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Review

Review

Global geographic trends in antimicrobial resistance: the role of international travel

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Abstract

Background: Rising antimicrobial resistance (AMR) is a threat to modern medicine, and increasing international mobility facilitates the spread of AMR. Infections with resistant organisms have higher morbidity and mortality, are costlier to treat, result in longer hospital stays and place a greater burden on health systems than infections caused by susceptible organisms. Here we review the role of travel in the international dissemination of AMR and consider actions at the levels of travelers, travel medicine practitioners and policymakers that would mitigate this threat.

Results: Resistant pathogens do not recognize international borders; travelers to areas with high AMR prevalence are likely to be exposed to resistant bacteria and return to their home countries colonized. Medical tourists go between health facilities with drastically different rates of AMR, potentially transmitting highly resistant strains. Drug-resistant bacteria have been found in every continent; however, differences between countries in the prevalence of AMR depend on multiple factors. These include levels of antibiotic consumption (including inappropriate use), access to clean water, adequate sanitation, vaccination coverage, the availability of quality healthcare and access to high-quality medical products.

Conclusions: Travelers to areas with high levels of AMR should have vaccines up to date, be aware of ways of treating and preventing travelers' diarrhea (other than antibiotic use) and be informed on safe sexual practices. The healthcare systems of low- and middle-income countries require investment to reduce the transmission of resistant strains by improving access to clean water, sanitation facilities and vaccines. Efforts are needed to curb inappropriate antibiotic use worldwide. In addition, more surveillance is needed to understand the role of the movement of humans, livestock and food products in resistance transmission. The travel medicine community has a key role to play in advocating for the recognition of AMR as a priority on the international health agenda.

Key policy recommendations: AMR is a threat to modern medicine, and international travel plays a key role in the spread of highly resistant strains. It is essential that this is addressed at multiple levels. Individual travelers can reduce antibiotic consumption and the likelihood of infection. Travelers should have up-to-date vaccines and be informed on methods of preventing and treating travelers' diarrhea, other than use of antibiotics and on safe sexual practices, such as condom use. Healthcare facilities need to be aware of the travel history of patients to provide appropriate treatment to those who are at high risk of exposure and to prevent further spread. Internationally, in countries without reliable and universal access to clean water, sanitation and hygiene, investment is needed to reduce the emergence and spread of resistance and ensure the antimicrobials available are of assured quality. High-income countries must ensure their use of antimicrobials is appropriate to reduce selection for AMR. Surveillance across all countries is needed to monitor and respond to this emerging threat.

Key words: antimicrobial resistance, medical tourism, travel, NDM, ESBL

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Introduction

Antimicrobial resistance (AMR) is a problem of increasing international concern. AMR is the ability of microbes to withstand the effects of the antimicrobial therapies that were previously effective in treating infections caused by such microbes. Drug-resistant pathogens have been found in humans and animals on all seven continents,[1] in the Arctic[2] and even on the international space station.[3] However, the prevalence of drug-resistant pathogens varies greatly across regions (Figure 1). Initiatives, such as ResistanceMap (resistancemap.org), have documented the geographic trends in AMR for several years, and more recently the World Health Organization's (WHO) Global Antimicrobial Resistance Surveillance System (GLASS) has begun to gather country-reported data using a standardized approach. In high-income countries, high levels of per capita antimicrobial consumption since the 1950s have driven the selection of resistant bacteria,[4] and recent initiatives to curb antimicrobial use have had limited impact on consumption.[5,6] In middle-income countries, which are rapidly converging to consumption levels found in high-income countries,[7] poor sanitation, a continued high background burden of bacterial infections and the increasing use of antibiotics have facilitated the rapid growth and spread of AMR.[8,9]

Recent analyses suggest that international mobility[10,11] and socio-economic standards[12] may play a greater role than previously understood in explaining the geographic trends in AMR, compared to national antimicrobial use levels. Antibiotic exposure may provide the selection pressure for the creation of resistant mutants but the movement of people, lack of access to clean water, poor hygiene, vaccine availability and healthcare facilities promote their broader dissemination.[12,13] Travelers to endemic areas are at risk of exposure to resistant pathogens and are likely to return colonized.[14] Human travelers are only one part of the mass global movement of live carriers capable of acting as vectors for resistant bacteria; wild animals, including migratory birds,[15,16] have also been implicated,[17] in addition to livestock animals,[18,19] fish and shrimp.[20–22] Legally and illegally imported meat can also carry drug-resistant organisms across international borders.[23,24]

For some countries, travel-associated infections with drug-resistant bacteria may represent a substantial fraction of the national AMR burden associated with foodborne pathogens. These are of particular interest as they colonize the human gut for extended periods of time[25] and transfer genes carrying drug resistance into the host microflora.[26] This has important public health and economic consequences. For example, in Norway, 65% of diarrhea cases were contracted abroad,[27] and in the USA, the cost of a single carbapenem-resistant *Enterobacteriaceae* (CRE) infection has been estimated at up to USD $66 031.[28] Such high costs have the potential to have a destabilizing impact on resources of healthcare systems worldwide.[29] We will focus on pathogens and/or particular strains that have a history of clinical failure due to their multidrug-resistant status. Here we summarize recent evidence on the international distribution and mobility of the common foodborne pathogens: *Campylobacter* and *Salmonella*. Then we look into the importance of intestinal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E). We then consider the role of travel in the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE) (Table 1). While MRSA and some VRE tend to be clonally spread, with genetically highly similar strains capable of rapidly propagating, a further risk is that a mobilized resistance gene may be brought by a traveler. This might begin in one bacterial host but rapidly spread via pathogenic or non-pathogenic bacteria that are highly virulent or adapted to the hospital environment. We discuss this in relation to the spread of New Delhi Metallo-β-lactamase (NDM)-1 and of colistin resistance via mobile colistin resistance (*mcr*) genes.

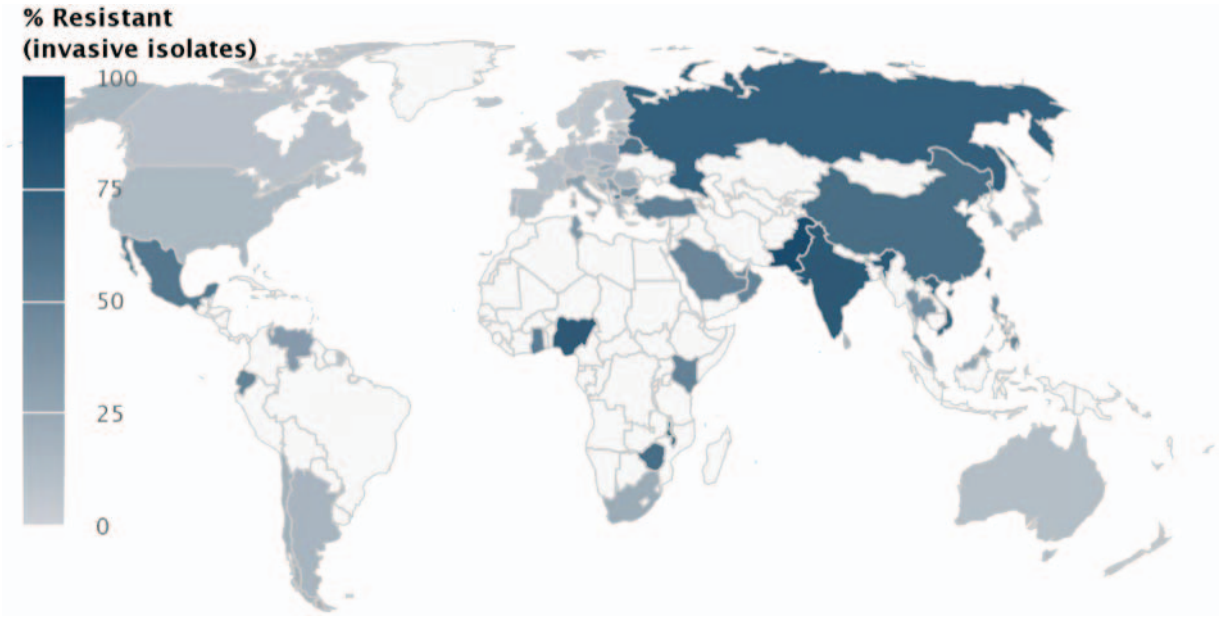

Figure 1. Resistance of *E. coli* to third generation cephalosporins (Center for Disease Dynamics, Economics & Policy, resistancemap.org).[158]

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Table 1. Summary table of the main pathogens

Pathogen	
Campylobacter	• Infections with *Campylobacter* spp. are a leading cause of diarrheal disease (109 700 deaths worldwide in 2010[30]). • Drug-resistant *Campylobacter* infections affect short-term leisure and business travelers[37,38] and military personnel.[39] • In the USA, UK, Switzerland and Canada, data have shown *Campylobacter* infections acquired abroad are more likely to be drug resistant.[33,40–42]
Salmonella	• Invasive non-typhoidal *Salmonella* caused 59 066 deaths in 2017.[43] • Drug resistance in many countries is increasing.[45–48] • Multidrug-resistant typhoid has been reported in travelers returning from the Indian subcontinent to Germany,[58] Japan[59] and the UK.[54]
ESBL-E	• ESBL-E are increasing worldwide,[62] and prevalence of infections is 25–50% in some tropical and subtropical regions, while baseline carriage in the healthy population is 20–40%.[65,67,71] • ESBL-E colonization is highest in visitors returning from high prevalence areas including the Indian subcontinent (29–88%), China and Southeast Asia (18–67%), Middle East (13–52%), Northern Africa (0–57%) and Central and South America (0–49%).[14,62,75] • Travelers have a 12% chance of transmitting an ESBL-E to colonize another household member on return from international travel.[76]
USA300 MRSA	• USA300 MRSA emerged in 1999[91] and by 2017, had spread across North America, South America, Asia, the Middle East, Europe and Africa.[100–108] • The international spread of MRSA strain USA300 was often associated with travel to the USA.[104,107,109,110]
VRE	• Ten years on from the first discovery of VRE in Europe over 25% of enterococci associated with bloodstream infections were VRE in US hospitals.[119] • Medical tourism may have contributed to the global spread of VRE, for example, in Singapore.[115,120] • VRE imported by four patients into a large Australian teaching hospital cost USD $1.5 million to eradicate; however, VRE is estimated to cost up to USD $27 000 per episode.[121]

The role of travel in the spread of drug-resistant organisms

Campylobacter

In 2010, infections with *Campylobacter* spp. were a leading cause of diarrheal diseases and were associated with 109 700 deaths.[30] In North America, Europe and Australia, there is a substantial increase in gastroenteritis caused by *Campylobacter*. This genus may also be frequently reported (in more than 1% of gastroenteritis) in parts of Africa, the Middle East and Asia, though data from these regions are limited.[31] The prevalence of drug resistance in *Campylobacter* has also increased across high- and low-income countries during recent decades.[32] In the USA, resistance to ciprofloxacin increased from 22.1% of *Campylobacter* cases, in the period 2004–2010, to 25.3%, in the period 2011–2012.[33] In the UK, ciprofloxacin-resistant *Campylobacter* increased from 7% to 38% of clinical isolates between 1995 and 2008[34] and, in China, from 50% (in 1994–1996) to 93.1% (in 2009–2010).[35] This trend is particularly worrying given that ciprofloxacin is commonly recommended as the first empirical treatment for diarrhea.[32] In humans, the epidemiology of multidrug-resistant *Campylobacter* is less documented or considered less important than that of *Salmonella*. For example, *Campylobacter* is not currently included in WHO's GLASS.

Campylobacter infections are common among international travelers. In Sweden, the highest infection rates were associated with visitors to the Indian subcontinent.[36] Infections with drug-resistant *Campylobacter* not only affect short-term leisure and business travelers[37,38] but also military personnel who are exposed to local food sources on a long range through long-term consumption of local food sources (Figure 2). One-third of diarrhea cases among US military personnel in Thailand were caused by *Campylobacter* species that were resistant to ampicillin and trimethoprim-sulfamethoxazole.[39] In the USA, 62.4% of *Campylobacter* infections acquired abroad were resistant to ciprofloxacin compared to 14.4% of domestic cases between 2004 and 2012.[33] *Campylobacter* infections in the UK were five times as likely to have been acquired abroad than domestically.[40] In Switzerland, 56.0% of travel-associated *Campylobacter* cases were quinolone-resistant compared to 39.4% of domestic cases.[41] In Montreal, Canada, 5.4% of *Campylobacter jejuni* isolates acquired abroad, between 2002 and 2013, were resistant to erythromycin, tetracycline and ciprofloxacin, whereas none of the domestic isolates showed resistance to these drugs.[42]

Salmonella

In 2017, invasive non-typhoidal *Salmonella* caused 59 066 deaths.[43] International travel has been identified as a risk factor for *Salmonella* acquisition.[44] Over the past few decades, the prevalence of antibiotic resistant salmonella has increased in several regions where surveillance is conducted, including Australia,[45] the USA[46] and the European Union.[47,48] As in the case of *Campylobacter*, recent reports have indicated that a large number of cases of salmonellosis were resistant to first-line treatment, such as ampicillin, and are increasingly resistant to fluoroquinolones.[49,50] Resistance to ciprofloxacin has been reported in multiple countries, principally originating from South Asia, including India, Pakistan and Vietnam.[49] It has been suggested that these increases are associated with the widespread use of antibiotics for prophylaxis, growth promotion and treatment in animals, as well as the use of counterfeit and substandard optimal drugs.[51]

Global travel has been shown to play a key role in the dissemination of antibiotic resistant *Salmonella*. Sequencing

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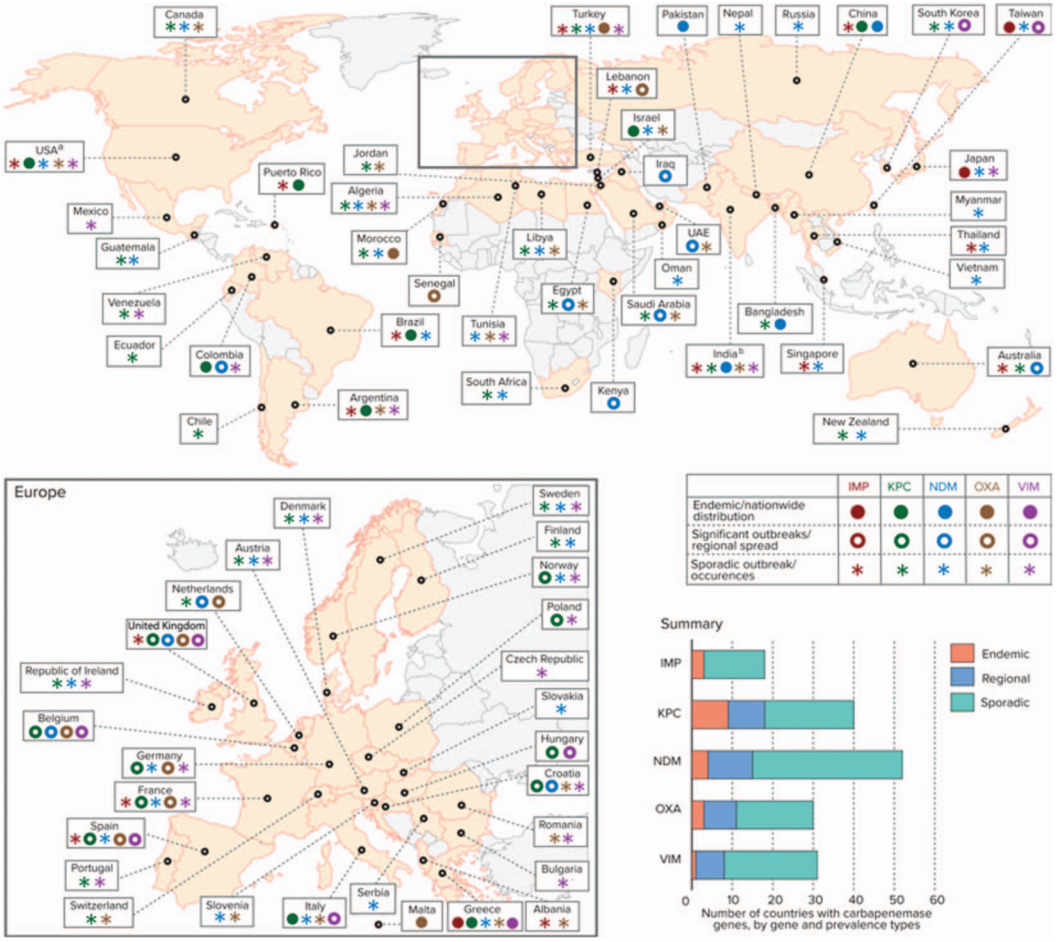

Figure 2. Global distribution of carbapenemase-producing *Enterobacteriaceae*, including NDM.[159] Other carbapenemase producers shown are *K. pneumoniae* carbapenemase (KPC), active on imipenem metallo-β-lactamase (IMP), OXA (referring to OXA-48, except in India, where it refers to OXA-181) and Verona integron-encoded metallo-β-lactamase (VIM)

of toilet waste from 18 international airplanes arriving in Copenhagen airport showed a flux of *Salmonella enterica*, and resistance genes of critical importance, such as $bla_{\text{CTX-M}}$ (an ESBL), which came predominantly from South Asia,[52] whereas other pathogens, such as *Clostridium difficile*, came primarily from the USA. As previously noted, the mass global movement of military personnel can also spread resistance genes. The overwhelming majority (94.6%) of isolates of non-typhoidal *Salmonella* from US military personnel travelling to Thailand between 1988 and 2013 had acquired resistance to one or more antimicrobials.[53]

Typhoidal *Salmonella* is also increasingly resistant to antibiotic treatment. In the UK, more than 90% of enteric fever cases are acquired abroad, the majority occurring in travelers returning from Pakistan, India and Bangladesh.[54] In travelers returning to London with enteric fever, 88% of *Salmonella* Paratyphi A isolates were resistant to ciprofloxacin, and almost 80% of *Salmonella* Typhi isolates were resistant to ciprofloxacin, 26% to ampicillin, 27% to chloramphenicol, 28% to trimethoprim and 28% to sulphonamides.[55] In this case, ciprofloxacin resistant *S.* Paratyphi A was associated with travel to India and Bangladesh but not to Africa. H58 *Salmonella* Typhi is multidrug-resistant and appears to be replacing sensitive strains as the dominant strain.[56] Genomic analysis suggests H58 originated in Asia and has travelled to Africa on multiple occasions.[57] In December 2017, a traveler returning from Pakistan to the UK was diagnosed with a bloodstream infection caused by H58 *S.* Typhi resistant to ceftriaxone, ceftazidime, ciprofloxacin and co-trimoxazole, prompting authorities to issue a public health resistance alert (PHRA).[54] PHRAs are used to inform microbiologists in the UK of emerging antimicrobial-resistant bacteria that could spread in the UK health service. A similar multidrug-resistant typhoid case was reported in a German traveler returning from India in the same year.[58] A Japanese traveler also returning from India carried a highly resistant strain of *S.* Paratyphi in 2013.[59] Cephalosporin resistance has also been reported in the Middle East and the Congo.[60,61]

ESBL-E

ESBL-E are increasing worldwide.[62] In contrast to many multidrug-resistant organisms (MDROs), for which expansion has occurred predominantly in hospitals, ESBL-E are often observed in community-acquired infections and in the intestine of healthy volunteers.[63–66] CTX-M-producing *Escherichia coli*

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are the most common ESBL-E and one of the key contributors to the expansion of these resistant strains in terms of both geography and host species.[67–70] The prevalence of ESBL-E infections has reached 25–50% in some tropical and subtropical regions, and baseline carriage in the healthy population is 20–40%, rendering these regions endemic for ESBL-E.[65,67,71] Poor hygiene and the overuse of antibiotics contribute to these high rates of carriage.[65] Given that these regions are tourism hotspots, travelers visiting ESBL-E areas are at risk of acquiring these bacteria and subsequently disseminating them in their country of origin upon return.[62]

Multiple ESBL-E colonization studies indicate that travel is a risk factor for developing an MDRO infection.[72–74] As one might expect, the prevalence of ESBL-E colonization was the highest in visitors returning from high prevalence areas including the Indian subcontinent (29–88%), China and Southeast Asia (18–67%), Middle East (13–52%), Northern Africa (0–57%) and Central and South America (0–49%), whereas the risk of colonization is lower in developed countries.[14,62,75] In another study, 75.1% of visitors to Southern Asia, 40–50% of those to central, eastern, or western Asia and northern Africa and 44.4% of those to Uganda acquired ESBL-E while travelling.[76] The acquisition rate being highest in India, at 88.6%. Aside from destination, other factors associated with ESBL-E acquisition include antibiotic consumption, traveler's diarrhea or other abdominal complaints, contact with orphan children, staying in rural areas and consumption of street food.[76–79] The food chain has been identified as a likely source of ESBL-E as molecular typing studies have identified ESBL-E to be closely genetically related to strains associated with food and the environment.[80–86]

Despite high colonization rates, the duration is often limited to the first 3 months after return from travel.[76,77] However, persistent colonization of up to 12 months has been observed in some cases.[76,77,80,84] Factors associated with persistence are not fully understood, but travel to Asia and a higher relative abundance of ESBL-E are associated with prolonged periods of carriage.[77] Colonization by multiple ESBL-E—polyclonal colonization—has been demonstrated in travelers returning from Asia.[68,77,80,84,86–88] Whether polyclonal colonization is due to a higher abundance of ESBL-E or due to a single dominant strain is unknown. Polyclonal colonization may increase the chance of resistance genes being transferred to other residents of the gut or increase the likelihood of acquiring a strain with characteristics that allow them to persist in the intestine for long periods of time.[77,80] Certain molecular features have been identified in connection with prolonged carriage; CTX-M-Group 9 is one example of this.[76]

One study noted a 12% chance of transmitting an ESBL-E that colonizes another household member after a return from international travel.[76] Follow-up studies indicate that the overall risk of developing an ESBL-E infection is low among those colonized,[77,78,89] and this decreases over time. Nonetheless, it is notable that individuals with an ESBL-E infection have a higher mortality rate in the intensive care unit, and patients colonized with EBSL-E have longer lengths of stay, highlighting the importance of these pathognes.[90] As the number of tourists to countries with ESBL-E endemic areas increases, travel is likely to facilitate the expansion and dissemination of these MDROs worldwide.

MRSA strain USA300

MRSA strain USA300 was first identified among prisoners in the US state of Mississippi in 1999 for causing skin and soft tissue infections.[91] Between 2000 and 2003, infections and outbreaks caused by MRSA strain USA300 occurred among athletes in Pennsylvania, Indiana and California and among prisoners in Georgia, California and Texas.[92,93] By 2011, strain USA300 had emerged as the leading cause of both community-acquired and hospital-acquired MRSA infections nationwide.[94–97] MRSA strain USA300 has been associated with increased in-hospital mortality, though, in some cases, with significantly lower mortality risk compared to other common MRSA strains.[98,99] By 2017, USA300 had been documented across North America, South America, Asia, the Middle East, Europe and Africa.[100–108]

The intercontinental spread of MRSA strain USA300 and other MRSA strains has been associated with international travel, migration, medical tourism and repatriation and transmission via water-related and sporting events.[107] In many cases, the international spread of MRSA strain USA300 was associated with travel to the USA. The first case of MRSA USA300 in Japan occurred in a 3-month-old girl who was born in a California hospital before moving to Tokyo.[104] In 2008, three family members traveled from Japan to Hawaii where one became infected with MRSA strain USA300; seven additional family members were subsequently infected.[109] Additionally, MRSA USA300 infections associated with travelers from the USA, or with travel to the USA, have also been reported in France, Germany, Ireland, Switzerland, Iraq and South Korea.[107,110] In Canada, Venezuela, Colombia and Ecuador, USA300 has become an endemic pathogen and the dominant MRSA strain.[107]

In other countries, MRSA strain USA300 prevalence remains low despite multiple introductions of the bacteria through international travel. In Switzerland, France and the UK, there were multiple instances of MRSA USA300 importation from the USA between 2011 and 2013, which went on to cause small, isolated clusters of infections but no further geographic spread.[111,112] It remains unclear as to why MRSA USA300 has failed to achieve widespread transmission in these countries. It has been suggested that this strain is in decline[113] and that the global burden of MRSA is decreasing.[114]

VRE

Vancomycin has been in use since the 1940s[115]; however, VRE were not reported in the UK and France until the late 1980s.[116] The emergence of vancomycin resistance has been associated with the extensive use of vancomycin to treat MRSA and *C. difficile* infections and resulted in the acquisition and spread of *van* genes in the genus *Enterococcus*. The emergence of VRE has also been associated with the use of avoparcin, an antibiotic that is structurally similar to vancomycin, in animals. However, the role this has played in the expansion of VRE in human populations is unclear. Reliable therapies for VRE were extremely limited until quinupristin-dalfopristin and linezolid became available in the early 2000s.[116,117] Emerging resistance is already rendering these treatments ineffective; in India, 2% of VRE isolates in one medical college were resistant to linezolid.[118] The spread of VRE is an example of how rapidly resistance can spread if not effectively contained. Ten years after VRE was first

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identified in Europe more than 25% of enterococci associated with bloodstream infections were VRE in US hospitals.[119]

Most hospital-derived strains of VRE found in Europe, the USA, South America and Asia are part of a single clonal lineage,[119] suggesting importation and spread through transfer of humans, livestock and animal products. There are two predominant genes carried by strains of VRE—*vanA* and *vanB*—both of which may be horizontally acquired. In the VRE strain circulating in Australia and Singapore *vanA* is dominant, and *vanB* is dominant in the VRE strain circulating in Europe, the USA and Korea.[115] In Singapore evidence suggests VRE strains causing early outbreaks were imported. The first case of VRE in Singapore occurred in 2004 in a patient from Indonesia and a subsequent case in 2005 occurred in a patient who had first been hospitalized in India.[115] It has been suggested, as Singapore has no significant agriculture, that VRE strains may have been imported by medical tourists, both those seeking care from abroad and Singaporeans travelling to other countries for care.[120] In Western Australia, VRE imported by four patients into one large teaching hospital cost USD $1.5 million to eradicate; however, this is in contrast to VRE attributable mortality that has been estimated to be as high as 37% with a cost per episode of up to USD $27 000.[121]

Movement of mobile genetic elements

Increasing long-distance travel and the increasing popularity of undertaking medical procedures abroad have increased the risk of highly resistant genes being transferred across borders.[122] The mobilization of resistance genes onto mobile genetic elements facilitates the speed of dissemination of these genes. The arrival of a new genetic element that is highly transmissible may give rise to multiple highly resistant organisms or combine with other resistant elements to form a multidrug-resistant pathogen. Colistin resistance, in the form of the *mcr-1* gene, has now been identified on plasmids alongside multiple other high-level resistance genes including ESBLs and carbapenemases.[123] New host pathogens may already be highly adapted to clinical and community environments, and resistance that is acquired in this way may incur low or insignificant fitness costs or have mechanisms of being maintained by bacteria.[124,125] This may make it more difficult to contain than resistance that arises via *de novo* mutations within a pathogen. Here we outline the worldwide spread of some of the most successful mobile resistance genes in recent years, NDM-1 and *mcr-1*.

NDM-1

NDM-1 is an enzyme that confers a high level of resistance to multiple antibiotics, including penicillins, cephalosporins and carbapenems, though susceptibility remains to aztreonam.[11,126] This is of particular concern as there are few treatment options beyond the carbapenems for infections caused by multidrug-resistant Gram-negative bacteria. Furthermore, NDM-1 has proved to be highly transmissible and capable of rapid dissemination. Of the NDM-1-producing *Enterobacteriaceae*, *Klebsiella pneumoniae* and *E. coli* are the most common; however, NDM-1 has also been described in *Klebsiella oxytoca*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus mirabilis*, *Salmonella* spp. and *Providencia* spp. NDM-1 has also been described outside of the *Enterobacteriaceae* in *Acinetobacter* spp. and *Pseudomonas aeruginosa*.[11]

At the beginning of the global outbreak, infections with NDM-1 producers were associated with previous hospitalization in the Indian subcontinent. NDM-1 was first isolated from a urinary tract infection (UTI) caused by *K. pneumoniae* in a Swedish traveler who had returned after treatment in India in 2007.[127] In the UK, between 2008 and 2009, of 29 patients with NDM-1-producing infections, 17 patients had a history of travel to India or Pakistan in the previous year. Fifteen of these patients had either travelled for cosmetic surgery or renal or bone marrow transplantation or had been hospitalized due to dialysis, stroke, chronic obstructive pulmonary disease, pregnancy, burns or traffic accidents.[128] Kumarasamy *et al*. were unable to prove the origin of British isolates despite comparison with sequences from across India; however, plasmids carrying $bla_{\text{NDM-1}}$ were readily transferable and prone to rearrangement, capable of losing or occasionally gaining DNA on transfer. This makes $bla_{\text{NDM-1}}$ not only able to rapidly spread but its plasticity may facilitate adaptation to new hosts. A subsequent analysis of 250 isolates from the UK, obtained between 2008 and 2013, found 52% of those for whom travel history was available had travelled to, or been hospitalized in, the Indian subcontinent.[129]

NDM-1-producing *Enterobacteriaceae* were subsequently isolated from a patient with a UTI returning to Canada who had been hospitalized in India.[130] This isolate belonged to the same sequence type as an isolate reported in Australia originating in a patient previously hospitalized in Bangladesh. Of 77 cases reported in 13 countries across Europe between 2008 and 2010, 31 had travelled, or had been hospitalized, in India or Pakistan and 5 had been hospitalized in the Balkan region.[131] A total of 13 of the 77 cases were associated with subsequent transmission within hospitals. It has been speculated that the Balkan region may serve as a secondary reservoir for NDM-1; however, strains in this region have also been attributed to patients travelling from the Balkans to Pakistan for kidney transplants.[132] By early 2010 isolates carrying NDM-1 had been isolated in three different US states,[133] and by the end of 2011, the presence of NDM-1 had been documented throughout all regions of the world except Latin America and Antarctica.[122] In 2013 evidence of the first NDM-1 isolate was published in Colombia and has rapidly spread throughout the region[134] (Figure 2).

Beyond nosocomial spread and risk factors associated with medical tourism, travelers may return from countries with a high prevalence of NDM-1, colonized with producing strains, without having ever been in contact with healthcare facilities.[132] Two backpackers returning from India to the Netherlands subsequently contracted NDM-1-producing infections despite not using medical facilities during their trip.[135] The spread of NDM-1 has been associated with the prevailing direction of people migrating between countries.[11]

mcr-1

Colistin resistance is of concern as this is a drug of last resort to which organisms that are highly resistant to other antibiotic classes are often susceptible.[136] It is one of the few drugs available still effective against some CRE, including NDM-1 producers.[123]

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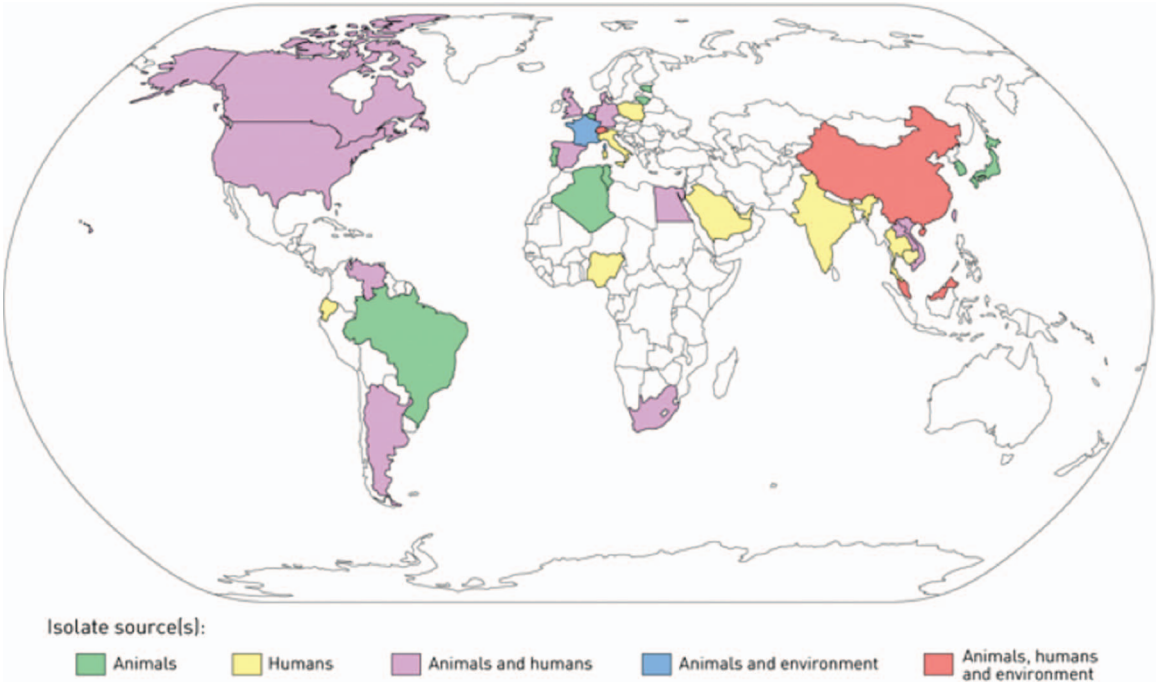

Figure 3. Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*, figure produced by Center for Disease Dynamics, Economics & Policy using data from Al-tawfiq *et al.*[136]

Hence, the recent emergence of the *mcr* gene, *mcr-1*, may herald the arrival of truly pan-resistant strains against which no antibiotic treatment is effective.

mcr-1 carriage was first detected in *E. coli* in a 2016 Chinese study that isolated *mcr-1* in 15% of 523 samples of raw meat and 21% of 804 animals during 2011–14, and, perhaps most worryingly, 1% of 1322 samples from inpatients with infections.[26] The *mcr-1* gene originates from an initial mobilization event in the 2000s, which is likely to have occurred on Chinese pig farms where colistin was commonly used to promote growth.[123] Once mobilized in this way, *mcr-1* was able to spread both horizontally between bacterial species and geographically between continents (Figure 3), facilitated by the transportation of food animals and meat products.[18,137]

The movement of both colonized and infected humans has also played a role in the spread of colistin resistance. Bacteria carrying *mcr-1* are capable of colonizing humans without prior exposure to colistin, including healthy volunteers.[138] The *mcr-1* gene was isolated in *E. coli* from six Dutch travelers returning to the Netherlands between November 2012 and November 2013. Two of whom had visited Peru and Bolivia, two had visited China, one had visited Tunisia and one had visited Thailand, Vietnam, Laos and Cambodia.[139] Even more worryingly, samples acquired from these travelers were also ESBL producers. A total of 16% of a sample of travelers visiting Vietnam from Japan were found to have acquired strains of *E. coli* positive for *mcr-1* during their trip.[140] Several of these travelers had stayed in four-star hotels, eaten in middle class restaurants and experienced upper class living in Vietnam; however, this did not prevent their colonization by colistin-resistant bacteria. A Canadian traveler who returned from 2-week stay in China, during which he had been hospitalized, was subsequently admitted to hospital with an infection that did not respond to treatment with colistin.[141] A total of 10.5% of stool samples belonging to travelers returning from India to the Netherlands were found to be carrying colistin-resistant *E. coli*.[142]

Discussion

In 2017, there were 1.3 billion international tourist arrivals worldwide,[143] and it has been predicted that this number will rise to 1.8 billion by 2030,[144] as travel becomes affordable for a growing share of the global population. Travelers may be more likely to self-treat with antibiotics, either because they are available over the counter in the country they travel to[145] or because they have brought them from home.[146] For instance, 5% of travelers to South and Southeast Asia at Hamburg airport between November 2014 and April 2015 carried ciprofloxacin.[147] Travelers to many parts of the world, including South(-east) Asia and Southern Africa, are at high risk of returning home colonized by a resistant pathogen.[139] They are also more likely to practice risky sexual behaviours while abroad,[148] enabling the spread of drug-resistant sexually transmitted infections, such as gonorrhea.[149]

Medical tourism has been associated with the spread of resistance genes, including NDM-1.[150] This industry has been predicted to reach USD $8 billion by 2020 in India alone,[151] as patients seek cheaper surgical procedures abroad that are available according to their timeline. Patients commonly travel for transplants, dentistry, cardiac surgery, orthopedic procedures and cosmetic surgery.[122] This flux of patients is multidirectional; those from developing countries may seek high-quality care in developed countries and those from high-income countries may seek lower cost and more convenient care in middle-income countries.

For travelers embarking on trips abroad, vaccines should be up to date; vaccination reduces transmission of resistant

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Table 2. Practices for travel medicine clinicians to help patients avoid colonization and infection with resistant bacteria

Recommendation	Rationale
Ensure vaccines are up to date	Vaccination reduces the transmission of resistant bacteria and the burden of cases that need to be treated with antibiotics.
Provide information on methods of preventing and treating travelers' diarrhea, other than use of antibiotics	This includes drinking from clean water sources, washing fresh fruit and vegetables with clean water, washing hands before eating and other basic hygiene practices. Treatment advice for diarrhea should include staying hydrated, taking oral rehydration solution, rather than immediately resorting to an antibiotic.
Provide information on safe sexual practices, such as condom use	Resistant infections can be transmitted through sexual contact, for example, multidrug-resistant gonorrhoea or syphilis. Even susceptible infections lead to antibiotic use, increasing selection for resistance.
Knowledge of recent trip to a country with high levels of resistance should inform treatment	Travellers to such countries are likely to return home colonized or infected with resistant bacteria.

strains and the consumption of antibiotics (Table 2).[152] Travelers' diarrhea is bacterial in origin in 80–90% of cases[147]; however, travelers should be informed on methods of preventing travelers' diarrhea, apart from antibiotics, including effective sanitation and hygiene practices in addition to ensuring access to clean water for drinking and washing of raw fruit and vegetables. Information on safe sexual practices, such as condom use, should be available to all travelers, including those going to high-risk countries, such as Thailand.[153] Hospital workers should be aware of patients with a history of travel to endemic regions as potential carriers of resistance. This would allow for the implementation of infection prevention control measures, such as increased hygiene and isolation.[11]

Ultimately, to curb travel-associated AMR, there needs to be global progress in addressing AMR. Resistance in any single country has the potential to reach everywhere. Investment is needed in the healthcare systems of low- and middle-income countries and greater attention to antimicrobial stewardship in high-income countries.[12] Globally, efforts to reduce inappropriate antibiotic use and improve surveillance need to be enhanced using a one health approach that incorporates both animal and human health. Opportunities to control typhoid with vaccination should not be overlooked, in addition to improving access to clean water, adequate hygiene and effective sanitation. Research efforts to document international trends in AMR have focused on analyzing levels of antimicrobial consumption between countries[154] and monitoring AMR prevalence where surveillance networks are in place.[155] Towards this goal ResistanceMap (resistancemap.org) is a freely available online platform that collates both consumption and resistance data.[156] Differences in resistance levels between countries show a clear association with levels of antibiotic consumption in some environments.[157] While antimicrobial consumption certainly has a role to play in all countries particularly those with strong public health systems, previous analyses have shown that reduced resistance is better correlated with the quality of healthcare systems, governance and a lower disease burden.[12] Following the emergence of *mcr-1*, its subsequent global dissemination was driven, not by colistin consumption levels, but most likely by the travel of colonized or infected humans[123,139] and the trade of live animals.[18] Such events highlight the importance of travel in the spread of resistance and the need to monitor the dissemination of both resistance genes and resistant pathogens in travelers visiting hotspots of resistance, such as China, Southeast Asia and the Indian subcontinent. The travel medicine community stands in a unique position to advocate for AMR and to ensure that it receives a high priority on the international agenda.

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I.F., T.P.V.B. and R.L. planned the review content and jointly wrote the introduction and conclusion. All authors participated in the writing and are responsible for the final version.

Conflict of interest

None declared.

References

1. Miller RV, Gammon K, Day MJ. Antibiotic resistance among bacteria isolated from seawater and penguin fecal samples collected near Palmer Station, Antarctica. *Can J Microbiol* 2009; **55**:37–45.
2. Mccann CM, Christgen B, Roberts JA *et al.* Understanding drivers of antibiotic resistance genes in High Arctic soil ecosystems. *Environ Int* 2019; **125**:497–504.
3. Urbaniak C, Sielaff AC, Frey KG *et al.* Detection of antimicrobial resistance genes associated with the International Space Station environmental surfaces. *Sci Rep* 2018; **8**:814.
4. Van Boeckel T, Gandra S, Ashok A *et al.* Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; **14**:742–50.
5. Goossens H, Guillemot D, Ferech M *et al.* National campaigns to improve antibiotic use. *Eur J Clin Pharmacol* 2006; **62**:373–9.
6. Duguid M, Cruickshank M. *Antimicrobial Stewardship in Australian Hospitals 2011*. Australian Commission on Safety and Quality in Health Care, 2011.

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7. Klein EY, Van Boeckel TP, Martinez EM *et al.* Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A* 2018; **10**:1–8.
8. Laxminarayan R, Duse A, Wattal C *et al.* Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; **13**:1057–98.
9. Okeke IN, Laxminarayan R, Bhutta ZA *et al.* Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis* 2005; **5**:481–93.
10. Wang R, van DL, Shaw LP *et al.* The global distribution and spread of the mobilized colistin resistance gene mcr-1. *Nat Commun* 2018; **9**:1179.
11. Dortet L, Poirel L, Nordmann P. NDM-type carbapenemases in gram-negative rods. In: *Human and Re-emerging Infections: Bacterial & Mycotic Infections*, Vol. **2**, 1st edn. 2016. https://www.researchgate.net/profile/Laurent_Dortet/publication/316392346_NDM-Type_Carbapenemases_in_Gram-Negative_Rods/links/5a2b0002a6fdccfbbf8522a3/NDM-Type-Carbapenemases-in-Gram-Negative-Rods.pdf
12. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Heal* 2018; **2**:e398–405.
13. World Bank. *Drug-Resistant Infections: A Threat to Our Economic Future*. Washington, DC: World Bank, 2017.
14. Ruppé E, Andremont A, Armand-Lefèvre L. Digestive tract colonization by multidrug-resistant Enterobacteriaceae in travellers: an update. *Travel Med Infect Dis* 2018; **21**:28–35.
15. Wang J, Ma Z, Zeng Z, Yang X, Huang Y, Liu J. The role of wildlife (wild birds) in the global transmission of antimicrobial resistance genes. *Zool Res* 2017; **38**:55–80.
16. Villa L, Guerra B, Schmoger S *et al.* Salmonella enterica serovar Corvallis strain isolated from a migratory wild bird in Germany. *Antimicrob Agents Chemother* 2015; **59**:6597–600.
17. Arnold KE, Williams NJ, Bennett M, Arnold KE. 'Disperse abroad in the land': the role of wildlife in the dissemination of antimicrobial resistance. *Biol Lett* 2016; **12**:20160137.
18. Grami R, Mansour W, Mehri W *et al.* Impact of food animal trade on the spread of mcr-1-mediated colistin resistance, Tunisia, July 2015. *Euro Surveill* 2016; **21**:30144.
19. Börjesson S, Guillard T, Landén A, Bengtsson B. Introduction of quinolone resistant Escherichia coli to Swedish broiler population by imported breeding animals. *Vet Microbiol* 2016; **194**:74–8.
20. Gianna D, Marshall DL. Ready-to-eat shrimp as an international vehicle of antibiotic-resistant bacteria. *J Food Prot* 2005; **68**:2395–401.
21. Almeida MVAD, Cangussú ÍM, Carvalho ALSD, Brito ILP, Costa RA. Drug resistance, AmpC-β-lactamase and extended-spectrum β-lactamase-producing Enterobacteriaceae isolated from fish and shrimp. *Rev Inst Med Trop Sao Paulo* 2017; **59**.
22. Ronholm J, Petrunka LJ, Banerjee SK. Antimicrobial resistance in Vibrio spp. isolated from Canadian imported shrimp, 2009–2014. *Int J Antimicrob Agents* 2015; **46**:475–6.
23. Jansen W, Müller A, Th N, Kehrenberg C, Muylkens B, Al S. Foodborne diseases do not respect borders: zoonotic pathogens and antimicrobial resistant bacteria in food products of animal origin illegally imported into the European Union. *Vet J* 2019; **244**:75–82.
24. Campos J, Mourão J, Silveira L, Saraiva M. Imported poultry meat as a source of extended-spectrum cephalosporin-resistant CMY-2-producing Salmonella Heidelberg and Salmonella Minnesota in the European Union, 2014–2015. *Int J Antimicrob Agents* 2018; **51**:151–4.
25. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature* 2012; **489**:220–30.
26. Liu Y, Wang Y, Walsh TR *et al.* Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 2016; **16**:161–8.
27. Vold L, Nygard K. Surveillance of travel-associated gastrointestinal infections in Norway, 2009–2010: are they all actually imported? *Euro Surveill* 2012; **17**:2009–10.
28. Bartsch SM, McKinnell JA, Mueller LE *et al.* Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. *Clin Microbiol Infect* 2017; **23**:48.e9–48.e16.
29. WHO. *Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter Baumannii and Pseudomonas Aeruginosa in Health Care Facilities*. 2017. https://apps.who.int/iris/bitstream/handle/10665/259462/9789241550178-eng.pdf;jsessionid=2090F4486A2171B98DEB4043E7E979FF?sequence=1 (22 May 2019, date last accessed).
30. Lozano R, Naghavi M, Foreman K *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**:2095–128.
31. Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global epidemiology of campylobacter infection. *Clin Microbiol Rev* 2015; **28**:687–720.
32. Sproston EL, Wimalarathna HML, Sheppard SK. Trends in fluoroquinolone resistance in campylobacter. *Microb Genomics* 2018; **4**: doi: 10.1099/mgen.0.000198.
33. Geissler AL, Carrillo B, Swanson K *et al.* Increasing Campylobacter infections, outbreaks, and antimicrobial resistance in the United States, 2004–2012. *Clin Infect Dis* 2017; **65**:1624–31.
34. Cody AJ, Clarke L, Bowler ICJW, Dingle KE. Ciprofloxacin-resistant campylobacteriosis in the UK. *Lancet* 2010; **11**:1987.
35. Zhou J, Zhang M, Yang W, Fang Y, Wang G, Hou F. A seventeen-year observation of the antimicrobial susceptibility of clinical Campylobacter jejuni and the molecular mechanisms of erythromycin-resistant isolates in Beijing, China. *Int J Infect Dis* 2016; **42**:28–33.
36. Ekdahl K, Andersson Y. Regional risks and seasonality in travel-associated campylobacteriosis. *BMC Infect Dis* 2004; **4**:54.
37. Post A, Martiny D, van Waterschoot N *et al.* Antibiotic susceptibility profiles among Campylobacter isolates obtained from international travelers between 2007 and 2014. *Eur J Clin Microbiol Infect Dis* 2017; **36**:2101–7.
38. Schwartz KL, Morris SK. Travel and the spread of drug-resistant bacteria. *Curr Infect Dis Rep* 2018; **20**:29.
39. Mason CJ, Sornsakrin S, Seidman JC *et al.* Antibiotic resistance in Campylobacter and other diarrheal pathogens isolated from US military personnel deployed to Thailand in 2002–2004: a case–control study. *Trop Dis Travel Med Vaccines* 2017; **3**:13.
40. Cody AJ, Mccarthy NM, Wimalarathna HL *et al.* A longitudinal 6-year study of the molecular epidemiology of clinical campylobacter isolates in Oxfordshire, United Kingdom. *J Clin Microbiol* 2012; **50**:3193–201.
41. Niederer L, Kuhnert P, Egger R, Büttner S, Hächler H, Korczak BM. Genotypes and antibiotic resistances of Campylobacter jejuni and Campylobacter coli isolates from domestic and travel-associated. *Appl Environ Microbiol Environ Microbiol* 2012; **78**:288–91.
42. Gaudreau C, Boucher F, Gilbert H. Antimicrobial susceptibility of Campylobacter jejuni and Campylobacter coli isolates obtained in Montreal, Quebec, Canada, from 2002 to 2013. *J Clin Invest* 2014; **52**:2644–6.
43. James SL, Abate D, Abate KH *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a

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systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**:1789–858.
44. Koch K, Kristensen B, Holt HM, Ethelberg S, Mølbak K, Schønheyder HC. International travel and the risk of hospitalization with non-typhoidal Salmonella bacteremia. A Danish population-based cohort study, 1999–2008. *BMC Infect Dis* 2011; **11**:277.
45. Williamson DA, Lane CR, Easton M *et al.* Increasing antimicrobial resistance in nontyphoidal Salmonella isolates in Australia from 1979 to 2015. *Antimicrob Agents Chemother* 2018; **62**:e02012–7.
46. Tadesse DA, Singh A, Zhao S *et al.* Antimicrobial resistance in Salmonella in the United States from 1948 to 1995. *Antimicrob Agents Chemother* 2016; **60**:2567–71.
47. Yoke-Kqueen C, Learn-Han L, Noorzaleha AS *et al.* Characterization of multiple-antimicrobial-resistant Salmonella enterica Subsp. enterica isolated from indigenous vegetables and poultry in Malaysia. *Lett Appl Microbiol* 2008; **46**:318–24.
48. Center for Veterinary Medicine. *National Antimicrobial Resistance Monitoring System—NARMS Now: Integrated Data*. https://www.fda.gov/animal-veterinary/antimicrobial-resistance/national-antimicrobial-resistance-monitoring-system
49. Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. *Vaccine* 2015; **33**:C21–9.
50. Lin D, Chen K, Wai-Chi Chan E, Chen S. Increasing prevalence of ciprofloxacin-resistant food-borne Salmonella strains harboring multiple PMQR elements but not target gene mutations. *Sci Rep* 2015;**5**:14754.
51. Hyeon J, Chon J, Hwang I *et al.* Prevalence, antibiotic resistance, and molecular characterization of Salmonella serovars in retail meat products. *J Food Prot* 2011; **74**:161–6.
52. Nordahl Petersen T, Rasmussen S, Hasman H *et al.* Meta-genomic analysis of toilet waste from long distance flights; a step towards global surveillance of infectious diseases and antimicrobial resistance. *Sci Rep* 2015; **5**:11444.
53. Srijan A, Lurchachaiwong W, Wongstitwilairoong B, Bodhidatta L, Mason C, Swierczewski B. Prevalence and antimicrobial resistance of non-typhoid Salmonella in military personnel, 1988–2013. *Asian Pac J Trop Med* 2018; **11**:387.
54. Public Health England. *UK Public Health Resistance Alert: Salmonella Typhi Resistant to Third-Generation Cephalosporins Isolated in England from a Traveller Returning from Pakistan*. 2017.
55. Dave J, Warburton F, Freedman J *et al.* What were the risk factors and trends in antimicrobial resistance for enteric fever in London 2005–2012? *J Med Genet* 2017; **66**:698–705.
56. Levine M, Simon R. The gathering storm: is untreatable typhoid fever on the way? *MBio* 2018; **9**:1–4.
57. Wong VK, Baker S, Pickard DJ *et al.* Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter-and intracontinental transmission events. *Nat Genet* 2015; **47**:632–9.
58. Kleine C, Schlabe S, Hischebeth GTR. Successful therapy of a multidrug-resistant extended-spectrum β-lactamase-producing and fluoroquinolone-resistant salmonella enterica subspecies enterica serovar Typhi infection using combination therapy of meropenem and fosfomycin. *Clin Infect Dis* 2017; **65**:1754–6.
59. Mawatari M, Kato Y, Hayakawa K, Morita M, Yamada K, Mezaki K. *Salmonella enterica* serotype Paratyphi A carrying CTX-M-15 type extended-spectrum beta-lactamase isolated from a Japanese traveller returning from India, Japan, July 2013. *Eurosurveillance* 2013; **18**:20632.
60. Rotimi VO, Jamal W, Pal T, Sovenned A, Albert MJ. Emergence of CTX-M-15 type extended-spectrum beta-lactamase-producing Salmonella spp. in Kuwait and the United Arab Emirates. *J Med Microbiol* 2008; **57**:881–6.
61. Phoba M, Barbé B, Lunguya O *et al. Salmonella enterica* serovar Typhi producing CTX-M-15 extended spectrum β-lactamase in the Democratic Republic of the Congo. 2017; **65**:1229–31.
62. Woerther P, Andremont A, Kantele A. *Travel-acquired ESBL-producing Enterobacteriaceae: impact of colonization at individual and community level*, 2017; **24**:S29–S34. doi: 10.1093/jtm/taw101.
63. Pitout JDD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) in the community. *J Antimicrob Chemother* 2005; **56**:52–9.
64. van Duin D, Paterson DL. Multidrug-resistant bacteria in the community: trends and lessons learned. *Infect Dis Clin North Am* 2016; **30**:377–90.
65. Woerther P-L, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev* 2013; **26**:744.
66. Coque TM, Baquero F, Cantón R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. *Eurosurveillance* 2008; **13**:19044.
67. Doi Y, Iovleva A, Bonomo RA. The ecology of extended-spectrum β-lactamases (ESBLs) in the developed world. *J Travel Med* 2017; **24**:S44–51.
68. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. *J Antimicrob Chemother* 2017; **72**:2145–55.
69. Cantón R, González-Alba JM, Galán JC. CTX-M enzymes: origin and diffusion. *Front Microbiol* 2012; **3**:110.
70. Ewers C, Bethe A, Semmler T, Guenther S, Wieler LH. Extended-spectrum beta-lactamase-producing and AmpC-producing Escherichia coli from livestock and companion animals, and their putative impact on public health: a global perspective. *Clin Microbiol Infect* 2012; **18**:646–55.
71. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. *Clin Infect Dis* 2016; **63**:310–8.
72. Laupland KB, Church DL, Vidakovich J, Mucenski M, Pitout JDD. Community-onset extended-spectrum β-lactamase (ESBL) producing Escherichia coli: importance of international travel. *J Infect* 2008; **57**:441–8.
73. van der Bij AK, Pitout JDD. The role of international travel in the worldwide spread of multiresistant Enterobacteriaceae. *J Antimicrob Chemother* 2012; **67**:2090–100.
74. Angue M, Allou N, Belmonte O *et al.* Risk factors for colonization with multidrug-resistant bacteria among patients admitted to the intensive care unit after returning from abroad. *J Travel Med* 2015; **22**:300–5.
75. Hassing RJ, Alsma J, Arcilla MS, van Genderen PJ, Stricker BH, Verbon A. International travel and acquisition of multidrug-resistant Enterobacteriaceae: a systematic review. *Eurosurveillance* 2015; **20**:30074.
76. Arcilla MS, van Hattem JM, Haverkate MR *et al.* Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis* 2017; **17**:78–85.
77. Ruppé E, Armand-Lefèvre L, Estellat C *et al.* High rate of acquisition but short duration of carriage of multidrug-resistant Enterobacteriaceae after travel to the tropics. *Clin Infect Dis* 2015; **61**:593–600.
78. Kantele A, Lääveri T, Mero S *et al.* Antimicrobials increase travelers' risk of colonization by extended-spectrum beta-

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lactamase-producing Enterobacteriaceae. *Clin Infect Dis* 2015; **60**: 837–46.
79. Kantele A, Mero S, Kirveskari J, Lääveri T. Increased risk for ESBL-producing bacteria from co-administration of loperamide and antimicrobial drugs for travelers' diarrhea. *Emerg Infect Dis J* 2016; **22**:117.
80. Pires J, Kuenzli E, Kasraian S *et al.* Polyclonal intestinal colonization with extended-spectrum cephalosporin-resistant Enterobacteriaceae upon traveling to India. *Front Microbiol* 2016; **7**: 1069–9.
81. Kuenzli E, Jaeger VK, Frei R *et al.* High colonization rates of extended-spectrum β-lactamase (ESBL)-producing Escherichia coliin Swiss travellers to South Asia—a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors. *BMC Infect Dis* 2014; **14**:528.
82. McNally A, Thomas CM, Piddock LJV, Hawkey PM. Acquisition and loss of CTX-M-producing and non-producing Escherichia coli in the fecal microbiome of travelers to South Asia. *MBio* 2018; **9**:e02408–18.
83. Vading M, Kabir MH, Kalin M *et al.* Frequent acquisition of low-virulence strains of ESBL-producing Escherichia coli in travellers. *J Antimicrob Chemother* 2016; **71**:3548–55.
84. Paltansing S, Vlot JA, Kraakman MEM *et al.* Extended-spectrum β-lactamase-producing Enterobacteriaceae among travelers from the Netherlands. *Emerg Infect Dis* 2013; **19**:1206–13.
85. Weisenberg SA, Mediavilla JR, Chen L *et al.* Extended spectrum beta-lactamase-producing Enterobacteriaceae in international travelers and non-travelers in New York City. *PLoS One* 2012; **7**:e45141.
86. Valverde A, Turrientes M-C, Norman F *et al.* CTX-M-15-non-ST131 Escherichia coli isolates are mainly responsible of faecal carriage with ESBL-producing Enterobacteriaceae in travellers, immigrants and those visiting friends and relatives. *Clin Microbiol Infect* 2015; **21**:252.e1–4.
87. Östholm-Balkhed Å, Tärnberg M, Nilsson M, Nilsson LE, Hanberger H, Hällgren A. Travel-associated faecal colonization with ESBL-producing Enterobacteriaceae: incidence and risk factors. *J Antimicrob Chemother* 2013; **68**:2144–53.
88. Lubbert C, Straube L, Stein C *et al.* Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. *Int J Med Microbiol* 2015; **305**:148–56.
89. Epelboin L, Robert J, Tsyrina-Kouyoumdjian E, Laouira S, Meyssonnier V, Caumes E. High rate of multidrug-resistant gram-negative bacilli carriage and infection in hospitalized returning travelers: a cross-sectional cohort study. *J Travel Med* 2015; **22**: 292–9.
90. Barbier F, Pommier C, Essaied W *et al.* Colonization and infection with extended-spectrum β-lactamase-producing Enterobacteriaceae in ICU patients: what impact on outcomes and carbapenem exposure? *J Antimicrob Chemother* 2016; **71**:1088–97.
91. Centers for Disease Control and Prevention. Methicillin-resistant Staphylococcus aureus skin or soft tissue infections in a state prison—Mississippi, 2000. *MMWR Morb Mortal Wkly Rep* 2001; **50**:919–22.
92. Centers for Disease Control and Prevention. Methicillin-resistant Staphylococcus aureus infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. *MMWR Morb Mortal Wkly Rep* 2003; **52**: 793–5.
93. Centers for Disease Control and Prevention. Methicillin-resistant Staphylococcus aureus infections in correctional facilities—Georgia, California, and Texas, 2001–2003. *MMWR Morb Mortal Wkly Rep* 2003; **52**:992–6.
94. Diekema DJ, Richter SS, Heilmann KP *et al.* Continued emergence of USA300 methicillin-resistant Staphylococcus aureus in the United States: results from a nationwide surveillance study. *Infect Control Hosp Epidemiol* 2014; **35**:285–92.
95. Centers for Disease Control and Prevention. *Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network Methicillin-Resistant Staphylococcus aureus*. 2012. Available via the Internet: http://www.cdc.gov/abcs/reports-findings/survreports/mrsa12.pdf\ignorespacesFor.
96. Challagundla L, Luo X, Tickler IA *et al.* Range expansion and the origin of USA300 North American epidemic methicillin-resistant Staphylococcus aureus. *MBio* 2018; **9**:e02016–7.
97. Carrel M, Perencevich EN, David MZ. USA300 methicillin-resistant *Staphylococcus aureus*, United States, 2000–2013. *Emerg Infect Dis J* 2015; **21**:1973.
98. Nair R, Ammann E, Rysavy M, Schweizer ML. Mortality among patients with methicillin-resistant Staphylococcus aureus USA300 versus non-USA300 invasive infections: a meta-analysis. *Infect Control Hosp Epidemiol* 2014; **35**:31–41.
99. Kempker RR, Farley MM, Ladson JL *et al.* Association of methicillin-resistant Staphylococcus aureus (MRSA) USA300 genotype with mortality in MRSA bacteremia. *J Infect* 2010; **61**: 372–81.
100. Tenover FC, Goering RV. Methicillin-resistant Staphylococcus aureus strain USA300: origin and epidemiology. *J Antimicrob Chemother* 2009; **64**:441–6.
101. David MZ, Rudolph KM, Hennessy TW *et al.* MRSA USA300 at Alaska Native Medical Center, Anchorage, Alaska, USA, 2000–2006. *Emerg Infect Dis* 2012; **18**:105–8.
102. Gottlieb T, Su W-Y, Merlino J, Cheong EY-L. Recognition of USA300 isolates of community-acquired methicillin-resistant Staphylococcus aureus in Australia. *Med J Aust* 2008; **189**: 179–80.
103. Planet PJ, Diaz L, Rios R, Arias CA. Global spread of the community-associated methicillin-resistant Staphylococcus aureus USA300 Latin American Variant. *J Infect Dis* 2016; **214**:1609–10.
104. Shibuya Y, Hara M, Higuchi W, Takano T, Iwao Y, Yamamoto T. Emergence of the community-acquired methicillin-resistant Staphylococcus aureus USA300 clone in Japan. *J Infect Chemother* 2008; **14**:439–41.
105. Witte W, Braulke C, Strommenger B. Community-associated methicillin-resistant Staphylococcus aureus ST8 ('USA300') in an HIV-positive patient in Cologne, Germany, February 2008. *Euro Surveill* 2008; **13**. https://edoc.rki.de/bitstream/handle/176904/767/230CGNxptjsQ.pdf?sequence=1
106. Otter JA, Havill NL, Boyce JM, French GL. Comparison of community-associated meticillin-resistant Staphylococcus aureus from teaching hospitals in London and the USA, 2004–2006: where is USA300 in the UK? *Eur J Clin Microbiol Infect Dis* 2009; **28**:835.
107. Zhou YP, Wilder-Smith A, Hsu L. The role of international travel in the spread of methicillin-resistant Staphylococcus aureus. *J Travel Med* 2014; **21**:272–81.
108. Strauß L, Stegger M, Eberechi P, Alabi A, Breurec S, Coombs G. Origin, evolution, and global transmission of community-acquired Staphylococcus aureus ST8. *Proc Natl Acad Sci U S A* 2017; **114**: e10596–604.
109. Yabe S, Takano T, Higuchi W, Mimura S, Kurosawa Y, Yamamoto T. Spread of the community-acquired methicillin-resistant Staphylococcus aureus USA300 clone among family members in Japan. *J Infect Chemother* 2010; **16**:372–4.
110. Huang X-Z, Cash DM, Chahine MA *et al.* Methicillin-resistant Staphylococcus aureus infection in combat support hospitals in three regions of Iraq. *Epidemiol Infect* 2011; **139**:994–7.

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111. Glaser P, Martins-Simões P, Villain A *et al.* Demography and intercontinental spread of the USA300 community-acquired methicillin-resistant Staphylococcus aureus lineage. *MBio* 2016; **7**: e02183–15.
112. Toleman MS, Reuter S, Coll F *et al.* Systematic surveillance detects multiple silent introductions and household transmission of methicillin-resistant Staphylococcus aureus USA300 in the east of England. *J Infect Dis* 2016; **214**:447–53.
113. Planet PJ. Life after USA300: the rise and fall of a superbug. *J Infect Dis* 2017; **215**:S71–7.
114. Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. Twenty-year trends in antimicrobial susceptibilities among Staphylococcus aureus from the SENTRY Antimicrobial Surveillance Program. *Open Forum Infect Dis* 2019; **6**:S47–53.
115. Molton JS, Tambyah PA, Ang BSP, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. *Clin Infect Dis* 2013; **56**:1310–8.
116. Chavers LS, Moser SA, Benjamin WH *et al.* Vancomycin-resistant enterococci: 15 years and counting. *J Hosp Infect* 2003; **53**:159–71.
117. Linden PK. Treatment options for vancomycin-resistant enterococcal infections. *Drugs* 2002; **62**:425–41.
118. Yadav G, Thakuria B, Madan M, Agwan V, Pandey A. Linezolid and vancomycin resistant Enterococci: a therapeutic problem. *J Clin Diagn Res* 2017; **11**:7–11.
119. Willems RJL, Top J, Van SM *et al.* Global spread of vancomycin-resistant enterococcus faecium from distinct nosocomial genetic complex. *Emerg Infect Dis* 2005; **11**:821–8.
120. Koh TH, Hsu LY, Chiu LL, Lin RVTP. Emergence of epidemic clones of vancomycin-resistant enterococcus faecium in Singapore. *J Hosp Infect* 2006; **63**:234–6.
121. Christiansen KJ, Tibbett PA, Beresford W, Pearman JW, Lee RC. Eradication of a large outbreak of a single strain of vanB vancomycin-resistant enterococcus faecium at a major Australian teaching hospital. *Infect Control Hosp Epidemiol* 2004; **25**: 384–90.
122. Wilson ME, Chen LH. NDM-1 and the role of travel in its dissemination. 2012; **14**:213–26.
123. Wang R, Van Dorp L, Shaw LP *et al.* The global distribution and spread of the mobilized colistin resistance gene mcr-1. *Nat Commun* 2018; **9**:1–9.
124. Vogwill T, MacLean RC. The genetic basis of the fitness costs of antimicrobial resistance: a meta-analysis approach. *Evol Appl* 2015; **8**:284–95.
125. Carattoli A. Plasmids and the spread of resistance. *Int J Med Microbiol* 2013; **303**:298–304.
126. Nordmann P, Poirel L, Toleman MA, Walsh TR. Does broad-spectrum beta-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria? *J Antimicrob Chemother* 2011; **66**: 689–92.
127. Yong D, Toleman MA, Giske CG *et al.* Characterization of a new metallo-beta-lactamase gene, bla NDM-1, and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. 2009; **53**:5046–54.
128. Kumarasamy KK, Toleman MA, Walsh TR *et al.* Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; **10**:597–602.
129. Jain A, Hopkins KL, Turton J *et al.* NDM carbapenemases in the United Kingdom: an analysis of the first 250 cases. 2014; **69**:1777–84.
130. Peirano G, Ahmed-bentley J, Woodford N, Pitout JD. New Delhi metallo-β-lactamase from traveler returning to Canada. *Emerg Infect Dis* 2011; **17**:2010–2.
131. Struelens MJ, Monnet DL, Magiorakos AP, Connor FSO, Giesecke J. New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe. *Euro Surveill.* 2010; **15**: pii=19716. Available online: http://www.eurosurveillance.org/ViewArticle.\ignorespacesaspx?ArticleId=19716.
132. Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-b-lactamase (NDM)-mediated carbapenem resistance. *J Med Microbiol* 2013; **62**: 499–513.
133. Centers for Disease Control and Prevention. Detection of Enterobacteriaceae isolates carrying metallo-beta-lactamase—United States, 2010. *MMWR Morb Mortal Wkly Rep* 2010; **56**:750.
134. Romero-alvarez D, Reyes J, Quezada V *et al.* First case of New Delhi metallo-beta-lactamase in Klebsiella pneumoniae from Ecuador: an update for South America. *Int J Infect Dis* 2017; **65**:119–21.
135. Leverstein-Van Hall M, Stuart JC, Voets GM, Versteeg D, Tersmette T, Fluit AC. Global spread of New Delhi metallo-β-lactamase 1. *Lancet Infect Dis* 2010; **10**:830–1.
136. Al-tawfiq JA, Laxminarayan R, Mendelson M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? *Int J Infect Dis* 2017; **54**:77–84.
137. Fernandes M, Moura Q, Sartori L *et al.* Silent dissemination of colistin-resistant Escherichia coli in South America could contribute to the global spread of the mcr-1 gene. *Euro Surveill* 2016; **21**:pii=30214. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.17.30214.
138. Wang Y, Tian G, Zhang R *et al.* Prevalence, risk factors, outcomes, and molecular epidemiology of mcr-1-positive Enterobacteriaceae in patients and healthy adults from China: an epidemiological and clinical study. *Lancet Infect Dis* 2017; **17**:390–9.
139. Von WCJH, Wolffs PFG, Van NJM *et al.* Detection of the plasmid-mediated colistin-resistance gene mcr-1 in faecal metagenomes of Dutch travellers. *J Antimicrob Chemother* 2016; **71**:3416–9.
140. Tatsuya Nakayama KY, Kawahara R, YamaguchiY T, Yamamoto Y. Carriage of colistin-resistant, extended-spectrum β-lactamase-producing Escherichia coli harboring the mcr-1 resistance gene after short-term international travel to Vietnam. *Infect Drug Resist* 2018; **11**:391–5.
141. Payne M, Croxen MA, Lee TD *et al.* mcr-1-positive colistin-resistant *Escherichia coli* in traveler returning to Canada from China. 2016; **22**:1673–5.
142. Bernasconi OJ, Kuenzli E, Pires J *et al.* Travelers can import colistin-resistant Enterobacteriaceae, including those possessing the plasmid-mediated mcr-1 gene. *Antimicrob Agents Chemother* 2016; **60**:5080–4.
143. World Tourism Organization. *2018 Edition UNWTO International Tourism Trends 2017*. 2018. https://www.e-unwto.org/doi/pdf/10.18111/9789284419876.
144. Glaesser D, Kester J, Paulose H, Alizadeh A, Valentin B. Global travel patterns: an overview. *J Travel Med* 2017; **24**:1–5.
145. Laxminarayan R, Matsoso P, Pant S *et al.* Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016; **387**:168–75.
146. Tribble DR. Resistant pathogens as causes of traveller's diarrhea globally and impact(s) on treatment failure and recommendations. 2017; **24**:6–12.
147. Hitch G, Fleming N. Antibiotic resistance in travellers' diarrhoeal disease, an external perspective. *Int Soc Travel Med* 2018; **25**: S27–37.

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148. Lejelind E, Westerling R, Sjögren Fugl-Meyer K, Larsson K. Condom use among Swedes while traveling internationally: a qualitative descriptive study. *Nurs Health Sci* 2017; **19**:257–63.
149. Lewis DA. The role of core groups in the emergence and dissemination of antimicrobial resistant N. gonorrhoeae. *Sex Transm Infect* 2013; **89**:iv47–51.
150. Chan HLE, Poon LM, Chan SG, Teo JWP. The perils of medical tourism: NDM-1-positive Escherichia coli causing febrile neutropenia in a medical tourist. *Singapore Med J* 2011; **52**: 299–302.
151. The Economic Times. *Indian Medical Tourism Industry to Touch $8 Billion by 2020: Grant Thornton*. 2015. https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/indian-medical-tourism-industry-to-touch-8-billion-by-2020-grant-thornton/articleshow/49615898.cms (22 May 2019, date last accessed).
152. Lipsitch M, Siber R. How can vaccines contribute to solving the antimicrobial resistance problem? *MBio* 2016; **7**:e00428–16.
153. Zöldi V, Sane J, Kantele A, Rimhanen-finne R, Salmenlinna S. Destination specific risks of acquisition of notifiable food and waterborne infections or sexually transmitted infections among Finnish international travellers, 1995–2015. *Travel Med Infect Dis* 2018; **25**:35–41.
154. World Health Organization. *WHO Report on Surveillance of Antibiotic Consumption*. 2018.
155. Tornimbene B, Eremin S, Escher M, Griskeviciene J, Manglani S, Pessoa-Silva CL. WHO Global Antimicrobial Resistance Surveillance System early implementation 2016–17. *Lancet Infect Dis* 2018; **18**:241–2.
156. The Center for Disease Dynamics Economics & Policy. *ResistanceMap: Antibiotic Resistance*. 2018. https://resistancemap.cddep.org/AntibioticUse.php (22 May 2019, date last accessed).
157. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**:579–87.
158. CDDEP. *ResistanceMap*. https://resistancemap.cddep.org/About.php (22 May 2019, date last accessed).
159. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. *J Infect Dis* 2017; **215**:1–9.

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