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Bacterial travellers' diarrhoea: A narrative review of literature published over the past 10 years

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ABSTRACT

Travellers' diarrhoea (TD) is the most frequent illness experienced by international travellers to lower-income countries with bacterial agents considered to account for 80–90% of cases. In this review, we summarise evidence published on bacterial TD over the past 10 years, focusing on the epidemiology and aetiology of TD. Diarrhoeagenic *Escherichia coli* (DEC) continue to be the most commonly implicated bacteria in TD, although Enteropathogenic *E. coli* (EPEC) and Enteroaggregative *E. coli* (EAEC) now appear to be predominant where Enterotoxigenic *E. coli* (ETEC) was previously considered most prevalent globally. Where fluroquinolone resistance had primarily been documented for *Campylobacter* in Southeast Asia, widespread resistance has been observed in most regions of the world for multiple enteropathogens, including *Shigella*, *Salmonella*, ETEC and EAEC. Implementation of novel molecular methods for pathogen detection has led to identification of bacterial pathogens, including *Clostridium difficile* (with and without the use of prior antibiotics), *Arcobacter* species and *Bacteroides fragilis*, as aetiological agents in TD. The widespread resistance to first-line antibiotics in multiple bacterial enteropathogens warrants continued surveillance and re-evaluation of current treatment practices. Further investigations are required to determine the prevalence and geographical distribution of bacterial enteropathogens that have been more recently implicated in TD.

1. Introduction

Travellers' diarrhoea (TD) is the most frequent illness experienced by international travellers to lower-income countries [1–5]. Classic TD has previously been defined as the passing of three or more unformed stools in a 24-h period accompanied by at least one enteric symptom [5–7]. However, guidelines published in 2017 recommend that TD should be classified using functional impact to define severity, instead of the traditional definitions, which are based on stool frequency. These new classifications define mild TD as diarrhoea that is tolerable and does not interfere with planned activities, moderate TD as diarrhoea that is distressing and impacts planned activities and severe TD as diarrhoea that is incapacitating and completely prevents planned activities, and includes all dysentery. Persistent diarrhoea is defined as lasting for at least 14 days [7].

TD usually manifests within the first days of contact with a pathogen after arrival in a new country [8]. Although diarrhoea usually resolves quickly within a few days, TD is a common reason for incapacitation, outpatient consultations and hospitalisations related to international travel [9]. Host risk factors for acquiring TD have been previously described elsewhere [5,8,10]. However, certain types of traveller may have an increased risk of TD, such as small children and younger travellers [4,11,12], backpackers [13,14] and healthcare and non-governmental organisation (NGO) volunteers [15,16]. TD is also a common reason for illness in deployed military personnel [17–20].

Infectious agents are the primary cause of TD. Bacterial infection is the most common cause of TD and is thought to be responsible for 80–90% of cases. Protozoal parasites are responsible for a small proportion of TD cases (approximately 10%) and approximately 2–15% of

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Abbreviations

AA	aggregative adherence
AAF	aggregative adherence fimbriae
CDI	*Clostridium difficile* infection
CF	colonisation factor
DEC	Diarrhoeagenic *Escherichia coli*
EAEC	Enteroaggregative *Escherichia coli*
EIEC	Enteroinvasive *Escherichia coli*
EHEC	Enterohemorrhagic *Escherichia coli*
EPEC	Enteropathogenic *Escherichia coli*
ETEC	Enterotoxigenic *Escherichia coli*
ESBL-PE	extended spectrum beta-lactamase-producing Enterobacteriaceae
IBD	inflammatory bowel disease
LT	heat-labile enterotoxin
MIC	minimum inhibitory concentration
MDR	multi-drug resistant bacteria
NGO	non-governmental organisation
PCR	polymerase chain reaction
PI-IBS	post-infectious irritable bowel syndrome
ST	heat-stable enterotoxin
Stx	shiga toxins
TD	travellers' diarrhoea
VFRs	visiting friends and relatives
WHO	World Health Organization

cases are thought to be caused by viral pathogens, though the latter are more frequently detected when multiplex molecular methods are implemented for diagnosis [6,8,21,22]. The purpose of this review is to provide an update on data that have been published within the past 10 years on the epidemiology and aetiology of bacterial TD. It should be noted that whilst we focus on the literature published over the past 10 years, much significant work on the aetiology of TD was carried out between 2000 and 2009 and thus predates 2010. This limitation may falsely diminish the relative importance of some emerging TD pathogens.

2. Methods

We performed a literature search and review and have provided a narrative review of the literature published on bacterial TD over the past 10 years. Searches of all fields were completed on March 12, 2020 in PubMed and April 13, 2020 in Embase using the key terms "travel*" and "diarrh*". A total of 1105 records were retrieved from the searches. After removal of duplicate records using Microsoft Excel, the abstracts of the retrieved records were screened against the pre-defined criteria for inclusion and exclusion. The inclusion criteria were clinical studies of any design and duration, meta-analyses, systematic reviews and narrative reviews (published after 2018) that specifically reported data relating to acute and chronic bacterial TD in humans, in English language only, published during the last 10 years (March 2010 to March 2020). The exclusion criteria were records for which the full text was not available, were not in English, case reports, commentaries, conference abstracts or posters, animal studies and studies relating to molecular aspects or vaccines. Narrative reviews published before 2018 were also excluded, as we believe that review articles published before this date would not give the most up-to-date clinical picture of TD. Articles of interest were retrieved, reviewed and relevant data extracted. Dual validation was not performed as the purpose of this review was not to provide a quantitative meta-analysis. Each record was critically evaluated according to the following: study design, study year, bacterial pathogens studied, geographical travel location, population, patient age group, patient characteristics and comorbidities, severity of TD (acute or chronic), diagnostic tests used, case criteria used to diagnose TD, treatment or intervention and study objective and clinical endpoints. A total of 831 records were excluded and 274 records were considered appropriate for inclusion. Geographical destinations were grouped according to the United Nations sustainable development goal regions and subregions [23]. The search did not identify any articles relating to rates of TD in Australia or Oceania; therefore, these regions were not included in the article.

3. Epidemiology

3.1. Global

Attack rate is defined as the number of cases of TD during a specified time interval. Differences between studies in the duration of exposure, population size and definition of TD make it difficult to compare data with precision; however, the percentage of international travellers who develop TD is estimated to range between 10% and 70% [11,15,24–35]. The results of a number of investigations suggested that rates of TD have decreased compared with figures published in the mid-2000's [26,27,32], when estimates exceeding 50% were reported in some destinations [10,26,32,36,37], though other recent studies have indicated that the risk of TD in international travellers remains high [27,28,30,31,34,35]. TD is most often observed in travellers to developing regions [8,38], although it should be noted that although rare, TD can occur after travel to high-income countries [39,40]. There is also a risk of diarrhoea at home [41].

3.2. Sub-Saharan Africa

Travellers to Sub-Saharan Africa are at high risk of TD; 11–87% of travellers acquire TD, depending on region [24–26,30,42,43]. Rates of TD range from 21 to 75% in East Africa [25,26,30,34], 22–87% in West Africa [25,26,30,42–44], 20–30% in Middle Africa [25,26] and 11–58% in Southern Africa [25,26,34]. The results of earlier investigations suggested that TD is less common during or after travel to South Africa; however, Mendelson et al. (2010) reported that the risk of diarrhoea in travellers to this region was similar to that of those visiting neighbouring countries such as Botswana, Lesotho and Swaziland [45].

3.3. Northern Africa and Western Asia

In Northern Africa and Western Asia, the percentage of travellers who acquire TD ranges between 6% and 50% [17,25,26,34,46].

3.4. Eastern and Southeastern Asia

Whilst the results of some investigations reported that risk of TD in Eastern and Southeastern Asia has decreased compared with estimates published in the early to mid-2000's [10,26,36,37,47], others indicated that the risk remains very high in these regions [25,30]. The percentage of travellers who acquire TD during or after travel to Eastern and Southeastern Asia is estimated to range between 9% and 79% [25,26,30,48–50], depending on region. Attack rates for TD are 12–79% in Southeast Asia [25,26,30,48,49], whilst 9–31% of travellers visiting Eastern Asia develop TD [25,26].

3.5. Central and Southern Asia

In Central and Southern Asia, estimated attack rates for TD range between 10% and 80% [13,30,51,52]. The estimated percentage of travellers who acquire TD in Southern Asia is 10–82% [13,30,34,51,52], whilst in Central Asia it is 26–52% [25,26,34].

3.6. Latin America and the caribbean

Estimated attack rates for TD in Latin America and the Caribbean range between 7% and 60% [24–28,30,53]. In South America, the estimated attack rate of TD is 15–44% [25–27], whilst estimates in Central America and the Caribbean range between 7–55% [25–27,53]. Some reports have suggested that rates of TD have decreased in some Latin American countries compared with estimates reported in studies published in the early-to-mid-2000's [10,26,36,37], although high attack rates have been reported in many other recent investigations [25,27,30].

3.7. Europe and Northern America

The risk of acquiring TD during or after travel to Europe and Northern America is generally low, with attack rates of 3–13% [28,34]. TD may be slightly more common after travel to regions in Eastern Europe, such as Russia, where there is an intermediate risk of acquiring TD [54].

4. Aetiology

4.1. Role of modern molecular techniques in determining the aetiology of TD

The prevalence of enteric pathogens in the stools of patients with TD by region is detailed in Table 1. There were very wide variations in the prevalence of several pathogens, which could be in part due to heterogeneity in study designs and differences in the rates of successful pathogen isolation [55]. Diagnosis of bacterial TD has traditionally relied upon culture-based methods for the identification of enteric pathogens [22]. These techniques fail to detect the aetiological agent in many cases and are resource intensive, with results often not available to clinicians for 48–72 h [22,56]. In recent years, diagnostic laboratories have started to implement multiplex polymerase chain reaction (PCR) technologies to identify TD enteropathogens [22]. These technologies can test for a broad range of pathogens simultaneously, including bacteria, viruses and parasites [56–60]. The findings of multiple studies have demonstrated that multiplex PCR panels have high sensitivity, high specificity and rapid turnaround compared with traditional diagnostic methods [56–58,61,62]. These technologies have led to a better understanding of the incidence of enteropathogens in TD, facilitated the detection of previously overlooked TD enteropathogens and given insight into the frequency of co-infections [22,43,56,58,59]. However, there is concern about irrelevant findings associated with colonisation by apathogenic bacteria and claims that evidence for a benefit to patients has been omitted [7,63].

4.2. Diarrhoeagenic Escherichia coli (DEC) pathotypes

Escherichia coli are one of the most frequent bacterial causes of TD worldwide [30]. The main DEC pathotypes include Enterotoxigenic *E. coli* (ETEC), Enteroaggregative *E. coli* (EAEC), Enteropathogenic *E. coli* (EPEC), Enterohemorrhagic *E. coli* (EHEC), Enteroinvasive *E. coli* (EIEC) and Shiga toxin-producing *E. coli* (STEC) [21].

4.2.1. Enterotoxigenic E. coli (ETEC)

ETEC is characterised by its ability to secrete one or both of two enterotoxins, called heat-labile (LT) enterotoxin and heat-stable (ST) enterotoxin [64]. Traditionally, ETEC has been recognised as the most common bacterial cause of TD in almost all regions of the world, with the exception of Southeast Asia [65]. However, the prevalence of ETEC as an aetiological agent in TD appears to be decreasing globally. The results of several investigations implementing novel molecular techniques for pathogen identification have indicated that alternative pathogens, such as EAEC and EPEC, are at least, if not more common than ETEC in patients travelling to Africa, Central and Latin America,

Table 1
Identification of enteric pathogens in stools of patients with TD by region.

	EAEC (%)	ETEC (%)	EPEC (%)	*Shigella* spp.[a] (%)	*Salmonella* spp. (%)	*Campylobacter* spp. (%)
Southeast and East Asia	2–37 [28,30,60,67,72]	5–36 [28,30,60,67,68,72]	8–42 [30,60,68]	2.0–13 [60,67,68,72]	1–17 [55,60,67,68,72]	15–63 [30,55,60,68,72,]
Southeast Asia	10–37 [28,30,60,67,72]	8–42 [30,60,68]	2.0–13 [60,67,68,72]	1–17 [55,60,67,68,72]	15–63 [30,55,60,68,72]	
East Asia	2 [28]	5–36 [28,30,60,67,68,72]	–	2.0–13 [60,67,68,72]	1–17 [55,60,67,68,72]	–
		5–6 [28]		–	–	
Southern and Central Asia	2–60 [28,30,73]	0–60 [28,30,73,76]	12–56 [30,76]	6–13 [73,76,92]	4–11 [73,76,92]	11–33 [30,73,76,92]
Central Asia	2 [28]	0 [28]	–	–	–	–
South Asia	3–60 [28,30,73]	0–60 [28,30,73,76]	12–56 [30,76]	6–13 [73,76,92]	0–11 [73,76,92]	11–33 [30,73,76,92]
North Africa and Western Asia	1–33 [28,68,70,71]	0–42 [18,28,68–71]	0–27 [68,70,71]	0–20 [18,68–71,92]	0–11 [68–71,92]	4–14 [18,68,69,92]
North Africa	16 [28]	17–42 [18,28]	–	0 [18]	–	10 [18]
Western Asia	1–33 [28,70,71]	0–41 [28,55,69–71]	3–27 [70,71]	1–20 [69–71]	0–11 [69–71]	12 [69]
Sub-Saharan Africa	0–59 [28,30,43,68]	0–56 [28,30,43,68]	0.5–77 [28,30,43,68]	6–18 [43,68,92]	2-6 [43,68,92]	0-9 [30,43,68,92]
West Africa	12–59 [28,30,43]	9–56 [28,30,43]	18 [43]	3 [43]	0–2 [30,43]	
East Africa	8–56 [28,30]	5–38 [28,30]	40–77 [30,43]	–	–	7 [30]
Middle Africa	0 [28]	0 [28]	44 [30]	–	–	–
Southern Africa	4 [28]	0–4.5 [28]	–	–	–	–
			–			
Latin America and the Caribbean	0–54 [28,30,59,68,72,73,75]	0–60 [28,30,59,68,72–75]	0–29 [30,68,75]	0–27 [68,72,73,75,92]	0–6 [59,68,72,73,75]	0–13 [30,59,68,72,73,75,92]
Central America	0–12 [28,73]	0–60 [28,73,74]	–	0 [73]	0–6 [73]	0–4 [73]
Caribbean	0 [28]	0 [28]	0 [75]	–	–	–
South America	4 [28,75]	6–11 [28,75]	–	6 [75]	0 [75]	9 [75]
		–		–	–	
Europe and North America[b]	0 [28]	0–5 [28]	–	–	–	–

EAEC, enteroaggregative *E. coli*; ETEC, enterotoxigenic *E. coli*; EPEC, enteropathogenic *E. coli*; EIEC, enteroinvasive *E. coli*; TD, travellers' diarrhoea.
[a] Some studies include combined estimates for *Shigella*/EIEC.
[b] Europe without Russia.

and Southern and Southeast Asia [28,30,43,61,66,67].

The prevalence of ETEC in TD by region is detailed in Table 1. ETEC is frequently identified in the stools of patients with TD during or after visiting Sub-Saharan Africa [28,30,43,68], in particular West and East Africa [28,30,43], as well as North Africa and Western Asia [18,28,68–71]. ETEC is a common cause of TD in Latin America and the Caribbean [28,30,59,68,72–75]. The prevalence of ETEC is also high in travellers visiting South and Southeast Asia [28,30,60,67,68,72,73,76], where the pathogen may be more common than previously reported [30]. The prevalence of ETEC is much lower in Europe and North America [28,30], although molecular characterisations of isolates collected from the Central and Far-Eastern regions of Russia suggest that the pathogen is in circulation in this area [77]. In addition to regional variation, ETEC infection rates vary significantly according to season. In countries such as Mexico, temperature variations significantly influence the rate of ETEC-associated diarrhoea in visitors [53].

ETEC occurs as a co-infection in approximately 40% of TD cases [59]. Co-infections with ETEC and EAEC are frequently observed in patients with TD [28,72]. This is most likely because they represent two of the most common pathogens in this population [72]. Additionally, mixed infections with ETEC and emerging causes of TD, including *Arcobacter butzleri* and enterotoxigenic *Bacteroides fragilis*, have been reported in travellers returning from India, Guatemala and Mexico [73].

The distribution of isolates expressing LT and ST enterotoxins may vary according to region [28,78], although worldwide, only 27% of ETEC strains express only LT, with the majority co-expressing the ST enterotoxin or expressing ST alone [78]. In a systematic review by Isidean et al. (2011), Latin America and the Caribbean was the region with the highest prevalence of LT-expressing strains among travellers, with a prevalence of 37.5% for LT-only strains, 29.6% for ST-only strains and 31.9% for LT/ST-producing strains [78]. The results of multiple investigations suggested that ST-ETEC is the most common phenotype in patients with TD visiting all other travel destinations [18,69,78–80]. However, one study by Paschke et al. (2011) reported that LT-ETEC was more common than ST-ETEC in a number of regions, including South Asia, Southeast Asia, Western Asia, Southern Africa and Europe [28], although a statistical analysis for the difference in abundance between the two strains was not conducted. It is possible that differences in the geographical distribution of LT-ETEC and ST-ETEC among studies arise due to variability in toxin detection methodologies. For example, genotypic methods can result in higher estimations for LT enterotoxin prevalence than phenotypic methodologies [78].

In addition to geographical variation, ETEC enterotoxin distribution may have also changed over time. In the Middle East, the prevalence of ST variant STp (porcine, bovine and human origin [81]) has significantly decreased, whilst the role of STh (human origin [81]) as a cause of diarrhoea has increased [79]. However, there is a possibility that this may reflect the analytical methods adopted rather than an actual change in enterotoxin prevalence over time, as adoption of more sensitive diagnostic methods may have resulted in the detection of more strains.

4.2.2. Enteroaggregative E. coli (EAEC)

The prevalence of EAEC in the stools of patients with TD varies by region and study and is detailed in Table 1. Although ETEC has traditionally been considered the predominant TD enteropathogen in almost all regions of the world [30,65], in recent years, EAEC is the most frequently detected pathogen in the stools of TD patients visiting East Africa [30,66], South Asia [28,30,66], and Latin America and the Caribbean [30,59,66] in some investigations. EAEC infection is also common during travel to Southeast Asia [28,30,60,67,72] and West Africa [28,30,43,66,67]. In high-income countries, EAEC has mostly been associated with foodborne disease [85]. In a 2018 study implementing multiplex PCR technology, EAEC was identified in 18% of stool samples from visitors to Europe; however, these travellers were not necessarily symptomatic [30].

Mixed infections with EAEC are common in patients with TD, as indicated in a multiplex PCR study by Zboromyrska et al. (2014), in which EAEC accounted for 35% of all coinfections identified in the stools of international travellers [59]. Similarly, analyses of stool samples from patients returning from West Africa showed that co-infections occur in 79% of TD cases, with EAEC and EPEC representing the most frequently detected co-pathogens [43]. TD can also result from co-infection with EAEC and viral pathogens, such as norovirus, as demonstrated in a case identified during a surveillance study of adult travellers visiting Peru [75]. In such cases, it may be difficult to determine which pathogen is responsible for the symptoms of TD, as norovirus and EAEC are both associated with acute, watery diarrhoea [21,85,86]. However, diarrhoea caused by norovirus typically resolves within 3 days and has been associated with outbreaks on cruise ships, and in dormitory rooms, camping sites and hotels [21]. EAEC infection typically results in a longer duration of symptoms (3–14 days) and has been associated with persistent diarrhoea in children [21].

4.2.3. Enteropathogenic E. coli (EPEC)

The role of EPEC as an aetiological agent in TD has not been studied to the same extent as those of ETEC or EAEC. However, the results of some investigations suggest that EPEC is more common than ETEC in patients who developed diarrhoea during or after travel to West Africa [30,43], East Africa, Southeast Asia, South Asia and Latin America and the Caribbean [30]. In a study published in 2014, EPEC was identified as the most common TD enteropathogen in travellers to West Africa [43]. Another study by the same authors suggested that EPEC is the most common pathogen in TD patients visiting Southeast Asia, where *Campylobacter* have been traditionally considered predominant [30]. However, other studies have suggested that *Campylobacter* are still the most prevalent TD-causing bacteria in this region [55,60,68,76].

4.3. Shigella species

The prevalence of *Shigella* spp. in TD varies by region and is detailed in Table 1. Although usually rare, TD caused by *Shigella* spp. has been detected in all lower-income destinations [30,43,59,60,67,68,72,75,76,92]. *Shigella* is much less commonly acquired during travel to higher-income regions such as Europe and North America [30,93]. In a 2010 paper, Baaten et al. (2010) reported that attack rates of shigellosis after travel to Latin America, the Middle East and Asia have significantly decreased since 1995 but remain high in Sub-Saharan Africa [94]. The *Shigella* spp. most commonly detected in the stools of patients with TD are *S. sonnei* and *S. flexneri*, accounting for 50.0% and 38.2% of *Shigella* isolates from patients with TD, respectively [41]. *Shigella* occurs as a co-infection in up to 75% of cases [59].

Shiga toxins (Stx) are cytotoxins that inhibit eukaryotic protein synthesis, resulting in host cell death [95]. Historically, only *S. dysenteriae* type 1 was thought to encode genes for Stx. However, novel strains of non-dysenteriae type-1 *Shigella* carrying *Stx* genes on a bacteriophage have been isolated from international travellers. Evidence suggests that these strains emerged as two distinct clusters from in Haiti and the Dominican Republic, having acquired *Stx* genes through horizontal phage transfer from *S. flexnari* 2a [95]. Likewise, cases of bloody diarrhoea caused by Stx-1-producing *S. sonnei* have also been reported in California. Although some early cases were associated with travel to Mexico, subsequent infections are thought to be the result of domestic transmission in the USA [96]. In a genomic analysis by Baker et al. (2018), importation of travel-associated sublineages of *S. flexnari* 2a and *S. sonnei* from Africa and Asia have also been reported in the UK (including Asian-travel related sublineages of both species with resistance to ciprofloxacin), further reinforcing how international travel is facilitating the dissemination of *Shigella* sublineages from areas where the pathogen is endemic to high-income nations [97]. In this study, the majority of domestically-acquired cases of travel-related sublineages were dead-end transmissions; however, one travel-imported antimicrobial resistant sublineage was found to contribute to a

domestically-transmitted epidemic [97].

In a 2018 study on the association between antibiotic use for TD and pathogen findings in the stools of returned travellers, infection with *Shigella* was more common in patients who received antibiotics compared with non-users (4% vs 1%). The authors postulated that this may be due to gut dysbiosis as a result of taking antibiotics, which facilitates infection and colonisation with pathogenic bacteria such as *Shigella* [66].

4.4. Campylobacter species

Table 1 details the prevalence of *Campylobacter* as a cause of TD by region. Though DEC are the most common cause of TD worldwide [98], *Campylobacter* have long been considered the predominant aetiological agent in TD acquired during travel to Southeast Asia [30,65]. Recent studies implementing novel molecular methods for pathogen detection contradict these previous observations, indicating that the role of *Campylobacter* may have been overestimated in Southeast Asia and that DEC are more common than originally reported in this region [30,72]. However, *Campylobacter* continue to be identified as the predominant diarrhoea-causing pathogen among travellers to Southeast Asia in other studies [55,60,68,76]. *Campylobacter* infection appears to be less common during travel to Latin America and the Caribbean, Sub-Saharan Africa, North Africa and Western Asia, with estimated rates of 0–14% in these areas [18,30,59,68,71–73,75,92]. *Campylobacter* infection is one of the leading causes of diarrhoea in both developing and developed countries. In an analysis of 5965 records of travellers who were unwell presenting to EuroTravNet centres, *Campylobacter* were identified as the leading cause of diarrhoea in travellers visiting Western Europe [99]. Interestingly, Schlagenhauf et al. (2015) reported that *Campylobacter* infection as a travel-related morbidity increased from 2008 to 2012 in travellers presenting to EuroTravNet centres for pre-travel advice [100]. The authors noted that pre-travel advice does not seem to be effective in the prevention of acute TD.

4.5. Salmonella species

Salmonella is one of the most frequently reported enteric pathogens in developed countries such as the USA [101,102] and represents another cause of travel-associated diarrhoea. As detailed in Table 1, the prevalence of *Salmonella* in the stools of patients with TD is 0–17%, depending on region [43,55,59,60,67,68,70,72,73,75,76,92].

4.6. Clostridium difficile

Traditionally considered a rare cause of diarrhoea in travellers [103], *C. difficile* infection (CDI) has been reported in travellers to all regions of the world, with the largest proportion of cases originating from Asia (31%), Latin America and the Caribbean (30%) and Africa (24%) [104]. Although CDI is reported most often after travelling to low- and middle-income countries, an analysis of 48 published cases of travel-associated CDI reported that ~20% of cases occur after travel to industrialised regions, such as the USA, Europe and Oceania [103]. Analyses of stool samples suggest that rates of *C. difficile* infection range between 1.2% and 1.4% in patients with TD [59,60], although in one 2018 study, 6.4% of international travellers returning with enteric symptoms were positive for this pathogen [56]. In studies in paediatric travellers with TD, *C. difficile* has been detected in stool samples at rates of 5–7% [57,58], although it is not yet clear whether children are a relevant community reservoir for *C. difficile* [57].

Antibiotic consumption is known to facilitate *C. difficile* colonisation through disruption of the intestinal microbiota and represents a significant risk factor for CDI [104–106]. In the aforementioned review of 48 travel-associated cases of CDI, 75% of patients for whom clinical data were available had consumed antibiotics prior to developing diarrhoea [103]. It is important to consider the impact of initial antibiotic treatment for TD on the development of *C. difficile*-associated diarrhoea. Norman et al. (2008) described six case studies in which patients developed CDI after receipt of antibiotic therapy for TD, with four of six patients having received ciprofloxacin [107]. However, further studies with larger sample sizes are necessary to determine the risks factors for CDI in travellers and their relevance today [104].

4.7. Other bacterial causes of TD

Other organisms implicated in TD include *Aeromonas* [60,108], *Yersinia* [70,93], and *Plesiomonas* spp. [60,108], all of which are less frequently isolated from travellers than those described previously [60,70,93,108,109]. A number of previously overlooked pathogens have also been identified as causes of TD. In a 2010 aetiological study, *Arcobacter* spp. and enterotoxigenic *Bacteroides fragilis* were identified in 8% and 7% of TD cases, respectively, experienced by US and European travellers returning from Mexico, Guatemala and India [73].

The results of a small-scale surveillance study suggested that *Tropheryma whipplei* may be associated with adult TD in Hajj pilgrims returning from Saudi Arabia [46]. In a similar investigation, *T. whipplei* was identified in the stools of travellers returning from Senegal [42], although further studies in larger cohorts are required to better understand the potential role of *T. whipplei* in TD [42,46].

Moreover, *Laribacter hongkongensis* was identified as the sole pathogen in a case of prolonged travel-associated gastroenteritis after travel to France. Although the role of *L. hongkongensis* in TD has not been fully elucidated, cases of *L. hongkongensis* have been reported in many countries including Hong Kong, China, Korea, Japan, Switzerland, USA, UK, Australia and Denmark, indicating that the pathogen is distributed worldwide [110].

Exposure to *Vibrio cholerae* is also a risk for travellers visiting endemic countries, although cholera is very rare in this population [111]. *V. cholerae* is isolated from the stools of 0–1.3% of travellers with diarrhoea [30,43,56,57,60,61,67,93]; however, cholera is often not distinguished from other causes of TD in most healthy travellers, meaning that cholera as a specific cause of diarrhoea is often under-reported [111].

5. TD enteropathogens and antimicrobial resistance

Antimicrobial resistance (AMR) is a major threat to global public health. Although antibiotics are effective in the treatment of TD [7,8,21,112], decreased susceptibility to first-line antibiotics has been observed in multiple TD enteropathogens, and in some cases has been reported to translate into clinical failure [41,92,108,113–115]. Antibiotic therapy is currently recommended by guidelines for the treatment of moderate to severe TD, with azithromycin (for TD including dysentery), fluroquinolones and rifaximin being the antimicrobials of choice for empirical antibiotic therapy [7]. Given that laboratory investigation is not necessary in most TD cases and it is common for international travellers to be provided with antibiotics for self-treatment in case they become unwell during travel [7,8], patients may receive empirical antibiotic therapy for TD without identification of the causative pathogen. Resistance surveillance data can therefore be used to guide recommendations for the choice of antibiotic for empirical therapy, based on the distribution of pathogens within the region and local resistance patterns [7,8].

Resistance rates in TD enteropathogens vary according to geography and are detailed in Table 2. There was wide variation in resistance rates for some areas, which could be in part due to differences in the methods used to derive antimicrobial resistance data [116]. Fluoroquinolones, such as ciprofloxacin and levofloxacin, have traditionally been used as first-line antimicrobials for the prevention and treatment of TD [21]. Increasing rates of fluoroquinolone resistance have been reported for a number of major bacterial causes of TD, including ETEC, EAEC, *Campylobacter* spp. and *Shigella* spp [41,92,113–115]. The results of

Table 2
Antibiotic resistance rates of TD enteropathogens by region.

Antibiotic	Global (%)	Southern and Central Asia (%)	East and Southeast Asia (%)	North Africa and Western Asia (%)	Sub-Saharan Africa (%)	Latin America and the Caribbean (%)	Europe and North America (%)
Amoxicillin-clavulanic acid	5.3–30.0 [41,164]	0.0–6.7 [41] [a]	–	9.4–43.2 [82] [b]	5.4 [41] [c]	0.0 [41] [d]	–
Ampicillin	35.5 [41]	0.0–49.4% [41,92,108] [a]	–	28.1–75.7 [82,92]	17.0–50.0 [92]	0.0–60.0 [41,92,108]	–
Azithromycin	5.0 [41]	0.0–24.5 [41,76,108] [a]	28.6–33.3 [115] [e]	–	0.0–25.0 [41,115] [i]	0.0–50.0 [41,108,114,115]	–
Aztreonam	–	10.3 [41] [a]	–	–	0.0 [41] [c]	0.0 [41] [d]	–
Cefepime	1.3–83.0 [41,164]	3.4 [41] [a]	–	–	0.0 [41] [c]	0.0 [41] [d]	–
Cefotaxime	2.6–96.0 [41,164]	3.3 [41] [a]	33.3–42.9 [115] [e]	–	0.0–6.3 [41,115] [c]	0.0 [41,115]	–
Ceftazidime	2.6–87.0 [41,164]	3.3 [41] [a]	–	–	0.0 [41] [c]	0.0 [41] [d]	–
Ceftriaxone	–	0.0–6.2 [108] [f]	–	–	–	0.0–20.0 [108] [g]	–
Chloramphenicol	–	–	–	2.7–6.3 [82] [b]	–	–	–
Ciprofloxacin	27.6–61.0 [41,113,164]	0.0–76.1 [41,76,113] [a]	41.7–68.0 [113,115] [e,h]	66.7 [113] [i]	2.7–52.0 [41,113] [c]	0.0–89.8 [108,113–115]	56.1 [113] [j]
Doxycycline	–	0.0–48.5 [108] [f]	–	–	–	0.0–60.0 [108] [g]	–
Erythromycin	4.6 [113]	15.2 [113] [k]	4.0 [113] [h]	2.8 [113] [i]	0.0–4.0 [113]	0.0–14.9 [113,114] [d]	2.4 [113] [j]
Gentamycin	39.0 [164]	–	–		–	–	–
Imipenem	1.0 [164]	–	–	–	0.0 [41] [c]	0.0 [41] [d]	–
Levofloxacin	–	0.0–40.8 [108] [f]	–	–	–	0.0–45.0 [108] [g]	–
Nalidixic acid	–	0.0–78.0 [76,108] [k]	64.3–66.7 [115] [e]	–	37.5–38.9 [115] [c]	0.0–38.5 [108,115]	–
Norfloxacin	–	64.0 [92] [k]	–	83.0 [92]	31.0 [92]	50.0 [92]	–
Rifaximin	–	0.0–29.4 [108] [f]	–	–	–	0.0–15.5 [108] [g]	–
Tetracycline	48.3 [113]	0.0–52.5 [108,113] [k]	56.0 [113] [h]	15.6–50.0 [82,113]	50.0–56.7 [113]	0.0–60.0 [108,113]	53.7 [113] [j]
Tobramycin	47.0 [164]	–	–	–	–	–	–
Trimethoprim/sulfamethoxazole	82.4 [41]	0.0–75.9 [41,76,92,108] [a]	35.7–50.0 [115] [e]	25.0–100.0 [82,92]	8.0–88.9 [41,92,115] [c]	0.0–75.0 [41,92,108,115]	–

TD, travellers' diarrhoea.
[a] Includes estimates for Asia as a whole, though most isolates originate from India.
[b] Estimates for Israel only.
[c] Includes estimates for Africa as a whole, though most isolates originate from Sub-Saharan Africa.
[d] Estimates for Southern and Central America only.
[e] Includes estimates for Southeast Asia/India.
[f] Estimates for India only.
[g] Estimates for Mexico and Guatemala only.
[h] Excludes East Asia.
[i] Estimates for North Africa only.
[j] Estimates for Europe only.
[k] Excludes Central Asia.

several studies have indicated that quinolone-resistant isolates are commonly identified in the stools in travellers visiting Southeast Asia and Southern Asia [76,92,113,115]. High levels of fluroquinolone resistance have also been reported in isolates from Latin America and North Africa [108,113,114]. Rates of *Campylobacter* resistance to fluroquinolones in these regions particular are concerning [113,114], and appear to be increasing, with rates of up to 90% being reported in Latin America [114]. Of most concern is evidence to suggest that fluroquinolone resistance translates into clinical failure. In an epidemiological study in travellers returning from the tropics, Bottieau et al. (2011) observed clinical failure in 33% of patients who received fluroquinolones for *C. jejuni*-associated diarrhoea [92].

Macrolides such as azithromycin and erythromycin are often used as an alternative treatment for TD. TD enteropathogens with reduced susceptibility to azithromycin have been documented in travellers to Asia [76,108,115], Africa [115], and Latin America and the Caribbean [41,108,114,115], with resistance rates of up to 33.3%, 25.0% and 50.0%, respectively (Table 2). Azithromycin and erythromycin are commonly used to treat *Campylobacter* infections, although significant increases in resistance to these antibiotics have been reported in regions such as Peru [114], where the prevalence of *Campylobacter* isolates that are co-resistant to both fluroquinolone and macrolides also appears to be increasing [114].

High rates of resistance have also been documented for ampicillin, nalidixic acid and trimethoprim-sulfamethoxazole (Table 2). Rates of trimethoprim-sulfamethoxazole resistance are particularly high in isolates from travellers to Africa, where up to 89% of *Shigella* isolates were found to be resistant to this agent [41]. Similarly, Bottieau et al. (2011) reported very high rates of resistance to trimethoprim-sulfamethoxazole in *Shigella* isolates from Sub-Saharan Africa, Latin America and the Caribbean, North Africa and Western Asia and *Salmonella* isolates from travellers to North Africa and Western Asia [92]. In a study of international travellers returning to Spain, rates of trimethoprim-sulfamethoxazole resistance were reported to have decreased during the period of 2008–2013 [41]. This may be in part due to the fact that these antibiotics are no longer recommended by the World Health Organization (WHO) as empirical treatment for *Shigella* infections [41].

In recent years, resistance to alternative agents to fluroquinolones and azithromycin, such as third- and fourth-generation cephalosporins (e.g., cefotaxime, ceftazidime and cefepime), has been reported (Table 2). Cephalosporin-resistant *Salmonella* isolates, in particular, have been identified in surveillance studies on the prevalence enteric pathogens acquired during Hajj pilgrimage to Saudi Arabia and appear

to be increasing with consecutive seasons [70,117].

The emergence of enteropathogens that are resistant to multiple antibiotic classes is of great concern. In an *in vitro* study by Ouyang-Latimer et al. (2011), EAEC isolates from travellers to Central America exhibited antibiotic resistance to all drugs tested, except rifaximin, including ampicillin, nalidixic acid, tetracycline, doxycycline and trimethoprim-sulfamethoxazole. Similar findings have been reported for EPEC, in which isolates from TD patients in Nepal have shown high levels of resistance to amoxicillin, trimethoprim-sulfamethoxazole and nalidixic acid [76].

In the aforementioned study by Ouyang-Latimer et al. (2011), ETEC and EAEC isolates showed lower levels of resistance to rifaximin compared with most other antibiotics tested [108], although *Campylobacter* isolates from South Asia exhibited resistance to this agent [108]. The results of several studies have indicated that rifaximin prophylaxis can reduce the occurrence of mild TD in travellers to Latin America, Western Asia, South Asia and Southeast Asia, with protective efficacies ranging from 48% to 67% [118–121]. As expected, based on *in vitro* findings on the susceptibility of *Campylobacter* to rifaximin, this agent was not effective for the prevention of Campylobacteriosis in clinical trials [122].

The spread of multidrug resistant (MDR) bacteria, such as extended β-lactamase producing Enterobacteriaceae (ESBL-PE), is a critical threat to global public health [123]. International travel represents an important mode for the acquisition and dissemination of MDR bacteria around the world [124]. Travel to Southern and Southeast Asia carries a particularly high risk of acquiring ESBL-PE [125–132], with acquisition rates of over 90% reported in travellers to India [133,134]. Travelling to Sub-Saharan Africa may carry a lesser but significant risk [125–129], although rates in North Africa and Western Asia may be similar to those recorded in South and Southeast Asia (Table 3) [127–129,132]. Although most travellers who become colonised remain asymptomatic [123], travellers may spread the bacteria within the community and facilitate further dissemination of MDR bacteria on their return [130].

TD has been identified as a significant risk factor for colonisation with MDR bacteria such as ESBL-PE in several studies [125,127,128,132,135–138]. The occurrence of diarrhoea or gastrointestinal disorders during travel may increase the risk of acquiring MDR Enterobactericeae by a factor of 2–3 [135]. Use of antibiotics during travel seems to further elevate this risk, as demonstrated by Kantiele et al. (2015), who reported that 80% of Finnish travellers with TD who also took antibiotics acquired ESBL-PE [128]. Other risk factors for acquiring MDR bacteria include a vegetarian diet [127,139], travel for >2 weeks [127,138], having contact with a healthcare system and backpacking [127]. Old age has also been indicated as a risk factor for colonisation, although the occurrence of TD appears to diminish the differences in ESBL-PE carriage between young and old patients [128]. In fact, Barreto Miranda et al. (2016) observed that old age was protective against ESBL-PE acquisition in German travellers with gastrointestinal complaints [126]. Carriage of MDR bacteria is transient and usually lasts for a few months [135]. However, in some patients, ESBL-producing bacteria can be detected up to 3 years post travel [140].

6. Long-term sequalae

TD can significantly increase the risk of developing functional gastrointestinal disorders, including constipation, post-infectious irritable bowel syndrome (PI-IBS) and dyspepsia [141–144]. PI-IBS in particular may be more common than previously thought in patients who have experienced TD [145]. The results of studies suggest that women and younger people are at higher risk of developing long-term sequalae such as PI-IBS [144,146], whilst longer stays and longer duration of TD symptoms have also been identified as risk factors for developing PI-IBS [143–145]. Development of PI-IBS has also been linked to ETEC, with students in Mexico with TD caused by LT-ETEC having a greater risk of developing persistent abdominal symptoms in one study [143]. In addition to functional gastrointestinal disorders, TD has been associated with a number of other long-term sequalae, including Guillain-Barre syndrome and reactive arthritis [147].

7. Special populations

7.1. Humanitarian aid workers

Diarrhoea is a significant burden in young travellers carrying out NGO placements or humanitarian aid work overseas. Wyler et al. (2012) reported that TD was the most frequently experienced health problem in volunteers working on short-term projects in developing countries [4], whilst in another retrospective study, 88.9% of NGO volunteers acquired acute diarrhoea whilst on placement [16]. Even though NGO volunteers may possess better knowledge regarding diarrhoea prevention than general travellers [148], the high rates of TD described elucidates the importance of tailored travel advice in this population [148].

7.2. Visiting friends and relatives (VFRs)

VFRs account for a substantial proportion of all international travellers. Though VFRs are at a high risk of acquiring TD, the frequency of diarrhoea appears to be lower in this population than in other travellers. This may be due to the fact that VFRs may preserve immunity from their previous residency in the country they are visiting [149]. In a prospective study on the risk factors of TD in children, Soriano Arandes et al. (2016) identified being a VFR child as a risk factor for development of gastrointestinal symptoms during travel. These travellers are often younger and tend to stay longer durations in high-risk areas of low-income countries. The authors highlighted that many VFR children lack appropriate pre-travel advice, vaccinations and malaria prophylaxis, possibly due to being perceived as low risk of acquiring TD, poor accessibility to travel clinics and a lack of resources to buy prophylactic medicines [150].

7.3. Military personnel

Military personnel on deployment represent a specific subset of travellers in which diarrhoea causes significant morbidity. The rate of TD in military personnel on deployment is estimated to range between 27% and 40%, depending on region [17,68,151,152]. Diarrhoea may be more severe during deployment to certain areas, as indicated in a prospective study that found that personnel deployed in Afghanistan were more likely to require intravenous rehydration and hospitalisation than soldiers in Lebanon and Cote d'Ivoire [153]. Specific risk factors for TD in military populations include being Caucasian, being an officer, eating outside the military living area, diarrhoea in the individual's close circle and shorter duration of deployment [18,19,154]. Diarrhoea experienced by this population significantly impacts readiness for duty and remains a threat to military efficiency [68].

7.4. Immunosuppressed travellers

Travel guidelines recommend that travellers who are immunocompromised, such as those on immunosuppressive agents or with inflammatory bowel disease (IBD), carry on-demand antibiotics due to an increased risk of infection [21]. However, there is little evidence to suggest that patients who are immunocompromised experience TD at a higher frequency than those who are not immunosuppressed. In a prospective study by Baaten et al. (2011), there was no difference in diarrhoea frequency or duration between patients with IBD or receiving immunosuppressive medications and the control group [29]. Similarly, van Aalst et al. (2018) found that the incidence of TD was similar between travellers who were immunocompromised and not immunocompromised in a questionnaire-based observational study. However, the symptoms of TD appeared to be more severe in patients who were

Table 3
Acquisition rates for multidrug resistant Enterobacteriaceae after international travel by region and subregion.

Study	Bacteria	Overall global acquisition rate (%)	South and Central Asia (%)			Southeast and East Asia (%)		North Africa and Western Asia (%)		Sub-Saharan Africa (%)				Latin America and the Caribbean (%)	Europe and North America (%)
			India only	South Asia	Central Asia	East Asia	Southeast Asia	Western Asia	North Africa	West Africa	East Africa	Central Africa	South Africa		
Arcilla et al. (2017) [125]	ESBL-PE	34.3	–	21.5	6.5		31.6	1.9	5.4	3.2		9.0	1.1	3.8–5.2	<1.0
Barreto et al. (2016) [126]	ESPL-PE	50.7	72.0	40.0[a]	–	–	59.0	–	33.3	33.3	40.0	–	0.0	20.0[b]	0.0[c]
Dall et al. (2019) [134]	ESBL-PE	–	93.2	–	–		–	–	–	–	–	–	–	–	–
Furuya-Kanamori et al. (2019) [127]	MRE	13.0–88.0	–	58.7		37.5		–	43.9			21.8		18.3	10.3–16.9
Kantele et al. (2015) [128]	ESBL-PE	20.9	–	45.9	–	33.3	32.7		33.3			11.9		0.0	0.0[d]
Kantele et al. (2016) [129]	ESBL-PE	26.0	–	54.3	–	50.0	38.5		40.0			12.3		0.0	0.0
Laaveri et al. (2018) [137]	ESBL-PE	–	–	–	–	–	–	–	42.9	10.0	16.2	26.7	6.9	–	–
Lausch et al. (2013) [138]	ESBL-EC	12.5	–		15.0–37.5[a]			50.0			11.1			–	0.0–12.5[e]
McNulty et al. (2018) [130]	ESBL-PE	8.8	33.7	38.5	–	–	17.4[f]	10.6			16.4			9.8–19.4	5.7–11.3
Ruppe et al. (2015) [133]	MRE	50.9	90.6			72.4			–			47.7		31.1	–
Tham et al. (2010) [131]	ESBL-PE	24.0	78.6	–	–	–	38.5[d]	40.0			11.8[g]			–	3.2[h]
Vading et al. (2016) [132]	ESBL-PE	32.0	–	49.2[a]	–	–	19.1	–	44.0	–	–	–	–	–	–

ESBL-EC, extended-spectrum β-lactamase-producing *E. coli*; ESBL-PE, extended spectrum β-lactamase-producing Enterobacteriaceae; MRE, multidrug-resistant Enterobacteriaceae.

[a] Includes the Indian subcontinent.
[b] Estimate for Central America only.
[c] Estimates for Europe and the USA only.
[d] Includes Australia.
[e] Estimates for Europe only.
[f] Includes Pacific Asia.
[g] Excludes Egypt.
[h] Europe excluding Sweden.

immunocompromised, with weight loss and fatigue as symptoms of gastrointestinal disorders reported more frequently in this group [155].

8. Discussion

The overall global attack rate for TD ranges between 10% and 70%, although estimates vary greatly among studies [1,11,15,24–34]. The results of some investigations indicated that rates of TD have decreased compared with percentages published in the 2000s [36,37,47], particularly in East Asia (including China), Southeast Asia and some Latin American countries [10,26,27,32]. Although differences in the methodology, rates of successful isolation of pathogens and definitions of TD used may account for the wide range of estimates among studies [27,31,55], improved socioeconomic conditions and hygienic standards may also account for a decline in rates of TD among visitors to some regions [32].

Globally, the aetiology of TD appears to have shifted. Where ETEC was previously considered the predominant aetiological agent in TD, EAEC and EPEC now appear to be more prevalent in almost all regions of the world [30,61]. The role of EAEC and EPEC in TD may have previously been overlooked as these pathogens were not investigated in many epidemiological studies in the past [61]. For EAEC, identification has previously relied on phenotypical methods that could not be easily implemented in routine surveillance laboratories, such as the Hep-2 cell assay [85]. Modern molecular techniques such as PCR have now largely replaced phenotypical assays for identification of EAEC and have been implemented in diagnostic laboratories, which could explain the increased reporting of EAEC in TD [85,88]. Even with the implementation of modern diagnostic techniques, heterogeneity in virulence factors and a lack of reliable diagnostic markers for pathogenic strains complicate diagnosis of EAEC and make it difficult to determine its epidemiological significance as a TD pathogen [85,89].

The emergence of EAEC, EPEC and ETEC as the predominant DEC pathotypes in Southeast Asia is interesting, given that *Campylobacter* have long been considered most prevalent in this region [30]. The limited coverage of DEC in earlier investigations of TD represents one possible reason why the prevalence of *Campylobacter* may have been overestimated in this region [30]. However, in other studies published during the past 10 years *Campylobacter* was the most frequent pathogen among travellers to Southeast Asia [55,60,68,76]. However, investigations into TD in this region are often conducted in a single country, such as Thailand or Nepal [60,76], or primarily focus on military personnel [55,68], meaning that the findings of these investigations may not be representative of general travellers visiting the region.

The identification of organisms such as *C. difficile*, *Arcobacter* spp., *B. fragilis*, *T. whipplei* and *L. hongkongensis,* as causes of TD warrants further investigation into their prevalence and geographical distribution [42,46,59,60,73,104,110]. The role of some of these pathogens may have been overlooked in the past due to a lack of conventional culture methods and commercial detection kits [56,157]. For example, there is significant heterogeneity in diagnostic practices for CDI between testing sites, meaning that variability in physician awareness of *C. difficile* in TD could be contributing to underdiagnosis [104]. The emerging role of *C. difficile* as a causative agent in TD brings into question the use of antibiotics in travel medicine. Given the strong association between CDI and antibiotic consumption in the general population and case studies that describe onset of CDI after antibiotic treatment for TD, CDI prevention represents another reason to encourage the judicious use of antibiotics in travellers [104].

Due to their efficacy reducing the symptoms and shortening illness duration [7,8,21,112], it had become commonplace for physicians to provide antibiotics for self-treatment of TD in travellers visiting moderate- and high-risk areas [116]. TD enteropathogens have shown increasing levels of resistance to first-line antibiotics over the past two decades [116], bringing these treatment practices into question. Where fluoroquinolone resistance had previously been described for *Campylobacter* spp. in South and Southeast Asia, widespread resistance has been reported in most regions of the world and for other enteropathogens, including *Shigella*, *Salmonella*, ETEC and EAEC [41,92,108,113–115]. Concerningly, high rates of clinical failure have been observed with fluroquinolone therapy [92]. In light of this evidence, it is clear that fluroquinolones should no longer be recommended as the drug of choice for management or prevention of TD. Azithromycin represents another first-line agent for the treatment for TD, recommended in regions where fluoroquinolone resistance is prevalent (e.g. Southeast Asia) or in cases of dysentery or febrile diarrhoea [7]. High levels of azithromycin resistance have now been recorded in Asia, Africa and Latin America and the Caribbean [41,76,108,114,115]. Although this resistance has not yet been demonstrated to have translated into clinical failure [92], continued surveillance is warranted to monitor the appropriateness of azithromycin therapy.

Travel guidelines recommend rifaximin for the treatment of moderate-to-severe, non-dysenteric TD [7]. The efficacy of this agent has been demonstrated for the treatment and prophylaxis of TD [119,158]. In the case of EAEC and ETEC, rates of resistance to rifaximin appear to be lower than those observed for other antibiotics and there is no indication that rifaximin minimum inhibitory concentrations (MICs) increase among recovered isolates [7,108], although data on resistance rates are limited [7]. Furthermore, rifaximin should not be used to treat *Campylobacter*-associated TD due to its high level of resistance and evidence of clinical failure [116,122,159] and is unsuitable for the treatment of invasive disease [7]. Since the aetiology of TD remains undetermined in 40–50% of cases [160], physicians should exercise caution when prescribing rifaximin in regions where *Campylobacter* or invasive pathogens are prevalent.

The spread of MDR bacteria further complicates decisions about recommendations for empirical antibiotic therapy. Though rifaximin appears to be an attractive choice given its efficacy and safety profile [119,158], there are concerns that rifaximin may select for MDR Enterobactericeae in the gut microflora of returning travellers [109,159]. Fluroquinolone use during travel has also been shown to select for fluroquinolone-resistant ESBL-PE in visitors to tropical and subtropical regions [136]. Interestingly, clinical studies have indicated that treatment with Rifamycin SV-MMX, a novel oral formulation closely related to rifaximin, does not result in increased colonisation with ESBL-PE [80]. The formulation was similar to ciprofloxacin in terms of efficacy, suggesting that Rifamycin SV-MMX could be a suitable first-line option for patients with non-dysenteric TD [80].

Given the widespread resistance to first-line antibiotics used for the treatment of TD [41,92,113–115], there is a clear need for effective prevention strategies for TD. Vaccines may represent a useful prophylactic measure that could reduce the morbidity and disruption to travel caused by TD. A number of vaccines for enteropathogens such as ETEC, *Shigella*, *Campylobacter jejuni* and *Clostridium difficile* are in development and have shown promise in pre-clinical studies [161–163]. Considering it is already commonplace for travellers to receive vaccines for the prevention of intestinal infections such as cholera and typhoid fever before travelling to high-risk destinations [6,8], the question is raised as to whether clinical practices could be reconsidered to include routine immunisation before travel as vaccines against TD enteropathogens become available.

9. Conclusions

Although improved hygienic conditions in low-income countries may have slightly decreased attack rates of TD in some regions, diarrhoea remains the most common health issue experienced by international travellers to lower-income countries. DEC have been identified as the most prevalent pathogens in all regions of the world, although where ETEC was previously considered the predominant aetiological agent in TD, EAEC and EPEC appear to be most common. A number of bacterial

pathogens such as *C. difficile*, *T. whipplei*, *B. fragilis* and *Arcobacter* spp. have now been implicated in TD. The increasing rate of antimicrobial resistance in TD enteropathogens elucidates the need for continued surveillance and reconsideration of current treatment practices, to balance the need for optimal clinical outcomes in those who need treatment with local antimicrobial resistance concerns. Considering the current situation of increasing and widespread resistance to first-line antimicrobials for TD, the development of effective vaccines against common gastrointestinal enteropathogens may represent a useful prophylactic measure that can reduce the morbidity and disruption caused by TD.

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