Asymptomatic Arbovirus, Campylobacter but no Hepatitis E Infections in German Travelers to Asia

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Research Article

Keywords: Dengue, Zika, Chikungunya, Hepatitis E, Camphylobacter jejuni, ELISA

Posted Date: March 16th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2516503/v2

Abstract

Purpose: Transmission of infectious travel diseases is increasing, especially in travelers from developed to developing countries. Still, the incidence of many travel diseases is not known, because retrospective surveillance systems do not detect asymptomatic infections.

Methods: We took medical history and blood samples of 81 German travelers before and after travelling to South and Southeast Asia. IgG, IgM, and if possible IgA antibody titers were measured for Dengue virus (DENV), Chikungunya virus (CHIKV), Zika virus (ZIKV), Hepatitis E virus (HEV), and Camphylobacter jejuni (C.jejuni) using commercial ELISA kits. Additionally, we tested for Cytomegalovirus and Helicobacter pylori.

Results: No symptoms were reported. Still, we found one anti-ZIKV and two anti-DENV IgG seroconversions. For CHIKV, we found three individuals who were IgG-positive before travel and negative afterwards. We found five IgG seroconversions for C.jejuni and zero for HEV. We also found one IgG seroconversion for CMV, and zero for H.pylori. Calculated incidences were between zero and 6.5%.

Conclusion: Using serological analyses, we found a small but significant number of travel infections that would have gone unnoticed by retrospectively asking for symptoms alone. This suggests that the risk for these infections may be higher than previously estimated.

Highlights

- Eighty-one consecutive travelers to Asia were tested for antiviral antibodies
- We tested pre and post travel for DENV, ZIKV, CHIKV, HEV, C. jejuni, CMV, and H.pylori
- None had any symptoms
- We found five IgG-seroconversions for C. jejuni, two for DENV, one for ZIKV
- We found no seroconversions for CHIKV and HEV

Introduction

Over the last decades, worldwide travel has seen an exponential increase, with a peak of 1,323,000,000 tourist arrivals in 2017 [1,2]. Exceptional events like the oil crisis of the 1970s, the 9/11 attacks of 2001, or the recent coronavirus pandemic have caused dents in this curve [3,4,5], but the general direction is clearly upwards [6,7].

Parallel to the development in worldwide travel, the incidence and prevalence of typical travel infections have multiplied as well, especially in travelers from developed to developing countries [8,9]. While all authors agree about this increase in principle, there is little precise data on the actual incidence of infections like vector-borne diseases (VBDs), or food and water-borne diseases (FWDs) in travelers [10,11,12,13]. One reason for this lack of information is that most studies on the subject are retrospective in

nature because they rely on surveillance data or spontaneously reported, symptomatic infections [14,15,16,17]. To overcome this hurdle, one study on Dengue virus (DENV) combined infection numbers with flight passenger data and calculated an incidence below one percent [18]. Another, also on DENV, used mathematical modeling to calculate an incidence between 0.2% and 0.91%, depending on the length of stay in an endemic region [19]. To our knowledge, there are no comparable studies on other travel infections.

So even if these models produce fairly precise numbers for clinically apparent infections, it would be desirable to assess the risk for apparent as well as for inapparent infections in endemic regions. A prospective, longitudinal serological investigation that also detects asymptomatic cases would be ideal here, but only few studies meet this standard: For VBDs like Dengue Virus (DENV), Chikungunya Virus (CHIKV), or Hepatitis E Virus (HEV) there is reliable data from the USA, Australia, and The Netherlands showing seroconversion rates from zero to 6.8% in travelers to endemic regions [20,21,22,23,24]. Regarding FWDs, reported seroconversion rates range between zero and 3.7% for hepatitis E virus (HEV), and up to 78% for Escherichia coli (ETEC), Salmonella, or Camphylobacter jejuni (C.jejuni) [25,26,27].

In this study, we longitudinally analyzed the sera of all individuals attending Hamburg-area travel health clinics from 2017 to 2018 who were planning journeys to South or Southeast Asia. Blood samples were drawn before and after travelling, antibody titers for typical travel diseases endemic in that region were determined, and a questionnaire about clinical symptoms and travel habits was filled out.

As examples for vector-borne diseases, we used DENV, CHIKV, and Zika virus (ZIKV). DENV and CHIKV were chosen because they have recently led to several outbreaks, they can be asymptomatic as well as highly symptomatic, and especially DENV can impose a life-threatening risk on a minority among those infected [28,29,30]. ZIKV, while causing milder symptoms, is linked with congenital microcephaly and autoimmune disorders and has seen several outbreaks, too [31,32,33,34]. So all of these share an epidemic potential and are of high clinical relevance. Additionally, they can be easily detected by standardized commercial ELISA kits. These kits, even if they are compromised by a relatively low specificity, are easier to use and better validated than comparable test systems for other relevant VBDs like malaria or leishmaniasis [35,36,37].

For FWD, we chose C.jejuni because it is one of the most widespread infectious diseases worldwide, because it is endemic in Asia [38], and because it can lead to severe clinical illness – sometimes with local or generalized long-term complications [39,40,41]. Hepatitis E virus (genotypes 1, and 2) is also endemic in south Asia. After several outbreaks in the last years, it is considered a disease on the rise [42,43,44]. Although symptoms are usually mild, HEV infections can become chronic in immunosuppressed individuals and may cause serious complications during pregnancy [45,46]. So much like the VBDs, both C.jejuni and HEV are of epidemiologic and clinical relevance, and they also can be reliably diagnosed using standard ELISA kits [47,48].

Finally, as a kind of “controls”, we chose CMV and H.pylori - two infectious agents that are neither FWD or VBD and that are not considered typical travel diseases.

Material And Methods

Proband selection

Eighty-one travellers attending Hamburg-area travel health clinics from 2017 to 2018 were prospectively enrolled before and followed until after travelling to endemic countries in South and Southeast Asia. All enrolled subjects reported no previous apparent infection with any of the investigated pathogens in the past. For the study, clinical data, travel destinations, durations and types of travel as well as symptoms were recorded (Table 1).

Serological test systems

Antibody titers were determined via ELISA in serum. In brief, sera were screened for anti-HEV IgA, IgG and IgM antibody titers using ELISA kits (# EI 2525-9601 A, # EI 2525-9601 G and # EI 2525-9601 M, Euroimmun AG, Lübeck, Germany). For DENV, IgG and IgM titers were determined (#EI 266a-9601-1 G and EI 266a-9601-1 M, Euroimmun AG, Lübeck, Germany). For CHIKV, IgG and IgM titers were determined (#EI 293a-9601 G and EI 293a-9601 M, Euroimmun AG, Lübeck, Germany). For ZIKV, IgG and IgM titers were determined (#EI 2668-9601 G and EI 2668-9601 M, Euroimmun AG, Lübeck, Germany).
For C.jejuni and H.pylori, IgA and IgG titers were determined (# EI 2091-9601 A and # EI 2091-9601 G, for C.jejuni; # EI 2080-9601 A and # EI 2080-9601 G, for H.pylori, Euroimmun AG, Lübeck, Germany). For CMV, IgG and IgM titers were determined (#EI 2570-9601 G and EI 2570-9601 M, Euroimmun AG, Lübeck, Germany). All tests were performed according to manufacturer’s instructions.

Data analysis

Descriptive statistics, student’s t-test and Fisher’s exact test were performed using GraphPad Prism (Graphpad Software Inc., version number 9.0).

Results

In 81 individuals, none reported any clinical symptoms.

Vector-borne diseases:

Out of 81 Individuals, 7 were seropositive for anti-DENV IgG before traveling, and 9 after traveling (9% vs. 11%; p=0.79); one was seropositive for anti-DENV IgM before traveling, and one after traveling (1.2% vs. 1.2%; p=0.99). Mean antibody titers before and after travelling were 7.79 RU/ml vs. 10.53 RU/ml (p=0.18) for IgG, and 0.21 vs. 0.21 for IgM (p=0.99). (Figure 1, Tables 2 and 3.)

For anti-CHIKV IgG, 5 individuals were seropositive before traveling, and 2 after traveling (6.5 % vs. 2.5%; p=0.44); for anti-CHIKV IgM, three were seropositive before traveling, and two after traveling (4% vs. 2.5%; p=0.99). Mean antibody titers before and after traveling were 4.76 RU/ml vs. 4.62 RU/ml (p=0.2) for IgG, and 0.24 RU/ml vs. 0.24 RU/ml for IgM (p=0.74). (Figure 1, Tables 2 and 3.)

For anti-ZIKV IgG, zero individuals were seropositive before traveling, and one after traveling (0 % vs. 1.2 %; p=0.99); for anti-ZIKV IgM, zero individuals were seropositive before traveling, and one after traveling (0 % vs. 1.2 %; p=0.99). Mean antibody titers before and after traveling were 3.28 RU/ml vs. 3.18 RU/ml (p=0.17) for IgG, and 0.07 RU/ml vs. 0.1 RU/ml for IgM (p=0.09). (Figure 1, Tables 2 and 3.)

Food and water-borne diseases:

Regarding FWDs, 14 individuals were seropositive for anti-C.jejuni IgG before traveling, and 19 after traveling (17% vs. 23.5%; p=0.44); 5 were seropositive for anti-C.jejuni IgA before traveling, and 4 after traveling (6% vs. 4.9%; p=0.99); zero were seropositive for anti-C.jejuni IgM before traveling, and zero after traveling (0% vs. 0%; p=0.99). Mean antibody titers before and after traveling were 13.83 vs. 21.77 RU/ml for IgG (p=0.05), 0.43 vs. 0.45 for IgA (p=0.06), and 0.08 vs. 0.08 for IgM (p=0.99). (Figure 2, Tables 4 and 5.)

For anti-HEV IgG, 9 individuals were seropositive before traveling, and 9 after traveling (11% vs. 11%; p=0.99); for anti-HEV IgA, 7 were positive before traveling, and 6 after traveling (9% vs. 7%; p=0.99); for anti-HEV IgM, zero were positive before traveling, and zero after traveling 0% vs. 0%; p=0.99). Mean antibody titers before and after traveling were 0.81 RU/ml vs. 0.65 RU/ml for IgG (p=0.09), 0.45 RU/ml vs. 0.44 RU/ml or IgA (p=0.47), and 0.08 RU/ml vs. 0.08 RU/ml for IgM (p=0.99). (Figure 2, Tables 4 and 5.)

Other diseases:

For anti-CMV IgG, 29 individuals were seropositive before traveling, and 29 after traveling (36% vs. 36%; p=0.99); for anti-CMV IgM, 5 were seropositive before traveling, and 6 after traveling (6% vs. 7%; p=0.99). Mean antibody titers before and after traveling were 43.27 RU/ml vs. 43.38 RU/ml for IgG (p=0.99), and 0.38 RU/ml vs. 0.40 RU/ml for IgM (p=0.07). (Figure 3, Tables 6 and 7.)

For anti-H.pylori IgG, 12 individuals were seropositive before traveling, and 12 after traveling (15% vs. 15%; p=0.99); for anti-H.pylori IgA, 13 were seropositive before traveling, and 18 after traveling (16% vs. 22%; p=0.43). Mean antibody titers before and after traveling were 19.13 RU/ml vs. 19.55 RU/ml for IgG (p=0.69), and 0.63 RU/ml vs. 0.67 RU/ml for IgA (p=0.24). (Figure 3, Tables 6 and 7.)

Discussion

It was the aim of this study to determine the risk for apparent as well as inapparent travel infections in a real-life scenario. We therefore chose a consecutive, longitudinal, single-center approach and objectively determined infections by seroconversion for specific antibodies against exemplary VBDs and FWDs.

If we count newly found seropositivity post travel as new infections, we found two DENV infections and one borderline result for ZIKV in the 81 individuals tested. Regarding CHIKV, there was one individual IgM-positive pre travel and negative post travel, which would theoretically hint to a symptomless infection at the beginning of the study that had healed in the meantime. Moreover, three individuals were positive for anti-CHIKV IgG pre travel and negative post travel. Although anti-CHIKV IgG can also vanish after an infection, it is rather unlikely that these three Germans were infected in the past and have lost their seropositivity just while traveling to Asia [49]. We rather suspect the aforementioned uncertain specificity of the ELISA test kits as the cause [36]. (Figure 1, Tables 2 and 3.)

None of the differences between pre and post travel values were formally significant, although it is obvious that when travelling from a non-endemic to an endemic region, every infection counts. Calculated incidences were 2% for DENV, 1.2% for ZIKV, and zero for CHIKV. This is slightly higher but still within the order of magnitude reported by others [21,23,24]. (Figure 1, Tables 2 and 3).

Regarding FWD, we found 5 seroconversions for anti-C.jejuni IgG, but none for IgA. This is not surprising, since the rise in IgA is usually transient and can be missed in a subclinical infection. No seroconversions for HEV were seen. The calculated incidence of 6.5% for C.jejuni is higher than expected, the incidence for HEV is, naturally, lower [26,27]. (Figure 2, Tables 4 and 5.)

In our “controls”, we found one CMV infection which would mean an incidence of roughly one percent. Regarding H.pylori, there were 5 anti-H.pylori IgA seroconversions and zero IgG seroconversions, hinting to transient contacts to helicobacter without any manifest infection (Figure 3, Tables 6 and 7).

Of note, none of the individuals reported any symptoms, and even those with seroconversions, when specifically asked, did not recall being ill. This would mean that none of these infections would have been detected in a retrospective surveillance system like GeoSentinel [50,51].

In conclusion, this study has confirmed the risk of FWD and VBD travel infections for these regions in Asia. While still low in absolute numbers, this risk is higher than what could be expected from retrospective surveillance data. The reason is that most – in our study: all – cases were asymptomatic.

Our study is not without flaws. First, because of its prospective, single-center nature, it was conducted on a relatively small sample size. Calculated incidences must therefore be seen as estimations rather than as precise epidemiologic data. Additionally, the aforementioned low specificity of the ELSA tests might skew the results even more. Finally, due to the nature of this study, only individuals who spontaneously attended travel health clinics to seek medical advice before departure were enrolled. We do not know if this population is more or less at risk compared to those who did not seek advice.

Tables

Table 1 Characteristics of all subjects included in the study.

Characteristic		
		total
Subjects		81
	Male	39 (48.2%)
	Female	42 (51.8%)
Age (yr)[a]		34.2 ± 13.9
	Male	33.8 ± 13.2
	Female	34.9 ± 14.1
Travel duration (d)[a]		23.2 ± 11.0
Travel destinations	India, Myanmar, Thailand, Cambodia, Laos, Nepal, Vietnam, Malaysia, Indonesia, Philippines, Sri Lanka	
Travel type	All inclusive tours, backpacker tours	

[a] The data are shown as means ± standard deviations.

Table 2 Seroprevalence for CHIKV, DENV, ZIKV[a]

Assay	CHIKV		DENV		ZIKV		
	IgG	IgM	IgG	IgM	IgG	IgM	N
Group							
Pre-travel	5 (6%)	3 (4%)	7 (9%)	1 (1.2%)	0 (0%)	0 (0%)	81
Post-travel	2 (2.5%)	2 (2.5%)	9 (11%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	81
P	0.44	0.99	0.79	0.99	0.99	0.99	

[a] The data are shown as no. of seropositive together with borderline cases (percentage).

Table 3 Antibody titers for CHIKV, DENV and ZIKV[a]

Assay	CHIKV		DENV		ZIKV		
	IgG [RU/ml]	IgM [Ratio]	IgG [RU/ml]	IgM [Ratio]	IgG [RU/ml]	IgM [Ratio]	N
Group							
Pre-travel	4.76 ± 4.74 (3.0)	0.24 ± 0.2 (0.2)	7.79 ± 18.94 (2.0)	0.21 ± 0.19 (0.2)	3.28 ± 2.7 (2.1)	0.07 ± 0.08 (0.1)	81
Post-travel	4.62 ± 4.05 (2.9)	0.24 ± 0.17 (0.2)	10.53 ± 25.01 (2.0)	0.21 ± 0.18 (0.2)	3.18 ± 2.62 (2.0)	0.1 ± 0.12 (0.1)	81
P	0.2	0.74	0.18	0.99	0.17	0.09	

[a] The data are shown as means ± standard deviations and (median).

Table 4 Seroprevalence for HEV and C.jejuni[a]

Assay	HEV			Campylobacter jejuni		
	IgA	IgG	IgM	IgA	IgG	N
Group						
Pre-travel	7 (9%)	9 (11%)	0 (0%)	5 (6%)	14 (17%)	81
Post-travel	6 (7%)	9 (11%)	0 (0%)	4 (4.9%)	19 (23.5%)	81
P	0.99	0.99	0.99	0.99	0.44	

[a] The data are shown as no. of seropositive together with borderline cases (percentage).

Table 5 Antibody titers for HEV and C.jejuni[a]

Assay	HEV			Campylobacter jejuni		
	IgA [Ratio]	IgG [IU/ml]	IgM [Ratio]	IgA [Ratio]	IgG [RU/ml]	N
Group						
Pre-travel	0.45 ± 1.11 (0.2)	0.81 ± 2.08 (0.2)	0.08 ± 0.1 (0.1)	0.43 ± 0.85 (0.2)	13.83 ± 19.72 (6.3)	81
Post-travel	0.44 ± 1.06 (0.2)	0.65 ± 1.5 (0.2)	0.08 ± 0.1 (0.1)	0.45 ± 0.85 (0.2)	21.77 ± 35.0 (7.6)	81
P	0.47	0.09	0.99	0.06	**0.05**	

[a] The data are shown as means ± standard deviations and (median).

Table 6 Seroprevalence for CMV and H.pylori[a]

Assay	CMV		Helicobacter pylori		
	IgG	IgM	IgA	IgG	N
Group					
Pre-travel	29 (36%)	5 (6%)	13 (16%)	12 (15%)	81
Post-travel	29 (36%)	6 (7%)	18 (22%)	12 (15%)	81
P	0.99	0.99	0.43	0.99	

[a] The data are shown as no. of seropositive together with borderline cases (percentage).

Table 7 Antibody titers for CMV and H.pylori[a]

Assay	CMV		Helicobacter pylori		
	IgG [RU/ml]	IgM [Ratio]	IgA [Ratio]	IgG [RU/ml]	N
Group					
Pre-travel	43.27 ± 60.4 (3.7)	0.38 ± 0.29 (0.3)	0.63 ± 0.79 (0.4)	19.13 ± 44.84 (4.0)	81
Post-travel	43.38 ± 60.1 (4.0)	0.40 ± 0.29 (0.3)	0.67 ± 0.87 (0.4)	19.55 ± 45.02 (4.3)	81
P	0.99	0.07	0.24	0.69	

[a] The data are shown as means ± standard deviations and (median).

Abbreviations

C.jejuni	-	Camphylobacter jejuni
CHIKV	-	Chikungunya Virus
CMV	-	Cytomegalovirus
DENV	-	Dengue Virus
ELISA	-	Enzyme Linked Immunoassay
FWD	-	Food- and Water-Borne Diseases
H.pylori	-	Helicobacter pylori
HEV	-	Hepatitis E virus
Ig	-	Immunoglobulin
IU	-	International Units
RU	-	Relative Units
VBD	-	Vector-Borne Diseases
ZIKV	-	Zika Virus

Declarations

Compliance with Ethical Standards:

All procedures were in accordance with the standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent or substitute was obtained from all subjects for the purpose of publication. This study was approved by the ethics committee of the Hamburg Chamber of Physicians (#PV5262).

Funding:

Funding was received by the B. Braun-Stiftung for the study originally entitled “Charakterisierung der Immunität gegen Hepatitis E-Viren bei Langzeitreisenden aus Deutschland in tropische Regionen Asiens und Afrikas“.

Competing Interests:

The authors declare that no competing interests exist.

Contributions:

WD planned and designed the study, performed analyses and statistics and co-wrote the manuscript. IEH, KB, SP, and CV cared for the patients, performed analyses, and edited the manuscript. FH supervised the study, researched literature and wrote the manuscript.

Data Availability Statement

All relevant data are within the paper.

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Figures

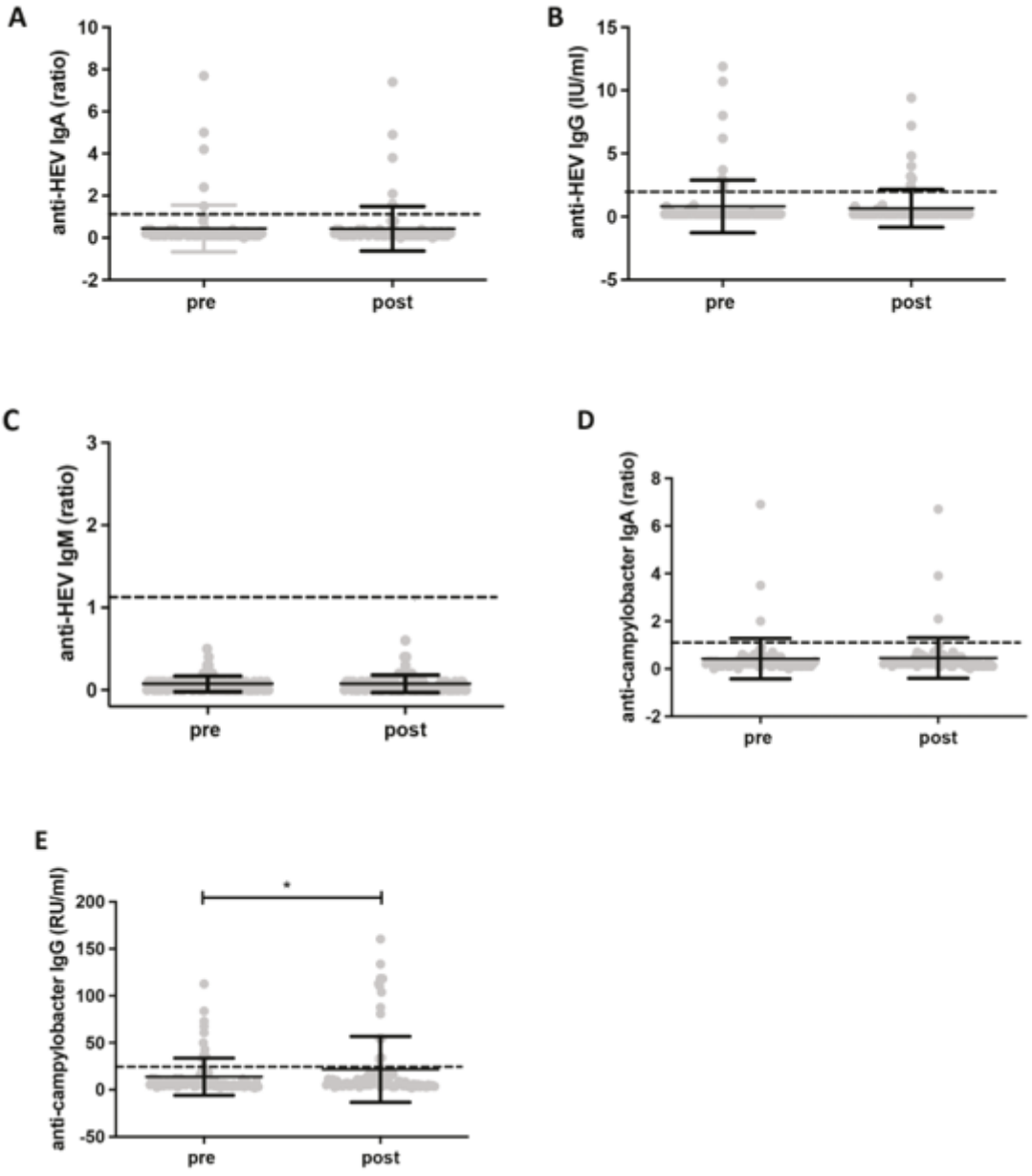

Figure 1

anti-CHIKV, -DENV and -ZIKV serology. Anti-CHIKV antibody titers were determined in serum for (A) IgG and (B) IgM. Anti-DENV antibody titers were determined in serum for (C) IgG and (D) IgM. Anti-ZIKV antibody titers were determined in serum for (E) IgG and (F) IgM. Mean time between start and end of travel was 2 months. All values are given as ratios or relative units per milliliter (RU/ml) including the mean. Dashed line signifies seropositivity cut-off. Inferential statistics was performed using student's t-test. Following symbol pinpoints significant differences: * ≤ 0.05. ** ≤ 0.01, *** ≤ 0.001.

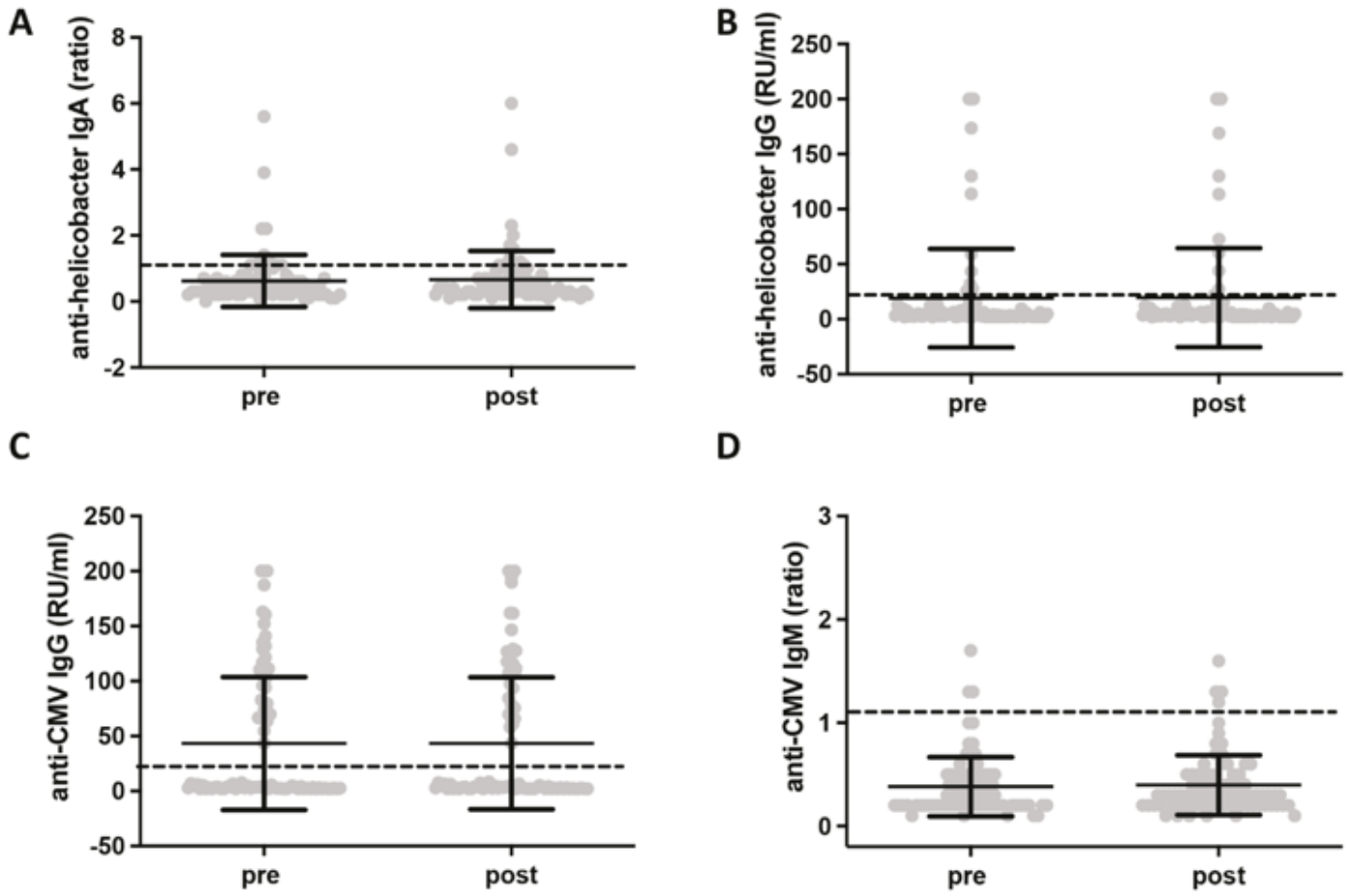

Figure 2

anti-HEV and anti-*Campylobacter jejuni*serology. Anti-HEV antibody titers were determined in serum for (A) IgA, (B) IgG and (C) IgM. Anti-*Campylobacter jejuni*antibody titers were determined in serum for (D) IgA and (E) IgG. Mean time between start and end of travel was 2 months. All values are given as ratios, international units per milliliter (IU/ml) or relative units per milliliter (RU/ml) including the mean. Dashed line signifies seropositivity cut-off. Inferential statistics was performed using student‘s t-test. Following symbol pinpoints significant differences: * ≤ 0.05. ** ≤0.01, *** ≤ 0.001.

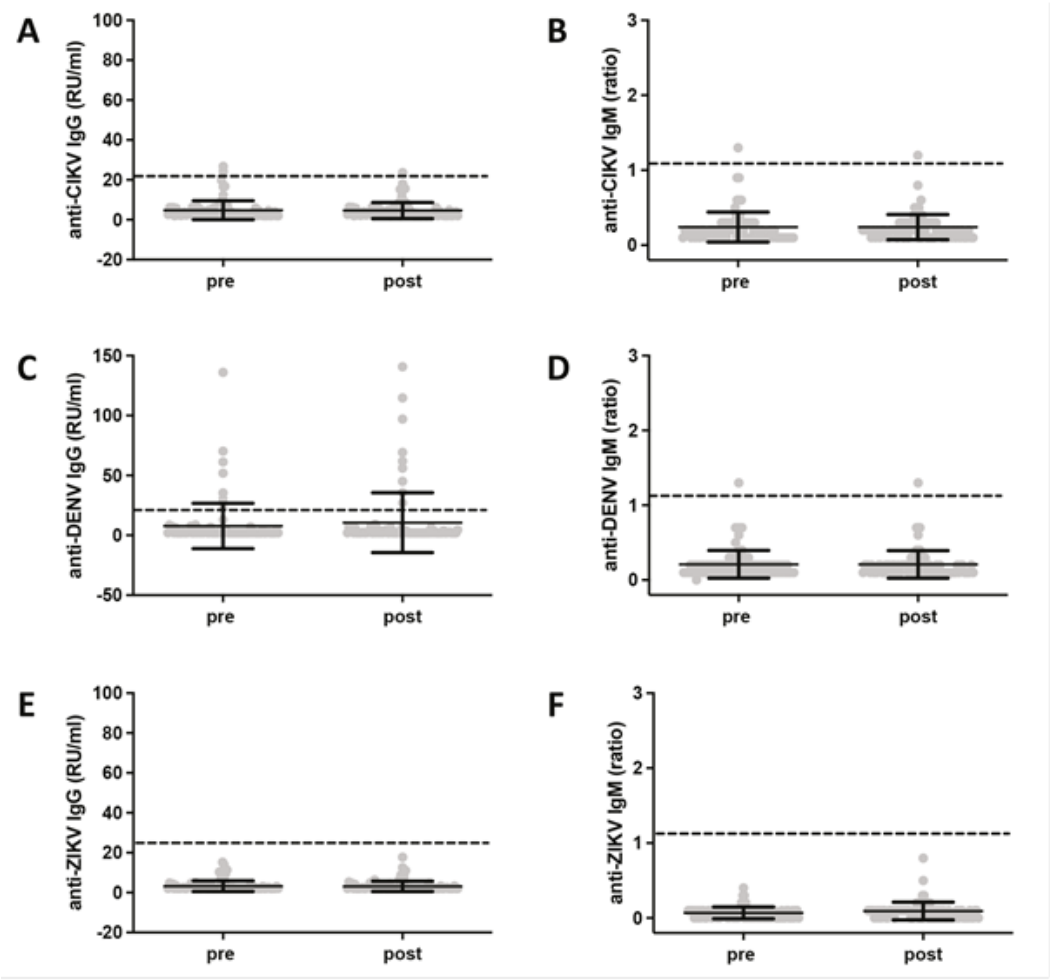

Fig. 3 anti-*Helicobacter pylori* and anti-CMV serology. Anti-*H.pylori* antibody titers were determined in serum for (A) IgA and (B) IgG. Anti-CMV antibody titers were determined in serum for (C) IgG and (D) IgM. Mean time between start and end of travel was 2 months. All values are given as ratios or relative units per milliliter (RU/ml) including the mean. Dashed line signifies seropositivity cut-off. Inferential statistics was performed using student's t-test. Following symbol pinpoints significant differences: * ≤ 0.05. ** ≤ 0.01, *** ≤ 0.001.

Figure 3

See above image for figure legend.