

Prescribing Patterns of Antibiotics for the Self-Treatment of Travelers' Diarrhea in Global TravEpiNet, 2009–2018

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Background. International travelers are often prescribed antibiotics for self-treatment of travelers' diarrhea (TD), but the benefits and risks of antibiotics are debated. We assessed the prescribing patterns of empiric antibiotics for TD in international travelers evaluated at Global TravEpiNet (GTEN) sites (2009–2018).

Methods. We performed a prospective, multisite cross-sectional study regarding antibiotic prescriptions for the self-treatment of TD at 31 GTEN sites providing pretravel consultations to adult international travelers. We described traveler demographics, itineraries, and antibiotic(s) prescribed. We used multivariable logistic regressions to assess the association of year of consultation with antibiotic prescribing (yes/no) and class (fluoroquinolones vs azithromycin). We performed interrupted time-series analyses to examine differences in prescribing before and after the Food and Drug Administration (FDA) warning on fluoroquinolones (July 2016).

Results. Antibiotics were not prescribed in 23 096 (22.2%) of 103 843 eligible pretravel GTEN consultations; azithromycin and fluoroquinolones were most frequently prescribed. Antibiotic prescribing declined significantly each year between 2009 and 2018 (odds ratio [OR], 0.84; 95% CI, 0.79–0.89), as did fluoroquinolone prescribing, relative to azithromycin (OR, 0.77; 95% CI, 0.73–0.82). The rate of decline in fluoroquinolone prescribing was significantly greater after the FDA fluoroquinolone warning (15.3%/year) than before (1.1%/year; $P < .001$).

Conclusions. Empiric antibiotics for TD were prescribed in >75% of pretravel GTEN consultations, but antibiotic prescribing declined steadily between 2009 and 2018. Fluoroquinolones were less frequently prescribed than azithromycin, especially after the 2016 FDA fluoroquinolone warning. Emphasis on the risks of antibiotics may influence antibiotic prescribing by providers for empiric treatment of TD.

Keywords. antibiotics; drug resistance; fluoroquinolones; travelers' diarrhea.

Travelers' diarrhea (TD) is the most common illness experienced during international travel, affecting 10%–60% of all travelers [1, 2]. Antibiotics, including azithromycin and fluoroquinolones, are active against common bacterial etiologies of TD and are frequently prescribed to international travelers for the empiric self-treatment of diarrhea [1]. Antibiotic self-treatment can lead to rapid recovery from TD, thereby minimizing disruptions to itineraries. It may also prevent postinfectious irritable bowel syndrome, which has been associated with prolonged and severe cases of TD [3, 4]. Although TD is common, many cases are mild and can usually be treated with supportive care alone [1, 4–6]. A recent systematic review

found that loperamide may have efficacy similar to that of antibiotics in treating mild or moderate TD [7], and the combination of loperamide and antibiotics is the most effective [8, 9]. Because the severity of TD can vary widely, pretravel antibiotic prescribing for the self-treatment of TD is common practice [1, 6].

Antibiotics have risks that may be underestimated by both providers and patients. Antibiotic therapy has been associated with adverse events including *Clostridium difficile* infection and QTc prolongation [10, 11]. The overuse of antibiotics has led to increasing antimicrobial resistance, an emerging public health concern [12, 13]. International travel itself is a risk factor for the acquisition of organisms with high antimicrobial resistance that can be transmitted upon return, leading some to call for greater antimicrobial stewardship efforts specifically targeted at international travelers [14–17]. In view of these factors, the International Society for Travel Medicine (ISTM) released new guidelines in 2017 recommending supportive care in lieu of antibiotic treatment for mild or “nondistressing” TD, with antibiotics recommended for moderate TD (weak recommendation) and severe TD (strong recommendation) [6].

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Fluoroquinolones, in particular, have been linked to serious adverse events. In 2016, the Food and Drug Administration (FDA) released a warning regarding “disabling and potentially permanent” musculoskeletal and central nervous system adverse events associated with fluoroquinolones and has subsequently released 2 additional warnings, further highlighting the risk of fluoroquinolone-related neuropsychiatric toxicity, aortic dissection, and long-term disability [18–21]. Although TD is not explicitly cited in the FDA warnings, fluoroquinolone antibiotics are no longer recommended for nonserious bacterial infections such as uncomplicated urinary tract infections [18].

Surveillance data demonstrate that bacterial pathogens associated with TD are increasingly resistant to fluoroquinolones. *Campylobacter* species comprise 15%–20% of TD etiologies in Southeast Asia, and fluoroquinolone resistance has reached 70%–80% in *Campylobacter* isolates from that region [2, 22–24]. In such settings, travelers who take fluoroquinolones for TD could be exposed to adverse events without clinical benefit. The 2017 ISTM guidelines explicitly recommended against prescribing fluoroquinolones to travelers visiting Southeast Asia [6]. Moreover, these guidelines also recommended azithromycin as first-line antimicrobial therapy for severe TD [6].

In this analysis, we first sought to describe antibiotic prescribing patterns for the self-treatment of TD for adult international travelers from 2009 through 2018. We next examined for associations between demographics and travel-related characteristics and the prescription of any antibiotic and, in particular, prescriptions for fluoroquinolones relative to azithromycin. Finally, we assessed time trends for antibiotic and fluoroquinolone prescribing over the study period.

METHODS

Study Setting

Global TravEpiNet (GTEN) is a Centers for Disease Control and Prevention (CDC)–sponsored consortium of clinics that provide pretravel health consultations. GTEN sites are geographically dispersed in the United States across the 4 Census regions: Northeast (9 sites), Midwest (3 sites), South (11 sites), and West (8 sites). The consortium is comprised of 20 academic centers (ie, affiliated with university hospitals or medical schools) and 11 nonacademic centers (7 public health clinics, 2 primary care clinics, 1 health network, and 1 pharmacy).

Study Population and Eligibility Criteria

We examined trends in antibiotic prescribing between January 12, 2009, and December 31, 2018. We excluded pretravel consultations in which travelers were younger than 18 years, reported an itinerary outside a World Health Organization (WHO)–defined region, received only prophylactic antibiotics, had an existing prescription or antibiotics from another provider, or indicated a travel time of 0 days or >2000 days.

Data Collection: Traveler Demographics, Travel-Related Characteristics, and Categorization of Antibiotic Prescribing

Data were prospectively collected at GTEN sites using a standardized online questionnaire completed by the traveler and provider. Travelers provided demographic information, including age, sex, self-reported medical history and allergies, and details regarding travel itinerary such as reason for travel, destination(s), and duration of travel. Providers confirmed these data and entered the vaccinations recommended and administered at the pretravel consultation, medications prescribed, and health advice discussed during the visit [25].

We categorized travelers by sex (male or female), age (ie, 18–49 years, 50–64 years, and ≥ 65 years), and self-reported drug allergies. We categorized travel destination into 6 WHO-defined regions [26]. Itineraries that included countries in >1 WHO region contributed data to multiple regions. Travelers specified their reason(s) for travel, which we categorized into 6 mutually exclusive categories in the following rank order: visiting friends and relatives (VFR), business, humanitarian service (including providing medical care, nonmedical service work, and missionary work), research/education, leisure, and other [25]. For example, travelers who selected both VFR and leisure contributed only to the VFR category. We categorized duration of travel into 3 groups: <14 days, 14–29 days, and ≥ 30 days.

We first categorized pretravel consultations by antibiotic prescribing (yes/no). We further categorized antibiotic prescribing into classes: azithromycin only, fluoroquinolone only, rifaximin only, other antibiotic only, and >1 antibiotic. Travelers receiving only doxycycline as malaria prophylaxis were categorized as receiving no antibiotics for TD.

Statistical Analyses

We obtained distributions of demographic and travel-related characteristics stratified by the categories of antibiotic prescribing used in this analysis. We obtained odds ratios (ORs) and 95% CIs from univariate and multivariable logistic regressions to assess the association of demographics, travel-related characteristics, and linear trends over time with (1) prescribing of any antibiotics compared with no antibiotics and (2) prescribing of fluoroquinolones compared with azithromycin. We considered the survey year of evaluation as a continuous variable to observe changes over the entire study period. We also performed interrupted time-series (ITS) analysis to examine fluoroquinolone prescribing practices before and after the FDA warning on fluoroquinolones (July 2016). From the ITS analysis, we estimated the effect of the intervention (the FDA warning) by comparing the trends in antibiotic prescribing before and after the intervention. We conducted our analyses using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), and SUDAAN 11.0.3 (RTI International, Durham, NC, USA) and considered a 2-sided P value <.05 to be significant.

IRB Approval

An institutional review board at all 31 participating sites either approved the study or considered it exempt from review.

Patient Consent Statement

We obtained institutional review board (IRB) approval at all participating GTEN sites; IRBs at each participating clinical site waived the need for written or oral informed consent because the study collected only deidentified data routinely collected during a standard clinical encounter.

RESULTS

Study Population

There were 121 295 pretravel consultations at participating GTEN sites between January 12, 2009, and December 31, 2018. We excluded 17 452 consultations for the reasons described above and included the remaining 103 843 pretravel consultations in this analysis (Figure 1).

Cohort Demographics

Among 103 843 eligible pretravel consultations, 45 282 travelers were male (43.6%), and 11 745 travelers (11.3%) were over age 65. Most travelers reported no drug allergies (79 724 [76.8%]); 626 (<1%) reported allergies to fluoroquinolones only, 1283 (1.2%) reported allergies to macrolides only, and 52 (<1%) had allergies to

both fluoroquinolones and macrolides. The most common destination region was Africa, followed by the Americas and Southeast Asia. Most travelers were planning itineraries for <14 days (43 868 [42.2%]) or 14–29 days (41 083 [39.6%]), and most were traveling for leisure (49 928 [48.1%]). Only 7527 (7.2%) travelers met criteria for VFR. Academic centers accounted for 87 975 (84.7%) of eligible pretravel consultations (Table 1).

Antibiotics Prescribed During Pretravel Consultations

Providers did not prescribe antibiotics in 23 096 (22.2%) pretravel consultations but did in 80 747 (77.8%) pretravel consultations (Figure 1). Among all pretravel consultations at GTEN sites, antibiotics prescribed included azithromycin only (42 697 [41.1%]), fluoroquinolone only (36 248 [34.9%]), rifaximin only (740 [<1%]), another antibiotic only (11 [<1%]), and >1 antibiotic (1051 [1.0%]) (Supplementary Table 1).

Predictors of Antibiotic Prescribing

Providers at GTEN sites were more likely to prescribe antibiotics for TD if travelers were 50–64 years old, reported an allergy to fluoroquinolones, were traveling to Southeast Asia or the Western Pacific, or were evaluated at an academic center. Providers were less likely to prescribe antibiotics to travelers who were traveling for ≥30 days, were VFR travelers, or were evaluated at GTEN clinics in the South (Table 2).

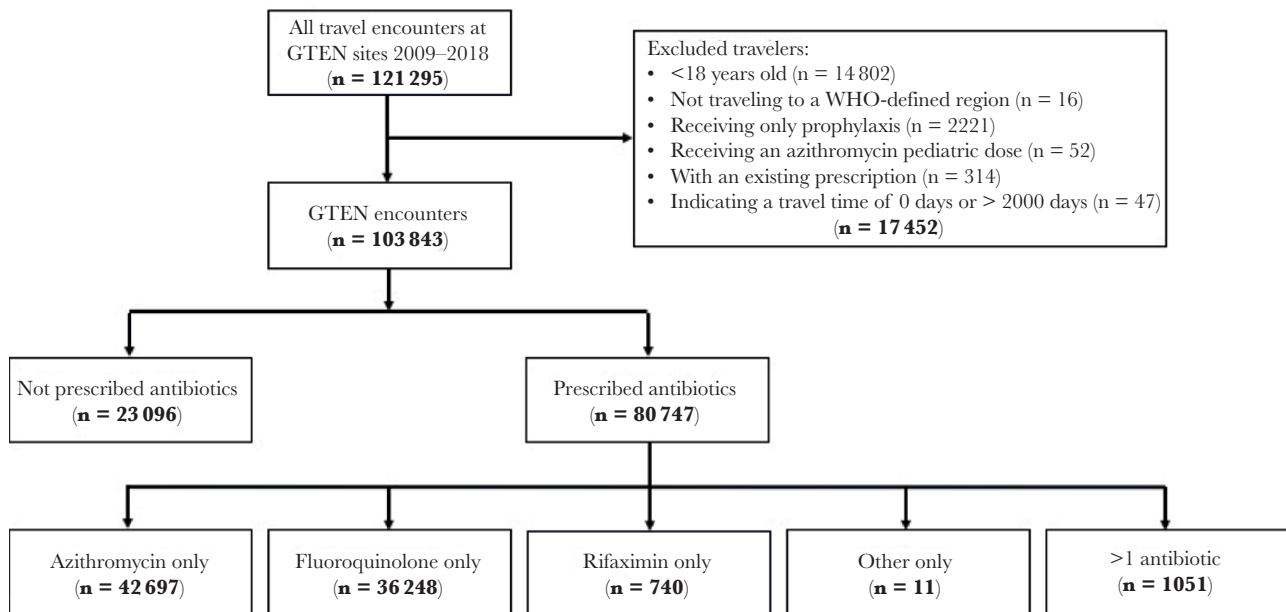


Figure 1. Flow diagram of travel encounters at GTEN sites (2009–2018). Between 2009 and 2018, 121 295 pretravel consultations were recorded at GTEN sites, of which 103 843 met the inclusion criteria of the study. Providers prescribed antibiotics for empiric treatment of TD in 80 747 pretravel consultations, of which 1051 received >1 antibiotic. The combinations of >1 antibiotic include azithromycin and fluoroquinolone (n = 825); azithromycin and rifaximin (n = 148); fluoroquinolone and rifaximin (n = 39); fluoroquinolone and other (n = 22); azithromycin and other (n = 9); fluoroquinolone, azithromycin, and rifaximin (n = 5); and fluoroquinolone, azithromycin, and other (n = 3). The other category included prescriptions for metronidazole, doxycycline, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanate for travelers’ diarrhea self-treatment and/or other nonmalaria prophylaxis indications (eg, respiratory infection, UTI). Abbreviations: GTEN, Global TravEpiNet; TD, travelers’ diarrhea; UTI, urinary tract infection; WHO, World Health Organization; WHO-defined regions: Africa, Americas, Southeast Asia, Europe, Eastern Mediterranean, Western Pacific.

Table 1. Demographics and Travel-Related Characteristics of Adult Travelers Evaluated at GTEN Sites (2009–2018)

Characteristics	No. (n = 103 843)	Not Prescribed Antibiotics (n = 23 096)	Prescribed Antibiotics (n = 80 747)
Sex, No. (row %)			
Male	45 282	9836 (21.7)	35 446 (78.3)
Female	58 561	13 260 (22.6)	45 301 (77.4)
Age, No. (row %)			
18–49 y	68 440	15 091 (22.0)	53 349 (78.0)
50–64 y	23 658	5263 (22.2)	18 395 (77.8)
≥65 y	11 745	2742 (23.3)	9003 (76.7)
Drug allergies, No. (row %)			
No allergies	79 724	18 346 (23.0)	61 378 (77.0)
FQ only	626	93 (14.9)	533 (85.1)
Macrolide only	1283	221 (17.2)	1062 (82.8)
FQ and macrolide	52	15 (28.8)	37 (71.2)
Other antibiotic allergy	22 158	4421 (20.0)	17 737 (80.0)
Duration of travel, No. (row %)			
<14 d	43 868	8630 (19.7)	35 238 (80.3)
14–29 d	41 083	7845 (19.1)	33 238 (80.9)
≥30 d	18 892	6621 (35.0)	12 271 (65.0)
Region of travel, No. (row %)^a			
Africa	37 604	10 804 (28.7)	26 800 (71.3)
Americas	29 845	6459 (21.6)	23 386 (78.4)
Southeast Asia	24 612	3169 (12.9)	21 443 (87.1)
Western Pacific	18 872	2977 (15.8)	15 895 (84.2)
Europe	5787	1202 (20.8)	4585 (79.2)
Eastern Mediterranean	5653	1434 (25.4)	4219 (74.6)
Reason for travel, No. (row %)			
Leisure	49 928	9227 (18.5)	40 701 (81.5)
Business	18 771	3231 (17.2)	15 540 (82.8)
Humanitarian service work	15 315	3704 (24.2)	11 611 (75.8)
Research/education	7784	1537 (19.7)	6247 (80.3)
VFR	7527	3250 (43.2)	4277 (56.8)
Other	4518	2147 (47.5)	2371 (52.5)
US Census region of clinic site, No. (row %)			
Northeast	45 817	5927 (12.9)	39 890 (87.1)
Midwest	8506	572 (6.7)	7934 (93.3)
South	26 145	12 419 (47.5)	13 726 (52.5)
West	23 375	4178 (17.9)	19 197 (82.1)
Type of clinic, No. (row %)			
Nonacademic center	15 868	10 169 (64.1)	5699 (35.9)
Academic center	87 975	12 927 (14.7)	75 048 (85.3)

Abbreviations: FQ, fluoroquinolone; GTEN, Global TravEpiNet; VFR, visiting friends and relatives.

^aTravelers can contribute to >1 region.

Antibiotic Prescribing Patterns From 2009 to 2018

When adjusting for demographic and travel-related predictors, a significant decline in antibiotic prescribing was observed over the study period (OR, 0.84; 95% CI, 0.79–0.89) (Table 2): from 92% of pretravel consultations in 2009 to 70% in 2018 (Figure 2A). The ITS analyses revealed no significant change in the rate of decline in antibiotic prescribing due to the intervention (ie, the FDA warning or ISTM guidelines).

Predictors of Fluoroquinolone Prescribing Compared With Azithromycin Prescribing

Relative to azithromycin prescribing, fluoroquinolone prescribing was associated with travel to Africa, the Americas,

Europe, or the Eastern Mediterranean. Providers were more likely to prescribe fluoroquinolones to travelers age 50–64 and were less likely to prescribe fluoroquinolones to travelers who were female, had a fluoroquinolone allergy, were traveling to Southeast Asia or the Western Pacific, or were evaluated at a GTEN clinic in the Midwest (Table 3). Among female travelers, fluoroquinolones were more likely to be prescribed to those age ≥50 years compared with females of childbearing age (18–49 years), after adjusting for other variables (OR, 1.42; 95% CI, 1.06–1.89). Similar predictors of fluoroquinolone prescribing, in addition to travel for business, were observed among travelers to Southeast Asia (Supplementary Table 2).

Table 2. Results From Logistic Regressions Assessing the Relationship of Demographics and Travel Characteristics With Prescribing Antibiotics for TD Among Travelers Evaluated at GTEN Sites (2009–2018)

Characteristics	Unadjusted OR (95% CI)	Unadjusted P Value	Adjusted OR (95% CI) ^a	Adjusted P Value ^a
Sex				
Male	Ref	.46	Ref	.77
Female	0.95 (0.82–1.10)		1.02 (0.89–1.18)	
Age				
18–49 y	Ref	.54	Ref	.045
50–64 y	0.99 (0.77–1.26)		1.14 (1.01–1.28)	
≥65 y	0.93 (0.73–1.18)		1.19 (0.92–1.54)	
Drug allergies				
No allergies	Ref	<.001	Ref	<.001
FQ only	1.71 (1.36–2.16)		1.67 (1.24–2.26)	
Macrolide only	1.44 (1.01–2.05)		1.12 (0.86–1.46)	
FQ and macrolide	0.74 (0.41–1.31)		0.75 (0.42–1.33)	
Other antibiotic allergy	1.20 (1.01–1.42)		1.14 (1.00–1.31)	
Duration of travel				
<14 d	Ref	<.001	Ref	<.001
14–29 d	1.04 (0.92–1.17)		0.99 (0.89–1.10)	
≥30 d	0.45 (0.31–0.66)		0.47 (0.32–0.70)	
Region of travel^b				
Africa	0.57 (0.35–0.90)	.013	1.01 (0.81–1.27)	.92
Americas	1.05 (0.72–1.54)	.79	0.95 (0.75–1.21)	.68
Southeast Asia	2.27 (1.68–3.07)	<.001	1.88 (1.50–2.35)	<.001
Western Pacific	1.66 (1.14–2.41)	.006	1.43 (1.17–1.74)	<.001
Europe	1.10 (0.76–1.58)	.61	0.90 (0.72–1.13)	.35
Eastern Mediterranean	0.83 (0.69–1.00)	.046	0.98 (0.82–1.16)	.79
Reason for travel				
Leisure	Ref	<.001	Ref	<.001
Business	1.09 (0.78–1.52)		1.03 (0.83–1.27)	
Humanitarian service work	0.71 (0.47–1.08)		0.76 (0.56–1.04)	
Research/education	0.92 (0.69–1.24)		1.17 (0.86–1.60)	
VFR	0.30 (0.13–0.70)		0.33 (0.13–0.84)	
Other	0.25 (0.13–0.49)		0.41 (0.28–0.59)	
US Census region of clinic site				
Northeast	Ref	.011	Ref	<.001
Midwest	2.06 (0.61–6.98)		1.52 (0.78–2.93)	
South	0.16 (0.03–0.99)		0.28 (0.11–0.69)	
West	0.68 (0.21–2.27)		0.79 (0.24–2.64)	
Type of clinic				
Nonacademic center	Ref	.014	Ref	.005
Academic center	10.36 (1.49–72.23)		7.30 (1.72–30.86)	
Survey year				
2009	Ref	<.001	Ref	<.001
Each year after 2009	0.88 (0.84–0.93)		0.84 (0.79–0.89)	

Abbreviations: FQ, fluoroquinolone; GTEN, Global TravEpiNet; OR, odds ratio; TD, travelers' diarrhea; VFR, visiting friends and relatives.

^aAdjusted results obtained from regressions that include all variables shown in the table.

^bReference: not traveling to that specific region. Travelers can contribute to >1 region.

Fluoroquinolone Prescribing Patterns From 2009 to 2018

Among all travelers, when adjusting for demographic and travel-related characteristics, fluoroquinolone prescriptions declined significantly each year from 2009 to 2018, compared with azithromycin prescriptions (OR, 0.77; 95% CI, 0.73–0.82) (Table 3). Notable decreases in any fluoroquinolone prescribing were observed between 2016 and 2018: from 57%

in July 2016 (FDA warning) to 46% in March 2017 (ISTM guidelines), and to 17% in December 2018 (final survey year). When examining for changes in practices after the release of the FDA warning, fluoroquinolone prescriptions declined 1.1%/year before July 2016 ($P = .027$) and 15.3%/year thereafter ($P < .001$) (Figure 2B). The rate of decline after July 2016 was greater and significant compared with

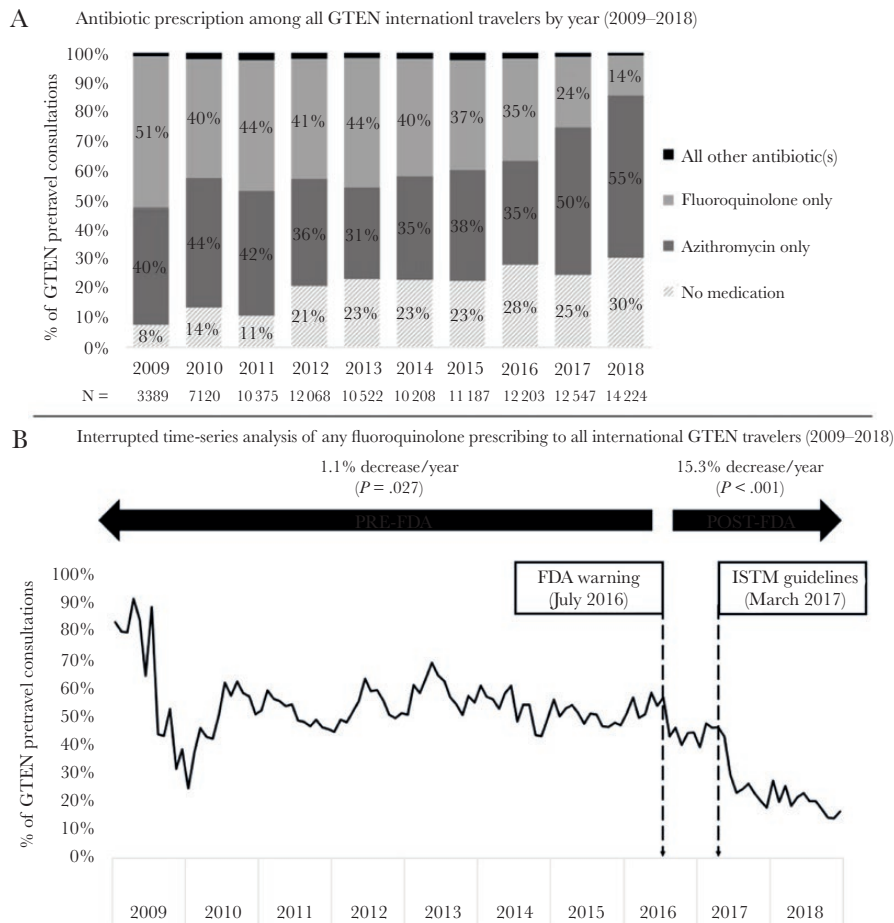


Figure 2. A, Antibiotic prescriptions among all GTEN travelers to any international destination (2009–2018). B, Interrupted time-series analysis showing the decrease in any fluoroquinolone prescriptions. A, Antibiotic prescription patterns for all travelers by year between 2009 and 2018. The x-axis represents the year, and the y-axis represents the proportion of pretravel consultations in which no antibiotics, azithromycin only, a fluoroquinolone only, and all other antibiotic(s) (including rifaximin only, another antibiotic, and >1 antibiotic) were prescribed. Among all GTEN travelers, antibiotic prescribing declined between 2009 and 2018. B, The proportion of pretravel consultations in which fluoroquinolone only was prescribed, by month, between 2009 and 2018. Interrupted time-series analysis shows the change in fluoroquinolone prescribing before and after the FDA warning on fluoroquinolones (July 2016). The rate of decrease in fluoroquinolone prescribing after the FDA warning was significant compared with that before the FDA warning ($P < .001$). Interrupted time-series analysis also revealed similar declines in fluoroquinolone prescribing before and after the release of the ISTM guidelines in March 2017 (before ISTM: 1.3%/year; $P = .002$; after ISTM: 13.6%/year; $P < .001$); when compared, the rates of decline were significantly different ($P = .002$). Abbreviations: FDA, Food and Drug Administration; GTEN, Global TravEpiNet; ISTM, International Society for Travel Medicine.

that before July 2016 ($P < .001$). Similar declines in fluoroquinolone prescribing were observed before and after the release of the ISTM guidelines in March 2017 (before ISTM: 1.3%/year; $P = .002$; after ISTM: 13.6%/year; $P < .001$); when compared, the rates of decline were significantly different ($P = .002$). As fluoroquinolone prescribing declined significantly over the study period, azithromycin prescribing increased significantly.

A dramatic decline was observed in fluoroquinolone prescribing to Southeast Asia travelers: from 36% in 2009 to 4% in 2018 (Supplementary Figure 1A), which was significant after adjusting for demographic and travel-related characteristics (OR, 0.77; 95% CI, 0.71–0.83) (Supplementary Table 2). Fluoroquinolone prescribing declined 3.9%/year before July 2016 ($P < .001$) and 2.6%/year thereafter ($P = .32$)

(Supplementary Figure 1B). Comparison of the rates of decline found no statistically significant difference ($P = .65$).

DISCUSSION

Providers prescribed antibiotics for the self-treatment of TD at >75% of GTEN pretravel consultations between 2009 and 2018. However, empiric antibiotic prescribing by providers declined significantly over the past 10 years (OR, 0.84; 95% CI, 0.79–0.89). Fluoroquinolone prescriptions, in particular, declined significantly between 2009 and 2018, whereas azithromycin prescriptions increased, especially for travelers visiting Southeast Asia.

The changes in observed prescribing practices may reflect ongoing efforts to reduce antibiotic adverse events and curb antimicrobial resistance by reducing antibiotic prescriptions for nonserious infections, such as mild TD. Such efforts include

Table 3. Results From Logistic Regressions Assessing the Relationship of Demographics and Travel Characteristics With Prescribing Fluoroquinolones Compared With Azithromycin for TD Among Travelers Evaluated at GTEN Sites (2009–2018)

Characteristics	Unadjusted OR (95% CI)	Unadjusted P Value	Adjusted OR (95% CI) ^a	Adjusted P Value ^a
Sex				
Male	Ref	.47	Ref	<.001
Female	1.02 (0.96–1.10)		0.94 (0.92–0.96)	
Age				
18–49 y	Ref	.063	Ref	<.001
50–64 y	1.22 (0.93–1.60)		1.34 (1.08–1.66)	
≥65 y	1.16 (0.84–1.62)		1.29 (0.86–1.94)	
Drug allergies				
No allergies	Ref	<.001	Ref	<.001
FQ only	0.08 (0.06–0.11)		0.04 (0.03–0.06)	
Macrolide only	4.53 (3.56–5.77)		7.68 (5.59–10.54)	
FQ and macrolide	0.74 (0.33–1.66)		0.41 (0.12–1.40)	
Other antibiotic allergy	1.04 (0.91–1.19)		1.02 (0.96–1.08)	
Duration of travel				
<14 d	Ref	.005	Ref	.002
14–29 d	0.76 (0.62–0.93)		0.91 (0.85–0.97)	
≥30 d	0.79 (0.65–0.95)		0.97 (0.85–1.10)	
Region of travel^b				
Africa	2.28 (1.62–3.19)	<.001	1.97 (1.31–2.95)	<.001
Americas	2.04 (1.44–2.90)	<.001	1.74 (1.22–2.48)	.002
Southeast Asia	0.15 (0.07–0.34)	<.001	0.17 (0.07–0.40)	<.001
Western Pacific	0.37 (0.27–0.50)	<.001	0.44 (0.38–0.51)	<.001
Europe	1.17 (1.02–1.35)	.019	1.22 (1.07–1.40)	.003
Eastern Mediterranean	1.03 (0.90–1.18)	.63	1.20 (1.03–1.40)	.017
Reason for travel				
Leisure	Ref	<.001	Ref	<.001
Business	1.00 (0.74–1.34)		1.10 (0.99–1.22)	
Humanitarian service work	1.77 (1.13–2.76)		0.91 (0.72–1.15)	
Research/education	1.38 (0.92–2.09)		1.05 (0.85–1.29)	
VFR	0.83 (0.58–1.20)		0.78 (0.57–1.07)	
Other	1.24 (0.96–1.59)		0.81 (0.66–0.99)	
US Census region of clinic site				
Northeast	Ref	<.001	Ref	<.001
Midwest	0.12 (0.06–0.26)		0.06 (0.02–0.13)	
South	2.14 (1.48–3.09)		2.47 (1.25–4.90)	
West	2.27 (1.77–2.91)		3.64 (2.66–4.99)	
Type of clinic				
Nonacademic center	Ref	.64	Ref	.24
Academic center	0.81 (0.32–2.07)		1.56 (0.72–3.39)	
Survey year				
2009	Ref	.023	Ref	<.001
Each year after 2009	0.88 (0.78–0.99)		0.77 (0.73–0.82)	

Abbreviations: FQ, fluoroquinolone; GTEN, Global TravEpiNet; OR, odds ratio; TD, travelers' diarrhea; VFR, visiting friends and relatives.

^aAdjusted results obtained from regressions that include all variables shown in the table.

^bReference: not traveling to that specific region. Travelers can contribute to >1 region.

policy changes like the 2016 FDA warning on fluoroquinolones and 2017 ISTM guidelines on the empiric treatment of TD. We found a consistent decline in any TD antibiotic prescribing among GTEN travelers over the past 10 years, but ITS analysis did not reveal significant changes in prescribing trends before and after these 2 policy interventions. As new data regarding the risks and benefits of antibiotics emerge, pretravel

providers play an important role in reducing antibiotic overuse to decrease the selective pressure for antimicrobial-resistant organisms among international travelers, a key at-risk population [14, 16, 17, 27]. As empiric antibiotic prescribing for TD remains common practice, providers must educate travelers about the risks and benefits of antibiotics and ISTM guideline-concordant management of TD (eg, recommending loperamide

for mild TD and antibiotics alone or with loperamide for moderate or severe TD) [6].

Although our findings suggest that clinical practice has been evolving, >70% of GTEN travelers were still prescribed antibiotics in 2018, which is consistent with CDC and ISTM guidelines, which continue to recommend antibiotics as primary treatment for TD [1]. Variability in oral antibiotic prescribing practices on the provider level is well described, and we similarly identified significant variation in clinical practice, even among specialized pretravel providers [28]. Providers at GTEN academic sites were significantly more likely to prescribe antibiotics for TD than providers at nonacademic sites, and prescribing practices also differed among geographic regions within the United States. Despite the heterogeneity in prescribing practices we observed, antibiotics were still widely prescribed by GTEN providers, which is consistent with the frequent antibiotic prescribing described in outpatient settings for other indications [29, 30]. Pretravel providers may choose to prescribe empiric antibiotics so that travelers can avoid seeking medical care while abroad, which may be inappropriate or harmful or include substandard or counterfeit antimicrobial drugs [31–33].

We found significant predictors for the prescribing of antibiotics to travelers, which highlight current clinical practice among experienced travel medicine providers. Travelers with longer trips (≥ 30 days) were less likely to be prescribed antibiotics than travelers with shorter durations of travel; it is possible that long-term travelers anticipate access to medical care while abroad and thus decline antibiotic prescriptions. We found that GTEN travelers visiting Africa were no more likely to be prescribed antibiotics than those visiting other regions, although travelers to Africa experience a high incidence of TD [4, 34]. VFR travelers were less likely to be prescribed antibiotics at GTEN sites. It is possible that VFR travelers may be less likely to accept pretravel advice despite the higher risk of some illnesses while abroad, that some providers may assume that VFR travelers have adequate access to medical care at the destination, or that providers may fail to offer adequate pretravel advice to VFR travelers [4, 35, 36]. Providers should be aware of potential disparities in pretravel care for VFR travelers, and these data highlight the importance of clinical guidelines to address high-risk groups of travelers.

We also found significant demographic and travel-related associations with prescribing fluoroquinolones relative to azithromycin. Females were less likely than males to be prescribed fluoroquinolones compared with azithromycin, perhaps due to concern for fetal and developmental toxicities with the use of quinolones during pregnancy [37]. Travelers with self-reported macrolide allergies were more likely to receive prescriptions for fluoroquinolones; the opposite trend was observed in travelers with self-reported fluoroquinolone allergies. Travelers visiting Southeast Asia and the Western Pacific were

less likely to be prescribed fluoroquinolones than azithromycin compared with those not visiting these regions, suggesting that providers may be increasingly aware of the prevalence of fluoroquinolone-resistant *Campylobacter* or responding to the 2017 ISTM guidelines [2, 6, 22–24].

We observed significant periods of decline in fluoroquinolone prescribing. The sharp decline observed in 2009 may reflect providers' response to a frequently cited 2007 study on increasing fluoroquinolone resistance among *Campylobacter* spp. among travelers visiting Thailand and recommendations suggesting azithromycin as first-line antibiotic treatment [38]. Among travelers to Southeast Asia, the differences in the rates of decline were not significant before and after the release of the 2016 FDA warning and 2017 ISTM guidelines; GTEN providers may have already been avoiding fluoroquinolone prescribing to these travelers. However, fluoroquinolone prescribing among all GTEN travelers declined at a significantly faster rate following the release of the 2016 FDA warning than before, suggesting its potential impact on pretravel clinical practices. These findings support a recently published analysis that reported a 7.6% decrease in in-hospital fluoroquinolone prescribing in July 2016, the month the FDA warning was released, and additional decreases thereafter (risk ratio, 0.89; 95% CI, 0.79–1.01) [39], although other studies have not demonstrated a significant effect of the 2016 FDA warning on outpatient fluoroquinolone prescribing [40, 41]. With the decline in fluoroquinolone prescribing, we observed corresponding increases in azithromycin prescribing, which support ISTM guidelines that recommend azithromycin for moderate to severe TD [6].

Although GTEN is the largest consortium of clinical sites that provide pretravel consultations in the United States, our analysis has limitations. Individuals seeking pretravel advice may be less likely to participate in risky behaviors, and providers may deem that counsel on the risks of TD and use of supportive care is sufficient for these travelers. Patient demographics and antibiotic prescribing practices at GTEN sites may not be generalizable to the general population of US travelers and providers, especially for VFR travelers. Additionally, we could not stratify antibiotic prescribing patterns by the training of GTEN pretravel providers (eg, physician, nurse, pharmacist). As in other GTEN analyses, we categorized travelers' itineraries by WHO geographic regions, which may not capture the details of TD risk during specific itineraries [25]. Given that the FDA warning and ISTM guidelines occurred within a year of each other, we were unable to discern the individual impact of these 2 public health interventions on antibiotic prescribing practices. Because these data capture antibiotic prescriptions at GTEN sites, our analysis does not include instances when loperamide was prescribed alone or with antibiotics, provider reasons for prescribing patterns, patient preferences, patient refusal of antibiotics, or actual antibiotic use among

travelers. However, these data regarding prescriber patterns remain vitally important and emphasize the changes in provider decision-making regarding antibiotic prescribing over the past 10 years.

In conclusion, our findings suggest that the prescribing of empiric antibiotics for travelers' diarrhea has declined significantly over the past 10 years but remains a common clinical practice at pretravel consultations. Specifically, we found that fluoroquinolone prescribing has dramatically declined, especially among travelers visiting Southeast Asia, while azithromycin is now the most frequently prescribed antibiotic for TD. Emerging data on the risks and benefits of antibiotics, recent antimicrobial stewardship efforts, and updated clinical practice guidelines may have contributed to the decline in antibiotic prescribing for TD, especially for fluoroquinolones.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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