Antimicrobial-resistant bacteria in international travelers

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Purpose of review
Antimicrobial resistance (AMR) in bacteria poses a major risk to global public health, with many factors contributing to the observed increase in AMR. International travel is one recognized contributor. The purpose of this review is to summarize current knowledge regarding the acquisition, carriage and spread of AMR bacteria by international travelers.

Recent findings
Recent studies have highlighted that travel is an important risk factor for the acquisition of AMR bacteria, with approximately 30% of studied travelers returning with an acquired AMR bacterium. Epidemiological studies have shown there are three major risk factors for acquisition: travel destination, antimicrobial usage and travelers' diarrhea (TD). Analyses have begun to illustrate the AMR genes that are acquired and spread by travelers, risk factors for acquisition and carriage of AMR bacteria, and local transmission of imported AMR organisms.

Summary
International travel is a contributor to the acquisition and dissemination of AMR organisms globally. Efforts to reduce the burden of AMR organisms should include a focus on international travelers. Routine genomic surveillance would further elucidate the role of international travel in the global spread of AMR bacteria.

Keywords
antimicrobial resistant bacteria, risk factors, travel

INTRODUCTION

Antimicrobial resistance (AMR) is a global public health threat, and its frequency is increasing [1–3]. AMR is directly correlated with antimicrobial usage, and its spread is driven by the transfer of resistant organisms and resistance genes between humans, other animals and the environment [4]. Recent models have suggested that without intervention, deaths attributable to AMR may reach 10 million by 2050, with disproportionate effects on individuals in low and middle-income countries (LMIC) [1,2]. This problem is compounded by the lack of novel antimicrobials and vaccines for many bacterial infections, and by high and inappropriate antimicrobial usage in many parts of the world, driving variable geographic patterns of AMR [1,3] The heavy use of antimicrobials for livestock, aquaculture and in routine clinical practice, and the environmental accumulation of antimicrobials through runoff, are widely recognized as important contributing factors in the rise of AMR [5–16]. As a result, there has been a steady increase in resistance, especially among gram-negative bacteria, to important classes of antimicrobials, including beta-lactams, fluoroquinolones and polymyxins [8,17,18]. The carriage of extended spectrum beta-lactamase (ESBL)-producing bacteria among healthy individuals has increased by 5% each year between 1978 and 2015 [19].

International travel has been identified as playing a role in the spread of resistance genes and

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KEY POINTS

- Antimicrobial resistance is growing rapidly globally.

- Approximately 30% of international travelers acquire ESBL-PE during travel; these are predominantly *E. coli* and often carry resistance to multiple antimicrobials.

- Risk factors for AMR bacterial acquisition include travel destination, antimicrobial usage and travelers' diarrhea.

- Substantial efforts are needed to address the increase in AMR associated with travel, and these efforts should prioritize genomic surveillance and improved antimicrobial stewardship in travelers.

organisms [12,20,21■,22■]. The ongoing COVID-19 global pandemic has highlighted the ease with which infectious diseases can be disseminated by international travel. Here, we review recent published data regarding the acquisition of AMR bacteria by international travelers and their role in the global spread of AMR.

TRAVELER PATTERNS

Except for the slowdown associated with the COVID-19 pandemic, international travel has been steadily increasing for decades. In 2019, there were 1.46 billion international tourist arrivals, representing an increase of 4% from the previous year [23]. This overall increase in travel has been paired with a concomitant increase in travel to and between countries with vulnerable health systems and inadequate public health infrastructure, as assessed by the Fragile States Index (FSI) [24■]. The FSI categorizes countries as Sustainable, Stable, Warning or Alert, and only countries listed as Sustainable are considered resilient to infectious disease threats [24■,25]. Currently, 84% of the world's population lives in Warning or Alert countries, and the greatest increase in travel since 2010 has been between Warning countries, with outbound travel from Warning countries increasing by 326 765 passengers per year [24■]. The widespread global presence of vulnerable health systems potentiates the risks of travel-associated AMR.

ANTIMICROBIAL RESISTANCE IN TRAVELERS

Most studies of AMR in travelers have been small convenience cohorts. To date, a small set of published studies have enrolled a sizable number (i.e. more than 100) of international travelers and have systematically characterized the acquisition of AMR bacteria in these cohorts (Table 1). All have focused on the acquisition of ESBL-producing gram-negative bacteria. More recent studies have assessed the presence of additional resistance genes, including those associated with carbapenem resistance and *mcr*-mediated colistin resistance. Here, we summarize the findings of seven large studies that have conducted recent analyses (Table 1).

Kantele *et al*. [26] performed a prospective study of pre and posttravel stool samples from 430 Finnish travelers between 2008 and 2010 at a travel clinic in Helsinki. Samples were screened for ESBL and carbapenemase-producing *Enterobacterales* (ESBL-PE and CPE, respectively). Sub-Saharan Africa was the top destination, followed by South East and South Asia. Twenty-one percent of travelers acquired ESBL-PE, the majority of which were *E. coli* [27■]. No carbapenemase-producing *Enterobacterales* were found [21■,26]. Of the travelers who acquired ESBL-PE, none had longitudinal carriage after one year.

The Carriage of Multiresistant Bacteria After Travel (COMBAT) study was a longitudinal multicentre cohort study that prospectively sampled stool from 2001 Dutch travelers and their nontravelling household members from November 2012 to November 2013 to investigate the acquisition of AMR *Enterobacterales* [28]. The most visited destinations by travelers were South East Asia, Eastern Africa and South Asia [28]. Thirty-four percent of travelers acquired ESBL-PE, mostly *E. coli*. A recent cross-sectional analysis of pre and posttravel ESBL-PE acquisition within the COMBAT cohort found that there were significant levels of coresistance to other antimicrobials found in ESBL-PE from returning travelers compared with ESBL-PE isolated from pretravel samples [29■]. However, carbapenem resistance was not identified in these returning travelers. The COMBAT study also found 8% onward transmission from ESBL-PE positive returning travelers to ESBL-PE negative household members [30,31].

The VOYAG-R study prospectively followed 574 French international travelers between 2012 and 2013 longitudinally up to 12 months, sampling stool pretravel and posttravel at 1, 2, 3, 6 and 12 months for ESBL-PE, CPE and plasmid-mediated AmpC (pAmpC)-type cephalosporinases [32,33]. The top travel regions were Asia, sub-Saharan Africa and Latin America, and 51% of travelers acquired an AMR organism, 92% of which were ESBL-PE, and which were predominantly *E. coli*. There was independent and concomitant pAmpC production, and three instances of CPE. There was a 16% carriage rate of travel-acquired bacteria after 1 month, which halved over each subsequent follow-up interval. A more recent analysis of 43 participants in the

Table 1. Recent large prospective studies of antimicrobial resistance in international travelers

Study.	Study years	Number of participants (Country of departure)	Top three travel regions	Resistance profiles phenotyped by selective growth	AMR genes assayed by genotyping	Resistance profiles found (genes found by genotyping)	Publications
Kantele *et al.*	2008–2010	430 (Finland)	Sub-Saharan Africa, South East Asia, South Asia	ESBL-P, CP-CR		ESBL-P	[21■,26,27■,49,55■■,82]
COMBAT	2012–2013	2001 (Netherlands)	East Africa, South Asia, South East Asia	ESBL-P	bla_{TEM}; bla_{SHV}; bla_{CTX-M}; mcr-1; CP-CRE by microarray	ESBL-P, CP-CR (bla_{TEM}; bla_{SHV}; bla_{CTX-M}; mcr-1)	[28,29■,30,31,52]
VOYAG-R	2012–2013	574 (France)	Asia, sub-Saharan Africa, Latin America	ESBL-P, CP-CR, pAmpC production (cefoxitin resistance)	bla_{CTX-M}; bla_{TEM}; bla_{SHV}; bla_{VEB}; pAmpc; bla_{KPC}; bla_{VIM}; bla_{IMP}; bla_{NDM}; bla_{OXA-48}; $bla_{OXA-181}$	ESBL-P, CP-CR, pAmpC (bla_{CTX-M}; bla_{NDM}, bla_{OXA-48})	[32,33,83]
Meurs *et al.*	2016–2017	230 (Germany)	South East Asia, East Africa, South America	ESBL-P	bla_{CTX-M}; bla_{VIM}; bla_{IMP}; bla_{NDM}; bla_{KPC}; bla_{OXA-48}	ESBL-P	[35■■]
Tufic-Garutti *et al.*	2015–2019	210 (Brazil)	Sub-Saharan Africa, South America	ESBL-P, CP-CR	bla_{TEM}; bla_{GES}; bla_{SHV}; bla_{CTX-M}; bla_{GIM}; bla_{IMP}; bla_{VIM}; bla_{SIM}; bla_{SPM}; bla_{NDM}; bla_{OXA}; bla_{GES}; bla_{KPC}; pAmpC; bla_{MOX}; bla_{CMY}; bla_{LAT}; bla_{DHA}; bla_{ACC}; bla_{MIR}; bla_{FOX}; PMQR genes (qnrD, qnrVC, qnrC, qnrB, qnrS, qnrA, aac(6')-Ib, qepA); mcr genes	ESBL-P, CP-CR; mcr genes; PMQR genes	[41■■]
Dao *et al.*	2017–2019	382 (France)	South East Asia, Africa, South Asia	ESBL-P, CP-CR	bla_{TEM}; bla_{SHV}; bla_{CTX-M}; bla_{OXA48}; bla_{NDM}; bla_{VIM}; bla_{IMP}; bla_{KPC}; mcr genes (1–6, 8)	ESBL-P, CP-CR, MCR (bla_{CTX-M}; bla_{TEM}; bla_{SHV}; mcr genes (1, 3, 8))	[37■■,38■■,40]
GTEN	2017–2019	608 (United States)	South Asia, South Africa, South America	ESBL-P, CP-CR, MCR	bla_{NDM}; bla_{CTX-M}; mcr genes; aac(3)-IIa; qnrS	ESBL-P, CP-CR, MCR (bla_{NDM}; bla_{CTX-M}; mcr genes; aac(3)-IIa; qnrS)	[22■,42■,44■]

ESBL-P, CP-CR, pAmpC production, and MCR were the only resistance profiles phenotypically measured; ESBL-P, extended-spectrum beta-lactamase-producing; CP-CR, carbapenemase-producing carbapenem-resistant; MCR, *mcr*-mediated colistin-resistant; PMQR, plasmid-mediated quinolone resistance.

VOYAG-R cohort investigated microbiota composition pre and posttravel, finding that diarrhea during travel was associated with a higher abundance of *Prevotella copri* but lower overall microbiome species richness [34▪].

Meurs *et al.* [35▪▪] conducted a prospective cohort study of 230 German international travelers visiting LMIC between 2016 and 2017, assessing pre and posttravel stool for ESBL-PE. The primary regional destinations were South East Asia, South America, and East Africa [35▪▪]. Twenty-three percent of returning travelers were colonized with ESBL-PE, of which 92% were *E. coli*. Of the ESBL-PE positive returning travelers, 42 were tested for carriage at 6 months posttravel; 17% remained colonized with ESBL-PE [35▪▪]. This study followed an earlier prospective cohort study of 205 German international travelers through the same travel clinic in 2013–2014, which found a 33% acquisition rate of ESBL-PE and no CPE; 97% of ESBL-PE were *E. coli* [36].

Dao *et al.* [37▪▪,38▪▪,39,40] conducted a prospective study of 382 French medical students interning internationally between 2017 and 2019 to assess acquisition of respiratory, enteric and vaginal pathogens. The top three destinations were South East Asia, Africa and South Asia. Twenty-nine percent of travelers acquired ESBL-PE, most of which were *E. coli*. A small proportion of acquired organisms were CPE (3%), and *mcr* genes were detected by PCR in 7% of returning participants [37▪▪,38▪▪].

Tufic-Garutti *et al.* [41▪▪] screened pre and posttravel stool samples of 210 Brazilian international travelers between 2015 and 2019, for ESBL-PE and CPE. Brazilian travelers most frequently traveled to sub-Saharan Africa and South America. Interestingly, over the study period, there was a 5% annual increase in pretravel carriage of ESBL-PE. Twenty-two percent of travelers acquired ESBL-PE; the majority of organisms were *E. coli* [41▪▪]. Within the ESBL-PE isolates, there was considerable concomitant resistance to other antimicrobials, including several observed instances of trimethoprim-sulfamethoxazole and quinolone resistance determinants [41▪▪].

More recently, the Global TravEpiNet (GTEN) study prospectively screened stool of 608 U.S. international travelers for ESBL-PE, CPE and *mcr*-mediated colistin-resistant *Enterobacterales* (MCRE) before and after travel from November 2017 to April 2019 [22▪,42▪–44▪]. Travelers most commonly visited India, South Africa and Peru. Thirty-eight percent of returning travelers acquired ESBL-PE, of which most were *E. coli*; CPE and MCRE were also detected independently and concomitantly with ESBL-PE [22▪,42▪]. There was a 30% carriage rate of acquired ESBL-PE at 3 months posttravel, and 10% at 1-year posttravel [22▪].

Overall, although there are some differences between these traveler cohort studies, there are clear trends indicating that ESBL-PE acquisition occurs in approximately 30% of travelers. The most recent studies have also observed acquisition of CPE and MCRE. These findings suggest continued evolution of AMR and an increase in circulating resistance genes, which may be readily acquired and transmitted by travelers.
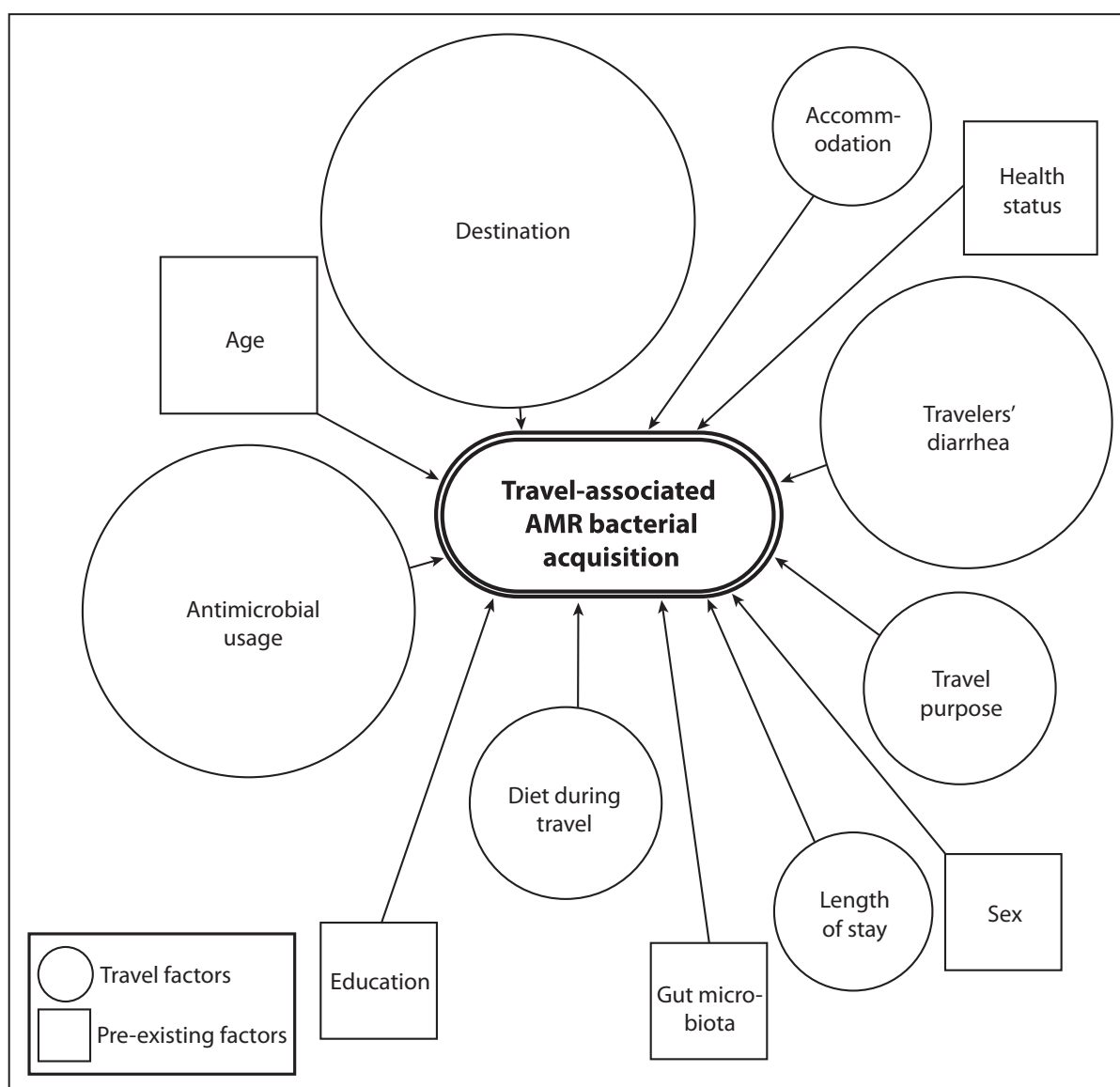
RISK FACTORS

Antimicrobial usage, travelers' diarrhea and destination have been repeatedly identified as risk factors for AMR bacterial acquisition during travel (Fig. 1) [22▪,26,29▪,37▪▪,41▪▪,45▪].

Antimicrobial usage

International travelers who visit travel clinics are frequently prescribed and consume antimicrobials. In 121 295 pretravel consultations at GTEN sites between 2009 and 2018, antimicrobials were prescribed 78% of the time; azithromycin (41%) and fluoroquinolones (35%) were prescribed most frequently [46▪]. An analysis of pretravel colonization by ESBL-PE within the COMBAT cohort found that antimicrobial usage in the three months pretravel was most predictive for ESBL-PE acquisition, and beta-lactam usage correlated most closely with the acquisition of ESBL-PE [29▪]. A meta-analysis of multidrug-resistant *Enterobacterales* acquisition risk factors found that during travel, the leading risk factor was antimicrobial consumption with an odds ratio of 2.38 [95% confidence interval (95% CI) 1.88–3.0] [47▪]. There was similarly an association between antimicrobial usage and multidrug-resistant *Enterobacterales* acquisition, and resistance was correlated with the antimicrobial used [41▪▪]. For instance, ciprofloxacin-resistance was found in 29% of Brazilian travelers who consumed ciprofloxacin compared with 11% who did not, and similar rates have been found in other cohorts [22▪,26,41▪▪].

Travel destination

Although *E. coli* are the most commonly acquired organisms in travelers, the resistance differs geographically. South East Asia, South Asia and North Africa have been identified as the riskiest destinations for AMR acquisition, and many of the travelers surveyed across studies visited one of these regions (Table 1) [22▪,30,35▪▪,37▪▪,48,49,50▪▪,51▪]. In addition, there is country-to-country variation in risk within a travel region; for example, travel to India and Vietnam within South and South East Asia,

FIGURE 1. Risk factors for the acquisition of travel-associated antimicrobial resistant bacteria. The three risk factors most commonly identified are destination, antimicrobial usage during travel and the occurrence of travelers' diarrhea. Risk factors have been distinguished by type (shape) and relative importance (size). The size of the shapes is a rough estimation of the relative importance of risk factors, based on the number of analyzed studies in which the risk factor was identified. The most common risk factor (destination) was identified in 13 out of 15 analyzed studies [22▪,26,28,29▪,30,32,35▪▪,36,37▪▪,38▪▪, 41▪▪,50▪▪,55▪▪,56▪,81▪].

respectively, appears to be higher-risk than other regional destinations [37▪▪]. Multiple studies have found that acquisition of *mcr*-mediated colistin-resistant organisms is highest following travel to Peru, although acquisition of *mcr* genes have also been reported from travelers to Vietnam, China and other destinations [20,22▪,37▪▪,41▪▪,52–54]. A study of 20 European travelers to Laos in 2015 found that 70% of participants were colonized at the end of the study. All participants had at least transiently acquired ESBL-PE, the majority of which were *E. coli*, and 28% of isolates had plasmid-mediated

colistin resistance [45▪]. Further evidence suggests that travel to Africa (other than Southern Africa) and South Asia increased risk of CTX-M group 1 acquisition; there appears to be a regional association with specific CTX genes encoding ESBL's [29▪].

Travelers' diarrhea

Travelers' diarrhea has repeatedly been identified as a risk factor for AMR bacterial acquisition. Kantele *et al.* [55▪▪] found that 68% of travelers in their Finnish cohort experienced travelers' diarrhea,

and there was greater acquisition of an AMR bacterium among those with travelers' diarrhea than without, regardless of antimicrobial usage. This association between travelers' diarrhea and AMR bacterial acquisition was also found in U.S. international travelers from the GTEN study, with travelers' diarrhea and antimicrobial usage independently increasing the likelihood of AMR acquisition [22■].

ENTERIC FEVER IN INTERNATIONAL TRAVELERS

Multidrug-resistant typhoidal and paratyphoid *Salmonella enterica* are a special concern with regard to international travel. Two recent studies have investigated travel-associated enteric fever. There were 68 reported cases of imported ESBL *Salmonella* Typhi and *Salmonella* Paratyphi in the UK between 2017 and 2020 [56■]. The majority of cases were associated with travel to Pakistan, where there is an ongoing outbreak of extremely drug-resistant *S.* Typhi in the Sindh province [57,58]. A separate multisite study of travelers with enteric fever found that 65% of *S.* Typhi isolates were resistant to multiple classes of antimicrobials [50■■]. Of the infected travelers, 59% (522/888) required hospitalization; in children, the rate of hospitalization was 61%. Of the surveyed travelers with *S.* Typhi (70 travelers), only 10% had received a typhoid fever vaccine. Interestingly, typhoid fever was more common in travelers visiting friends and relatives, whereas paratyphoid fever was more common in leisure travelers [50■■].

AREAS IN NEED OF FURTHER INVESTIGATION

Many gaps remain in our understanding of travel-associated AMR. The breakdown in regular healthcare due to COVID-19 may have exacerbated AMR challenges, and this lends urgency to increased efforts to monitor and combat AMR [59]. Here, we highlight four areas in need of further investigation and development.

Genomic surveillance

Recent work has indicated there may be transmission of ESBL *Enterobacterales* from travelers to previously uncolonized household members, and further genomic investigations could confirm such links [30]. There has also been evidence of secondary transmission of *Shigella* spp. and *E. coli* in the Netherlands with genomic similarity to travel-associated clusters [60■]. Many studies have tracked the spread of New Delhi metallo-beta-lactamase 1 (NDM-1) and more recently the dissemination of

mcr-1, showing that these resistance elements have spread geographically and become endemic in some parts of the world [61–72]. One recent example of this is nearly identical plasmids with *bla*NDM-5 and *qepA* in *E. coli* found in Pakistan and Canada [73]. Existing efforts to follow AMR and specific pathogens include GeoSentinel, NARMS and PathogenWatch, and such efforts could be implemented more broadly [50■■,74–77]. New genomic surveillance efforts have been implemented during the COVID-19 pandemic, and prioritizing the development and support for such infrastructure is crucial for global AMR control efforts as well [78–80].

Role of the microbiome

Another gap in understanding is how the gut microbiome influences and is influenced by travel-associated AMR. ESBL *Enterobacterales* acquisition and carriage have been shown to be temporal and highly dynamic, but it is unclear what the ramifications of that are for gut microbial communities and risk of infection [45■]. There is some evidence that *Actinobacteria* species richness pretravel lowers the risk of ESBL-E acquisition during travel, and the VOYAG-R study found that higher abundance of *Prevotella* species is correlated with during-travel diarrhea; further studies would be valuable in determining the relationship between the gut microbiome and travel-associated AMR acquisition, carriage and longitudinal gut health [34■,81■].

Broader sampling for antimicrobial resistant organisms

AMR analyses in travelers have largely been conducted from stool samples; however, there may be value in evaluating nasal, skin and vaginal samples, as there may be important organisms and resistance mechanisms missed by focusing solely on stool [37■■]. In addition, past traveller studies have been biased in sampling primarily European and American travelers. Analyzing more diverse populations and samples will provide greater insight into AMR patterns.

Clinical strategies and interventions

Travel-associated AMR has implications for clinical practice. Medical practitioners should be aware of travel history as a risk factor for AMR. Clinicians providing pretravel health consultation should also consider antimicrobial stewardship principles and be cautious about the prescription of broad-spectrum antimicrobials for empiric use by travelers. Recent analyses have shown that although the occurrence of travelers' diarrhea cannot be controlled for, reducing

the use of empiric antimicrobial treatment for travelers' diarrhea may be useful for lowering the acquisition of travel-associated AMR bacteria [21■,55■■,82].

CONCLUSION

Research over the past decade has shown that approximately 30% of international travelers acquire AMR bacteria during travel, indicating that international travel is one component of the global problem of AMR. Surveillance, antimicrobial stewardship in travelers and novel strategies to decrease AMR acquisition by international travelers are essential for mitigating the global spread of AMR.

Conflicts of interest

There are no conflicts of interest.

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