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Stand-by antibiotics encourage unwarranted use of antibiotics for travelers' diarrhea: A prospective study☆

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ABSTRACT

Background: As antibiotics predispose travelers to acquiring multidrug-resistant intestinal bacteria, they should no longer be considered a mainstay for treating travelers' diarrhea. It has been claimed that stand-by antibiotics are justified as a means to avoid visits to local healthcare providers which often lead to polypharmacy.
Method: We revisited the traveler data of 316 prospectively recruited volunteers with travelers' diarrhea by retrieving from questionnaires and health diaries information on antibiotic use, stand-by antibiotic carriage, and visits with local healthcare. Multivariable analysis was applied to identify factors associated with antibiotic use.
Results: Among our 316 volunteers with travelers' diarrhea, however, carrying stand-by antibiotics seemed not to reduce the rate of healthcare-seeking; on the contrary, antibiotic use was more frequent among stand-by antibiotic carriers (34%) than non-carriers (11%). Antibiotics were equally taken for severe and incapacitating travelers' diarrhea, but compared to non-carriers, stand-by antibiotic carriers resorted to medication also for mild/moderate (38% vs. 4%) and non-incapacitating disease (29% vs. 5%). Antibiotic use was associated with stand-by antibiotic carriage (OR 7.2; 95%CI 2.8–18.8), vomiting (OR 3.5; 95%CI 1.3–9.5), incapacitating diarrhea (OR 3.6; 95%CI 1.3–9.8), age (OR 1.03; 95%CI 1.00–1.05), and healthcare visit for diarrhea (OR 465.3; 95%CI 22.5–9633.6).
Conclusions: Carriage of stand-by antibiotics encouraged less cautious use of antibiotics. Recommendations involving prescription of antibiotics for all travelers require urgent revision.

1. Introduction

Travelers' diarrhea (TD) remains the most common health problem encountered by travelers to low-income regions [1–4]. At present, its treatment is hotly debated. Traditionally, antibiotics used to be the mainstay of TD treatment [5], and even prophylaxis [6,7], yet recently the justification for this approach has been questioned due to the upsurge in antimicrobial resistance (AMR) [8–10]. AMR rates are highest in developing countries because of insufficient hygiene and lax/non-existent antibiotic policy; approximately 20–70% of travelers to these areas become colonized by multidrug-resistant (MDR) intestinal bacteria, especially extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) [11]. More importantly, several studies have demonstrated antibiotic treatment of TD to predispose travelers to colonization by ESBL-PE [11–16]. Very recently, it was shown that antibiotics, indeed, select ESBL-PE with the broadest spectrum of co-resistance [17]. Several guidelines have now been revised to direct health practitioners toward less liberal writing of prescriptions [18], and antibiotics are no longer recommended for mild/moderate TD [19,20].

Seeking background data for advice on how to prevent unwarranted antibiotic use, we applied three approaches: (1) identifying risk factors associated with antibiotic treatment of TD among 316 prospectively recruited Finnish travelers who had contracted TD, (2) surveying their use of stand-by antibiotics, and (3) looking at the medications provided by healthcare abroad.

Abbreviations: SBA, stand-by antibiotics; TD, travelers' diarrhea; MDR, multidrug-resistant; AMR, antimicrobial resistance

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2. Material and methods

2.1. Study design

Data for this prospective study were retrieved from the database of our previous research [4]. We included all 316 volunteers who had traveled to the (sub)tropics (duration of stay 4 days–6 months) and contracted TD. The travelers, all recruited at a pre-travel visit to the Aava Travel Clinic in Helsinki, had filled in (1) questionnaire 1 (Q1) on that occasion, (2) a health diary during the journey, and (3) questionnaire 2 (Q2) at home, within two days after return. Our inclusion criteria included having returned Q1 and Q2. The study protocol had been approved by the Ethics Committee of the Helsinki University Hospital; informed consent had been obtained from all volunteers.

2.2. Questionnaires

The two questionnaires Q1 and Q2 consisted of 103 multiple-choice or open-ended questions. The health diary collected more detailed information on daily symptoms and behavior, with a special focus on severity of illness, duration of symptoms, disability, and antibiotic use.

2.3. Definitions

TD was defined according to the WHO criteria as passage of loose or liquid stools more frequently than is normal for the individual [21]. The severity of TD was evaluated by two different approaches: (1) using the definition “severe TD” to refer to cases with ≥6 diarrheal stools/day, hemorrhagic diarrhea, or diarrhea accompanied by fever (> 37.5 °C) (all others defined as mild/moderate TD), and (2) using the definition “incapacitating TD” to refer to diarrhea that had, as reported by the travelers themselves, disrupted or prevented activities planned for the day.

2.4. Destinations

Destinations were categorized into geographical regions. A modification of the UN definition was used, and eight regions were formed [22]: Latin America and the Caribbean, Southern Asia, South-Eastern Asia, Eastern Asia and Central Asia, Northern Africa and Western Asia, Western Africa and Middle Africa, Eastern Africa, and Southern Africa (Table 1). For travelers visiting several destinations, the one with the greatest risk of diarrhea was selected as primary destination. As a reference map of diarrhea risk, we used the one published by Steffen et al. [2].

2.5. Analysis

Univariable and multivariable models were applied. A p-value < 0.05 was considered significant in Pearson Chi-square and Fisher's exact tests. Factors with a p-value < 0.20 in univariable analysis were chosen for the Firth regression model, and their adjusted odds ratios and 95% confidence intervals were calculated. Missing values were assumed to be missing at random (MAR), and multiple imputations in SPSS and Stata were performed. Due to complete separation, Firth logistic regression model was fitted to the data. We also compared the results to a logistic regression model. The statistical analyses were carried out with SPSS Statistics (version 24.0.0.1, IBM Corp., Armonk, NY) and Stata (version 15, StataCorp LLC, College Station, TX).

3. Results

3.1. Cohort population

All 316 volunteers filled in Q1 and Q2 (inclusion criteria). The health diary was returned by 74% (237/316) of the travelers. Information on diarrhea characteristics was available for 94% (298/316) and incapacitation level for 67% (213/316) of the participants. Data on whether or not SBA had been prescribed before travel was provided by 84% (266/316); 20% (54/266) had been given SBA. In 98% (53/54) of the cases, SBA had been prescribed to be used for severe diarrhea symptoms (fluoroquinolone or macrolide), and in one for skin infection (cephalexin). Demographic data are presented in Table 1 and flowchart of study protocol with central results in Fig. 1. Treatment of TD is described in Supplementary Table 1.

3.2. Stand-by antibiotics

Of our 53 travelers carrying SBA for TD, 69% (36/52) did not use them at all, 29% (15/52) used for TD, and 2% (1/52) for prevention of skin infection; data were incomplete for one traveler. Among those using SBA, the criteria of severe TD were met by 36% (5/14) of the cases, and mild/moderate TD by the rest (64%). Respectively, 54% (7/13) categorized their TD as incapacitating, and the rest (46%) as non-incapacitating (Table 2).

SBA carriers and non-carriers differed with regard to the rate of using antibiotics for non-severe TD (SBA carriers 38%; 10/26 vs. SBA non-carriers 4%; 4/96, OR 14.4, 95% CI 4.0–51.5) or non-incapacitating TD (SBA carriers 29%; 7/24 vs. SBA non-carriers 5%; 5/95, OR 7.4, 95% CI 2.1–26.1).

In univariable analysis seeking risk factors predisposing SBA carriers to using SBA for TD, vomiting (OR 3.9, 95% CI 1.1–14.3) was the only factor identified (Table 2). No significant difference was found between those using versus not using SBA with respect to the various demographic (Supplementary Table 2) or behavioral factors (Supplementary Table 3), with the exception of type of toilet.

The risk factors for using SBA in the group of SBA carriers differed from those predisposing to antibiotic use among SBA non-carriers (liquid stools, fever, duration of TD, number of stools per day, severity of TD, incapacitation level of TD; Table 2). The only risk factor shared by SBA carriers and non-carriers was vomiting.

3.3. Risk factors for using antibiotics for travelers' diarrhea

TD was treated with antibiotics by 16% (52/316) of the travelers. To identify factors predisposing to antibiotic use, the data of all 316 travelers with TD were subjected first to univariable and then to multivariable analysis (Supplementary Table 2, Table 3). The following were identified as risk factors in multivariable analysis: carriage of SBA (OR 7.2, 95% CI 2.8–18.8), vomiting (OR 3.5, 95% CI 1.3–9.5), incapacitating diarrhea (OR 3.6, 95% CI 1.3–9.8), age (OR 1.03, 95% CI 1.00–1.05), and seeking healthcare for TD (OR 465.3, 95% CI 22.5–9633.6). Severe TD proved not to be a significant risk factor. When the Firth results were compared with ordinary logistic regression, all effects and p-values were very close in both models except for the variable whose maximum likelihood estimation did not exist.

3.4. Healthcare visits

Seeking healthcare for TD was associated in the univariable model with vomiting (OR 8.0, 95% CI 3.2–20.2), severe diarrhea (OR 16.4, 95% CI 3.7–73.0), incapacitating diarrhea (OR 12.7, 95% CI 3.6–45.4), fever over 37.5 °C (OR 10.5, 95% CI 4.0–27.4), longer duration (> 3 days) of diarrhea (OR 4.1, 95% CI 1.6–10.0), liquid stools (OR 7.3, 95% CI 1.7–32.1), slimy stools (OR 5.8, 95% CI 2.1–15.8), and increased number of stools (≥6 stools/day; Table 4).

When comparing by univariable analysis those only using SBA for TD and those seeking healthcare because of TD, the latter had more commonly had severe (OR 36.0, 95% CI 3.2–405.9) or incapacitating diarrhea (OR 12.0, 95% CI 1.2–123.7), and fever (OR 33.0, 95% CI 3.2–342.3). No difference was found between these two groups in occurrence of vomiting, duration of diarrhea, type of diarrheal feces,

Table 1
Demographics, travel information, and antibiotic use among 316 travelers with diarrhea, initially recruited at a pre-travel visit to a Finnish travel clinic in Helsinki between December 2008 and February 2010, all staying in the (sub)tropics for more than four days and less than six months.

	Total	SBA (n = 266), no. (%)		OR (95% CI)	P-value
	No. (%)	Non-carriers (n = 213)	Carriers (n = 53)		
Sex (md = 0)					0.018
Male	112 (35)	81 (38)	11 (21)	1.0	
Female	204 (65)	132 (62)	42 (79)	2.3 (1.1–4.8)	
Age, years, median (IQR) (md = 0)	33 (27–52)	33 (26–50)	43 (28–60)		0.360
0–17	17 (5)	13 (6)	1 (2)	1.0	
18–29	100 (32)	70 (33)	13 (25)	2.4 (0.3–20.1)	
30–54	134 (42)	89 (42)	24 (45)	3.5 (0.4–28.2)	
55–64	44 (14)	27 (13)	9 (17)	4.3 (0.5–37.9)	
65–	21 (7)	14 (7)	6 (11)	5.6 (0.6–52.7)	
Duration of travel, median in days (IQR) (md = 1)	18 (14–30)	18 (14–30)	21 (14–38)		0.088
4–7 (md = 0)	8 (3)	7 (3)	0 (0)	«1[a]	
8–29	223 (71)	153 (72)	33 (62)	0.6 (0.3–1.1)	
30–160	85 (27)	53 (25)	20 (38)	1.0	
Purpose of travel (md = 1)					0.009
Vacation	261 (83)	181 (85)	36 (68)	1.0	
Business	25 (8)	16 (8)	7 (13)	2.2 (0.8–5.7)	
Other/multiple purposes	29 (9)	15 (7)	10 (19)	3.4 (1.4–8.1)	
Geographical region (md = 0)					0.222
South-Eastern Asia	83 (26)	58 (27)	10 (19)	1.0	
Eastern Africa	72 (23)	51 (24)	11 (21)	1.3 (0.5–3.2)	
Western Africa, Middle Africa	57 (18)	36 (17)	14 (26)	2.3 (0.9–5.6)	
Southern Asia	56 (18)	42 (19)	7 (13)	1.0 (0.3–2.7)	
Latin America and the Caribbean	23 (7)	12 (6)	4 (8)	1.9 (0.5–7.2)	
Southern Africa	15 (5)	9 (4)	3 (6)	1.9 (0.4–8.4)	
Northern Africa, Western Asia	6 (2)	3 (1)	2 (4)	3.9 (0.6–26.1)	
Eastern Asia, Central Asia	4 (1)	2 (1)	2 (4)	5.8 (0.7–46.0)	
Antibiotic for TD	52 (16)	23 (11)	18 (34)	4.2 (2.1–8.7)	< 0.001

Abbreviations: missing data – md; travelers' diarrhea – TD; stand-by antibiotics – SBA; maximum likelihood estimation – MLE; loperamide – LO; antibiotic – AB.
[a] MLE of variable duration of travel 4–7 days does not exist.

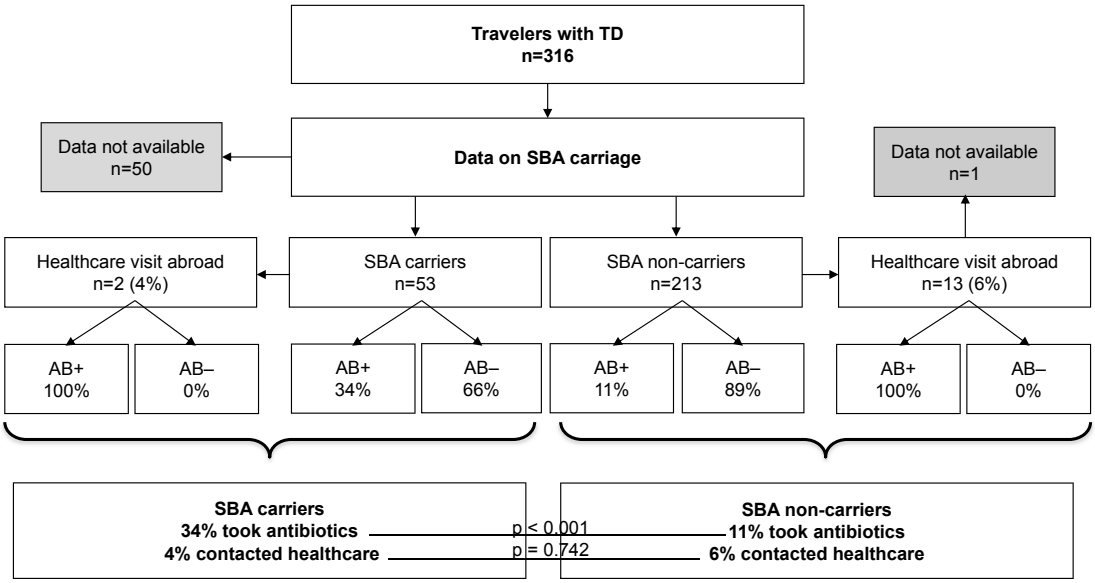

Fig. 1. Flowchart of study protocol with central results.

number of stools per day, or TD-related symptoms at return home (data not shown).

The primary indication of SBA carriers to seek healthcare was gastroenteritis. In univariable analysis, the rate of TD-related healthcare visits did not differ significantly between SBA carriers and non-carriers (3.8% (2/53) versus 6.1% (13/212); OR 0.6, 95% CI 0.1–2.7; Fig. 1, Table 4). In multivariable analysis covering four TD-related factors (SBA carriage, vomiting, number of stools/day as a continuous factor, fever plus TD) SBA carriage did not decrease the rate of healthcare visits (data not shown, OR 0.41, 95% CI 0.04–4.5).

3.5. Antimicrobials given at healthcare visits

All the 21 travelers who had consulted local healthcare practitioners or had been hospitalized for TD symptoms had been provided antibiotics (Fig. 1, Table 5): 24% (5/21) had been given parenteral antibiotics, and 57% (12/21) more than one regimen. SBA had been carried by 13% (2/15) of those seeking medical care for TD symptoms. The antibiotic most commonly provided abroad was ciprofloxacin. Two different fluoroquinolone regimens had been co-administered to two travelers.

Table 2
Study of 316 prospectively recruited travelers with diarrhea: univariable analysis of TD-related factors correlating with the use of SBA for TD among SBA carriers and use of antibiotic for TD among SBA non-carriers.

	SBA carriers who used SBA for TD			SBA non-carriers who used AB for TD		
	No. (%)	OR (95% CI)	P-value	No. (%)	OR (95% CI)	P-value
Total, proportions of all	15/53 (28)			23/213 (11)		
Liquid stools	11/31 (35)	3.3 (0.8–13.7)	0.091	20/115 (17)	8.8 (2.0–39.0)	0.001
Loose stools	10/36 (28)	1.2 (0.3–4.4)	1.000	12/134 (9)	0.6 (0.2–1.4)	0.201
Slimy stools	1/4 (25)	0.9 (0.1–9.4)	1.000	3/19 (16)	1.6 (0.4–6.0)	0.444
Hemorrhagic stools	–	–	–	0/3 (0)	«1 [a]	1.000
Fever plus TD	3/11 (27)	0.9 (0.2–4.1)	1.000	12/37 (32)	7.2 (2.9–18.1)	< 0.001
Duration of TD, days			1.000			0.049
1–3	11/39 (28)	1.0		13/152 (9)	1.0	
> 3	3/13 (23)	0.8 (0.2–3.3)		9/48 (19)	2.5 (1.0–6.2)	
Stools per day, median (IQR)	4.5 (2.3–5.0)		1.000	7.0 (4.0–11.3)		0.001
0–2	3/8 (38)	1.0		1/39 (3)	1.0	
3–5	7/21 (33)	0.8 (0.2–4.5)		5/73 (7)	2.8 (0.3–24.8)	
≥6	2/7 (29)	0.7 (0.1–5.9)		8/25 (32)	17.9 (2.1–154.5)	
Vomiting	7/14 (50)	3.9 (1.1–14.3)	0.046	11/29 (38)	8.8 (3.4–22.7)	< 0.001
Severity of TD[b]			0.722			< 0.001
Mild/moderate TD	9/26 (35)	1.0		4/96 (4)	1.0	
Severe TD	5/17 (29)	0.8 (0.2–2.9)		13/49 (27)	8.3 (2.5–27.2)	
Incapacitation level of TD [b]			0.148			< 0.001
Non-incapacitating TD	6/24 (25)	1.0		5/95 (5)	1.0	
Incapacitating TD	7/13 (54)	3.5 (0.8–14.6)		16/43 (37)	10.7 (3.6–31.8)	
TD-related symptoms on arrival	4/14 (29)	1.0 (0.3–3.8)	1.000	8/62 (13)	1.3 (0.5–3.3)	0.558
Healthcare visit for TD	2/2 (100)	»100 [a]	0.076	13/13 (100)	»100 [a]	< 0.001

[a] MLE of variables hemorrhagic stools and healthcare contact for TD does not exist.

[b] Diarrhea was defined by WHO criteria (passage of ≥3 loose or liquid stools per day, or more frequently than normal for the individual). Severe TD: diarrhea accompanied by fever, hemorrhagic diarrhea, or diarrheal stools ≥6 per day. Non-severe TD: diarrhea not filling the criteria of severe TD. Incapacitating TD: diarrhea that disrupted or completely prevented activities planned for the day. Non-incapacitating TD: diarrhea not meeting the criteria of incapacitating TD.

4. Discussion

SBA has long been prescribed to a substantial proportion of travelers [1,23]. Recently, however, this practice has been challenged, since antibiotic use has been shown to predispose travelers to contracting intestinal MDR bacteria [11–16]. At the same time, prescribing SBA has been justified by its assumed effect of decreasing the rate of seeking healthcare while abroad. This study exploring data on SBA among 316 Finnish travelers found that, as opposed to common belief, carrying SBA did not keep travelers from seeking healthcare. And, in fact, SBA increased their use of antibiotics.

4.1. Use of stand-by antibiotics

One of our major findings was that antibiotics were taken for TD more frequently by SBA carriers (34%) than non-carriers (11%) (Fig. 1). While we did not find any other studies comparing specifically SBA use among carriers and non-carriers, our rates of antibiotic use in the two groups accord with previous research focusing on TD in general, yet also providing data on SBA carriage: Stoney et al. [23] presents 163 SBA carriers with TD, 36% of whom had treated it with antibiotics, and a report by Belderok et al. [24] describes 597 SBA non-carriers with TD, only 5% of whom had taken antibiotics.

All travelers with SBA had been advised to use their SBA only for TD symptoms they considered severe. Despite this, comparisons between the two subgroups, SBA carriers and non-carriers, revealed that SBA carriers treated mild/moderate TD with antibiotics more frequently (38% vs. 4%, OR 14.4); a similar difference was recorded for non-incapacitating diarrhea (29% vs. 5%, OR 7.4). As regards of severe and incapacitating TD, by contrast, the rates of antibiotic use did not differ significantly between SBA carriers and non-carriers. Carrying SBA thus appears to lead to less cautious use of antimicrobials, *i.e.* treating mild/moderate and non-incapacitating TD with antibiotics, and, in one case, even taking SBA for another indication than TD.

4.2. Use of antibiotics for travelers' diarrhea

Earlier studies report rates of antibiotic use for TD ranging from 5% to 45% [1,24–26], the huge difference between the scanty (Netherlands [24]) and the wide (USA [1]) use correlating with differences in rates of prescribing SBA; in an investigation by Hill [1] among US travelers, 89%–92% had been prescribed antibiotics, while in another by Belderok et al. [24] among Dutch travelers, none had. In a study by Pitzurra et al. [25] among Swiss travelers, only 7% had taken antibiotics for TD. The rates of SBA carriers are not provided in the report, but all travelers had obtained written instructions on how to use antibiotics [25]. In an investigation by Soonawala et al. among Dutch travelers, 7% had carried SBA and 9% had used antibiotics for TD [26]. In our study, respectively, of all volunteers, 20% had carried SBA and 16% had taken antibiotics to treat TD. Taken together, these data suggest a connection between the rates of SBA carriage and recourse to antibiotics for TD, which accords with our finding that SBA carriage predisposes to antibiotic use.

4.3. Treatment of severe versus incapacitating TD with antibiotics

In multivariable analysis, treating TD with antimicrobials correlated with incapacitating but not severe diarrhea (antibiotics taken by 45% vs. 32%, respectively). Likewise, the use of any medication (antibiotic or loperamide) appeared more common among those with incapacitating (77%) than severe TD (59%). The data indicate that recourse to antibiotics or any medication depends more on travelers' subjective experience of incapacitation than objective symptoms, such as fever or number of stools.

Our data demonstrate that neither severe nor incapacitating diarrhea always *require* antibiotic treatment. In the severe TD group, 26% used only loperamide and 41% no medications at all, *i.e.* 67% managed without antibiotics. In the incapacitating groups, the respective figures were 32%, 23%, and 55% (Supplementary Table 1). Thus, even if a case meets the criteria of severe/incapacitating diarrhea, that does not

Table 3
Univariable and multivariable analyses of factors correlating with antibiotic use for TD.

	AB for TD No. (%)	Univariable OR (95% CI)	P-value	Multivariable AOR (95% CI) for using AB for TD [a]	P-value
Total, proportions of all (md = 0)	52/316 (16)				
Age [b] , median (IQR) (md = 0)	32 (27–59)		0.144 [c]	1.03 (1.00–1.05)	0.047
0–17	3/17 (18)	1.0			
18–29	19/100 (19)	1.0 (0.3–4.2)			
30–54	16/134 (12)	0.6 (0.2–2.4)			
55–64	7/44 (16)	0.9 (0.2–3.9)			
65–	7/21 (33)	2.3 (0.5–11.0)			
Severe diarrhea (md = 92)	13/130 (10)	3.6 (1.8–7.1)	< 0.001 [c]		
Incapacitating diarrhea (md = 103)	37/81 (46)	6.9 (3.4–13.9)	< 0.001 [c]	3.6 (1.3–9.8)	0.011
Vomiting (md = 0)	26/54 (48)	8.4 (4.3–16.5)	< 0.001 [c]	3.5 (1.3–9.5)	0.012
Carrying stand-by antibiotics (md = 50)	18/53 (34)	4.2 (2.1–8.7)	< 0.001 [c]	7.2 (2.8–18.8)	< 0.001
Healthcare visit (md = 0)			< 0.001 [c]		
No	30/278 (11)	1.0		1.0	
For TD	21/21 (100)	»100 [d]		465.3 (22.5–9633.6)	< 0.001
For other reason	1/17 (6)	0.5 (0.1–4.0)		0.7 (0.1–5.1)	0.731
Location (md = 16)			0.636		
City	13/83 (16)	1.0			
Countryside/jungle	39/217 (18)	1.2 (0.6–2.3)			
Accommodation (md = 7)			0.956		
Hotel	18/108 (17)	1.0			
Guest house/home of a local	34/201 (17)	1.0 (0.5–1.9)			
Type of toilet (md = 5)			0.085 [c]		
WC as a toilet	46/254 (18)	1.0		1.0	
Other type of toilet	5/57 (9)	0.4 (0.2–1.1)		0.3 (0.04–1.5)	0.125
Used other than bottled water (md = 2)	3/16 (19)	1.2 (0.3–4.3)	0.735		
Alcohol consumption (md = 41)			0.025 [c]		
0–2 units per day	37/204 (18)	1.0			
3– units per day	5/71 (7)	0.3 (0.1–0.9)			
Site of meals (md = 9)			0.588		
Restaurant more than 50% of meals	44/257 (17)	1.0			
Own household and sometimes elsewhere	7/50 (14)	0.8 (0.3–1.9)			
Ate uncooked meat/fish (md = 2)	6/35 (17)	1.0 (0.4–2.7)	0.922		
Did not wash hands always/often (md = 10)	4/40 (10)	0.5 (0.2–1.5)	0.207		
Ate salads (md = 19)	38/238 (16)	0.7 (0.3–1.4)	0.269		
Diet (md = 102)			1.000		
Omnivore	35/190 (18)	1.0			
Vegetarian	4/24 (17)	0.9 (0.3–2.8)			
Used milk as part of diet (md = 102)	36/210 (17)	0.6 (0.1–6.1)	0.535		
Did not always use utensils (md = 16)	19/96 (20)	1.3 (0.7–2.5)	0.377		
Was in contact with freshwater (md = 108)	22/82 (27)	3.2 (1.5–6.8)	0.002 [c]		
Walking barefoot often/sometimes (md = 3)	34/223 (15)	1.4 (0.4–1.4)	0.306		
Unprotected sex with local (md = 18)	2/7 (29)	1.9 (0.4–10.2)	0.352		
Other close contact with local (md = 19)	11/63 (17)	1.0 (0.5–2.1)	0.991		
Insect stings (md = 15)	40/249 (16)	0.7 (0.3–1.5)	0.374		

[a] Firth logistic regression was used with multiple imputations (70 data sets). Backward selection using p-values eliminated from those included in the first stage multivariable model: duration of travel (continuous variable), duration of diarrhea (two categories), number of stools/day (three categories), type of diarrhea (two categories), fever (three categories), BMI (two categories), purpose of travel (two categories), consumption of alcohol (two categories), and contact with freshwater (two categories).

[b] Analyzed as continuous variable.

[c] Factor with p-value less than 0.20 in univariable analyses were chosen for the multivariable model. Severe TD and incapacitating TD were analyzed in separate models.

[d] MLE of variable healthcare visit for TD does not exist due to low numbers.

indicate a necessity to take antibiotics, merely suggests antibiotics to be considered. This finding supports guidelines not recommending antibiotics for any cases of non-severe or non-incapacitating TD. Moreover, our results encourage stricter policies for antibiotic use than recently suggested [27].

4.4. Risk factor analyses

When analyzing risk factors predisposing to antibiotic use, our findings revealed substantial differences between SBA carriers and non-carriers. Among the SBA carriers, the various symptoms of TD (except for vomiting) were not found to correlate with recourse to SBA. Among those not carrying SBA, the risk factors for antibiotic use included liquid stools, fever, duration of TD, high number of stools, vomiting, and symptoms consistent with severe or incapacitating diarrhea, i.e. factors akin to those associated with healthcare visits. In fact, these factors also accord with the instructions given on SBA use by the doctor who had initially prescribed the drugs in Finland before departure.

In multivariable analysis of antibiotic use for TD covering the entire cohort, five risk factors were identified: age, incapacitating TD, vomiting, SBA carriage, and TD-related healthcare visits. As far as we know, this is the first study to explore and identify SBA carriage as a risk factor for antibiotic use among travelers. Identification of SBA carriage as a risk factor is highly relevant when looking for means to cut back on antibiotic use. While seeking medical care always seems to lead to antibiotic use, carrying SBA appears not to solve the problem either.

4.5. Alternatives to antibiotic treatment

Recommendations for cautious use of antibiotics in TD treatment have raised valid questions about non-antibiotic alternatives. Attention has centered on loperamide, a drug widely used for decades. It is

Table 4
Univariable models on TD-related factors correlating with healthcare visit due to TD.

	Healthcare visit due to TD		
	No. (%)	OR (95% CI)	P-value
Total, proportions of all	21/315 (7)		
Liquid stools	18/173 (10)	7.3 (1.7–32.1)	0.002
Loose stools	10/197 (5)	0.5 (0.2–1.3)	0.133
Slimy stools	7/31 (23)	5.8 (2.1–15.8)	0.002
Hemorrhagic stools	0/4 (0)	«1[a]	1.000
Fever plus TD	14/61 (23)	10.5 (4.0–27.4)	< 0.001
Duration of TD, days			0.003
1–3	10/228 (4)	1.0	
> 3	11/70 (16)	4.1 (1.6–10.0)	
Stools per day, median (IQR)	7.0 (5.0–10.0)		< 0.001
0–2	0/57 (0)	«1[a]	
3–5	6/106 (6)	0.2 (0.1–0.7)	
≥6	9/44 (20)	1.0	
Vomiting	12/54 (22)	8.0 (3.2–20.2)	< 0.001
Severity of TD			< 0.001
Mild/moderate TD	2/137 (1)	1.0	
Severe TD	17/87 (20)	16.4 (3.7–73.0)	
Incapacitation level of TD			< 0.001
Non-incapacitating TD	3/139 (2)	1.0	
Incapacitating TD	16/73 (22)	12.7 (3.6–45.4)	
TD-related symptoms at arrival	7/87 (8)	1.3 (0.5–3.4)	0.571
SBA			0.742
Non-carriers	13/212 (6)	1.0	
Carriers	2/53 (4)	0.6 (0.1–2.7)	

[a] MLE of variables hemorrhagic stools and 0–2 stools per day does not exist.

effective for TD; in fact, comprehensive data that would show antibiotics given singly to be superior to loperamide has not been presented so far [28]. Taken singly, loperamide does not increase the risk of contracting ESBL-PE [29]. Taken together with antibiotics, the drug has been found effective in treating TD [30], but the combination does predispose to MDR colonization [29]. Further, it should be noted that in our study 31% (98/316) of the travelers successfully treated their TD with only loperamide.

Racecadotril is efficacious for infectious diarrhea [31,32], yet studies among travelers are lacking. As regards probiotics, we found no data to support their use in treating TD.

4.6. Local healthcare abroad

Prescribing SBA has been justified as a means to prevent healthcare-seeking abroad which is generally associated with polypharmacy [33]. Indeed, in our study all healthcare visits led to antibiotic treatment and half of them to polypharmacy. Our results suggest, however, that carrying SBA does not decrease the number of heath care visits, thus disputing the justification for prescribing SBA (Fig. 1).

Future studies should address the impact of SBA on unwarranted use of antibiotics and rates of healthcare visits *if* the SBA is given with written, detailed instructions or the option of remote consultation to obtain accurate guidance. Another pertinent project might research into carrying non-antibiotic medication (loperamide, racecadotril) and written advice on antibiotic regimen and route of administration to be handed out to local practitioners, should care be sought.

Table 5
Data on 21 travelers who contacted local healthcare because of TD.

Destination in subtropics	Sex	Severe/ incapacitating TD	Fever/ Vomiting	Carried SBA	Self-reported diagnosis	Antimicrobial treatment	Parenteral/no. of regimens
Gambia	F	Yes/-	Yes/no	No	TD, fever	Ciprofloxacin	No/1
Gambia, Senegal	F	-/yes	No/yes	No	Gastroenteritis	Unknown antibiotic	No/1
Ghana, Benin	F	Yes/no	Yes/no	No	TD, suspected malaria	Ciprofloxacin, ceftriaxone, artemether/lumefantrine, quinine	Yes/5
India	F	Yes/yes	Yes/yes	No	Gastroenteritis, flu	Ciprofloxacin	No/1
India	F	Yes/yes	Yes/no	No	TD	Ofloxacin, tinidazole	No/2
India	F	Yes/yes	Yes/yes	No	Food poisoning	Ofloxacin, two unknown antibiotics	Yes/3
India	F	Yes/yes	Yes/yes	Yes[a]	Food poisoning	Ciprofloxacin, tinidazole	No/2
Indonesia	F	Yes/no	Yes/yes	–	TD, cystitis, otitis, pneumonia (in Finland)	Unknown antibiotic	No/1
Indonesia, Singapore	M	Yes/yes	Yes/no	–	TD	Ciprofloxacin	No/1
Indonesia, Singapore	F	Yes/yes	Yes/yes	No	Amebiasis	Ciprofloxacin, metronidazole	Yes/2
Mexico	F	-/yes	No/yes	No	TD	Ciprofloxacin, ofloxacin	No/2
Namibia, Swaziland	F	Yes/yes	Yes/yes	No	Gastroenteritis	Ciprofloxacin, amoxicillin	No/2
Nigeria	F	No/yes	No/no	No	TD, malaria	Ciprofloxacin, metronidazole, artemether/lumefantrine	No/4
Peru	F	No/yes	No/yes	–	TD (salmonella + giardia)	Ciprofloxacin, levofloxacin, secnidazole, tinidazole	No/4
Singapore, Malaysia, Myanmar	M	Yes/yes	Yes/yes	No	"I do not recall"	Ciprofloxacin, unknown antibiotic x2	No/3
Tanzania	F	Yes/yes	No/yes	–	Gastroenteritis	Ciprofloxacin	No/1
Tanzania	M	Yes/-	Yes/yes	Yes[a]	Food poisoning	Ciprofloxacin, mebendazole	Yes/2
Thailand	M	Yes/no	No/no	–	TD, external otitis	Unknown antibiotic	Yes/1
Thailand, Cambodia, Vietnam	M	Yes/yes	Yes/no	No	TD	Ciprofloxacin, nifuroxazide	No/2
Thailand, Laos, Indonesia	M	Yes/yes	No/no	No	TD	Unknown antibiotic	No/1
Thailand, Laos, Vietnam, Cambodia	M	Yes/yes	Yes/no	–	Food poisoning (no rotavirus or parasite)	Ciprofloxacin	No/1
Summary	F 14/21	18/19 / 16/19	14/21 / 12/ 21	2/15			5/21 median 2

[a] Both (2/2) SBA carriers used it for TD.

4.7. Limitations

Some drawbacks of this study need to be addressed. First, the number of travelers and SBA carriers was limited, restricting the statistical power of some analyses. This may apply especially to healthcare visits. However, even if SBA would further decrease the initially low rates of healthcare visits reported in many studies (3%–10%) [24,26,34–36], the increase caused by antibiotic use for non-severe diarrhea among SBA carriers would by far exceed the small benefit the decreased number of healthcare contacts might bring.

Second, the personalities of those carrying SBA may have had some impact on the outcome. SBA was prescribed probably mostly for those actively requesting; thus this group may have included overly concerned persons. However, such personality may not necessarily correlate with more liberal use of antibiotics, but instead, the travelers may simply wish to be well-prepared. In the present study, the SBA carrier and non-carrier groups were similar with regard to particulars, yet the former included more females, who might have been more eager to ask for prescriptions. It is noteworthy, however, that the rates of recourse to antibiotics did not differ between females and males in the SBA group. Moreover, the OR for SBA carriage as risk factor for antibiotic use was exceptionally high (OR 7.2, 95% CI 2.8–18.8), which makes it highly unlikely that a possible bias in the estimate would account for all of it.

5. Conclusions

In our data, seeking medical care for TD while abroad led to antibiotic use without exception, and often to polypharmacy. However, carrying SBA appeared not to prevent medical visits either. On the contrary, it encouraged less cautious use of antibiotics. Not only did SBA carriers resort more to antibiotics, but the drugs were mostly taken for non-severe and non-incapacitating diarrhea. To cut back on unwarranted use of antibiotics for TD, new approaches need to be explored.

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Authors' contributions

Study concept and design: AK; acquisition of data: KV, SHP, AK; analysis of results: KV; interpretation of results: KV, AK; drafting of manuscript: KV, AK; critical comments on manuscript: SHP, TL; final approval of submitted version: KV, SHP, TL, AK.

Potential conflicts of interest

KV, TL and SHP declare no conflicts of interest. AK received an honorary for lectures (Pfizer, MSD, Valneva, Immuron) and two investigator-initiated grants (Pfizer, Valneva), and on two occasions has consulted on an advisory board (Valneva); none of these are, however, relevant to the current manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tmaid.2018.06.007.

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