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SHORT COMMUNICATION

Seroprevalence of Dengue Virus, West Nile Virus, Chikungunya Virus, and Zika Virus in International Travelers Attending a Travel and Migration Center in 2015–2017, Southern Italy

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Abstract

International travelers to areas endemic for vector-borne diseases (VBDs) may be at risk of contracting and spreading these diseases. The aim of this study was to evaluate the prevalence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies that are specific for Dengue Virus (DV), West Nile Virus (WNV), Chikungunya Virus (CHIKV), or Zika Virus (ZV) in a cohort of international travelers. The study enrolled travelers who attended the Travel Medicine and Migration outpatient service of Local Health Unit of Bari, Italy, in March 2015–June 2017 for counseling and vaccine prophylaxis before travel. After receiving informed consent, post-travel blood samples were tested for IgM and IgG antibodies specific for DV, WNV, CHIKV, and ZV. Of the 207 travelers attending the vaccine service, 156 (75%) were enrolled. Of the 156 subjects, 23 (14.7%) had IgM and/or IgG antibodies specific for at least one VBD. Of these, 12 (52%) were asymptomatic. Nineteen (12.2% of the whole cohort), nine (5.8%), nine (5.8%), and two (1.3%) subjects had IgM and/or IgG antibodies specific for DV, WNV, CHIKV, and ZV, respectively. Ten subjects (6.4%) harbored antibodies that were specific for more than one VBD. A significant number of the international travelers were DV-positive. Our findings suggest that international travelers should undergo serological surveillance, particularly those who travel frequently and for long periods to areas that are endemic for hemorrhagic dengue. Due to a possible risk of introducing VBDs into nonendemic areas, increased awareness among physicians and travelers and appropriate laboratory detection are crucial. There are currently no licensed vaccines for these VBDs in Italy or other European countries; the main preventive measures are protection from mosquito bites and vector control.

Keywords: travelers, Dengue Virus, West Nile Virus, Chikungunya Virus, Zika Virus, seroprevalence

Introduction

Vector-borne diseases (VBDs) are common in tropical and subtropical areas (WHO 2014). Climate changes, movement of population and goods, and changes in vector ecology (*e.g.*, adaptation to new habitats) may influence emergence of VBDs (Confalonieri et al. 2007, Campbell-Lendrum et al. 2015, Negev et al. 2015).

VBDs symptoms are often mild and infection may go unrecognized (WHO 2014), leading to spread of VBDs and importation of pathogens into nonendemic areas; thus it is important to assess the prevalence of these infections in travelers to VBD-endemic areas.

To the best of our knowledge, no serosurvey of VBDs is available for international travelers in Italy. Therefore, the aim here was to examine the prevalence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies specific for Dengue Virus (DV), West Nile Virus (WNV), Chikungunya Virus (CHIKV), and Zika Virus (ZV) in a cohort of international travelers who received counseling and vaccine prophylaxis at

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Table 1. Patterns of Immunoglobulin M and/or Immunoglobulin G Seropositivity for Vector-Borne Diseases in International Travelers

Patient/ gender	Country of travel (Continent)	Symptoms	DV		Classification of infection	WNV		Classification of infection	CHIKV		Classification of infection	ZV		Classification of infection
			IgM	IgG		IgM	IgG		IgM	IgG		IgM	IgG	
1/Female	Venezuela (America)	No	−	+	Previous	−	+	Previous	−	−		−	−	
2/Male	Venezuela (America)	No	−	+	Previous	−	+	Previous	−	+	Previous	−	−	
3/Male	Dominican Republic (America)	Yes	−	+	Previous	−	−		−	−		−	−	
4/Female	Burkina (Africa)	No	−	+	Previous	−	+	Previous	−	−		−	−	
5/Male	Angola (Africa)	Yes	−	+	Previous	+	+	Recent	+	+	Recent	+	−	Dubious
6/Male	India (Asia)	No	−	−		−	−		−	+	Previous	−	−	
7/Female	Senegal (Africa)	Yes	−	−		−	−		+	−	Dubious	−	−	
7/II[a]			−	−		−	−		+	−	No infection	−	−	
8/Female	Nigeria (Africa)	No	−	+	Previous	−	+	Previous	−	−		−	−	
9/Male	Nigeria (Africa)	No	−	+	Previous	−	−		−	−		−	−	
10/Male	Thailand (Asia)	Yes	+	+	Recent	−	−		−	−		−	−	
11/Male	South America	No	−	+	Previous	−	−		−	−		−	−	
12/Female	Uganda (Africa)	No	+	−	Dubious	−	−		+	−	Dubious	−	−	
12/II[a]			−	−	No infection	−	−		+	−	No infection	−	−	
13/Male	Brasil (America)	No	+	−	Dubious	−	−		−	−		−	−	
14/Female	Brasil (America)	Yes	+	+	Recent	−	−		−	−		−	−	
15/Female	Bali (Asia)	Yes	+	+	Recent	−	−		−	−		−	−	
16/Female	Cuba (America)	Yes	−	−		−	−		+	−	Dubious	−	−	
17/Female	Dominican Republic (America)	No	+	−	Dubious	+	−	Dubious	+	−	Dubious	−	−	
18/Male	Cuba (America)	Yes	−	−		−	−		−	−		+	+	Recent
19/Male	Caribbean (America)	No	+	−	Dubious	+	−	Dubious	+	−	Dubious	−	−	
20/Male	Seychelles (Africa)	Yes	+	−	Dubious	+	−	Dubious	−	−		−	−	
20/II[a]			+	+	Recent	−	−	No infection	−	−		−	−	
21/Female	Bahamas (America)	No	+	−	Dubious	+	−	Dubious	+	−	Dubious	−	−	
22/Male	Benin (Africa)	Yes	+	+	Recent	−	−		−	−		−	−	
23/Female	Thailand (Asia)	Yes	+	+	Recent	−	−		−	−		−	−	

[a]Patients from whom a second serum sample was obtained.

Classification of infection: previous = VBD-specific IgG without IgM; recent = VBD-specific IgM and IgG detected in either the first or second sample; dubious = first sample was IgM-positive/IgG-negative; no second blood sample was available; no infection = no IgG detected in the second sample, with or without IgM (if IgM was still present in the second sample, it was considered a false-positive test).

DV, Dengue Virus; WNV, West Nile Virus; CHIKV, Chikungunya Virus; ZV, Zika Virus; +, positive; −, negative; VBD, vector-borne diseases; IgM, immunoglobulin M; IgG, immunoglobulin G.

the Travel Medicine and Migration Center of Bari (Southern Italy).

Materials and Methods

The study population comprised all consecutive international travelers who attended the Travel Medicine and Migration outpatient service at the Department of Biomedical Sciences and Human Oncology in the Hygiene Section/Local Health Unit of Bari in March 2015–June 2017 for counseling and vaccine prophylaxis before traveling to VBD-endemic regions. On average, 100 travelers visit the vaccine service each year. This study did not require local ethics committee approval since all serologic tests were routine, with no data collection above that required for routine care. All participants provided written consent to participate. The study was conducted in accordance with Italian and Institutional standards, with the principles set down in the Declaration of Helsinki and its revisions, and with local legislation.

Four weeks after returning from travel, each participant completed a data collection form, which asked about the length, destination, and reason for travel, and whether the subject had developed any symptoms of VBDs. The reasons for travel were categorized as work/study, volunteering, domicile, tourism, and visiting friends and relatives (VFR). The length of travel (days spent abroad) was also recorded. Subjects were considered symptomatic for one of the four VBDs if, during or after the last journey, they had one or more symptoms (WHO 2014).

All subjects were also bled 4 weeks after their travel. Blood samples were tested for IgM and IgG antibodies specific for DV, WNV, CHIKV, and ZV by enzyme-linked immunosorbent assays (Euroimmun Italia, Padua, Italy) conducted at the Hygiene and Preventive Medicine Unit of Policlinico Hospital, Bari, Italy. Some asymptomatic IgM-positive IgG-negative subjects provided a second sample 4 weeks later to ascertain whether seroconversion had occurred. Neutralization tests to confirm IgM positivity were not performed, as none were available.

Statistical analysis was performed using STATA 12.0 (Student's *t*-test or chi-squared/Fisher's exact test).

Results

During the study period, 207 travelers attended the vaccine service and 156 (75%) were enrolled. Three patients provided a second sample.

Of the 156 subjects, 79 were male (51%) and 77 were female (49%). The median age was 33 years (interquartile range (IQR): 27–43). The most visited continent was Africa (37.8%), followed by America (35.9%), Asia (25.6%), and Europe (0.6%). The most common reason for travel was tourism (51.9%), followed by volunteering (28.8%), work/study (15.4%), domicile (1.9%), and VFR (1.9%). The median length of the journey was 21 days (IQR: 14–32).

Of the 156 travelers, 23 (14.7%) had IgM and/or IgG antibodies specific for at least one of the four VBDs (Table 1). Of these, 12 (52%) were asymptomatic. No symptomatic patient was hospitalized. The median journey length for seropositive subjects was 21 days (IQR: 12–136) and that for seronegative subjects was 16 days (IQR: 11–29). VBD-seropositive patients made significantly longer journeys than VBD-seronegative subjects ($p = 0.0007$); this was also true for DV-, WNV-, CHIKV-, and ZV-seropositive versus DV-, WNV-, CHIKV-, and ZV-seronegative subjects ($p < 0.01$). America was the most visited continent (Table 1). The main travel motivation of seropositive individuals was tourism (43.5%), followed by volunteering (21.7%), work/study (13%), domicile (13%), and VFR (8.7%). Domicile was the only motivation statistically associated with seropositivity for any VBDs, and with seropositivity for DV or WNV ($p < 0.01$).

Of the whole cohort, 19 (12.2%), 9 (5.8%), 9 (5.8%), and 2 (1.3%) had IgM and/or IgG antibodies specific for DV, WNV, CHIKV, and ZV, respectively (Table 1). The first serum sample from 10 subjects (6.4%) had antibodies against more than 1 VBD. One patient experienced a recent DV infection (patient no. 20, Table 1).

Six subjects positive for anti-DV IgG reported a travel history to Africa and five to America. A subject with a recent ZV infection had visited Cuba (patient no. 18, Table 1).

Discussion

Here, we showed that 14.7% of the enrolled subjects had antibodies specific for at least one of the four vector-borne pathogens, suggesting that international travelers are at risk of contracting VBDs. Dengue was the most common infection (12.2%). This is consistent with the results of other studies (Leder et al. 2013, Wilder-Smith 2017).

The main limitation was the small number of subjects, all of whom were recruited from a single outpatient service; thus they may not be representative of the traveling population. Furthermore, no neutralization tests were performed.

Nevertheless, our finding that travelers were frequently positive for DV, and that more DV infections were imported into Italy by travelers over recent years, suggests a risk that DV may emerge in Italy (Quam et al. 2015). This underlines the need for systematic pretravel counseling and surveillance of international travelers visiting endemic areas. This is particularly true for those traveling frequently or for long periods to areas endemic for hemorrhagic DV (Ayukekbong et al. 2017, Wilder-Smith 2017).

We confirmed that VBDs are often asymptomatic. This is concerning because both asymptomatic and symptomatic travelers could spread VBDs when competent vectors are present, leading to autochthonous cycles of infection (Venturi et al. 2017, Wilder-Smith 2017).

Conclusions

Europe has no licensed vaccines for the VBDs studied herein; the main preventive measures are protection from mosquito bites and vector control.

In light of the recent Chikungunya epidemic in Italy (ECDC 2017, Venturi et al. 2017), early detection of imported viremic cases is crucial. Increased awareness among physicians and travelers and appropriate laboratory detection (ECDC 2017) are paramount. Further studies should elucidate the role of travelers in introducing these infections to previously uninfected areas (Wilder-Smith 2017).

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Author Disclosure Statement

No conflicting financial interests exist.

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