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Travel Characteristics and Yellow Fever Vaccine Usage Among US Global TravEpiNet Travelers Visiting Countries with Risk of Yellow Fever Virus Transmission, 2009–2011

Emily S. Jentes,* Pauline Han, Mark D. Gershman, Sowmya R. Rao, Regina C. LaRocque, J. Erin Staples, Edward T. Ryan, and the Global TravEpiNet Consortium

Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, Atlanta, Georgia; Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts; Center for Health Quality, Outcomes, and Economic Research, Bedford Veterans Administration Medical Center, Bedford, Massachusetts; Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, Ft. Collins, Colorado; Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts; Department of Medicine, Harvard Medical School, Boston, Massachusetts

Abstract. Yellow fever (YF) vaccine-associated serious adverse events and changing YF epidemiology have challenged healthcare providers to vaccinate only travelers whose risk of YF during travel is greater than their risk of adverse events. We describe the travel characteristics and YF vaccine use among US travelers visiting Global TravEpiNet clinics from January of 2009 to March of 2011. Of 16,660 travelers, 5,588 (34%) had itineraries to areas with risk of YF virus transmission. Of those travelers visiting one country with YF risk (N = 4,517), 71% were vaccinated at the visit, and 20% were presumed to be immune from prior vaccination. However, travelers visiting friends and relatives (odds ratio [OR] = 2.57, 95% confidence interval [95% CI] = 1.27–5.22) or going to Nigeria (OR = 3.01, 95% CI = 1.37–6.62) were significantly more likely to decline vaccination. To optimize YF vaccine use, clinicians should discuss an individual's risk–benefit assessment of vaccination and close knowledge gaps regarding vaccine use among at-risk populations.

INTRODUCTION

Yellow fever (YF) is caused by infection with a flavivirus (family *Flaviviridae*) that is transmitted to humans primarily through the bite of *Haemagogus* spp. and *Aedes* spp. mosquitoes in South America and Africa, respectively. YF virus infection can be asymptomatic or cause a spectrum of disease ranging from a mild non-specific febrile illness to hemorrhagic fever with multiorgan failure and death. The number of YF cases reported widely varies, with approximately 50–5,000 cases per year.[1] However, this estimate is likely an underestimate of the true number of cases, because only a limited percentage of cases are identified because of underdiagnosis and underreporting.[2]

The epidemiology of YF continues to change, which is evidenced by a recent outbreak in Paraguay in 2008 and an increase in reported cases in Central and East Africa in 2010–2012.[3–6] Travel to countries with emerging economies, including nations where YF is endemic, has become more common, increasing from 31% of international tourist arrivals in 1990 to 47% in 2010.[7] Specifically, many popular destinations in South America and sub-Saharan Africa include areas with risk of YF virus transmission (i.e., areas endemic or partially endemic for YF).

Prevention of YF in travelers is critical, because no specific treatment of YF disease exists. Effective prevention strategies include the use of personal protective measures, such as insect repellent on skin and clothing, staying in accommodations with screens or air conditioning, and vaccination. The YF 17D vaccine has historically been considered one of the safest vaccines, with more than 500 million doses delivered globally.[1] However, reports of serious adverse events have been associated with the vaccine, including YF vaccine-associated neurologic disease (YEL-AND) and more recently, YF vaccine-associated viscerotropic disease (YEL-AVD).[8] YEL-AVD results from the replication and dissemination of YF vaccine virus, producing a clinical syndrome similar to wild-type YF disease; it is fatal in approximately 65% of cases.[2] Although reporting rates of both YEL-AND and YEL-AVD are higher in selected populations, young healthy adults have also developed these serious adverse events.[8,9] Because of these safety concerns, it is essential that healthcare providers vaccinate only those travelers whose risk of YF during travel is estimated to be greater than their risk of serious adverse events from vaccination.[2]

The objective of this study was to describe the characteristics of US travelers planning to visit countries with risk of YF virus transmission and YF vaccine usage. Specifically, we analyzed the demographics, itineraries, and YF vaccine use among travelers to countries with risk of YF virus transmission who visited Global TravEpiNet (GTEN) providers for pre-travel consultations.

METHODS

GTEN is a consortium of US travel health practices; a detailed description of the consortium was published previously.[10] Enrollment of clinics and patients in GTEN began in January of 2009 and is ongoing; this analysis uses data collected from January of 2009 to March 31, 2011. Of note, these data were collected before the release of the revised 2012 YF vaccine recommendation maps for international travelers on April 1, 2011.[11–13] The types of the GTEN practices include academic practices, health maintenance organizations, private practices, pharmacy-based practices, and public health clinics. All GTEN consortium members are designated YF vaccine administration sites. An institutional review board at each participating site reviewed and approved analyses of the data.

We used an online tool to collect data routinely recorded on all individuals seen for pre-travel consultations in GTEN clinics. No personal identifiers were collected. For each consultation, travelers self-reported medical history, travel itinerary details, reasons for seeking pre-travel advice, and purpose

*Address correspondence to Emily S. Jentes, Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-03, Atlanta, GA 30333. E-mail: ejentes@cdc.gov

of travel (e.g., leisure, business, returning to country of origin of self or family to visit friends and relatives, research/education, or non-medical service work). Multiple responses were allowed for some variables, including purpose of travel, reasons for seeking pre-travel consultation, and destination.

GTEN healthcare providers verified traveler responses and entered information into the tool about vaccination history, vaccines administered (including YF vaccine), medications prescribed, and travel health advice provided during the clinic visit. If YF vaccine was not administered to travelers visiting areas with risk of YF virus transmission, the tool prompted healthcare providers to give a reason; available options included pre-existing immunity, vaccine not indicated, referred to primary care provider for vaccination, patient declined, medical contraindication, insufficient time, or vaccine not available. Pre-existing immunity to YF virus was defined as self-reported vaccination within the 10 years before the current clinic visit; evidence of previous vaccination usually involved presentation of a YF vaccination certificate, but no serologic tests were performed to confirm immunity.

We used the 2009–2010 US Centers for Disease Control and Prevention (CDC) YF maps to identify countries classified as either entirely or partially endemic.[14] Travelers going to destinations with risk for YF virus transmission were defined as those travelers visiting countries considered entirely endemic (and therefore, YF vaccine was always recommended) and/or countries considered partially endemic, for which the provider noted that YF vaccine was indicated by the traveler's stated itinerary. Hence, travelers going to partially endemic countries and for whom the provider chose vaccination not indicated for this itinerary were excluded from analyses. Travelers who selected returning to country of origin of self or family to visit friends and relatives (VFR) and who were visiting at least one low or low–middle income country according to the 2009 World Bank World Development Report (available at: http://econ.worldbank.org) were further defined as VFR travelers as described by the CDC.[11,15]

The demographics, travel characteristics, vaccination status, and contraindications were characterized for GTEN travelers visiting areas with risk for YF virus transmission. If the

Table 1
Demographic and travel characteristics of US Global TravEpiNet travelers visiting countries with risk of YF virus transmission

Characteristics	Total	Travel to		
		South America only*	Africa only	Both
Total (row %)	5,588	1,734 (31)	3,773 (68)	81 (1)
Age (*n*, column %)				
≤ 9 months	19 (< 1)	1 (< 1)	18 (< 1)	0 (0)
10 months to 12 years	426 (8)	71 (4)	350 (9)	5 (6)
13–18 years	280 (5)	93 (5)	185 (5)	2 (2)
19–59 years	4,047 (72)	1,238 (71)	2,747 (73)	62 (77)
60–69 years	615 (11)	245 (14)	362 (10)	8 (10)
70–79 years	175 (3)	71 (4)	100 (3)	4 (5)
> 80 years	26 (< 1)	15 (1)	11 (< 1)	0 (0)
Sex (*n*, column %)				
Female	3,101 (55)	914 (53)	2,142 (57)	45 (56)
Male	2,487 (45)	820 (47)	1,631 (43)	36 (44)
Reason for seeking pre-travel health advice†‡ (*n*, column %)				
Referral from primary care physician	760 (19)	208 (17)	540 (20)	12 (19)
Read information on the internet	465 (12)	170 (14)	285 (10)	10 (16)
Travel agent suggested making the appointment	254 (6)	75 (6)	179 (6)	0 (0)
Employer suggested making the appointment	390 (10)	92 (8)	286 (10)	12 (19)
Family member or friend suggested making the appointment	641 (16)	195 (16)	436 (16)	10 (16)
Public health announcement prompted scheduling appointment	35 (< 1)	13 (1)	22 (1)	0 (0)
Concern about health issues related to travel	1,293 (32)	390 (32)	876 (32)	27 (44)
Type of destination† (*n*, column %)				
Urban	4,984 (89)	1,599 (92)	3,304 (88)	81 (100)
Rural	4,216 (75)	1,401 (81)	2,758 (73)	57 (70)
Type of accommodation† (*n*, column %)				
Camping	533 (10)	183 (11)	330 (9)	20 (25)
Dormitory or hostel	979 (18)	360 (21)	596 (16)	23 (28)
Home stay with relatives	1,137 (20)	170 (10)	962 (26)	5 (6)
Home stay with non-relatives	782 (14)	278 (16)	481 (13)	23 (28)
Hotel	3,512 (63)	1,295 (75)	2,147 (57)	70 (86)
Other	903 (16)	249 (14)	638 (17)	16 (20)
Top three purposes of travel† (*n*, column %)				
Leisure§	2,976 (53)	1,245 (72)	1,684 (45)	47 (58)
VFR§¶	887 (16)	64 (4)	819 (22)	4 (5)
Business§	827 (15)	202 (12)	602 (16)	23 (28)

Travelers include those travelers visiting countries where the entire country is considered endemic and/or travelers visiting countries considered partially endemic where the healthcare provider noted that vaccine was indicated. Individuals going to partially endemic countries where the healthcare provider chose vaccination not indicated for this itinerary were excluded. Data were collected from January of 2009 to March 31, 2011.

*South America includes the Central American country of Panama and the Caribbean islands of Trinidad and Tobago.

†Travelers could choose more than one answer.

‡The question regarding the traveler's reason for seeking travel advice is not a required field; there are 1,549 missing values for this question.

§More travelers to Africa indicated VFR (22% versus 4%, $P < 0.0001$) and business (16% versus 12%, $P < 0.0001$) than travelers to South America; however, more travelers indicated leisure to South America than Africa (72% versus 45%, $P < 0.0001$). Comparisons were made by looking at travelers to Africa only or South America only and whether they indicated leisure travel versus any other type of travel, whether they indicated VFR versus any other type of travel, and whether they indicated business travel versus any other type of travel.

¶Travelers participating in GTEN who selected returning to country of origin of self or family to visit friends and relatives and were visiting low or low–middle income countries according to the 2009 World Bank World Development Report (available at http://econ.worldbank.org) were termed VFR travelers as defined previously by the CDC. Travelers choosing returning to country of origin of self or family to visit friends and relatives but who did not meet the criteria for visiting low or low–middle income countries included travelers to Venezuela ($N = 2$), Panama ($N = 2$), Brazil ($N = 35$), Argentina ($N = 2$), Gabon ($N = 2$), and Equatorial Guinea ($N = 1$).

healthcare provider specified that vaccine was contraindicated, the traveler's medical history was reviewed for a clinical reason, because the tool did not prompt the provider to denote the condition(s) that contraindicated the vaccine. Using the list of contraindications and precautions to YF vaccine designated by the Advisory Committee on Immunization Practices (ACIP) in 2010, we inferred from the patient's medical history the potential clinical reasons why the provider determined the vaccine was contraindicated.[2]

Two-sided χ^2 tests of independence were used for categorical comparisons. Bivariate and multivariable logistic regressions were used to evaluate the association of age, sex, purpose of travel, duration of travel, destinations, and type of destination with whether travelers declined or received YF vaccination. Regression analyses were limited to travelers only listing one destination country, listing one purpose of travel, and declining or administered vaccine at the clinic visit. Because of possible between-clinic variation, random intercept models with clinic site as the random effect were used in both the bivariate and multivariable regressions. A correction was also made to reduce bias because of small numbers of clusters (clinic sites).[16] A two-sided P value < 0.05 was considered to be significant. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Demographics and travel characteristics of GTEN travelers visiting areas with risk for YF virus transmission. Of 16,660 total GTEN travelers, 5,588 (34%) had itineraries that included travel to an area with risk for YF virus transmission. Table 1 outlines the demographic and travel characteristics of those 5,588 travelers; 19 (< 1%) were ≤ 9 months of age, 816 (15%) were ≥ 60 years of age, and more than one-half (55%) were women. The two most frequent reasons travelers selected for seeking pre-travel consultations were concern about health issues related to travel (32%) and referral from their primary care physician (19%). Thirty-one percent of travelers planned to visit South America only, 68% were visiting Africa only, and 1% planned to visit both continents. Travelers

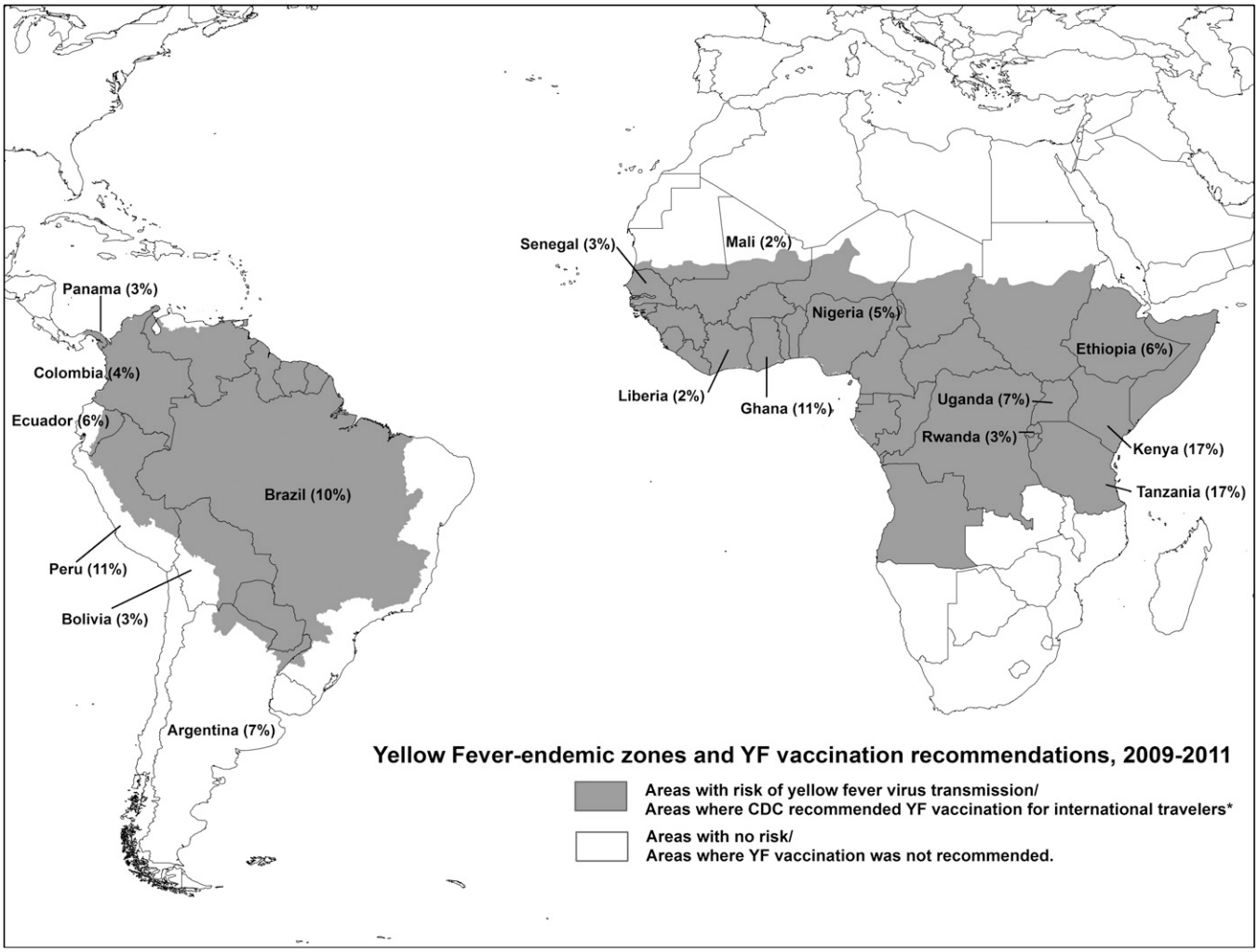

FIGURE 1. Top travel destinations among US Global TravEpiNet travelers visiting countries with risk of YF virus transmission in 2009–2011 (country [% of trips]). The map is the YF risk map that was available to clinicians during the period of data collection described in this analysis (January of 2009 to March 31, 2011). Top travel destinations for travelers included persons traveling to more than one country. The total number of trips for travelers going to areas with risk of YF virus transmission was 7,081. For all YF-endemic countries for which no labels and percentages are listed, the percentages of all travelers' trips are ≤ 1%.

to both South America and Africa reported that they were visiting both urban and rural areas (89% and 75%, respectively). Most travelers reported that they were spending some or the entire trip in hotels (63%), although among travelers to Africa, 26% were spending some or their entire trip in a home with relatives. The top three purposes of travel were leisure (53%), VFR (16%), and business (15%). There were more travelers to Africa who indicated VFR or business than travelers to South America (22% versus 4%, $P < 0.0001$; 16% versus 12%, $P < 0.0001$); however, more travelers indicated leisure trips to South America than Africa (72% versus 45%, $P < 0.0001$).

The top travel destinations of GTEN travelers visiting countries with risk of YF transmission are shown in Figure 1. The 10 most common destinations, in descending order, were Kenya, Tanzania, Ghana, Peru, Brazil, Argentina, Uganda, Ethiopia, Ecuador, and Nigeria. Of 5,588 total travelers to YF-endemic countries, 4,396 (79%) were traveling to at least 1 of these 10 destination countries. Leisure travel was the most common purpose for travel for these travelers. However, 42% of travelers to Ethiopia and 40% of travelers to Nigeria indicated VFR as their purpose of travel (Figure 2). Other common purposes of travel included business (Kenya, Brazil, and Uganda), research/education (Argentina, Uganda, and Ecuador), and adventure (Tanzania and Peru).

YF vaccination status of GTEN travelers. Among all travelers going to entirely endemic or partially endemic countries, 90% and 93% of travelers, respectively, received vaccination at the current clinic visit or were presumed to have pre-existing immunity based on reported YF vaccination within the last 10 years (Table 2). Of all 3,207 travelers receiving vaccine at the clinic visit, only 149 (5% overall) reported having been vaccinated more than 10 years before. Seventeen travelers, eight to entirely endemic and nine to partially endemic areas, were referred to another provider for vaccination. For 34 travelers, vaccine was reportedly not available at the time of their clinic visit.

Of those travelers visiting 1 of the top 10 most commonly visited countries with risk of YF virus transmission, the highest proportion of immune travelers (vaccinated at the visit or had pre-existing immunity) was traveling to Ghana (96%) and Uganda (96%). The highest proportions of non-immune travelers who were not vaccinated before their current trips were individuals planning travel to Ethiopia and Nigeria (22% and 16%, respectively); the most common reason reported for not vaccinating was that the traveler declined vaccination (Table 2). Among all travelers to entirely endemic countries who declined vaccination, almost one-half (45%) planned travel to either Ethiopia or Nigeria.

Providers reported that vaccine was contraindicated for 110 (2%) of all travelers visiting areas of YF virus transmission (Table 3). The most commonly reported medical conditions in these travelers were cancer (17%); immune-suppressing

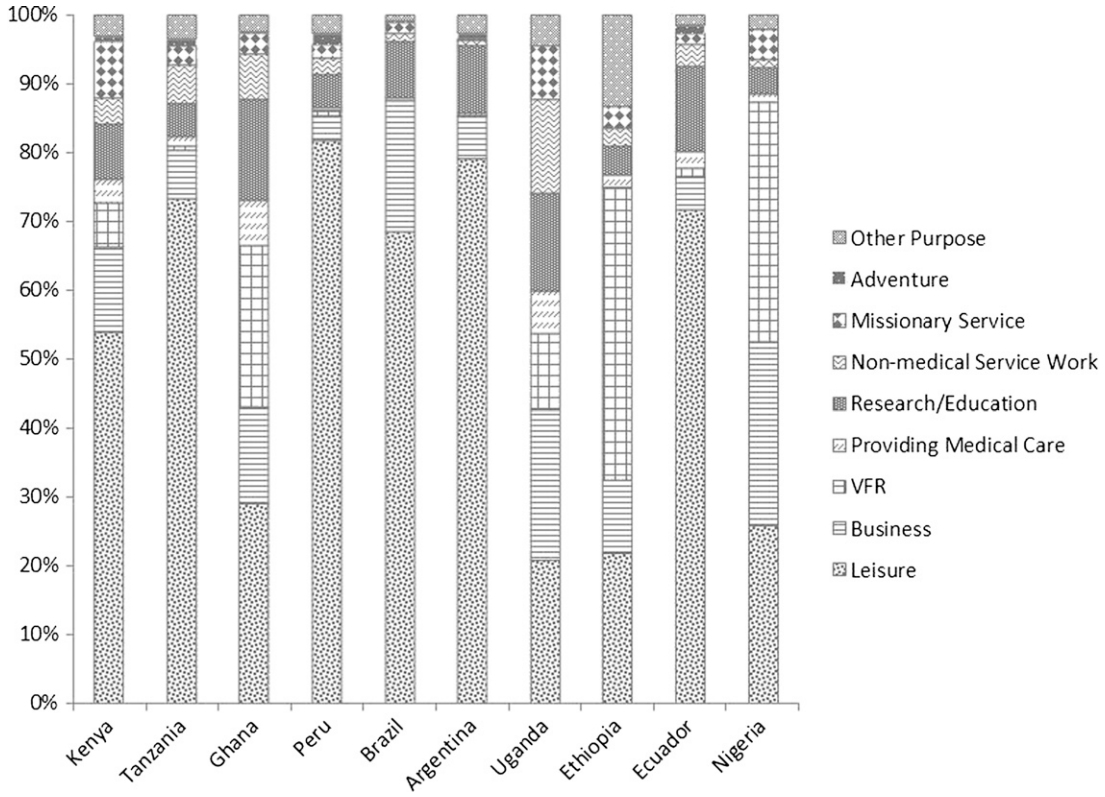

FIGURE 2. Purposes of travel to the top 10 destination countries of US Global TravEpiNet travelers visiting areas with risk of YF virus transmission. Travelers who included only one purpose of travel and traveled to at least one of the top 10 countries included in the graph (N = 4,116) are shown. Travelers who identified only one purpose of travel represented 78% of the dataset (4,379/5,588). Of 5,588 total travelers, 4,396 (79%) were traveling to at least one of these 10 destination countries. Travelers participating in GTEN who selected returning to country of origin of self or family to visit friends and relatives and were visiting low or low–middle income countries according to the 2009 World Bank World Development Report (available at http://econ.worldbank.org) were termed VFR travelers as defined previously by the CDC. Other activities includes self-described other activities, attending gatherings, military, receiving medical care, or adoption.

TABLE 2
YF vaccination status among US Global TravEpiNet travelers visiting the top 10 countries with risk for YF virus transmission

Destinations	Vaccination administered with this visit	Reasons for non-vaccination *n* (row %)							Total
		Pre-existing immunity*	Not indicated for this itinerary	Referred to primary care physician	Medical contraindication	Patient declined	Insufficient time to complete before departure	Vaccine not available	
Entirely endemic									
All†	2,244 (69)	664 (21)	76 (2)	8 (< 1)	59 (2)	152 (5)	1 (< 1)	29 (1)	3,233
Tanzania	408 (70)	111 (19)	33 (6)	0 (0)	4 (< 1)	12 (2)	1 (< 1)	10 (2)	579
Kenya	374 (71)	105 (20)	15 (3)	2 (< 1)	9 (2)	22 (4)	0 (0)	0 (0)	527
Ghana	427 (77)	101 (18)	1 (< 1)	3 (< 1)	9 (2)	8 (1)	0 (0)	3 (< 1)	552
Ethiopia	169 (57)	63 (21)	11 (4)	0 (0)	12 (4)	37 (12)	0 (0)	5 (2)	297
Nigeria	145 (58)	66 (26)	0 (0)	0 (0)	5 (2)	32 (13)	0 (0)	2 (1)	250
Uganda	170 (69)	68 (27)	0 (0)	0 (0)	3 (1)	2 (1)	0 (0)	5 (2)	248
Partially endemic									
All‡	963 (75)	234 (18)	N/A§	9 (1)	17 (1)	50 (4)	3 (< 1)	5 (< 1)	1,281
Peru	256 (73)	68 (19)	N/A§	6 (2)	3 (1)	17 (5)	0 (0)	2 (1)	352
Brazil	257 (83)	33 (11)	N/A§	0 (0)	3 (1)	13 (4)	1 (< 1)	0 (0)	307
Ecuador	129 (72)	41 (23)	N/A§	2 (1)	2 (1)	3 (2)	1 (1)	2 (1)	180
Argentina	84 (71)	22 (19)	N/A§	0 (0)	1 (1)	8 (7)	1 (1)	0 (0)	118

Analysis is limited to travelers listing only one destination country ($N = 4,518$); vaccination status was missing for four travelers.
*Pre-existing immunity is defined as the patient having reported receipt of the YF vaccine within 10 years before the current clinic visit.
†All entirely endemic countries include but are not limited to Tanzania, Kenya, Ghana, Ethiopia, Nigeria, and Uganda.
‡All partially endemic countries include but are not limited to Peru, Brazil, Ecuador, and Argentina.
§Includes those travelers visiting countries where the entire country is considered endemic and/or travelers visiting countries considered partially endemic where the healthcare provider indicated vaccine might be indicated. Individuals going to partially endemic countries where the healthcare provider chose vaccination not indicated for this itinerary were excluded.

medication/chemotherapy or steroids by mouth in the last 3 months (17%); other immune system issue (12%); or age less than 6 months (9%).

Comparison of travelers who declined with travelers who received YF vaccine. Table 4 outlines both the bivariate and multivariable comparisons of the demographic and travel characteristics of travelers who declined or were administered YF vaccination. Travelers to either Ethiopia or Nigeria were included to assess whether they still were more likely to decline than those travelers going to other countries after the data were controlled for all other variables. Specifically, travelers to Ethiopia were compared with travelers going to countries other than Ethiopia and Nigeria. Similarly, travelers to Nigeria were compared with travelers going to countries other than Nigeria and Ethiopia. Furthermore, leisure travelers and VFRs were compared separately with those travelers traveling for other reasons. In the multivariable model, there was significant variance attributed by clinic differences on the outcome of receiving or declining YF vaccine (variance = 1.46, standard error = 0.64, $P = 0.035$). Adjusting for all other variables in the model, males were less likely to decline vaccine than females (odds ratio [OR] = 0.633, 95% confidence interval [CI] = 0.41–0.99). VFRs were significantly more likely to decline YF vaccination than receive it compared with non-VFR/non-leisure travelers (OR = 2.57, 95% CI = 1.27–5.22). Finally, travelers to Nigeria were 3.01 (95% CI = 1.37–6.62) times more likely to decline vaccination than receive vaccination compared with travelers to other countries.

TABLE 3
Characteristics or medical conditions of US Global TravEpiNet travelers visiting areas with YF virus transmission for whom the provider specified that vaccine was contraindicated ($N = 110$)

Characteristics or medical conditions*	Total (*n*, %)
Have cancers or blood disorders	19 (17)
Received immune-suppressing medication/chemotherapy or took steroids by mouth in the last 3 months	19 (17)
Other immune system issue(s)	13 (12)
< 6 months old	10 (9)
Pregnant	5 (5)
6–8 months old	4 (4)
≥ 60 years	4 (4)
Hypersensitivity to eggs	4 (4)
HIV: most recent CD4 = 200–500	3 (3)
HIV: most recent CD4 < 200	2 (2)
Received organ or bone marrow transplant	1 (1)
Breastfeeding	1 (1)
History of having spleen removed	0 (0)
Thymus disease or history of thymectomy	0 (0)

Analysis includes all travelers visiting areas with risk of YF virus transmission ($N = 5,588$). Data on the specific medical conditions were missing for 41 (37%) travelers.
*More than one response allowed.

DISCUSSION

Our study found that approximately one-third of GTEN travelers were visiting areas with risk of YF virus transmission; most (> 90%) were vaccinated at their pre-travel health consultation or reported YF vaccination within the past 10 years. We also found that VFR travelers behave differently than those travelers traveling for other purposes with regard to acceptance of YF vaccination. Furthermore, travelers to Nigeria and females were also more likely to decline vaccine.

Few published studies have focused on the pre-travel preparation of travelers going to areas with risk of YF virus transmission; however, the prevalence of YF vaccination in our study was higher (> 90%) than the prevalence described in an airport study in South Africa, in which only 76% of travelers to YF risk areas could produce proof of vaccination.[17] Another study comparing VFR travelers with tourist travelers found that 90% of adult tourists were vaccinated against YF virus compared with 66% of adult VFR travelers.[18]

Previous studies have found that VFR populations are less likely to seek care than those travelers traveling for other purposes and are at greater risk for acquiring diseases while abroad.[18–21] In this study, VFR travelers who did seek pre-travel care were approximately three times more likely to decline YF vaccination than those travelers who were traveling for non-VFR/non-leisure purposes. VFR travelers, like other travelers in our study, reported that they sought care at

TABLE 4

Comparison of US Global TravEpiNet travelers who declined versus travelers who were administered YF vaccine before visiting areas with risk for YF virus transmission

Characteristics	YF vaccine status		Bivariate*		Multivariable*	
	Declined (N = 156) N (%)	Vaccine administered (N = 2,510) N (%)	OR	95% CI	OR	95% CI
Age (years)						
≤ 12†	34 (22)	247 (10)	1.41	0.65–3.06	0.94	0.45–1.96
13–18	10 (6)	150 (6)	0.94	0.33–2.70	0.84	0.32–2.17
19–59	89 (57)	1812 (72)		Referent		
≥ 60	23 (15)	302 (12)	1.42	0.50–4.00	1.55	0.58–4.13
Sex						
Female	96 (62)	1,362 (54)		Referent		Referent
Male	60 (38)	1,149 (46)	0.67	0.43–1.06	0.63	0.41–0.99
Purpose of travel						
Leisure	51 (33)	1,172 (47)	1.61	0.96–2.70	1.59	0.86–2.92
VFR‡	73 (47)	417 (17)	3.02	1.59–5.73	2.57	1.27–5.22
Non-leisure/non-VFR	32 (21)	922 (37)		Referent		Referent
Duration of travel (days)						
≤ 14	58 (37)	1,359 (54)		Referent		Referent
15–30	52 (33)	719 (29)	1.64	0.72–3.72	1.28	0.49–3.31
≥ 31	46 (29)	433 (17)	1.21	0.69–2.12	1.02	0.52–1.99
Destinations						
Ethiopia	24 (15)	142 (6)	1.83	1.06–3.13	1.43	0.69–2.96
Nigeria	25 (16)	112 (4)	3.39	1.70–6.74	3.01	1.37–6.62
Other countries¶	107 (69)	2,257 (90)		Referent		Referent
Type of destination‖						
Urban	94 (60)	1,540 (61)		Referent		Referent
Rural	13 (8)	318 (13)	1.04	0.58–1.88	1.12	0.54–2.30
Both urban and rural	650 (26)	49 (31)	0.74	0.50–1.10	0.72	0.40–1.32

Analysis is limited to travelers who only listed one destination country, listed one purpose of travel, declined vaccine, or were administered vaccine at the clinic visit (N = 2,666).

*Bivariate and multivariable modeling were done using a random intercept model with clinic site as the random effect; a correction was also made to reduce bias caused by small numbers of clusters (clinic sites).[16] There was significant variance attributed by clinic differences on the outcome of receiving or declining YF vaccine (variance = 1.46, standard error = 0.64, P = 0.035).

†Only one traveler under 9 months of age was included in children less than 12 years. For unknown reasons, this child was vaccinated, although YF vaccination is not routinely recommended for children less than 9 months of age.

‡Travelers participating in GTEN who selected returning to country of origin of self or family to visit friends and relatives and were visiting low or low–middle income countries according to the 2009 World Bank World Development Report (available at http://econ.worldbank.org) were termed VFR travelers as defined previously by the CDC.

§Non-leisure/non-VFR travelers were defined as those travelers traveling for business, adventure, missionary service, non-medical service work, research/education, providing medical care, receiving medical care, attending a gathering, military, adoption, or self-described other activities.

¶Other countries were defined as all other countries with risk for YF virus transmission except for Ethiopia and Nigeria.

‖Travelers could choose more than one answer.

GTEN clinics, because they were concerned about health issues or referred to the clinic by their primary care physicians. The finding that VFRs are more likely to decline vaccination underscores the need for both primary care and travel medicine providers to identify these persons before they embark on international travel and thoroughly discuss the risk and benefits of vaccination. Furthermore, VFR travelers might be more likely to return to the same country in the future; therefore, providers should discuss the repeated risk of multiple trips and the value of the vaccine as an investment in future travel.[22] Interestingly, VFR travelers in our study were more likely to be traveling to Africa.

Our multivariable model also found that travelers to Nigeria were more likely to decline vaccine. In Nigeria, YF outbreaks occur frequently.[23] A review in 2002 estimated that the risk of YF illness in travelers to West Africa for a 2-week trip is 1:2,000 during interepidemic periods and 1:267 during epidemic periods, although the risks might vary according to the season.[24,25] Because passive surveillance systems are often insensitive in identifying cases, the true number of cases is unknown. Furthermore, the implementation of mass preventive YF vaccination campaigns in certain countries has increased the proportion of residents with immunity to YF virus and consequently, led to a decrease in the number of cases of YF.[26] The paucity of reported YF cases in such countries might falsely reassure travelers, specifically VFR travelers who are still at risk for contracting YF disease if they have never been immunized.

We also found that females were more likely to decline vaccine than males after the data were adjusted for age, purpose of travel, duration of travel, destination, and type of destination. Although the GTEN tool does not collect the reason for the traveler's declining recommended vaccination, possible reasons may include cost, the patient's perceptions of the risk of vaccination, or the patient's perception of the disease risk from travel (especially in the absence of ongoing outbreaks).[20,27,28]

Interestingly, a small percentage of GTEN travelers were referred to other providers for YF vaccination. Because all GTEN clinics are designated as YF vaccination centers and most specialize in travel medicine, it is unclear why these travelers would have been referred elsewhere. This finding may reflect intermittent shortages of vaccine. For a number of travelers, the reported reason for not administering YF vaccine was vaccine not available. During several months in 2008, Sanofi Pasteur (the sole manufacturer–distributor of YF vaccine in the United States) reported that single-dose vials of YF vaccine were in short supply, although five-dose vials were still available.[29] A similar shortage occurred in 2009. Clinics can monitor national shortages or supply issues through the US Food and Drug Administration (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm) and the CDC (http://www.cdc.gov/vaccines/vac-gen/shortages). Although logistically difficult, clinics can also arrange times for multiple travelers to be seen simultaneously for YF vaccination; this strategy takes advantage of multiple-dose vials

that might be more readily available. Travelers should verify before their pre-travel consultation that YF vaccine will be available, if indicated, for their travel.

Our study data were collected before the revised global YF risk map and country-specific vaccination recommendations for travelers were published on April 1, 2011.[11–13] These recommendations downgrade Tanzania from a country for which all travelers had previously been recommended to receive YF vaccination to one where YF vaccination would be recommended only for travelers who expect increased risk of exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites.[11–13] If the revised recommendations had been in effect during our study period, at least 17% of trips to areas with risk of YF (e.g., those travelers traveling to Tanzania) captured in GTEN might have been affected by this change. Although the GTEN tool does not collect subnational data, future studies of GTEN data could compare the vaccine status of travelers to destination countries before and after the change in recommendations and estimate the number of travelers affected.

Our study has a number of limitations. The primary limitation of this study is that it is an analysis of data for individuals who sought pre-travel advice. Studies have found that most travelers do not seek pre-travel health advice. One study conducted at John F. Kennedy International Airport in New York found that only 36% of travelers sought pre-travel advice before traveling to high-risk destinations.[28] An airport study at Boston's Logan International Airport found that only 46% of travelers to low/low–middle income countries sought pre-travel advice.[19] Furthermore, the same study found that, among travelers to low/low–middle income countries who sought pre-travel advice, 38% did so from primary care physicians, and only 30% from travel medicine specialists.[19] Considering these findings and the fact that all the GTEN practices are designated YF vaccination centers, travelers seeking care at GTEN clinics may not be representative of the general population of US travelers. YF vaccine is only authorized to be administered at clinics designated by state or territorial health departments; such clinics are listed on the YF Vaccination Center Registry maintained by the CDC and publicly accessible online (http://www.cdc.gov/travel/yellowfever-vaccination-clinics/search.htm). Therefore, travelers planning to visit countries with YF vaccination requirements or desiring to comply with CDC's YF vaccination recommendations for travel to endemic countries without requirements must visit one of these designated clinics. The representativeness of the GTEN clinics to other clinics listed on the YF Vaccination Center Registry is unknown; however, GTEN clinics represent < 1% of all designated YF vaccination centers in the United States.

Another limitation is that we had to assume that all YF vaccination decisions made by GTEN clinicians were correct, because the dataset did not allow us to identify errors in these decisions. Also, limiting the multivariable analysis to travelers who listed only one destination and purpose of travel might have influenced the results. Our results may also have been influenced by using only low or low–middle income countries outlined in the 2009 World Bank World Development Report for the definition of a VFR. Finally, the revised ACIP recommendations for the use of YF vaccine were published in the middle of our study period (July of 2010) and might have affected provider and traveler decisions regarding vaccination.[2]

This study showed that, although most GTEN travelers visiting areas with risk of YF virus transmission were vaccinated at the pre-travel clinic visit or within 10 years before the clinic visit, VFR travelers, specifically those travelers traveling to Nigeria, were more likely to decline YF vaccination recommended for their itineraries. Clinicians seeing VFR travelers should thoroughly discuss destination-specific health risks, insect bite prevention, and benefits of vaccination, especially if future travel to areas with risk of YF virus transmission is expected. Travelers should be encouraged to seek pre-travel consultations 4–6 weeks in advance to allow adequate time for the administration of all other vaccines recommended and ensure that YF vaccine is available. Additional studies are required to identify travelers' reasons for declining recommended YF vaccination and evaluate the effect of the revised country-specific YF vaccination recommendations on YF vaccination patterns. Data regarding the reasons for refusal of YF vaccination by VFR travelers could inform the development of future outreach and education programs targeted to these travelers.

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Authors' addresses: Emily S. Jentes, Pauline Han, and Mark D. Gershman, Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, Atlanta, GA, E-mails: ejentes@cdc.gov, hfd7@cdc.gov, and dvj8@cdc.gov. Sowmya R. Rao, Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, and Center for Health Quality, Outcomes, and Economic Research, Bedford Veterans Administration Medical Center, Bedford, MA, E-mail: sowmya.rao@va.gov. Regina C. LaRocque and Edward T. Ryan, Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, E-mails: rclarocque@partners.org and etryan@partners.org. J. Erin Staples, Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, E-mail: auv1@cdc.gov.

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