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Travel-related hepatitis E: a two-decade GeoSentinel analysis

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Author contributions

L.A.N. Made the study design, manuscript writing and data interpretation; A.D.V. helped in the manuscript writing and prepared the figure; R.J.S. made the data analysis; K.M.A. did the data interpretation and critical revision of the manuscript; M.G., P.G., P.J.J.G., E.B., K.L., H.A., D.T.L., B.C., P.P., F.T., F.G., F.C. helped in the data collection and critical revision of the manuscript; M.B. did the critical revision of the manuscript and supervision; and D.H.H. made the study design with L.A.N. study design, data interpretation and critical revision of the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

Supplementary data

Supplementary data are available at *JTM* online.

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Abstract

Background: Hepatitis E virus (HEV) is widely distributed worldwide and is endemic in developing countries. Travel-related HEV infection has been reported at national levels, but global data are missing. Moreover, the global availability of HEV diagnostic testing has not been explored so far. The aim of this study is to describe the epidemiology of HEV infections in returning travellers and availability of HEV diagnostic testing in the GeoSentinel surveillance network.

Methods: This was a multicentre retrospective cross-sectional study. All confirmed and probable HEV travel-related infections reported in the GeoSentinel Network between 1999 and 2018 were evaluated. GeoSentinel sites were asked to complete a survey in 2018 to assess the availability and accessibility of HEV diagnostic procedures (i.e. serology and molecular tests) throughout the study period.

Results: Overall, 165 travel-related HEV infections were reported, mainly since 2010 (60%) and in tourists (50%). Travellers were exposed to hepatitis E in 27 countries; most travellers (62%) were exposed to HEV in South Asia. One patient was pregnant at the time of HEV infection and 14 had a concomitant gastrointestinal infection. No deaths were reported. In the 51% of patients with information available, there was no pre-travel consultation. Among 44 GeoSentinel sites that responded to the survey, 73% have access to HEV serology at a local level, while 55% could perform (at a local or central level) molecular diagnostics.

Conclusion: Reported access to HEV diagnostic testing is suboptimal among sites that responded to the survey; this could negatively affect diagnosing HEV. Pre-travel consultations before travel to South Asia and other low-income and high-prevalence areas with a focus on food and water precautions could be helpful in preventing hepatitis E infection. Improved HEV diagnostic capacity should be implemented to prevent and correctly diagnose travel-related HEV infection.

Keywords

HEV; hepatitis; epidemiology; travel; geosentinel

Background

Hepatitis E virus (HEV) is an hepatotropic virus belonging to the genus Hepevirus in the Hepeviridae family.[1] HEV was first identified in stools of affected soldiers after an outbreak of unexplained hepatitis at a military camp, during the Soviet occupation of Afghanistan in the 1980s. A pooled fecal extract was ingested by a scientist of the research team, who consequently developed HEV-related disease; the virus was detected in his stool, demonstrating fecal–oral transmission.[2] Currently, HEV is recognized as universally distributed and identified as a leading cause of acute viral hepatitis in developing countries. In developing countries, HEV genotypes 1 and 2 are prevalent and infection is mainly

related to ingestion of unsafe water.[3, 4] In industrialized countries, sporadic cases are related to HEV genotypes 3 and 4, and zoonotic transmission via the consumption of infected pork or game meat is the more frequent transmission route.[3,4] Furthermore, HEV infection is possible through blood and vertical transmission and potentially by sexual intercourse.[3–5]

A combination of serological and molecular methods is recommended for early detection and accurate diagnosis of acute HEV infection.[6] However, serological assays are affected by discrepancies in sensitivity and specificity.[6, 7] Moreover, molecular testing may not be affordable in developing countries where specialized laboratory equipment are limited.

Few data are available on the epidemiology of hepatitis E virus (HEV) infection among international travellers. A study from The Netherlands demonstrated an incidence rate of 1.2–1.8 per 1000 person-weeks of travel to the tropics and subtropics, and it may be higher among long-term travellers and those traveling to the tropics.[8] Studies conducted in UK and France reported recent international travel in 23 and 1.8% of HEV cases, but authors did not evaluate the impact of travelling on HEV risk.[9, 10] A Norwegian study found that travel was not significantly associated with the risk of developing HEV infection,[11] and in an Israeli study on a small cohort of travellers returning with acute hepatitis, 39% were determined to be HEV related.[12] Although these studies contribute to further understanding of HEV infection among international travellers, they are from single countries and do not provide information on the current global epidemiology of travel-related HEV infections.

GeoSentinel, a global clinician-based sentinel surveillance network that monitors travel-related illnesses among international travellers and migrants, is a collaboration between the U.S. Centres for Disease Control and Prevention (CDC) and the International Society of Travel Medicine.[13, 14] The network was started in 1995 to track emerging infections and to provide a description of specific travel-related diseases, including those that are of public health importance. Limitations of the network include the absence of denominator data precluding the estimation of relative risk of specific travel-acquired illnesses.[13]

The objective of this study was to describe the epidemiology of acute HEV infection among returning international travellers who presented to the GeoSentinel surveillance network during the last 20 years. A secondary objective was to assess the availability of HEV diagnostic testing in 2018 at participating surveillance sites.

Methods

Data source

GeoSentinel currently consists of 70 specialized travel and tropical medicine sites across 31 countries.[13] Case status, traveller demographics, trip details, clinical information and region or country of exposure are collected. In October 2015, data on highest level of care (e.g. hospitalization) and diagnostic testing were added to the data collection form. GeoSentinel's data collection protocol has been reviewed by a human subjects advisor at CDC's National Centre for Emerging and Zoonotic Infectious Diseases and is classified as public health surveillance and IRB review is not required. Sites obtained additional ethical clearance as required by their respective institutions.

Inclusion criteria

Patients reported to GeoSentinel from January 1999 to December 2018 with confirmed or probable HEV infection as their final diagnosis were included.

Confirmed HEV is defined as a compatible clinical history plus either virus isolation, positive nucleic acid testing or seroconversion/rising titre on serology, while probable infection is defined as a compatible clinical history plus a single positive IgM serology. The distinction between confirmed and probable infection was available only since October 2015; before this, HEV infection was ascertained by the site personnel and diagnostic testing information was not collected.

Records were excluded if the region of exposure was not ascertainable, or if there was a confirmed acute infection concomitant to HEV and data clearly referred to the infection other than HEV. Food or waterborne (e.g. *Campylobacter*, *Giardia*) concomitant acute infection were retained, as records on clinical presentation, lab test results and transmission routes were attributed to HEV infection.

Survey

Because different HEV assays are available worldwide, GeoSentinel sites were asked to complete a survey in 2018 to identify the availability and accessibility of HEV diagnostic procedures (i.e. serology and molecular tests) throughout the study period (Supplementary 1).

Statistics

Data were managed using Microsoft Access (Redmond, Washington, USA), and all analyses were performed using SAS Version 9.4 (Cary, North Carolina, USA).

Results

A total of 165 records were included; 137 were confirmed cases of HEV and 28 were probable cases. Travellers were residents of 42 countries and were exposed to HEV in 27 countries. Most travellers were male (60%), the median age was 37 years (range 4–74), and most were diagnosed since 2010 (60%), travelled for tourism (50%), and were exposed to HEV in South Asia (62%) (Table 1). The most frequent countries of exposure were on the Indian subcontinent: India (41%), Nepal (8%), Pakistan (6%) and Bangladesh (6%) (Figure 1). Of 130 travellers with information available, 66 (51%) did not have a pre-travel consultation. Among 25 travellers with information available, 14 (56%) were hospitalized. Overall, 14 travellers presented with an additional food or waterborne-infection, including *Giardia* spp. ($n = 6$), *Campylobacter spp.* ($n = 4$), hepatitis A ($n = 1$), entero-aggregative *Escherichia coli* ($n = 1$), *Salmonella enterica* serovarparatyphi ($n = 1$) and *S. typhi* ($n = 1$). Jaundice was reported in 16 (10%) travellers. There was only one pregnant traveller with HEV infection. Among 42 travellers with information available, the median time from symptom onset to GeoSentinel site presentation was 13 days (interquartile range [IQR]: 8–26 days). Although GeoSentinel does not systematically capture deaths since patients are seen at a single point in time, no deaths were reported.

Forty-four (65%) of 68 GeoSentinel sites responded to the survey on the availability of HEV diagnostics (Table 2); 15 (34%) had access to HEV diagnostic tests locally, while the remaining reported sending samples to an external reference laboratory. Most sites (73%) reported access to HEV serology (IgM and IgG in western countries and IgA in Japan), while 55% of sites could perform (at a local or central level) molecular diagnostics. A wide variety of different serological tests from different manufacturers are used. Among 24 sites with access to molecular diagnostics, 11 (46%) used in-house assays and 11 used a commercially available assay (information missing for the remaining 2 sites). Beyond blood (either whole blood, plasma or serum), 12 sites (18%) performed HEV molecular testing on stool, 2 on cerebrospinal fluid and 2 on solid tissue.

Discussion

This global report contributes to increasing knowledge on the epidemiology of travel-related HEV infections. Current evidence shows that HEV affects 20 million people annually, with a mortality rate of 3.3%.[15] HEV is endemic in low- and middle-income countries,[1, 16–18] while in high-income countries, it causes sporadic infections.[19, 20] However, a few high prevalence areas (e.g. Germany, The Netherlands, France) have been recognized in Europe.[20–22] In spite of the existence of high prevalence areas in high-income countries, only two HEV cases were reported in western Europe. This is consistent with the different source of HEV infection identified in low- and high-income countries, being the consumption of raw food (instead of unsafe water) the most frequent in the latter.[3, 4] On the other hand, most HEV-infected travellers reported to the GeoSentinel network returned from the tropics, most frequently from South Asia, and notably from India. These results highlight that travellers who develop acute hepatitis should be tested for HEV infection especially if they return from South Asia.

Tourists accounted for 50% of travel-related HEV infections and a substantial proportion of travellers did not attend to a pre-travel consultation with a healthcare provider. A recent systematic review reported that lack of perceived risk while travelling was the predominant reason for not seeking pre-travel consultation and that adherence to food and water precautions was low for long-term and younger travellers.[23] In this GeoSentinel experience, several travellers experienced a concurrent gastrointestinal infection. As HEV in endemic countries is mainly transmitted via consumption of contaminated water or food, these findings further highlight the need for pre-travel counselling of travellers to endemic countries, particularly tourists who may be unfamiliar with local hygiene standards. Although a single pre-travel consultation cannot address prevention for every travel-related infection, especially in the absence of some disease-specific recommendations, every effort should be made to improve travellers' perception of risk and adherence to prevention of food and water-borne infections. On the other hand, our data do not support a recommendation for HEV vaccination to all travellers visiting high-prevalence areas, as we did not collect data regarding HEV incidence in returning travellers. Another option for prevention is vaccination. However, the only commercially available recombinant HEV vaccine has been tested and approved only in China, where both genotypes 1 and 4 co-circulate with the zoonotic genotype 4 predominating. Seroprotection rates and protection against symptomatic infections exceed 98.7 and 97%, respectively,[24] but no data are available on

vaccine efficacy against HEV genotypes 2 and 3. Thus, the potential benefit of administering HEV vaccine to travellers to high-prevalence areas deserves further study.

Our data included only one pregnant woman, so although the mortality of HEV-related hepatitis is higher in this setting,[25, 26] we were unable to assess HEV among pregnant travellers.

Given the burden of disease, limited options available for diagnosis, treatment and control and limited research funding targeted towards the disease, HEV was recently proposed as a neglected tropical disease.[27] In the absence of HEV diagnostic tests, HEV infection can remain undiagnosed and potentially spread to other persons via fecal-oral, bloodborne, sexual or vertical transmission.[3, 28] Consistent with the known limitations in diagnostic capacity, the GeoSentinel diagnostics survey demonstrated that availability of HEV serology and molecular diagnostics remain sub-optimal even among the specialised tropical medicine and infectious diseases centres in GeoSentinel.

This analysis has some limitations. GeoSentinel data are not population based; therefore, rates or risk estimates cannot be derived. Detailed clinical presentations and outcomes or risk factors are not routinely reported in the GeoSentinel dataset. In addition, there was substantial under-reporting of pre-travel visits, so these could not be assessed for all travellers with hepatitis E infection. Also, although the surveillance definition for hepatitis E was constant throughout the analysis, the diagnostic test result used to classify HEV cases reported before October 2015 could not be validated since diagnostic testing information was not collected before this time. Additionally, 28 probable cases recorded after 2015 were not confirmed by positive nucleic acid testing or seroconversion/rising titre on serology. Thus, as sensitivity and specificity of the HEV serological tests may vary, some episodes may have been missed and others erroneously attributed to HEV infection. However, all cases included had a compatible clinical presentation for whom other possible diagnoses were ruled out.

This report on HEV infection among international travellers serves as a reminder to healthcare providers to consider HEV during their diagnostic work-up, particularly among travellers returning from South Asia. Reliable HEV diagnostics should be more readily available for diagnostic evaluation of returning travellers with acute hepatitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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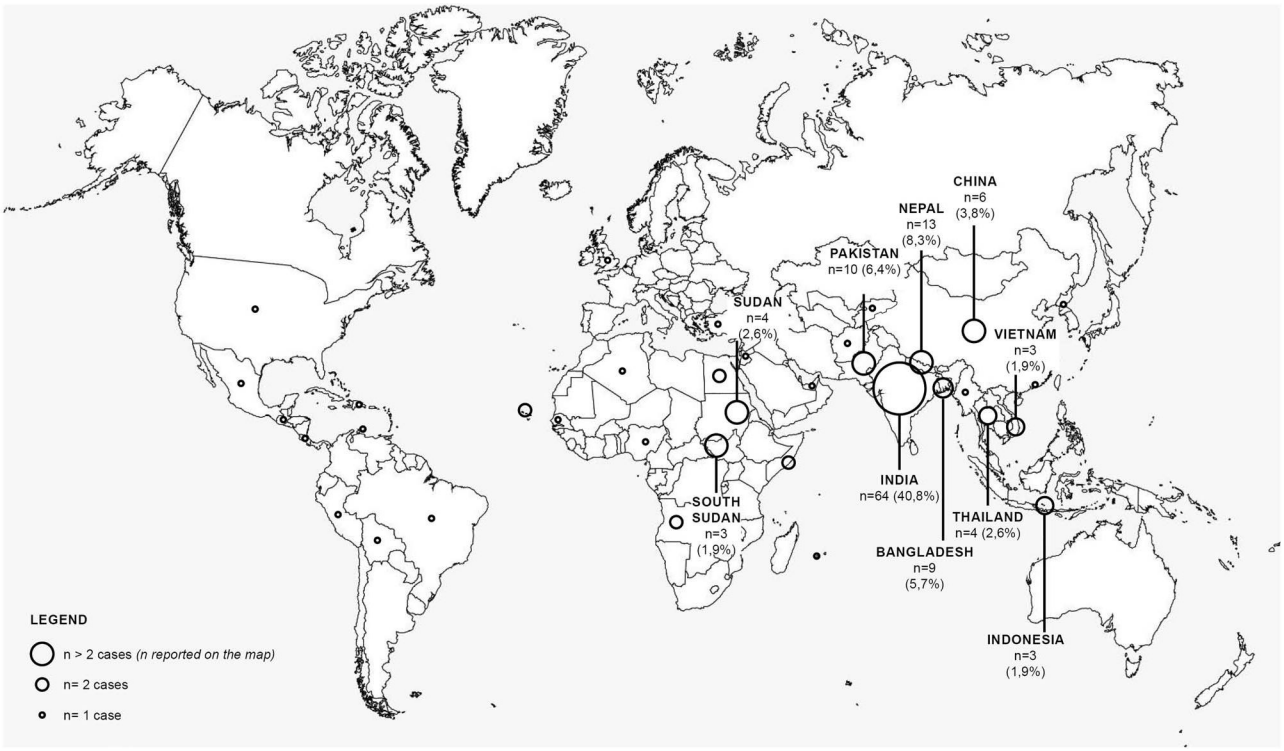

Figure 1.

Countries of exposure among travellers with hepatitis E virus infection reported to GeoSentinel, 1999–2018; footnote includes 157 (95%) of 165 travellers with a single country of exposure listed in the patient record

Table 1.

Characteristics of international travellers diagnosed with hepatitis E in GeoSentinel 1999–2018 (n = 165)

Characteristic	Travellers *n* (%)*
Male	99 (60)
Age†	
< 20 years	10 (6)
20–39 years	86 (54)
40–59 years	50 (31)
≥ 60 years	13 (8)
Year of inclusion in GeoSentinel for HEV diagnosis††	
1999–2002	4 (2)
2003–2006	31 (19)
2007–2010	32 (24)
2011–2014	55 (33)
2015–2018	36 (22)
Reason for travel	
Tourism	82 (50)
Visiting friends and relatives	35 (21)
Missionary/humanitarian/volunteer/community service	21 (13)
Business/corporate/conference	20 (12)
Migration	5 (3)
Education/student	2 (1)
Region	
South Central Asia	103 (62)
Central Asia	1 (1)
Sub Saharan Africa	16 (10)
South East Asia	16 (10)
North East Asia	8 (5)
North Africa	7 (4)
South America	4 (2)
Central America	3 (2)
Middle East	3 (2)
Caribbean	2 (1)
North America	1 (<1)
Western Europe	1 (<1)

*Percentages may not sum to totals due to rounding

†Missing for six patients

††Missing for seven patients

Table 2.

Results of the HEV Diagnostic Testing Site Survey

HEV diagnostic testing question	Answerss *N* (%)
Type of referral laboratory for HEV diagnostics [1]	
Local hospital lab	15 (34)
Academic research lab	2 (5)
Private reference lab	13 (30)
Public reference lab (e.g. state, provincial or national lab)	19 (43)
HEV IgG availability on site	
Yes	32 (73)
No	12 (27)
HEV IgM availability on site	
Yes	32 (73)
No	12 (27)
Recent change of on-site available serological HEV testing	
Yes	4 (9)
No	20 (45.5)
Not applicable/unknown	20 (45.5)
Local availability of molecular HEV diagnostics	
Yes	24 (55)
No	20 (45)
Type of molecular HEV assay currently used	
Commercially available assay	11 (25)
In-house assay	11 (25)
Not applicable/unknown	22 (50)
Recent change of on-site available molecular HEV testing	
Yes	2 (5)
No	19 (43)
Not applicable/unknown	23 (52)
Type of samples that can be potentially tested with molecular assays [1]:	
Plasma	18 (41)
Serum	20 (45)
Stool	12 (27)
Whole blood	12 (27)
Other	5 (11)
Not applicable/unknown	18 (41)
Access to HEV sequencing (both at local or referral centre)	
Yes	16 (36)
No	26 (59)
Unknown	2 (5)

[1]The sum is more than 44 as more than one response was allowed; percentages are referred to 44 responses.