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TROPICAL, TRAVEL, AND EMERGING INFECTIONS (L CHEN AND A BOGGILD, SECTION EDITORS)

Travel and the Spread of Drug-Resistant Bacteria

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Abstract

Purpose of Review The rise in antimicrobial resistance is an urgent public health threat which, in the absence of intervention, may result in a post-antibiotic era limiting the effectiveness of antibiotics to treat both common and serious infections. Globalization and human migration have profoundly contributed to the spread of drug-resistant bacteria. In this review, we summarize the recent literature on the importance of travelers in the spread of drug-resistant bacterial organisms. Our goal was to describe the importance of travel on a variety of clinically relevant drug-resistant bacterial organisms including extended-spectrum β-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, *Salmonella* species, as well as other enteric infections.

Recent Findings Travelers from high income countries, visiting low and middle income countries, frequently acquire drug-resistant bacteria, particularly extended-spectrum β-lactamase-producing Enterobacteriaceae. The highest risk is associated with travel to the Indian subcontinent. Multidrug-resistant enteric infections in travelers from *Salmonella* spp., *Campylobacter* spp., and *Shigella* spp. are increasing. Refugees, pilgrimages, and medical tourists are associated with considerable risk of multiple forms of drug resistance.

Summary This review highlights the importance of antimicrobial stewardship, infection control, and surveillance; particularly in low and middle income countries. International leadership with global coordination is vital in the battle against antimicrobial resistance.

Keywords Travel · Migration · Antimicrobial stewardship · Antimicrobial resistance · Public health

Introduction

The emergence of drug-resistant bacteria poses a major threat to global public health. On September 21, 2016, the United Nations convened a general assembly for member states to coordinate a strategy to curb the spread of drug-resistant bacteria. This representing only the fourth time in history the United Nations has met for a health issue. It was recognized that "antimicrobial resistance threatens the achievement of the Sustainable Development Goals and requires a global response" [1]. According to a report commissioned by the UK, in the absence of intervention, in the year 2050, annual deaths attributable to drug-resistant infections are estimated to be 10 million, surpassing cancer and motor vehicle collisions combined. The estimated global economic losses as a result of antimicrobial resistance are estimated to be $100 trillion USD [2•].

Our objective was to review and summarize the recent literature on the importance of travel to the spread of drug-resistant bacteria (Table 1). For the purpose of this review, travel was defined as movement of persons from low and middle income countries in Asia, Africa, and South America, to high income countries in Europe plus the USA, Canada, Australia, and New Zealand.

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Table 1 Summary table on travel and the spread of drug-resistant bacteria

Travel-associated bacteria	Highlights from summary of recent literature
Extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae	There is a global trend of rising ESBL Enterobacteriaceae. Over 60% of travelers to the Indian subcontinent return colonized with an ESBL organism
Carbapenem-pesistant Enterobacteriaceae (CRE)	The importance of travel to CRE varies by resistance mechanism. Approximately 0.4% of travelers to the Indian subcontinent return colonized with a CRE
Methicillin-resistant *Staphylococcus aureus* (MRSA)	MRSA acquisition is relatively less common; detected in 0.006% of travelers to Africa and the Middle East
Salmonella typhi and *paratyphi*	Approximately 80% of enteric fever cases from the Indian subcontinent have reduced susceptibility to ciprofloxacin
Nontyphoidal *Salmonella enterica*	Approximately 60% of travel-associated cases have reduced susceptibility to ciprofloxacin as well as a rising trend in ceftriaxone nonsusceptible strains
Campylobacter spp.	Approximately 60% of travel-associated cases are ciprofloxacin-resistant
Shigella spp.	Approximately 90% of isolates from India had reduced ciprofloxacin susceptibility

Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae

For purposes of this review, we classified bacteria as extended-spectrum β-lactamase (ESBL) if described by the authors as either containing a known ESBL resistance mechanism or third-generation cephalosporin resistance phenotype. The first study to prospectively evaluate travel as a risk factor for acquisition of ESBL-producing Enterobacteriaceae was by Tangden et al. in 2010. This study enrolled 100 ESBL negative Swedish participants prior to international travel. Upon return to Sweden, 24 were colonized with an ESBL-producing *Escherichia coli*, with stark differences based on country of travel. India and other parts of Asia were associated with the greatest risk of colonization [3].

The risk of ESBL colonization varies by location of travel. The greatest risk is seen in travelers to the Indian subcontinent with an average 64% becoming colonized. The risk was 50% from other parts of Asia, 36% from the Middle East, 34% from Africa, and 19% from South and Central America (Fig. 1) [4, 5••, 6, 7•, 9–26]. Other important risk factors include development of traveler's diarrhea (TD) [4, 5••, 6, 7•, 10, 11] and receipt of antibiotics while traveling [5••, 6, 7•, 22]. The effect sizes of these risk factors were consistently associated with a two to four times increased odds of ESBL colonization in returning travelers. This finding was confirmed in the largest study to date, performed with 1847 Dutch travelers [5••]. The colonization rate was 34% (95% CI 32–37%), with the highest risk in travelers from Southern Asia (75%, 95% CI 68–81%). The risk factors in this study were antibiotic use during travel (adjusted OR 2.7, 95% CI 1.9–4.1), TD (2.3, 1.4–3.8), and pre-existing chronic bowel disease (2.1, 1.1–3.9).

Kantele et al. identified a 70% risk of ESBL colonization with the combination of antibiotics and loperamide. They propose that by slowing intestinal transit time with loperamide, contact time between antibiotics and intestinal microbiota is increased resulting in greater selection pressure for resistance. However, the risk with the combination of antibiotics and loperamide in this study was not statistically significantly greater than antibiotics alone in persons with TD [7•].

A systematic review in 2016 synthesizing the literature on ESBL fecal colonization pooled 66 studies on 28,909 healthy individuals. The global ESBL colonization rate was 14%, ranging from 2% in the Americas to 46% in Asia and Africa. The most significant risk factors were international travel (RR = 4.1, 95% CI 1.33–12.41) and antibiotic use in the previous 4–12 months (RR = 1.58, 95% CI 1.16–2.16). This study looked at the trend in global ESBL colonization rates over a 20-year period and estimated an annual increase of 5.4% ($R^2 = 12.2$, $p = 0.003$) [27•].

A number of studies have evaluated the duration of colonization following travel. Approximately 75% of travelers colonized with ESBL organisms after returning from travel will be negative by 6 months [9–11, 14, 18]. In the largest study of travel-associated ESBL acquisition, the median colonization time was 30 days [5••]. Colonization with ESBL *Klebsiella pneumonia* and travel to western Asia were associated with the shortest colonization times. Travelers colonized with CTX-M group 9 ESBL had the longest colonization times. Overall 11% remained colonized at 12 months, suggesting vigilance for drug-resistant colonization is required for at least 1-year post-travel. This study also screened household contacts of travelers and identified a 12% risk of spreading the drug-resistant organism, highlighting the importance of questions regarding travel of household contacts when assessing a patient, particularly in those who are higher risk based on age or immune status [5••].

Studies from Denmark, Sweden, Australia, and the USA have identified travel as a significant risk factor for urinary tract infections from ESBL-producing Enterobacteriaceae [28–31]. A study evaluating infective complications post-transrectal prostate biopsies found a bacteremia rate of 5%.

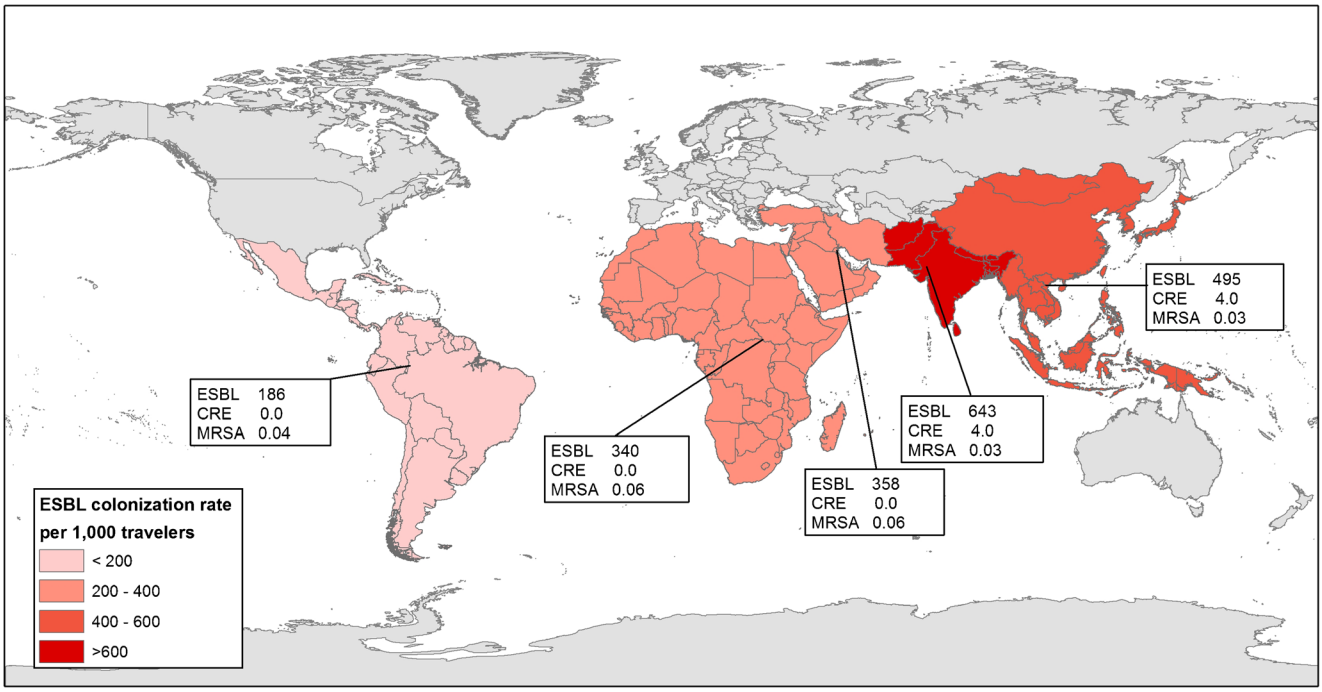

Fig. 1 The number of drug-resistant organisms detected per 1000 healthy travelers. The risk of travelers returning with a drug-resistant bacterial organism varies by region visited and type of organism. The highest risk has been observed in travelers from the Indian subcontinent. ESBL = extended-spectrum beta-lactamase; CRE = carbapenem-resistant Enterobacteriaceae; MRSA = methicillin-resistant *Staphylococcus aureus*. Data for figure based on weighted average of published studies [3, 4, 5••, 6, 7•, 8–17]

Risk factors for ESBL-associated bacteremia included travel within 4 weeks of the procedure (RR = 2.7, 95% CI 1.0–7.1) [32]. A matched case-control study of US children with ESBL infections also identified international travel in the previous 6 months as a significant risk factor (OR = 8.9, 95% CI 2.9–27.8) [33].

The body of literature surrounding the importance of travel to ESBL acquisition is robust with three important take home points:

1. Patients should be counselled regarding the risk of ESBL colonization during pre-travel assessments. This is important information for travelers when evaluating the risks associated with potential itineraries [34–36].
2. The risks of ESBL colonization should be considered when prescribing antibiotics for TD. Recent guidelines on the treatment of TD encourage supportive care only for mild TD. Furthermore, antibiotic prophylaxis for TD should be discouraged in average risk travelers to minimize the risk of acquiring and spreading drug-resistant bacteria [37•].
3. Clinicians should be cognisant of patient's travel history within the last 12 months when treating a bacterial infection commonly caused by Enterobacteriaceae, particularly in travelers from the Indian subcontinent and consider coverage for presumed ESBL-producing Enterobacteriaceae in patients with severe invasive disease.

Carbapenem-Resistant Enterobacteriaceae

Carbapenem-resistant Enterobacteriaceae (CRE) have been steadily increasing globally. In Europe, 6% of all *K. pneumoniae* bloodstream infections are carbapenem-resistant. There is substantial variability with rates of < 1% for most European countries, compared to two-thirds of the isolates from Greece [38]. CRE bloodstream infections are associated with a high mortality of 40–70%, partially attributable to suboptimal therapeutic options [38–40].

There are three epidemiologically relevant carbapenemases, which confer carbapenem resistance: class A *K. pneumonia* carbapenemases (KPCs), class B metallo-β-lactamases (MBLs) including New Delhi MBL (NDM-1), and class D β-lactamases including oxacillinases (OXA-48). KPCs are the most common CRE in North America and tend to spread clonally within healthcare facilities. NDM-1 is thought to have originated in the Indian subcontinent and tends to spread between bacterial species on a transposon [41]. NDM-1 is widely spread in hospital and community settings in areas with limitations in sanitation and hygiene. OXA-48 is primarily a plasmid-based resistance gene that was originally identified in the Mediterranean region with sporadic cases reported globally [40].

The first reported case of NDM-1 was isolated from the urine of a hospitalized patient in Sweden following transfer from a New Delhi hospital in 2007 [41]. Retrospective

analyses identified NDM-1s in India from 2006 but virtually nonexistent from other parts of the world until 2009. Over the last decade, NDM-1 has been reported in multiple bacterial species from all continents [42].

Travel, and medical care while traveling, has been strongly linked to CRE risk. A cohort study from Canada identified 261 CRE isolates from 238 patients representing a 5-year incidence of 0.07/1000 admissions. KPCs comprised 65% of the identified resistance mechanisms. For patients where travel history was available, 24% had recent travel and most (87%) sought medical care while abroad. Notably, 55% of all cases were associated with nosocomial transmission [43]. A study from the UK summarized 250 patients with NDM-1; of those with a travel history available, 52% had traveled to the Indian subcontinent, 7% had traveled elsewhere, and 41% had no travel history. While most CRE isolates are from hospitalized patients, 12% from this cohort were from primary care [44]. Among 2001 travelers returning to the Netherlands, only 5 (0.2%) had a CRE organisms detected upon returning [16]. CRE colonization is largely limited to travelers from Asia and is much less common than ESBLs (Fig. 1).

Colistin is increasingly being used as a last resort antibiotic in the treatment of CRE. However, a mobile, plasmid-associated resistance element, MCR-1, has recently been described [45]. A Dutch study identified this resistance mechanism in 5% of travelers after returning from Asia and Africa suggesting this resistance mechanism is already widespread [46].

The global spread of CRE is a major public health concern. While travel is clearly playing an important role in the international spread of CRE, it is likely that local efforts in the countries of origin including strengthening infection prevention and control, as well as antimicrobial stewardship, are necessary to minimize the spread of these extensively resistant organisms.

Methicillin-Resistant *Staphylococcus aureus*

S. aureus bacteremia, including methicillin-resistant *S. aureus* (MRSA), is one of the most common healthcare-associated infections. Individuals born in the USA may be at higher risk for MRSA skin and soft tissue infections (SSTI) than those born outside of the USA [47]. However, travelers who return with SSTI are more likely to have both multidrug-resistant *S. aureus* and Panton-Valentine leukocidin positive (PVL+) virulence gene detected [48, 49]. International travel has been implicated as the origin in both patients and hospital staff. This was highlighted by a neonatal intensive care unit outbreak in the UK of PVL+ MRSA infections traced back to a nurse who brought this clone from the Philippines [50].

The evidence for spread of the virulent PVL+ MRSA clones has been previously summarized. Five major routes of intercontinental exchange were observed including the USA300 (ST8) clone that spread from the USA to Europe, USA400 (ST1) clone that spread from the USA to Europe and Asia, the USA1000 (ST59) clone that spread from the USA to Asia, the ST80 clone spread from Europe to Asia, and finally the ST30 clone spread from Oceania to Europe [51]. The overall risk of acquiring MRSA is 5.8 cases per 1,000,000 travelers, with a range of 0.1 per 1,000,000 travelers from Nordic countries to 60 per 1,000,000 travelers from Africa and the Middle East [52].

International travel has been important for the global spread of MRSA clones. However, compared to drug-resistant Enterobacteriaceae, the risk to individual travelers is substantially lower (Fig. 1).

Drug-Resistant Enteric Infections

Enteric Fever

Enteric fever is a systemic febrile illness caused by *Salmonella enterica* subsp. *enterica* serovar Typhi (typhoid fever) and *S. enterica* subsp. *enterica* serovar Paratyphi A, B, or C (paratyphoid fever). Humans are the only reservoir for *S. typhi* and *S. paratyphi*, which are spread via the fecal-oral route. Few bacterial infections cause a significant global morbidity and mortality as does enteric fever. The WHO estimates there are approximately 21 million incident cases of enteric fever per year and 222,000 deaths [53].

Increasing global resistance in *S. typhi* and *S. paratyphi* has been well described [54] and is now reflected in isolates in travelers who return to high income countries following travel to low and middle income countries. Multidrug-resistant (MDR) typhoid is defined as infection with *S. typhi* that is resistant to early first line recommended drugs including chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMX), and ampicillin. More recently, resistance to naladixic acid and decreased sensitivity to ciprofloxacin (NAL-R/DSC) has been described. Unsurprisingly, these resistant organisms have been imported into higher income countries.

Between 2008 and 2012, there were 2341 enteric fever cases (80% typhoid and 20% paratyphoid A) reported to the USA CDC National Typhoid and Paratyphoid Fever Surveillance system and the National Antibiotic Resistance Monitoring System (NARMS) [55•]. Most of these cases (86% typhoid and 92% paratyphoid) were associated with travel to south Asia. NAL-R/DSC was particularly common in cases originating in South Asia. Notably, 53% of cases from Pakistan were NAL-R/DSC and MDR. None of the cases were resistant to azithromycin or ceftriaxone (though one case exhibited decreased sensitivity). Similar patterns of imported

enteric fever antibiotic resistance have been reported from Canada [56], Spain [57], and Switzerland [58].

A large study of enteric fever in London, UK from 2005 to 2012 examined 496 isolates of *S. typhi* and 382 isolates of paratyphoid A with known travel abroad for trends in antimicrobial resistance [59•]. This study found increasing resistance over time to naladixic acid and ciprofloxacin (80% of *S. typhi* and 88% of *S. paratyphi* A were ciprofloxacin resistance). A bivariate analysis of *S. typhi* isolates found that travel to Pakistan (OR 5.11, 95% CI 3.19–8.21) or Bangladesh (OR 3.82, 95% CI 2.34–6.22) was associated with multidrug and ciprofloxacin resistance. Notably, this study did not find any resistance to ceftriaxone. Although no clinical breakpoints are available to define azithromycin sensitivity, ≤ 16 μg/mL is generally considered to be wild-type organism that is responsive to treatment. A study from the Netherlands found azithromycin MICs > 16 μL/mL in 16.1% of travel-related *S. typhi* and S. *paratyphi* isolates [60].

Nontyphoidal *Salmonella*

There are over 2500 serovars of nontyphoidal *S. enterica*, many of which are major causes of human foodborne illness and that can cause gastrointestinal or invasive disease. Resistance to quinolones, ESBLs, and CREs has been described in travelers who have acquired disease abroad.

The CDC NARMS routinely collects nontyphoidal isolates of *Salmonella* and other enteric pathogens and tests for antimicrobial sensitivity. Through linkage with FoodNet, a multi-organization US-based collaboration, which conducts active surveillance for laboratory confirmed pathogens transmitted through food, 368 isolates of *S. enterica* serovar Enteritidis with a known travel history were identified between 2004 and 2010. The proportion of isolates from patients with recent international travel among those with naladixic acid resistance was significantly higher than those without travel (64 vs 17%, $p < 0.05$). The Dominican Republic and Mexico were the most common countries associated with naladixic acid resistance [61].

A large scale study from the UK screened over 31,000 isolates of *S. enteritidis* collected between 2005 and 2010. A plasmid containing gene that confers resistance to multiple antibiotics including ampicillin, chloramphenicol, streptomycin, sulfonamides, tetracycline, and trimethoprim was identified from 11 isolates, most from African travelers [62].

In part because of increasing resistance to other agents, third-generation cephalosporins have been increasingly used to treat invasive infections or severe diarrhea from *Salmonella* spp. However, there have been increasing reports of ESBL and AmpC beta-lactamase-producing *Salmonella* spp. in returned travelers. Between 1993 and 2011, over 43,000 *S. enterica* isolates were sent to the National Salmonella Reference Centre in Finland and 225 (0.5%) were found to be cefotaxime nonsusceptible and there was a significant increasing trend in the proportion of nonsusceptible isolates in more recent years [63]. From 2006 to 2011, most ESBL positive isolates came from Southeast Asia, 61% were in those with a recent travel history to Thailand, and most were *S. enterica* serovar Typhimurium.

More recently, there have been reports of carbapenemase-producing *S. enterica* isolates. A French study identified a *S. enterica* serotype Kentucky strain producing carbapenemase OXA-48 in a traveler returning from Egypt [64]. A UK study described a *S. enterica* serovar Senftenberg strain with NDM-1 [65]. The overlapping areas of circulation of different *S. enterica* serovars circulating in the same areas as plasmid-borne carbapenemases, these mechanisms of resistance will probably become more common in *Salmonella* species in the future.

Campylobacter spp.

Campylobacter jejuni and *C. coli* are common causes of diarrhea in travelers. A US study from FoodNet and NARMS found that 18% of isolates from patients with known travel status had a recent history of international travel. Quinolone and macrolide resistance were both more common in patients with a history of international travel than in those with no travel (61 vs 14% for quinolones and 4 vs 1% for macrolides, respectively). While most of the travel was to Latin America, rates of quinolone and macrolide resistance were both highest with travel to Asia [66]. A Belgian study of 261 isolates obtained between 2007 and 2014 found high levels of ciprofloxacin resistance in travelers to all regions (overall resistance rate 61%) with the highest being in those with travel to South America (80%) and South Asia (76%) [67]. Resistance to macrolides was much lower (5% overall) but again relatively higher in travel to South Asia (15% resistance). The high rates of ciprofloxacin resistance among *Campylobacter* spp. isolates suggest that this antibiotic is suboptimal for treatment of severe travelers' diarrhea.

Shigellosis

Shigellosis is an enteric bacterial infection caused by *Shigella* spp. (most commonly *Shigella sonnei*). Shigellosis is most often associated with travel and has demonstrated increasing antimicrobial resistance [68]. A FoodNet NARMS collaborative study between 2000 and 2010 in the USA found that persons reporting a history of international travel in the 7 days prior to specimen collection were more likely to have strains resistance to TMP-SMX (75 vs 39%, $P < 0.0001$) and also more likely to have MDR strains [69]. In a Pennsylvania study, of 102 isolates from travelers, 81 (79%) were resistant to multiple antibiotics compared to 52% from domestically acquired *Shigella* infections. Fluoroquinolone resistance was

also more common in travelers (28 vs 4%) [70]. India has also been identified as the major risk factor for acquisition of ciprofloxacin resistant *Shigella* among European [71] and Australian travelers, with 90% of isolates of Indian origin having reduced susceptibility to ciprofloxacin [72].

Special Populations

Refugees

It is estimated that over 65 million people have been forced from their homes and that there are over 22 million refugees, more than half of whom are children [73]. Nearly half of all refugees come from just two countries, Syria (5.5 million) and Afghanistan (2.5 million). Of the high income countries included in this review, it is the European countries that make up the top hosting countries for these refugees.

It is not a surprise that refugees are at relatively high risk for colonization with, and disease from, resistant organisms. Recent papers from various European countries have documented this in different populations. Three German studies show increased rates of drug-resistant organisms in adults, children, and pregnant women, respectively. A study of hospitalized adults in Frankfurt performed rectal and nasal swabs on 143 refugee and 1489 nonrefugee patients [74]. The positive rates for MDR gram negative bacilli (61%) and ESBL *E. coli* (34%) were all more common in refugee patients. Over half of the refugees in this study were from Syria, and more than 20% were from each of Afghanistan and Iraq. A similar German study in children found 34% of the children screened positive for MDR organisms. The majority (84%) of the resistant organisms identified were ESBL or MDR gram negatives, 16% were MRSA, and 0.7% VRE [75]. Finally, a hospital-based case-control study from Munster, Germany, compared colonization rates with antibiotic-resistant organisms between 50 pregnant refugee women and 50 pregnant nonrefugee controls [76]. The countries of origin of the refugees in this study were similar with 70% coming from the Middle East. MRSA colonization was higher in the refugee group (6 vs 0% in control group, $p < 0.001$). Taken as a whole, the German literature suggests that resistance rates are higher among refugee populations of all types, particularly those from the Syria and Afghanistan.

Hospitalized Abroad

Travelers may receive medical care and be hospitalized abroad for several reasons. While some contact with the medical system in foreign countries is unplanned and/or emergent, medical tourism, in which patients travel abroad specifically to receive care that may be less expensive, unavailable, or have a long wait time at home, is increasing. Patients hospitalized abroad who return to the health care system in their home countries are now recognized as being at increased risk for colonization with antibiotic-resistant organisms. In a French study, patients admitted to the ICU who had been hospitalized abroad, and received antibiotic treatment, were at greatly increased risk of being colonized with MDR bacteria (OR 10.7, 95% CI 4.2–27.3) compared to those without foreign hospitalization [77]. In this study, nearly 90% of the foreign hospitalizations occurred in Madagascar, Comoros, or Mauritius. Another French study [78] identified longer foreign hospital stays, and hospitalization in a high risk unit, as independent risk factors for colonization with MDR bacteria. A Finnish study found that hospitalization abroad in a lower income country is higher risk for importation of MDR organisms than is hospitalization in a higher income country [79]. This study compared travelers to temperate zones (North America, Europe, and Oceania) to those who traveled to tropical and subtropical zones as surrogates for higher and lower income countries, respectively. This study found that the risk for MRSA (55.2% vs 16.8, $p < 0.001$), ESBL (12.4 vs 0.4%, $p < 0.001$), and CRE (3.2 vs 0.4%, $p < 0.001$) were all more common in those hospitalized in the tropics and subtropics. MDR colonization rates were highest in those returning from South Asia (78%), Latin American (60%), Africa (60%), and Southeast Asia (53%). A study of ICU patients transferred from hospitals abroad to Switzerland suggests that colonization with resistant bacteria is not only common but importantly can lead to worse health outcomes [80]. In this study, being colonized with a MDR organism was associated with an increase length of ICU stay (8 vs 3.5 days, $p = 0.001$) and a higher risk of death (OR 5.2, 95% CI 1.3–20.2).

Mass Gatherings

There are several recurring annual gatherings, often related to religion or athletics, to which large numbers of people travel from all parts of the world. Such large gatherings have been the site of infectious disease outbreaks and the transmission of resistant bacteria that may then be imported back to home countries. The annual Hajj pilgrimage in Saudi Arabia is one of the largest mass human gatherings with an estimated two to three million people travelling to Mecca each year. Several recent French studies are representative of this risk. A cohort of 129 pilgrims travelling to Mecca with a single French travel agency were screened pre- and post-travel with rectal swabs for resistant bacteria and found an increase post-travel in ESBL-producing *E. coli* (14% colonized post-travel vs 4% before, $p = 0.008$) [81]. In the same cohort, CTX-M genes were found in the stool of 33% of Hajj pilgrims post-return vs 10% before departure ($p < 0.001$). Risk factors for acquisition of CTX-M genes include being of Moroccan origin, using beta-lactam antibiotics, and shortness of breath or diarrhea [82]. The same group also found six samples positive for

third-generation cephalosporin-resistant *S. enterica* [83]. Perhaps of even more concern, a study of pilgrims from France to the 2014 Hajj found 42 isolates of *Acinetobacter baumannii* in pharyngeal and rectal swabs taken during and after travel compared to none before, with 32% of the samples harboring the OXA-51 carbapenemase gene [84].

Conclusion

Globalization and the rise in international travel have contributed to the spread of antimicrobial resistance from low and middle income to high income nations. This is particularly apparent for bacterial organisms spread via a fecal-oral route, such as drug-resistant Enterobacteriaceae. Future research should focus on strategies to reduce transmission of these organisms; including optimal management of traveler's diarrhea and identifying and reducing high risk behaviors while traveling. Global efforts to improve antimicrobial stewardship efforts, infection control practices, and antimicrobial resistance surveillance, particularly in low and middle income countries, are urgently needed. This body of evidence highlights the importance of international leadership and coordination to effectively combat the rise of antimicrobial resistance.

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Compliance with Ethical Standards

Conflict of Interest Kevin Schwartz and Shaun Morris declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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