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ORIGINAL RESEARCH

Prevalence of Hepatitis E Virus Infection Among Blood Donors in the Eastern Province of Saudi Arabia

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Purpose: Hepatitis E virus (HEV) causes acute hepatitis in humans and constitutes a major problem for immunocompromised patients, patients with hematological diseases, and pregnant women. It is transmitted mainly through fecal oral route; however, transmission through blood and blood products is reported globally and becoming a health concern. We sought to determine the prevalence of HEV among blood donors in the Eastern Province of Saudi Arabia using molecular as well as serological assays to assess the safety of blood transfusion and the need for HEV screening among blood donors.

Patients and Methods: A total of 806 whole blood samples were collected from blood donors between May and November 2020 and tested for anti-HEV IgG and IgM antibodies by ELISA and for HEV RNA by RT-PCR.

Results: The overall seroprevalence of HEV IgG antibodies was 3.2% with no statistically significant difference between the non-Saudis (3.28%) and Saudis (3.17%) (p value 0.929) or between males (3.14%) and females (4.88%) (p value 0.527). None of the IgG positive individuals had IgM antibodies. HEV RNA was not detected in any of the blood donors.

Conclusion: HEV seroprevalence is low among blood donors in the Eastern Province of Saudi Arabia and may constitute minimal risk for transfusion associated infections.

Keywords: HEV, IgG, IgM, seroprevalence, ELISA, RT-PCR

Introduction

Hepatitis E virus (HEV) is a single-stranded positive sense RNA, non-enveloped, icosahedral virus that belongs to the genus *orthohepevirus* of the family *Hepeviridae*. Like other hepatitis viruses, members of this genus affect the liver and cause acute hepatitis in humans and various mammals. Immunocompromised patients and pregnant women are also a cause of chronic hepatitis.[1,2] A key feature of HEV, unlike other hepatitis viruses, is its ability to infect animals as well. Phylogenetically, the genus Orthohepevirus A is divided into eight genotypes (HEV 1–8) with different host specificity and geographical localization. HEV-1 and HEV-2 are mostly associated with human infection, while HEV-3 and HEV-4 can infect humans and animals, such as swine, deer, goats, Bottlenose dolphins and boars.[3–5] HEV-5 and HEV-6 were found in wild boar in Japan, while HEV-7 and HEV-8 have only been isolated from camels in China.[6] Geographically, genotype 1 is most commonly reported in the countries of Asia and Africa, while genotype 2 is most common in Mexico, Nigeria, and Chad.[3] Genotype 3 is limited to Japan, Korea, and Taiwan, while genotype 4–8 is restricted to Asia.[3,6]

The first epidemic of HEV infection was reported in India as icteric hepatitis in 1955, after which the oral route of infection was documented in a Russian military

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camp in 1990.[7,8] Although HEV infection is mostly self-limiting and can cause asymptomatic disease, infection of immunocompromised, thalassemic, HIV patients, and pregnant women can cause mild forms of hepatitis, extra-hepatic manifestations, and death in some cases.[9]

HEV infection is mostly ecologically dependent and is associated with travel history to endemic regions or low sanitary conditions, involving water-borne and fecal oral routes as the predominant route of transmission.[9] However, evidence of HEV transmission through blood and plasma has been reported globally.[7,10–13] According to a report from the World Health Organization (WHO), about 118.2 million blood donations were collected in 118 countries globally in the year 2013, and nearly 21 million blood components were transfused annually in the USA alone.[14] But HEV is not included in routine testing for pathogens before blood transfusion. A number of surveillance studies have been done to detect the prevalence of HEV in blood donors, indicating that the sero-positivity of HEV among blood donors ranges from 2% to 49% in different parts of the world.[4,9,11–55] Some studies reported active viremia in blood donors, indicating a direct risk to blood or blood components recipients.[7,12,18,21–24,29,30,32,34–41,45,46,48,52–54,56–58] Table 1 summarizes studies in the literature concerning HEV-seroprevalence among blood donors.

The transfusion-related HEV transmission, which is reported in several studies, strongly suggests the need for HEV screening of donated blood. No study from Saudi Arabia so far has investigated the prevalence of HEV RNA in blood donors to estimate the risk of HEV transmission from blood transfusion. In our study, we sought to determine the prevalence of HEV among blood donors in the Eastern Province of Saudi Arabia using molecular as well as serological assays.

Materials and Methods

Inclusion and Exclusion Criteria

All blood donors attend the blood bank section of the Laboratory department of king Fahd Hospital of the University of Al-Khobar between May 15 and November 31, 2020. Blood donors who did not gave consent to participate in the study were excluded.

Sample Collection

A total of 806 blood samples were collected in EDTA tube from the blood donors attending the blood bank section of King Fahd hospital of the University (KFHU) in Al-Khobar, Saudi Arabia. Blood samples were centrifuged, then the plasma was separated and stored at −80°C. Written ethical consent was taken from the participating volunteers, including information on their age, gender, and nationality. All the volunteers were informed about the purpose of study in accordance with the declaration of Helsinki.

Ethical approval for the study was obtained from ethical committee of the Institution Review Board (IRB) at Imam Abdulrahman Bin Faisal University (IAU) (number IRB-2020-01-149).

Serological Tests

All plasma samples were tested qualitatively for anti-HEV antibodies of IgG type using an indirect enzyme-linked immuno-sorbent assay, Human Hepatitis E Virus IgG (HEV IgG) ELISA Kit (Abbexa Ltd, Cambridge, UK).[60] Positive HEV IgG plasma samples were further tested for Anti-HEV IgM antibodies against Orthohepevirus A genotypes, using Human Hepatitis E Virus IgM (HEV IgM) ELISA Kit (Abbexa Ltd, Cambridge, UK) following the manufacturer's instruction.[60,61]

The HEV IgG & IgM ELIZA plates are coated with Recombinant HEV ORF-2/ORF-3 antigen and Mouse-anti -human IgM (μ chain), respectively. These ELIZA kits can detect IgG/IgM antibodies against Orthohepevirus A genotypes. The sensitivity and specificity of HEV-IgM (abx055720) is 99.6% and 99.2%, while HEV-IgG (abx364866) is 99.5% and 99.3%, respectively.

NAT Testing

RNA was extracted from plasma samples using QIAamp Viral RNA mini kit (Qiagen, Hilden Germany), as per the manufacturer's instructions. All samples were spiked with internal control from the employed detection kit. All plasma samples were tested for HEV RNA using RealStar HEV RT-PCR Kit 2.0 (Altona Diagnostics GmbH, Hamburg, Germany).[62] The assay was run on the Applied Biosystem QuantStudio™ 5-Realtime PCR system (Thermo Fisher Scientific, MA, USA). Quantification standards provided with the kit were used with each run. The standards are designed in accordance with the first World Health Organization International Standard for Hepatitis E Virus RNA Nucleic Acid (NAT)-Based Assays (PEI code 6329/10). The analytical sensitivity of the kit is 95%. It specifically detects all relevant genotypes of HEV and does not cross-react with viruses causing similar symptoms.[62]

Table 1 Summary of the HEV Seroprevalence Studies in Blood Donors in Multiple Geographical Areas

Continent	Country	Year and Study Duration	HEV IgG Seroprevalence		HEV IgM Seroprevalence		HEV Viremia		
			Sample Size	% Positive	Sample Size	% Positive	Sample Size	% Positive	Ref
Europe	Central Italy	Feb-Mar 2013 Feb-Mar 2014	198	3.5	198	1.01	198	0.5	[15]
	Central Italy	Feb-March 2014	313	49	313	0.6	313	0.6	[46]
	Overall Italy	2015–2016	10,011	8.7	10,011	0.4	10,011	0	[47]
	Ireland	Dec 2013-Jun 2014	1076	5.3	57	2	24,985	0.02	[54]
	Serbia	2010	200	15	ND	ND	200	0	[55]
	Spain	Jun-Dec, 2013	1082	19.96	216	13	9998	0.03	[58]
	Bulgaria	Jun-Oct, 2020	555	25.9	ND	ND	ND	ND	[69]
	Germany	2009–2010	ND	ND	ND	ND	1185	1.18	[31]
	Germany	Jul-Sept 2011	349	6.3	349	4.3	16,125	0.08	[32]
	France	Nov-2012–14	183 pools	175 pools	175 pools	2 pools	53,234	3.94	[35]
	France	Sept,2003-May, 2004	512	52.5	ND	ND	ND	ND	[36]
	Southern France	Oct 01–14, 2011	3,353	39.1	3353	3.31	591[c]	0.16	[68]
	Paris	Jan 12-Feb 13, 2015	11	45.45	11	36.36	25,637	0.04	[37]
	Upper Austria	Feb 2013-Apr 2014	1203	13.55	7	6	58,915	0.01	[34]
	UK/ Southeast England	Oct 8, 2012- Sep 30, 2013	79	29	79	29	225 000	0.04	[7]
	Netherland	Jan 2013-Dec 2014	45	24	ND	ND	59,474	0.0069	[39]
	Netherland	Nov 2011-Jan 2012 Apr-May 2012 Mar-2011 (3Days)	5239	26.7	1401	3.5	45,415	0.028	[40]
	UK/ Scotland	2004–2008 2nd set 2012	1559 528	4.7 5.7	1559 528	0 0	43,560	0.0069	[29]
	UK/ Scotland	Aug 2014 to Sept 2015 Feb 2016-Feb 2017 Mar-May 2017	1714	6.1	38	21.05	94,302	0.04	[30]
Africa	Egypt	Sept, 2005- Sept 2006	ND	ND	760	0.45	3[a]	66.66[a]	[21]
	Egypt/ Dakahlia Governorate	Jan 2017-Jan 2018	200	25	200	5	200	3	[22]
	Sudan	Apr-Jul, 2014	90	26.7	ND	ND	ND	ND	[26]
	Ghana	Unknown	239	4.6	239	5.9	239	0	[51]

(*Continued*)

Table 1 (Continued).

Continent	Country		Year and Study Duration	HEV IgG Seroprevalence		HEV IgM Seroprevalence		HEV Viremia		
				Sample Size	% Positive	Sample Size	% Positive	Sample Size	% Positive	Ref
Asia	Nepal		Feb-Mar 2014	581	9.5	581	4.6	27[a]	1.54	[23]
	Pakistan		Jan-Jun 2020	5230	3.49	5230	2.04	107[a]	0.70	[24]
	India, Northern region		Jun-Jul, 2016 Nov-Dec, 2016	633	60.5	ND	ND	1799	0	[44]
	India, Pune,		Jan-Aug, 2017	2447	17.70	2447	0.20	5[a]	40	[45]
	Philippines		Unknown	85	11.8	85	2.4	ND	ND	[25]
	Thailand		Oct-Dec 2015	26	23.08 Emurium 34.6 wantai	26	7.69 Emurium 0 Wantai	30,115	0.086	[41]
	China		Dec 2002-Oct 2008	44,816	32.60	44,816	0.94	420[c]	7.14	[48]
	China		Jan-Dec, 2012	816	21.1	816	0.5	816	0	[49]
	East China, Jiangsu Province,		Jan-Jun, 2011	486	23.3	ND	ND	ND	ND	[79]
	Japan		2004–2014	36	19.44	36	5.5	620,140	0.007	[52]
	Cambodia		Jul-Aug 2014	301	28.2	301	0.3	301[a]	0.3	[53]
	Saudi Arabia	Al-Qassim	Jan-Apr, 2019	Total: 1078 Saudis: 85.7 Non-Saudis: 14.3	5.7	1078	1.3	ND	ND	[65]
		Jeddah	1995	593	16.9	ND	ND	ND	ND	[42]
		Makkah.	Mar-Aug, 2009	900	18.7 Saudis:15.18 NonSaudi:23.32	900	4.3 Saudis: 4.3 Non-Saudi: 4.4	ND	ND	[43]
	UAE-Abu-Dubai		Feb-Apr, 2015	318	10.69	ND	ND	ND	ND	[17]
	Qatar		Jun 2013-May 2016	5854	20.5	5854	0.58	34[a]	11.7[a]	[18]
	Iran/Central province		Sept, 2012	530	14.3	ND	ND	ND	ND	[19]
	Iran/Khuzestan		May-Dec 2005	400	11.5	ND	ND	ND	ND	[20]
Australia	Australia		May 16- Dec 02, 2016	1	100	1	100	74,131	0.0013	[80]
	Australia		Sept-Oct 2014	1	0	1	0	14,799	0.0068	[38]
	New Zealand		Nov 11, 2014-Mar 10, 2015	1013	9.7 8.1	ND	ND	5103	0	[27]

(*Continued*)

Table 1 (Continued).

Continent	Country	Year and Study Duration	HEV IgG Seroprevalence		HEV IgM Seroprevalence		HEV Viremia		
			Sample Size	% Positive	Sample Size	% Positive	Sample Size	% Positive	Ref
North America	USA	Jul 20-Aug 29, 2015	3	33.33	3	0	128,021	0.002	[56]
	USA	Feb-Jul, 2013	4499	7.3	4499	0.58	18,829	0.39	[57]
	Canada	Jul 2013- Dec 2015	4102	5.9	241	1.65	13,993	0	[33]
	USA/ South Caribbean	Unknown	600	4.2	600	0.17	25[b]	0	[59]

Notes: [a]Only IgM positive samples were tested for HEV viremia, [b]only IgG reactive samples were tested for HEV viremia, [c]random samples were tested for HEV viremia.

Additionally, a 10-fold serial dilution of the highest HEV RNA standard concentration was performed and tested in triplicates using the above-mentioned kit and thermocycler (Figure 1). The limit of detection of the kit was 0.1 IU/ul (Figure 1). The dilution of 0.01 IU/ul gave a positive RT-PCR result in one out of the three measurements at a Ct of 40.23.

Statistical Analysis

All data were tabulated in Excel spreadsheets to calculate frequencies. The chi-square test was calculated using the OpenEPI webpage (https://www.openepi.com/Menu/OE_Menu.htm). For the age groups, the chi-square for linear trend was used. The post-hoc analysis was used to calculate the chi-square for the difference among nationalities by testing each value of one nationality versus the sum value of all other nationalities. P value was considered significant if less than 0.05.

Results

Of the 806 blood donors, 765 (94.91%) were males and 41 (5.08%) were females. 410 (50.8%) of the blood donors were Saudis, while 396 (49.1%) were non-Saudis from India, Yemen, Philippine, Egypt, Syria, Sudan, and Bangladesh (Table 2). Median age of the participants was 32 years (range 18–85 years).

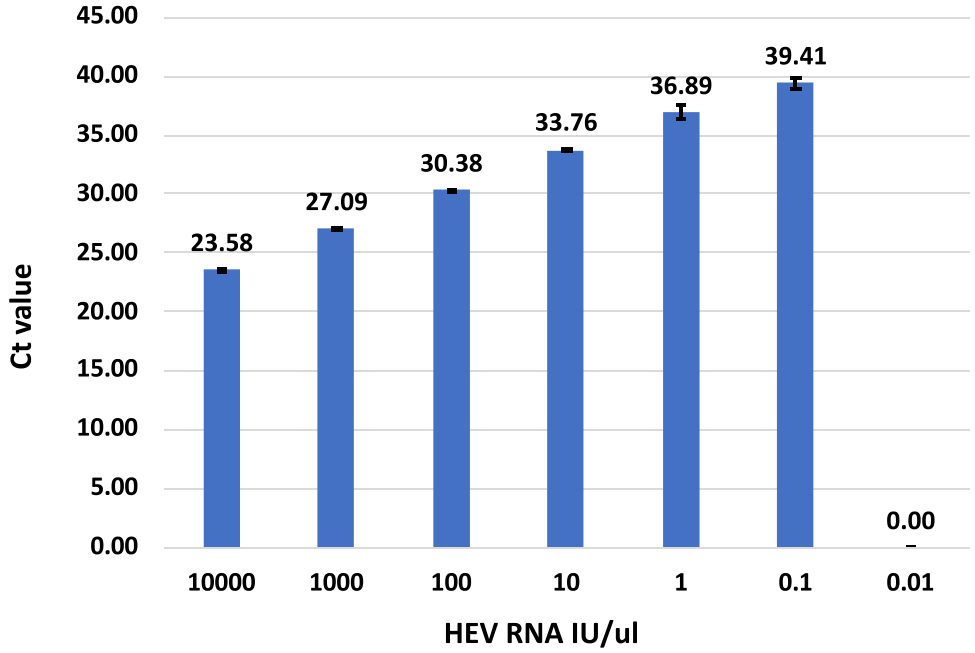

Figure 1 A 10-fold Serial dilution of HEV RNA detected by RealStar HEV RT-PCR Kit. The results show the average Ct from three measurements. The dilution 0.01 IU/ul gave a positive result in one out of the three readings with a Ct of 40.23.

Table 2 Prevalence of Anti-HEV IgG Antibodies Among Blood Donors in the Eastern Province of Saudi Arabia

	Positive		Negative		Total	P value
	N	%	N	%		
Gender						
Male	24	3.14	741	96.86	765	0.527
Female	2	4.88	39	95.12	41	
Age groups						
18 to <25	5	3.76	128	96.24	133	0.589*
25 to <35	10	2.90	336	97.1	346	
35 to <45	8	3.96	194	96.04	202	
45 to <55	3	3.16	92	96.84	95	
≥55	0	0	30	100	30	
Nationality**						
Philippine	2	6.25	30	93.75	32	0.356
Sudan	1	5.26	18	94.74	19	0.589
Bangladesh	1	5.26	18	94.74	19	0.589
India	3	4.48	64	95.52	67	0.532
Egypt	2	3.51	55	96.49	57	0.838
Saudi Arabia	13	3.17	397	96.83	410	0.929
Syria	1	2.27	43	97.73	44	0.906
Yemen	2	2.04	96	97.96	98	0.522
Kuwait	1	100	0	0	1	0.064
Others	0	0	59	100	59	0.268

Notes: *Chi square for linear trend. **The p value is calculated for each nationality against the sum of all other nationalities.

Anti-HEV IgG antibodies were detected by ELISA in 26 (3.23%) donors, and there was no statistically significant difference between non-Saudis (3.28%) and Saudis (3.17%). Anti-HEV IgG antibodies were detected in 3.14% (24/765) of the males and in 4.88% (2/41) of the females with no statistically significant difference (Table 2). Additionally, there was no statistically significant tendency with different age groups.

The highest IgG antibody prevalence was observed among the blood donors from the Philippines followed by blood donors from Sudan, Bangladesh, India, Egypt, and Saudi Arabia (Table 2). One case was from Kuwait and was positive for HEV IgG. There was no statistically significant difference in the positivity among different nationalities (Table 2).

Anti-HEV IgM antibodies were not detected in any of the 26 samples IgG positive samples.

HEV-RNA was not detected in any of the 806 samples.

Discussion

In the current study, we tested 806 blood donors from the Eastern Province of Saudi Arabia for hepatitis E virus RNA, and HEV IgG and IgM antibodies. The seroprevalence for Anti-HEV IgG was found to be 3.23%. None of the donors was positive for HEV RNA or Anti-HEV IgM. Additionally, there was no significant difference in IgG seroprevalence between Saudis (3.17%) and non-Saudis (3.28%) with any age or gender presence. Despite the fact that we have looked for IgM antibodies in IgG positive donors only, we believe that it is less likely to have missed IgM positive donors who are IgG negative for the following reason: According to the known information about the course of the HEV infection, IgM antibodies appear with the peak of RNA titer.[63–65] IgG antibodies appear at the peak of IgM antibodies and continue to be positive for a long time. IgM antibodies can still be detected until week 14 post-infection along with IgG antibodies.[63–65] Therefore, there is no window where IgG antibodies are positive and IgM antibodies are negative during an acute infection and hence it is less likely that we have missed a patient with an acute infection because all patients were negative for RNA, and the IgG positive samples are negative for IgM. This means that all IgG positive blood donors in our study had past infections.

An approximately similar HEV IgG antibody prevalence was reported from another recent study from the middle region (Qasim) of Saudi Arabia (5.7%).[66] This is lower than the previously reported HEV IgG seroprevalence before 2013, where it ranged between 14% and 18% from the southern and western regions, respectively.[16,42,43,67] This could indicate a reduction in the HEV exposure in the past few years or a regional difference in the country. The western region (Mecca and Jeddah) receives the majority of Saudi Arabia's visitors for religious purposes, who may import a silent infection and increase the exposure of the local population. Two studies have previously reported the detection of anti-HEV IgM antibodies without the confirmation of a current HEV infection with RNA detection.[16,43] It is worth noting that HEV seroprevalence in countries of the expatriate who are involved in our study is also moderate, such as Philippines (11.8%), Sudan (26%), and Egypt (25%).[21,25,26]

It is also important to note that the seroprevalence of Anti HEV-IgG in our study is less than neighboring

Middle Eastern countries like Qatar (20.5%) Iran (14.3% and 11.5%), Egypt (25%) and Abu-Dhabi (10.69%) and African countries like Sudan (26%), Ghana (4.6%) and Asian countries from where most of the non Saudis belong to like Nepal (9.5%) Pakistan (3.5%) Philippines (11.8%) China (23.3%, 21.1%) Cambodia (28.2%) Japan (3.7%) and India (17.70% and 60.5%) and European countries like Scotland (4.7%, 6.1%) France (3.94% and 52.5%) Italy (8.7% and 49%) Netherland (26.7%) Ireland (5.3%) Spain (19.9%) and Bulgaria (25.9%).[15,17–21,23–26,29,30,35,36,44–48,50,51,53,54,58,59,68–70] However, this tremendous variation in seroprevalence among different countries is expected due to differences in assays, sample size and geography.

Our study was the first to look for HEV RNA in blood donors in the country. The lack of RNA detection in our study cannot be attributed to the reduced sensitivity of the employed RT-PCR kit, especially with the absence of IgM antibodies among the donors. Our analytical sensitivity analysis shows that the kit can detect as low as 0.1 IU/ul of HEV RNA consistently in three different measurements. This could, however, suggest the need for a much larger sample size to detect such a low prevalent virus. Additionally, a short duration of HEV viremia during the course of infection could have been missed by our one-time sampling strategy.

Transfusion-transmitted hepatitis E is gaining growing attention, particularly among blood donors, because of the increased number of reported cases in multiple countries. More importantly, HEV infections in high-risk individuals, such as pregnant women, immunocompromised patients and patients with hematological diseases, have been associated with fulminant hepatitis and chronic hepatitis, which can lead to liver cirrhosis and liver failure with high fatality. Furthermore, vertical transmission in pregnant women has been reported with high risk of transmission and high neonatal fatality.[71,72]

In response to the emerging pattern of transfusion-transmitted hepatitis E, screening programs for HEV in blood donors are being implemented in many countries including Austria, the Netherland, Ireland, UK, France, Spain, Germany, Luxembourg,[73,74] Switzerland[76] and Japan[75] and being evaluated in others. Hepatitis E screening programs for blood donors have been implemented using different modalities, which include universal screening vs selective screening and individual vs pooled samples screening.[77] Cost-effectiveness studies showed variable impact[78,79] primarily due to variations in HEV prevalence in different parts of the world.

This study reports a low seroprevalence of HEV in the blood donor population in the eastern province of Saudi Arabia and no detectable HEV viremia, which alone cannot rule out the risk of transfusion associated with hepatitis E in the area, particularly for high-risk individuals. One main limitation of this study is the sample size, which contributes to the lack of detection of HEV viremia and this necessitates the need for large-scale studies and evaluation of the cost-effectiveness of blood donor HEV screening programs in the kingdom in order to quantify the risk and propose a cost-effective preventive tool.

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Disclosure

The authors report no conflicts of interest in this work.

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