carriers of MRE. For example, studies have reported an association between international travel and extended-spectrum β-lactamase-producing (ESBL) *E. coli* bacteraemia post trans-rectal ultrasound guided prostate biopsy[16,17] raising the question of the role of screening and antibiotic prophylaxis in this group of patients.

In 2015, Hassing et al. conducted a systematic review that compiled the evidence of MRE detection among international travellers.[18] However, they did not quantitatively analyse the data. Additionally, since the publication of the systematic review, findings from the COMBAT study,[13] the largest study on MRE in travellers with over 2000 participants have been published. In this systematic review and meta-analysis, we update the evidence by including the most recent studies and quantifying the risk factors for MRE colonisation among international travellers.

Methods

The protocol was prospectively registered in PROSPERO (CRD42018076853) and the findings of this systematic review and meta-analysis are presented according to PRISMA reporting guidelines.[19]

Search strategy and selection criteria

The original search strategy was designed in PubMed and converted for use in Web of Science and Scopus. The search included all articles published from 2000 until February 2019, and the search was updated in July 2019. Search terms related to "travel", "*Enterobacteriaceae*", and "drug resistance" were included. To achieve a comprehensive evaluation of the published evidence, the systematic search was supplemented with a forwards and backwards citation search as well as retrieving the first 20 similar articles from PubMed

for each of the studies included from the initial search. In addition, all references from relevant previous systematic reviews were hand searched to identify possible missed studies.

Eligible studies were analytical epidemiological studies among international travellers that reported the rate or risk (and protective) factors (i.e. compared MRE carriers versus non-carriers) for MRE acquisition (e.g. due to contaminated food), colonisation (e.g. due to an underlying condition such as inflammatory bowel disease), or selection (due to use of antibiotics) on return, where data were available in an extractable format. Among the risk factors of interest were demographic characteristics, travel characteristics, past medical history, medication use and medical problems while overseas, food exposure, and reason for travel. Potential protective factors included vaccines, probiotics, and hand hygiene. MRE included ESBL, AmpC β-lactamase, or carbapenemase-producing *Enterobacterales*. For a study to be included, it must have reported the country/region of travel and screened all participants on return for MRE and not just targeting symptomatic participants (e.g. with diarrhoea or fever on return). Given that the aim of the review was to describe the current situation of MRE among international travellers, only studies containing data post-2000 were included.

Studies reporting MRE acquisition among military personnel, refugees and asylum seekers, adoptees, travellers seeking medical attention, international inpatient transfers, or during mass gatherings (e.g. Hajj, Olympic games) were not included as these travellers were considered at higher risk and not deemed representative of the average traveller. Exclusion criteria also included studies conducted on animals, in vitro studies, conference abstracts or proceedings, descriptive studies (e.g. case series), and ecological studies. No language restriction was imposed.

Study selection and data extraction

Titles and abstracts of all papers were extracted and uploaded to the Rayyan platform (http://rayyan.qcri.org/)[20] for screening. Two authors (LFK and JS) independently screened the titles and abstracts on the Rayyan platform. The same authors examined the full-text papers for eligibility in accordance with the review protocol. Any disagreements were resolved through consensus.

Data from the included studies were extracted and summarised in a spreadsheet, the recorded fields included 1) first author and year of publication; 2) country and study setting; 3) study population characteristics (e.g. mean/median age, proportion of females, number of travellers); 4) travel characteristics (e.g. travel destination, duration of travel); 5) rate of MRE detection (i.e. number of travellers that tested positive for MRE on return among the number of travellers that tested negative for MRE before travel); 6) risk (and protective) factors for MRE acquisition, colonisation, or selection; and 7) MRE isolate characteristics (e.g. type of bacteria and resistance genes). Adjusted effect estimates and 95% confidence intervals of the risk factors were extracted. If adjusted effect estimates were not available, unadjusted estimates were extracted or computed based on the sample size and number of events (i.e. MRE post-travel) in the exposed and unexposed groups.

Statistical analysis

Two effect measures of interest were examined, the proportion of MRE detected and the odds ratio (OR) for risk factors. Previous reviews[18,21,22] have reported large heterogeneity in the proportion of detection across studies, suggesting the absence of a common worldwide effect estimate for the proportion of MRE detection. Countries were grouped into geographical regions (i.e. South Asia, Asia [excluding countries in South Asia], Northern Africa, Sub-Saharan Africa, South and Central America, North America, Europe, and Oceania) as in a previous systematic review by Hassing et al.[18] The detailed list of countries per region can be

found in the supplementary material (S1). A meta-regression was fitted to examine if region of destination was a predictor for the observed heterogeneity. It was found that region of destination was the best predictor (accounted for over 45% of the observed variance) of MRE detection. Therefore, the proportions of MRE detection were pooled by the region of destination using the inverse variance heterogeneity (IVhet) model.[23] Adjusted and unadjusted (when adjusted were not available) estimates along with their 95% confidence intervals were pooled for the different risk factors using the IVhet model. The secondary objective of the systematic review was to describe the most common bacteria isolated from the travellers as well as report the distribution of resistance genes. Proportion meta-analysis using the IVhet model was applied to pool the data from the types of bacteria and resistance genes in travellers. Statistical heterogeneity was assessed using the I^2. Publication bias was assessed using the Doi plot and LFK index.[24] All the analyses were conducted in MetaXL version 5.3 (EpiGear Int Pty Ltd; Sunrise Beach; Australia; http://www.epigear.com).

Results

Studies identified

The search identified 725 publications, 177 articles remained after the title and abstract screening. Full-text review of 177 publications was conducted, and 28 met the eligibility criteria. It was noted that there was overlap in participants in five sets of publications. Four[13,25-27] and two[28,29] publications used data from the COMBAT and VOYAG-R studies, respectively. Three publications[30-32] reported results from a Finnish cohort of travellers, two publications[33,34] from a cohort of Australian healthcare volunteers, and two publications[35,36] from a cohort of Dutch travellers. Therefore, 20 datasets (from 28 publications) with 5253 travellers were included in this meta-analysis (S2).

Characteristics of the included studies

All the studies were conducted in Europe (The Netherlands,[12,13,35,37,38] Sweden,[39-42] Switzerland,[43,44] France,[28,45] Germany,[38,46] Finland,[30] United Kingdom,[10] and Denmark[47]) except for three that were conducted in Australia,[33] Japan,[48,49] and the USA.[49] The median age of the participants ranged from 25 to 66 years. Overall more females (n=3028, 57.6%) were included in the studies. The sample size ranged from 18 to 1847 participants. The median duration of travel ranged from 7 to 45 days, with 75% of the studies having a median duration of travel between 14 and 21 days. Thirteen studies collected stool samples,[10,13,28,30,35,38-40,42,43,46,48,49] five studies used rectal swabs,[12,33,41,44,45] and two studies use a combination of both types of samples.[37,47] Collection of the post-travel sample was done within one month after return in 70% of the studies. The majority of studies (n=19, 95%) used selective media for MRE detection that were mainly followed by genotyping confirmation, while one study only used meta-genomic approach for MRE detection[35] (Table 1).

Quantitative analysis

Proportion of MRE detection by region of destination

Overall, there was a wide variability in the proportion of MRE detected, ranging from 13% to 88% and considerable heterogeneity across studies was observed. Heterogeneity substantially decreased when estimates were pooled by regions. South Asia (58.7%, 95%CI 44.5-72.5%), Northern Africa (43.9%; 95%CI 37.6-50.3%), and Asia (37.5%; 95%CI 23.6-51.9%) were the travel destinations with the highest proportion of MRE detection. These regions were followed by Sub-Saharan Africa (21.8%; 95%CI 12.0-32.4%), South and Central America (18.3%; 95%CI 8.8-28.9%), and North America (16.9%; 95%CI 2.6-35%); while the lowest proportion of detection were observed in Europe (10.3%; 95%CI 5.5-16.1%) and Oceania (6.9%; 95%CI 0-21.1%) (Figure 1).

Risk factors

MRE detection was not associated with sex, age, or duration of travel, but it was dependent on the travel destination. In terms of past medical history, it was found that inflammatory bowel disease (OR 2.1; 95%CI 1.2-3.8) was a significant risk factor for MRE colonisation. While overseas, use of antibiotics (OR 2.4; 95%CI 1.9-3.0) was the strongest risk factor; antimalarial prophylaxis (OR 1.0; 95%CI 0.8-1.4) was not associated with MRE colonisation, but it should be noted that commonly used antimalarial medications include doxycycline (a broad spectrum antibiotic) as well as other medications (e.g. mefloquine, atovaquone/proguanil, chloroquine) that would not be expected to have an effect on selection of AMR *Enterobacterales*. Other factors associated with MRE colonisation were experiencing traveller's diarrhoea (OR 1.7; 95%CI 1.3-2.3) and having contact with the healthcare system either as inpatients or outpatients (OR 1.5; 95%CI 1.1-2.2). With regards to food exposure, having a vegetarian diet (OR 1.4; 95%CI 1.0-2.0) was found to increase the odds of acquiring MRE compared to other diets, and consuming only bottled water/beverages did not have an impact on MRE colonisation. Among the interventions that were examined for their potential impact in decreasing the risk of MRE colonisation, meticulous (as defined by primary study authors) hand hygiene and probiotics had no effect, while oral cholera vaccine (OR 1.6; 95%CI 1.0-2.5) was found to increase the odds of MRE colonisation, possible due to confounding by indication (see discussion). Backpacker travellers had a 50% (OR 1.5; 95%CI 1.2-1.8) increased odds of acquiring MRE compared to other types of travellers (Table 2).

Aetiology and resistance genes

Of the 2276 MRE isolates, the vast majority were *E. coli* (92.0%; 95%CI 84.9-97.3%) followed by *K. pneumoniae* (5.9%; 95%CI 1.2-11.8%). The remaining 2% of isolates included

Citrobacter spp. (*freundii* and *amalonaticus*), *Proteus* spp. (*vulgaris* and *mirabilis*), *Enterobacter cloacae, Enterococcus faecium*), *Acinetobacter baumannii*, *Morganella morganii,* and a case of non-Typhi *Salmonella enterica*.

bla$_{\text{CTX-M}}$ (92.3%; 95%CI 44.6-100%) was the most frequent resistance gene found in the MRE isolates. CTX-M group 1 was the most common followed by CTX-M groups 9 and 4. *bla*$_{\text{SHV}}$ and *bla*$_{\text{TEM}}$ were found in 3.0% (95%CI 0-2.0%) and 2.0% (95%CI 0-1.8%) of the isolates, respectively. *Enterobacterales* with carbapenem- (*bla*$_{\text{OXA}}$[28,37,45] and *bla*$_{\text{NDM}}$[28,44,45]) and colistin- (*mcr*[48]) resistance genes were also isolated. Fifty isolates with carbapenem-resistant genes were identified mainly from travellers returning from Southeast Asia and the Indian subcontinent,[28,37,44,45] while the three isolates with colistin-resistant genes were from travellers returning from Vietnam.[48]

Discussion

In this systematic review and meta-analysis, we compiled data from 20 different studies with over 5000 travellers to update the evidence on the proportion and risk factors for MRE detection in international travellers. The highest proportions of MRE detection were observed from travellers returning from South Asia, Northern Africa, Asia, Sub-Saharan Africa, and South and Central America; our findings correspond with the global epidemiology of AMR[4] and the ESBL producing *Enterobacterales* colonisation prevalence among healthy individuals.[50] In a meta-analysis by Karanika et el., international travellers were found to be four times more likely to be colonised by ESBL producing *Enterobacterales* than non-travellers.[50] These findings highlight the importance of international travel to low- and middle-income countries in the global spread of MRE.[51,52] In recent years, dissemination of emerging pathogens such as NDM-1 carbapenem-resistant *K. pneumoniae* from India[53] and mcr-1 colistin-resistant *E. coli* from China[54] were facilitated by international travel.[55,56] Of concern is

that our review revealed that carbapenem-[28,37,44,45] and colistin[48]-resistant *Enterobacterales* are being detected in international travellers. Investment in infrastructure to provide access to clean water, and adequate sanitation and hygiene may reduce transmission in low- and middle-income countries,[4] and possibly reduce the global spread of AMR.

Contact with the healthcare system, traveller's diarrhoea, and antibiotic use while travelling were strongly associated with MRE detection. The possibility that these factors are associated through reverse causality with MRE cannot be excluded (i.e. MRE infection leading to contact with the healthcare system, traveller's diarrhoea, and/or use of antibiotics). Even in the event the observed associations are due to reverse causality, these factors are markers for MRE detection and can be used to identify travellers at higher risk of being colonised by MRE. Among the risk factors identified, one that travellers have control over is antibiotic consumption, thus during pre-travel consultations, healthcare professionals need to emphasise the use of antibiotics only when is required.

Acute diarrhoea is the most common condition affecting travellers to South and Central Asia and the second most common among travellers worldwide.[57] Therefore, priority areas of research have been identified to generate evidence-based recommendations for preventing traveller's diarrhoea.[58] In line with the research priority areas, inflammatory bowel disease, a vegetarian diet, and backpacking were identified as host risk factors for MRE detection. Although it was not possible to examine the exposure to different classes and doses of antibiotics in the current review, findings by Ruppe et al.[28] indicate that use of different classes of antibiotics have distinct effects on the risk of MRE selection. They found that antibiotics used for malaria prophylaxis (i.e. doxycycline) did not to increase the risk of MRE selection (OR 0.9; 95%CI 0.6-1.6), while beta-lactams were associated with an increase in risk (OR 4.2; 95%CI 1.5-12.1).[28]

Non-antibiotic approaches to prevent MRE colonisation were also examined. Findings from the current review align with a recent randomised controlled trial that found that *Lactobacillus rhamnosus* GG did not reduce MRE colonisation in travellers.[59] The effect of oral cholera vaccine was also assessed, and paradoxically it was found that cholera vaccine was associated with an increase in the risk of MRE colonisation. Considering that the oral cholera vaccine provides some cross-protection against *enterotoxigenic E. coli*, one of the most common causes of traveller's diarrhoea, this association may seem contradictory. The most likely explanation for the observation is that unadjusted estimates were analysed and the result is affected by confounding by indication, i.e. travellers going to regions with higher risk of MRE are more likely to receive oral cholera vaccine. In our previous study of MRE detection in Australian travellers, those travelling to the Indian subcontinent were more likely to receive oral cholera vaccine than travellers going to other destinations; when the analysis was adjusted for travel destination and traveller's comorbidities, the point estimate indicated a protective effect of oral cholera vaccine against MRE colonisation.[60] To prevent confounding by indication, randomised controlled trials are needed to provide robust evidence on the effect of potentially protective interventions.

It is clear that international travellers are a high risk group; over 50% of travellers returning from South Asia are asymptomatic MRE carriers and there is increasing evidence of subsequent household transmission of MRE.[12,13] Cases of ESBL-producing *E. coli* bacteraemia have been reported after prostate biopsies[17] and international travel has been identified as the risk factor for fluoroquinolone-resistant and ESBL-producing *E. coli* infections.[16,61] Therefore, the role of screening and contact precaution of returned travellers from clinical and public health perspectives need to be further examined.[62] It is unfeasible to screen all returning travellers, but in a healthcare setting, it may be feasible to screen those who are planning to undergo higher risk medical procedures; although current evidence suggest that ESBL-

producing *E. coli* is less likely to spread between patients in hospitals than other *Enterobacterales* species.[63] Current studies on international patient transfers have shown that targeted screening programs of high-risk patients may be a more cost-effective strategy than mass screening[64] and contact precaution and environmental cleaning with chlorine-based disinfectant can prevent transmission.[65] Given that prolonged MRE carriage is uncommon, most travellers (~90%) are culture-negative within 6 months,[28,33,46] strategies should aim to reduce transmission and avoid elective surgical interventions within this period.

The findings of our systematic review and meta-analysis should be understood in light of some of the limitations. Estimates extracted and synthesized from observational studies included adjusted as well as unadjusted estimates, thus pooled estimates may be affected by confounding variables. This may be the case of potential protective interventions, where paradoxical findings were observed. To examine regional and within-country differences in MRE detection, as well as the risk of different antibiotic classes and doses, more granular data are required. Individual patient data meta-analysis may provide valuable information to answer these questions. The current review examined the risk factors relevant to average travellers from high-income countries, thus findings may not be applicable to special groups of travellers such as military personnel, refugees and asylum seekers, or hospital transfers as they may have different risk profiles. The median age of travellers in the included studies ranged from 25 to 66 years, so findings may not be generalizable to children. Some studies collected post-travel samples between 3 and 12 months post travel, thus we cannot rule out the possibility that the participants became colonised after their return.

In conclusion, international travel is an important driver for MRE spread worldwide. South Asia as a travel destination is a major risk factor for MRE acquisition. Additional risk factors for individuals to become colonised, include inflammatory bowel disease, use of antibiotics, traveller's diarrhoea, contact with the healthcare system, having a vegetarian diet,

and backpacking. Future research needs to identify effective interventions to reduce the risk of MRE colonisation and design strategies to reduce local transmission on return, including transmission to household and community members, as well as wider dissemination into the environment and animal populations

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Conflicts of interest

The authors do not have any conflicts of interest to declare.

Authors' contribution

Conception and design of the study: LFK, DJM, CLL

Collection and assembly of the data: LFK, JS

Analysis and interpretation: LFK, LY, DJM, CLL

Manuscript writing: All authors

Final approval of manuscript: All authors

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Table 1. Characteristics of the included studies

First author, year of publication	Country	Study period	Study population	Mean/median age (in years)	Proportion of females (%)	Sample size	Type of sample	Collection of sample post-travel	Laboratory detection method	Most common travel destinations	Mean/median duration of travel (in days)	Proportion of MRE detection (%)
Angelin 2015[42]	Sweden	2010-2014	Healthcare students travelling for clinical courses	25	78	99	Stool sample	1-2 weeks after return	Selective media	89% South East Asia and Africa	45	35
Arcilla 2017[13]	The Netherlands	2012-2013	Patients attending travel clinics	51	54	1847	Stool sample	Immediately after return	Selective media + microarray genotyping	82% Asia and Africa	20	34
Bernasconi 2016[43]	Switzerland	2015	People living in Switzerland	44	68	38	Stool sample	Within 1 week after return	Selective media + microarray genotyping	India	18	76
Bevan 2018[10]	UK	NR	Healthy volunteers	30	NR	18	Stool sample	NR	Selective media + PCR genotyping + whole genome sequencing	India and Sri Lanka	21	89
Kantele 2015[30]	Finland	2009-2010	Patients attending a travel clinic	40	61	430	Stool sample	First or second stool after return	Selective media + PCR genotyping	83% Asian and Africa	19	21
Kennedy 2010[33]	Australia	2008-2009	Hospital staff and contacts	45	62	102	Rectal swab	Within 2 weeks after return	Selective media + PCR genotyping	77% South East Asia and Europe	21	49
Kuenzli 2014[44]	Switzerland	2012-2013	Patients attending travel clinics	41	56	170	Rectal swab	Directly after return	Selective media + microarray and PCR/DNA sequence genotyping	India, Bhutan, Nepal, and Sri Lanka	18	69
Lausch 2013[47]	Denmark	2011	Inpatients with travel history in the last 3 months	37	57	88	Rectal swab and stool sample (if patient had diarrhoea)	Up to 3 months after return	Selective media	52% Asia and Africa	NR	13
Lubbert 2015[46]	Germany	2013-2014	Patients attending a travel clinic	34	57	191	Stool sample	Within 1 week after return	Selective media + PCR genotyping	88% Asia and Africa	21	30
Macaux 2018[45]	France	2014-2016	Inpatients with travel history in the last 12 months	62	34	138	Rectal swab	Up to 12 months after return	Selective media	83% Asia, Sub-Saharan Africa, and the Mediterranean	NR	NA
Nakayama 2018[48]	Japan	2015-2016	Japanese travellers to Vietnam	37	42	19	Stool sample	Within 3 weeks after return	Selective media + PCR genotyping	Vietnam	7	88
Ostholm-Balkhed 2013[39]	Sweden	2008-2009	Patients attending vacation clinics	54	59	226	Stool sample	Up to 4 months after return	Selective media + PCR genotyping	57% Sub-Saharan Africa and Asia	16	30

Paltansing 2013[12]	The Netherlands	2011	Patients attending a travel clinic	33	63	338	Rectal swabs	Immediately after return	Selective media + microarray genotyping	49% South East Asia and Central Africa	21	33
Reuland 2016[37]	The Netherlands	2012-2013	Patients attending a vacation clinic	33	58	418	Rectal swab or stool sample	Within 2 weeks after return	Selective media + microarray genotyping	Africa, Asia, and Latin America	14	23
Ruppe 2015[28]	France	2012-2013	Patients attending international vaccination centres	36	61	574	Stool sample	Within 1 week after return	Selective media + PCR genotyping	Sub-Saharan Africa, Asia, and Latin America	20	50
Schaumburg 2019[38]	Germany and The Netherlands	2016-2018	Patients attending vaccination centres	32	59	132	Stool sample	Within 1 week after return	Selective media + molecular assay	68% Asia and Africa	18	46
Tangden 2010[40]	Sweden	2007-2009	Patients attending travel clinics	43	55	100	Stool sample	NR	Selective media + PCR genotyping	65% Africa and Asia	14	24
Vading 2016[41]	Sweden	2013-2015	Patients attending a travel clinic	49	68	175	Rectal swab	NR	Selective media + PCR genotyping	South East Asia, India, Northern Africa and Turkey	14	38
von Wintersdorff 2014[35]	The Netherlands	2010-2012	Patients attending travel clinics	43	58	122	Stool sample	Immediately after return	Meta-genomic	48% South East Asia and India	21	32
Weisenberg 2012[49]	USA	2009-2010	Patients attending a travel clinic	66	68	28	Stool sample	Within 1 week after return	Selective media + PCR genotyping	54% Sub-Saharan Africa and South Asia	16	25

NR not reported; *NA* not applicable, the study was a matched case-control

Table 2. Risk factors for acquisition of multidrug-resistant *Enterobacterales*

	OR (95% CI)	I^2 (%)	Number of studies with adjusted estimates/ Total number of studies
Demographic			
Sex (female)	0.91 (0.80-1.03)	0	2 / 14
Age (per 10 year increase)	1.01 (0.97-1.06)	0	2 / 5
Travel associated data			
Duration of travel (per week increase)	1.02 (0.99-1.06)	0	1 / 5
Travel destination (reference Europe)*	1	NA	0 / 10
South Asia	**1.52 (1.31-1.76)**		0 / 19
Northern Africa	**1.33 (1.25-1.43)**		0 / 11
Asia	**1.26 (1.17-1.35)**		0 / 16
Sub-Saharan Africa	1.12 (0.99-1.28)		0 / 15
Americas	**1.11 (1.02-1.20)**		0 / 16
Past medical history			
Inflammatory bowel disease	**2.09 (1.16-3.77)**	0	1 / 3
Chronic disease	1.01 (0.65-1.57)	57	2 / 5
Admitted to a hospital in the previous 3-6 months	1.79 (0.09-36.63)	68	1 / 2
Antibiotic use in the previous 3-12 months	1.00 (0.76-1.32)	12	3 / 4
Medical history while overseas			
Antibiotic use	**2.38 (1.88-3.00)**	0	4 / 12
Anti-acid use	1.08 (0.59-1.97)	25	0 / 5
Antimalarial prophylaxis	1.04 (0.75-1.44)	10	0 / 3
Travellers' diarrhoea	**1.69 (1.25-2.30)**	46	5 / 13
Contact with healthcare system	**1.53 (1.09-2.15)**	20	1 / 10
Food exposure			
Vegetarian diet	**1.41 (1.01-1.96)**	0	0 / 5
Only consume bottled water/beverages	1.29 (0.50-3.34)	77	1 / 6
Protective factors			
Oral cholera vaccine	**1.61 (1.04-2.50)**	0	0 / 2
Meticulous hand hygiene	1.10 (0.81-1.49)	0	1 / 4
Probiotics	1.06 (0.78-1.45)	0	0 / 2
Type of traveller			
Backpackers	**1.46 (1.20-1.78)**	0	2 / 7
Holiday makers	0.99 (0.70-1.38)	0	0 / 4
Visiting friends and relatives	0.95 (0.55-1.63)	29	0 / 5
Business travellers	0.78 (0.46-1.30)	0	0 / 4

OR odds ratio; *CI* confidence interval; *NA* not applicable

* OR obtained through meta-regression. Americas include North, Central, and South America. Oceania was excluded from the analysis because too few studies (3) reported data for this region.

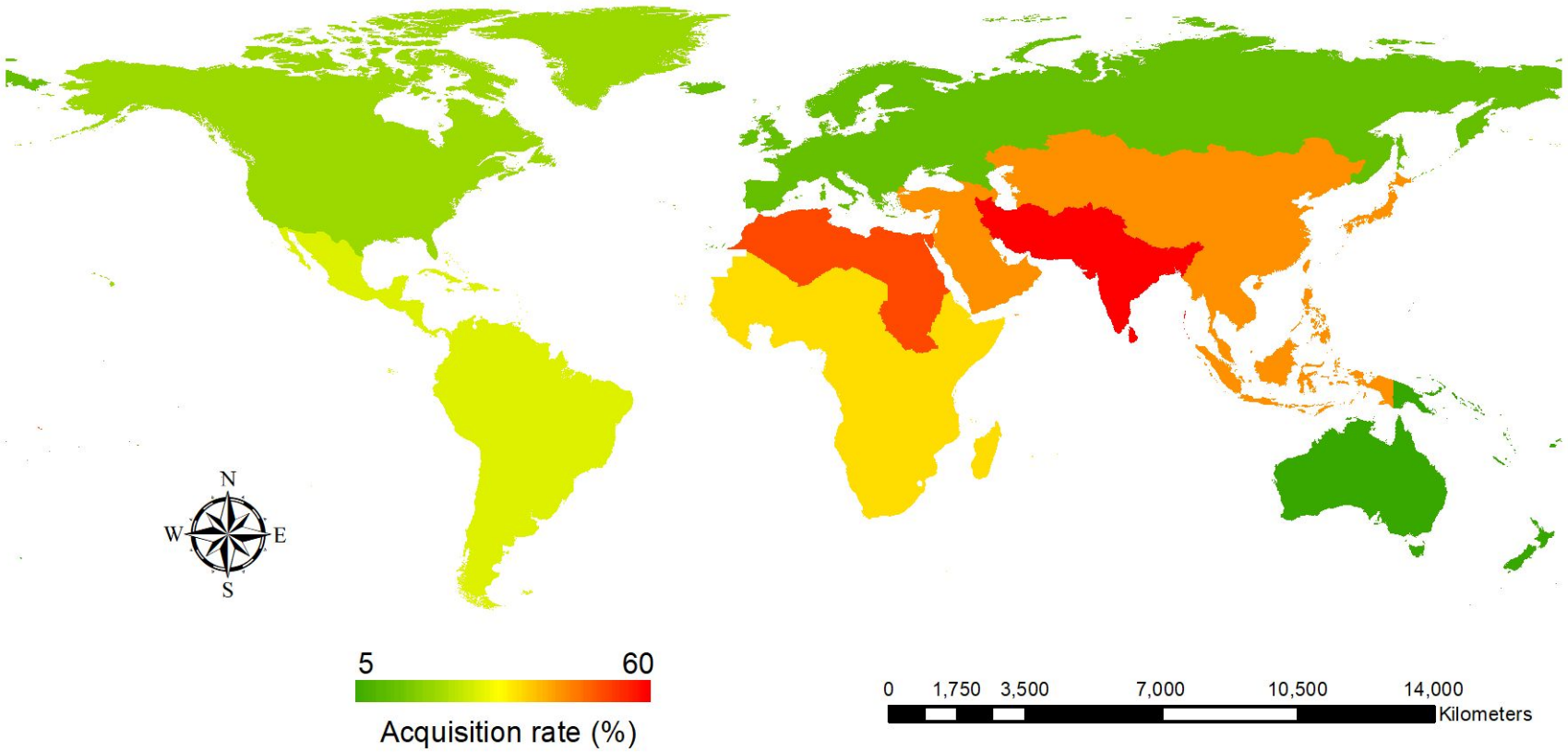


Figure 1. Proportion of acquisition of multidrug-resistant *Enterobacterales* by region of destination

Supplementary material

S1. Countries by region

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

Asia (without South 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, Vietnam, Yemen.

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

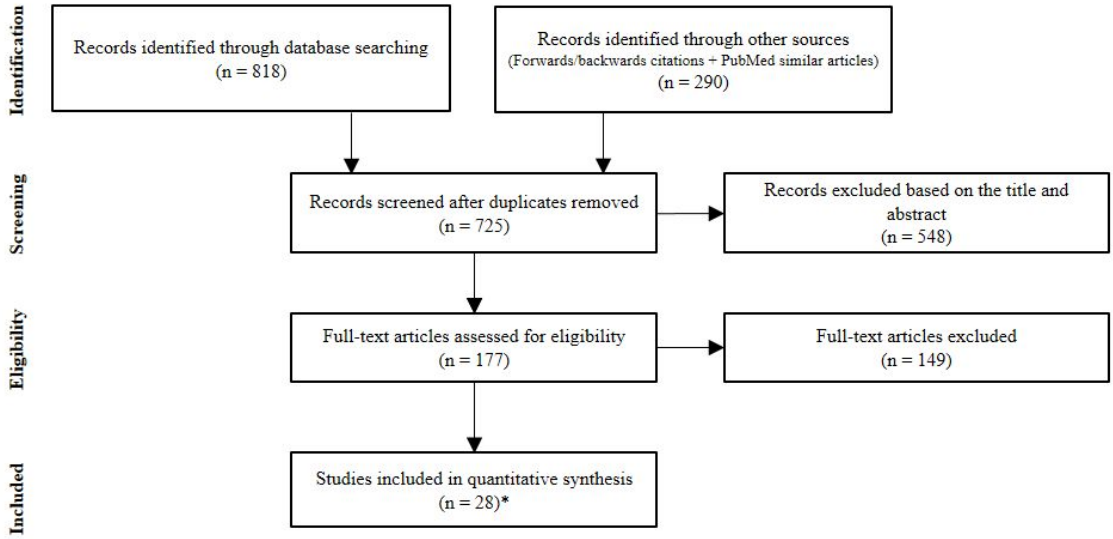
Sub-Saharan Africa: Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo (Brazzaville), Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Reunion, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Swaziland, Tanzania, The Gambia, Togo, Uganda, Zambia, Zimbabwe.

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, Curacao, Dominica, 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-Barthelemy, 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: Aland 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, Slovakia, Slovenia, Spain, Svalbard and Jan Mayen, Sweden, Switzerland, Ukraine, United Kingdom.

Oceania: American Samoa, Australia, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia, Nauru, New Caledonia, New Zealand, Niue, Norfolk Island, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn Islands, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna.



S2. PRISMA flow diagram for the selection of studies

*28 studies comprising 20 datasets