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Acute hepatitis A in international travellers: a GeoSentinel analysis, 2008–2020

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Abstract

Background: Non-immune international travellers are at risk of acquiring hepatitis A. Although hepatitis A vaccination is recommended for unvaccinated travellers to high or intermediate hepatitis A virus endemicity, compliance with this recommendation is not universal. The main objective was to describe the demographic and travel characteristics of international travellers infected with hepatitis A during travel.

Methods: Available data on travellers with confirmed (positive molecular test) or probable (symptomatic individuals with a single positive IgM test) hepatitis A diagnosed during and after travel from January 2008 to December

2020 were obtained from the GeoSentinel Surveillance Network database. We analysed demographic and travel characteristics of infected travellers.

Results: Among 254 travellers with hepatitis A (185 confirmed and 69 probable), the median age was 28 years (interquartile range: 19–40), 150 (59%) were male, and among 54 travellers with information available, 53 (98%) were unvaccinated. The most common reasons for travel included tourism ($n = 120$; 47%) and visiting friends or relatives (VFR; $n = 72$; 28%). About two-thirds of VFR travellers with hepatitis A ($n = 50$; 69%) were younger than 20 years old. Hepatitis A was acquired most frequently in South-Central Asia ($n = 63$; 25%) and sub-Saharan Africa ($n = 61$; 24%), but 16 travellers (6%) acquired hepatitis A in regions with low endemicity including Western Europe ($n = 7$; 3%), the Caribbean ($n = 6$; 2%) and North America ($n = 3$; 1%). Median duration from illness onset to GeoSentinel site presentation was ~7 days (interquartile range : 4–14 days). Among 88 travellers with information available, 59% were hospitalized.

Conclusions: Despite availability of highly effective vaccines, travellers still acquire hepatitis A, even when traveling to low-endemicity destinations. Providing pre-departure hepatitis A vaccine to susceptible travellers is crucial to reducing travel-associated hepatitis A and should be offered to all travellers as part of the pre-travel consultation, regardless of destination.

Key words: hepatitis A vaccine, endemicity, immunization, epidemiology, COVID-19

Background

Globally, an estimated 1.4 million cases of acute hepatitis A occur every year, with most occurring in Asia, Africa, Eastern Europe and Central and South America.[1,2] Over the past two decades, some countries have decreased their hepatitis A virus (HAV) incidence rates from high [defined as age at midpoint of population immunity (AMPI) < 5 years] to intermediate (AMPI approximated at late adolescence) and low (AMPI estimated at middle childhood)[3,4] by improvements in sanitation, access to clean water, implementation of childhood hepatitis A vaccination programs and economic development as reflected by an increase in gross domestic product.[5] Despite this shift, some countries or specific regions within countries remain highly endemic for HAV infection.

Travelers to endemic countries with no immunity to HAV infection from previous exposure or vaccination are at risk of acquiring hepatitis A. The risk increases with longer duration of stay and travel to areas where sanitation facilities may be inadequate and hygiene practices suboptimal.[6] The World Health Organization (WHO), the United States Advisory Committee for Immunization Practices (ACIP) and most national travel health expert groups (with some exceptions in northern Europe) recommend hepatitis A vaccine for international travellers going to regions that have high or intermediate hepatitis A virus endemicity.[7–11] In some countries including the USA, universal hepatitis A vaccine is recommended for children beginning at age 1 as well as special populations, men who have sex with men (MSM), persons experiencing homelessness and those who have been recently incarcerated; immunization can begin at 6 months of age for infants traveling internationally.[7,12]

Many international travellers do not have a pre-travel consultation with a health care provider or do not inform their provider about upcoming travel and may therefore miss an opportunity to receive a hepatitis A vaccine.[5,13,14] Not receiving pre-travel consultation and increasing international travel to low- and middle-income countries where HAV infection is still endemic pose a threat to the health of travelers.[15] We used the GeoSentinel Surveillance Network database to assess demographic and trip characteristics of international travellers who acquired acute hepatitis A during travel over a 13-year period (2008–2020).

Methods

GeoSentinel—a collaboration between the Centers for Disease Control and Prevention (CDC) and the International Society of Travel Medicine (ISTM)—is a global clinician-based sentinel surveillance system that monitors infectious diseases and other adverse health events that affect international travelers.[16] GeoSentinel comprises 68 sites in 28 countries, where clinicians diagnose patients and collect demographic and travel-related information on infections acquired during travel. GeoSentinel's data collection protocol was reviewed by a human subjects advisor at the CDC National Center for Emerging and Zoonotic Infectious Diseases and has been classified as public health surveillance and not human subject research. Additional ethics clearance was obtained by sites as required by their respective institutions.

Definitions

For this analysis, *high endemicity* is defined as countries with age at midpoint of population immunity (AMPI; youngest age at which 50% of the population develop immunity to HAV infection) <5 years.[4] *Intermediate endemic countries* are countries with an AMPI between adolescence and adulthood, whereas *low endemic countries* are countries with AMPI in middle adulthood.[22] *Foreign-born* is defined as individuals whose country of birth differs from their country of residence. *Confirmed* cases had a compatible clinical history in addition to a positive nucleic acid amplification test (NAAT) or evidence of antibody seroconversion. *Probable* cases were defined as travellers with an acute illness with symptoms and signs consistent with acute viral hepatitis and a single positive immunoglobulin M (IgM) antibody to HAV.

Inclusion/exclusion criteria

For our analysis we included confirmed and probable hepatitis A cases recorded from 1 January 2008 to 31 December 2020, which were travel-related and had an ascertainable region of exposure; travellers with additional diagnoses other than hepatitis A were

excluded. Confirmed and probable cases were combined into one group for analysis.

Data extraction

Data about traveller demographics (e.g. sex and age), GeoSentinel site, visit date, travel details (e.g. reason for travel, dates of travel, country/region of hepatitis A acquisition, having a pre-travel consultation) and clinical information (e.g. date of illness onset, diagnostic method[s], hospitalization and hepatitis A vaccination status) were extracted.

Statistical analysis

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

Results

Overall, 254 travellers with acute hepatitis A presented to a GeoSentinel site during or after international travel between 2008 and 2020 and met inclusion criteria (Table 1). The median age was 28 years (range: 1–75 years); 59% were male. Among 54 travellers with information available, 53 (98%) were not vaccinated against hepatitis A; one traveller was vaccinated with a single dose of Vaqta® vaccine approximately more than one year before acquiring hepatitis A in India. The median duration between onset of illness and GeoSentinel site presentation was 7 days [interquartile range (IQR): 4–14 days]. Hospitalization information was available for 88 travellers; 52 (59%) were hospitalized and no deaths were reported. The median duration of travel was 30 days (IQR: 14–62 days). Travelers were most frequently tourists ($n = 120$; 47%), followed by those visiting friends and relatives (VFRs; $n = 72$; 28%) and business travellers ($n = 36$; 14%). Most VFR travellers were younger than 20 years of age ($n = 50$; 69%) and their median age was 11.5 years (range: 1–68 years). Among VFR travellers younger than 20 years of age ($n = 50$), 12 (24%) were foreign born. VFRs aged 60 years or older represented fewer than 2% of VFRs ($n = 1$).

Among 202 travellers with information available, 158 (78%) did not have a pre-travel consultation with a health care provider (Table 1). Differences among travellers who had or did not have a pre-travel consultation are available in Table 1. VFRs notably more frequently did not have a pre-travel consultation with a health care provider.

Hepatitis A was most frequently acquired among travellers visiting South Central Asia ($n = 63$; 25%), sub-Saharan Africa ($n = 61$; 24%) and North Africa ($n = 44$; 17%; Table 1). Travelers also acquired hepatitis A in regions with low endemicity, including Western Europe ($n = 7$; 3%), the Caribbean ($n = 6$; 2%) and North America (USA) ($n = 3$; 1%). Seventy-seven countries were identified as the country of exposure among 244 (96%) of travellers with information available. Eleven (5%) travellers visited countries of low endemicity, including the USA ($n = 3$; 27%), Thailand ($n = 3$; 27%) and Spain ($n = 2$; 18%; Table 2). In contrast, 243 (96%) infections were acquired in intermediate-/high-endemicity countries including Morocco ($n = 25$; 10%), India ($n = 25$; 10%), Pakistan ($n = 20$; 8%) and

Table 1. Travel and demographic characteristics of international travellers with diagnosis of hepatitis A ($N = 254$) reported to GeoSentinel sites (January 2008–December 2020)

Traveller characteristics	*N*	%
Male	150	59.1
Median age, years (range)	28 (1–75)	
Age category		
<20 years	68	26.8
20–39 years	120	47.2
40–59 years	52	20.5
>60 years	14	5.5
Reason for travel		
Tourism	120	47.2
Visiting friends or relatives (VFRs)	72	28.4
Business/occupational	36	14.2
Missionary/volunteer/ humanitarian/researcher/aid work	13	5.1
Migration	8	3.2
Education/student	4	1.6
Military	1	<1
Severity[a], *n* (%)		
Outpatient	36	40.9
Inpatient	52	59.1
Endemicity [13]		
Intermediate/high	243	95.7
Low	11	4.3
Region of exposure		
South Central Asia	63	24.8
Sub-Saharan Africa	61	24.0
North Africa	44	17.3
Southeast Asia	19	7.5
South America	17	6.7
Central America	11	4.3
Middle East	8	3.2
Eastern Europe	8	3.2
Western Europe	7	2.8
Caribbean	6	2.4
North East Asia	5	2.0
North America	3	1.2
Oceania	2	<1
Travelers without a pre-travel encounter[b]	158	78.2
Male	96	60.8
Median age, years (range)	27 (1–75)	
Top 3 reasons for travel		
Tourism	89	56.3
Visiting friends or Relatives (VFRs)	38	24.1
Business	19	12.0
Top 3 countries of exposure[c]		
Morocco	21	13.5
India	15	9.7
Pakistan	12	7.7

Continued

Table 1. Continued

Traveller characteristics	N	%
Travelers with a pre-travel encounter[b]	44	21.8
Male	25	56.8
Median age, years (range)	33 (3–71)	
Top 3 reasons for travel		
Tourism	24	54.5
Missionary/volunteer/ humanitarian/researcher/ aid work	8	18.2
Business	7	15.9
Top 3 countries of exposure[d]		
India	3	7.5
Kenya	3	7.5
Nepal	3	7.5
VFR traveller characteristics ($n = 72$)		
Median age, years (range)	11.5 (1–68)	
Age category (VFR)		
<20 years	50	69.4
20–39 years	18	25.0
40–59 years	3	4.2
>60 years	1	1.4

[a]Information was available for 88 (35%) travellers.
[b]Pretravel clinic visit information was available for 202 (80%) travellers.
[c]Information was available for 155 (98.1%) travellers.
[d]Information was available for 40 (90.9%) travellers.

Egypt ($n = 14$; 6%). Travelers to low endemicity countries (vs those to intermediate or high endemicity countries) were more frequently male (91% vs 59%), tourists (91% vs 47%), and did not have a pretravel encounter with a health care provider (100% vs 78%). During the coronavirus disease of 2019 (COVID-19) pandemic and the preceding year, 19 travellers were reported to have acquired hepatitis A (from January 2019 to December 2020).

Discussion

HAV infection has a worldwide distribution although incidence and seroprevalence differ widely among countries. Similar to previous studies, these GeoSentinel data demonstrate that most travellers acquired HAV infection in countries with high or intermediate endemicity.[4,17] Thus, traveller vaccine recommendations have been based on travel to destinations fitting these endemicity classifications. Our study demonstrates that transmission occurs among travellers who visit even low endemic, high- or high–middle-income countries. Some travellers in our study had HAV exposure during travel to the USA, Thailand, Belgium, Spain, Croatia, Czech Republic and Kingdom of Saudi Arabia. Because these countries have low rates of hepatitis A, travellers visiting these countries or other similar countries would be unaware of the HAV risk and thus might not have a pretravel visit and therefore, not be offered hepatitis A vaccine before travel. In fact, all travellers to low-endemicity countries in this analysis with information available did not have a pretravel encounter with a health care provider and none with information available were vaccinated against hepatitis A. Although the number of people who acquired infection in low-endemicity countries represented

Table 2. Characteristics of travellers to countries with low hepatitis A endemicity ($n = 11$)

Characteristics	N	%
Male	10	90.9
Median age, years (range)	27 (9–43)	
Age category		
<20 years	2	18.2
20–39 years	7	63.6
40–59 years	2	18.2
>60 years	0	0
Reason for travel		
Tourism	10	90.9
Business	1	9.1
Severity[a]		
Inpatient	2	50.0
Outpatient	2	50.0
Travelers without a pretravel encounter[b]	8	100
Exposure country		
USA	3	27.3
Thailand	3	27.3
Spain	2	18.2
Belgium	1	9.1
Croatia	1	9.1
Saudi Arabia	1	9.1

[a]Information was available for 4 (36.4%) travellers.
[b]Information was available for 8 (72.7%) travellers.

4% of our study population, the risk of HAV exposure remains. Although these countries have low HAV infection rates, their seroprevalence rates may differ by rural or urban population, interaction with an at-risk group (including MSM), quality of water treatment in areas visited and location-specific socioeconomic status.[8,18,19] Vaccination of susceptible travellers visiting low-endemicity countries could further reduce the burden of travel-associated HAV acquisition.

Organizations such as the WHO, ACIP and national health expert groups currently recommend vaccination of individuals who intend to travel to countries with intermediate or high hepatitis A virus endemicity.[20] Countries are classified based on endemicity (low, intermediate and high).[4] This classification provides a crude assessment of hepatitis A rates in different countries, and it only accounts for the specific age group at which mid-point population immunity was attained. More extensive and representative seroprevalence studies are needed since sub-national prevalence may vary and this additional information may impact travel vaccine recommendations. Seroprevalence is also important in developing region-specific or country-wide vaccination programs, ascertaining the effectiveness of these programs and recommending appropriate preventive measures. In our cohort, most travellers infected with hepatitis A acquired infection in countries with intermediate or high hepatitis A virus endemicity, which demonstrates there were missed opportunities for vaccination.

In our study, the sub-group of travellers between 20 and 39 years of age accounted for nearly half of hepatitis A cases. This

observation parallels population-based studies of HAV infection among returned travelers.[23,24] One possible reason for this observation is that hepatitis A vaccine was not recommended in the country they lived in when they were young children. Hepatitis A vaccine was introduced in Europe in 1992 and the USA in 1994–1995.[21–23] During this period, hepatitis A vaccine was recommended only for at-risk populations. In the USA, routine childhood vaccination was recommended in 1999–2000 for children residing in 11 states with the highest hepatitis A incidence.[24] By 2005, the US Food and Drug Administration reduced the age for vaccination from 24 to 12 months. Soon after, the vaccine was incorporated into the childhood immunization schedule for all eligible children in the USA.[25] In 2010, a survey in the European Union (EU), Norway and Iceland that assessed mandatory and recommended vaccinations revealed that 25 countries were considering hepatitis A vaccination for their childhood immunization program.[26] Additional reasons for why travellers between 20 and 39 years of age accounted for nearly half of hepatitis A cases include possibly riskier food and water consumption practices while traveling, local spread among MSM and older persons acquiring immunity from previous infection.

The reason for travel for a substantial number of travellers in our study was to visit friends and relatives. Immigrants, who are returning to their home or birth countries, have an increased risk of travel-related hepatitis A infection.[21,25] Further stratification based on country of birth revealed that some returning travellers in our study were foreign born. A subgroup of travellers aged 20–25 years were born in countries with intermediate to high endemicity for HAV infection such as India, Pakistan, Burkina Faso, Bangladesh and Morocco. Despite being born in an intermediate- or high-endemicity country, depending on their age of immigration to a low-endemicity country, these travellers likely did not have protection afforded by early childhood HAV infection. During the last two decades, many countries with intermediate and high seroprevalence for hepatitis A have had an epidemiological shift to low and intermediate/transitional HAV endemicity, respectively. For example, a decreasing seroprevalence of hepatitis A among Asian youth has been attributed to a reduction in endemicity level over time due to enhanced hygiene and sanitation, improved housing conditions, socioeconomic factors, upgrade in health care expenditure and delay in age of first HAV exposure.[4,17,27] There are documented reports of individuals with travel-associated hepatitis A infection during the COVID-19 pandemic. However, the reported numbers are likely lower than expected because of the pandemic and the resulting lockdowns, travel restrictions, disruptions in reporting of diseases and travel-related control measures.[28]

There are several limitations to this analysis. Some of these limitations are inherent to the approach that the GeoSentinel Network uses for surveillance.[17] GeoSentinel sites are travel and tropical medicine centres that see returning travellers who represent a convenience sample rather than a systematically collected cohort of returning travellers. Although strength of the Network is the large number of sites around the world, many of which see large volumes of returning travellers and migrants, there are some important countries that are not represented in the Network so there is not access to a representative array of ill travellers. GeoSentinel data are not generalizable or population-based, and there is no denominator data, therefore, risk and infection rates cannot be calculated. In the GeoSentinel database, vaccination status was not available for all travellers in this report; however, given the immunogenicity of hepatitis A vaccine at preventing illness, it is likely the vast majority of travellers in this cohort were unvaccinated. Breakthrough infections in travellers have been observed[29]—the only traveller in this analysis who acquired hepatitis A after being partially vaccinated had received the dose of Vaqta® vaccine over one year before their hepatitis A exposure. Detailed exposure information (e.g. sanitation and hygiene) is not routinely collected, although among those travellers with a pretravel consultation, guidance about sanitation, hygiene and safe food and water is usually communicated. The lack of risk information precludes us from making inferential statements on independent risk factors for acute hepatitis A among travellers. Also, deaths associated with travel-related hepatitis A may have been missed. Lastly, clinical information on patient comorbidities is not routinely collected by GeoSentinel.

Surveillance for acute hepatitis A among travellers by region/country of disease acquisition, the purpose or reason for travel and sentinel site, is important for understanding the public health impact of hepatitis A.[30] Despite the availability of a highly effective hepatitis A vaccine, travellers still acquire hepatitis A, even during travel to low-endemicity destinations. Providing predeparture hepatitis A vaccine to susceptible travellers is crucial to reducing travel-associated hepatitis A and should be offered to all travellers as part of the pre-travel consultation, regardless of destination. It is essential to offer hepatitis A vaccines for all travellers along with easy access to pretravel consultation—given the availability of an effective vaccine, hepatitis A should not be a concern for any international traveller, regardless of destination. Approaches that improve the training of primary care providers about hepatitis A vaccination for their patients who plan to travel and integrating travel medicine consultations into primary health care visits may improve vaccination uptake and reduce preventable cases of hepatitis A among travellers.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' Contributions

All authors contributed substantially to the study design, analysis, interpretation, reporting and manuscript writing. The authors also played a significant role in manuscript revisions and approved the final version of the paper.

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