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REVIEW ARTICLE

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Assessment of Hepatitis E virus transmission risks: a comprehensive review of cases among blood transfusion recipients and blood donors

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ABSTRACT

Background: Hepatitis E Virus is a major cause of acute and fulminant hepatitis, particularly in developing countries. While the virus is commonly spread through the fecal-oral route, numerous cases of transfusion transmitted Hepatitis E Virus (TT-HEV) have been reported, raising concerns about its transmission via blood transfusions, especially in industrialized countries. The high prevalence of antibodies and viremia among asymptomatic blood donors further heightens the risk of transfusion-related transmission. However, there is still debate about the best strategy to minimize TT-HEV.

Objective: The review was conducted to Summarize the literature on TT-HEV infection cases and the prevalence of HEV among blood donors.

Methods:

- The databases PubMed, Scopus, Web of Science, Embase, and CINAHL were searched for relevant studies from 2000 to 2022.
- Serological and molecular screening data of HEV in blood donors were used to gather prevalence and incidence rates.
- TT-HEV cases were reviewed by examining evidence of HEV infection before and after transfusion.

Results: A total of 121 manuscripts reports the prevalence and incidence of HEV among blood donors and cases of TT-HEV. Twenty-six articles reported confirmed cases of TT-HEV and 101 articles reported on HEV prevalence or incidence among blood donors.

Conclusion:

- TT-HEV transmission through blood products is a real concern, especially for immunocompromised patients.
- The risk and severity of infection could vary between immunocompetent and immunosuppressed patients.
- To increase transfusion safety, the evaluation recommends HEV screening protocols, especially in endemic region.

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Introduction

Hepatitis E virus (HEV) is the causative agent of viral Hepatitis E and is classically considered one of the common causes of acute hepatitis worldwide. HEV was formerly known as non-A non-B hepatitis virus [1]. The first record for HEV was traced back to 1978 in India from the hepatitis epidemic due to fecal contamination of drinking water. This was initially ascribed as a Hepatitis A outbreak. However, it was later attributed to HEV infection on retrospective analysis [2]. Similar outbreaks and epidemics were also documented in Nepal, Bangladesh, Burma, Pakistan, Mexico, and China, whereas in developed countries, sporadic and autochthonous cases were reported [3]. In 2015, World Health Organization (WHO) estimated that about 20 million people were affected annually with HEV, of which 3.3 million were symptomatic cases [4]. Major outbreaks and epidemics of HEV have been reported in Asia, Africa, and South American continents [5].

HEV belongs to the *Paslahepevirus* genus of the *Hepeviridae* family, and it consists of single-stranded positive-sense, quasi-enveloped ribonucleic acid (RNA). The size of the virion ranges from 27 to 34

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nm. The genome length is approximately 7.2 kb with three open reading frames (ORF1 to ORF3) [5]. The genus *Paslahepevirus balayani* had a total of eight HEV genotypes that have been identified so far, of which four genotypes such as genotype-1 (HEV1), genotype-2 (HEV2), genotype-3 (HEV3), and genotype-4 (HEV4) commonly infect humans. Among these genotypes HEV1 and HEV2 infect only humans, while HEV3 and HEV4 exhibit a wide range of host with swine and wild boar being the main reservoir [6]. These HEV genotypes were further sub-divided into sub-genotypes [3]. Apart from its natural modes of transmission via fecal-oral routes, zoonotic route is considered the most common one in high income countries, further, parenteral transmission of HEV through blood transfusion and its components have been reported [7]. However, HEV is self-limiting and asymptomatic in most cases. Patient such as pregnant women, compromised immune systems such as organ transplant recipients, individuals with HIV, and those receiving cancer treatment, may face challenges in effectively clearing infections. It was well documented that HEV3 infection among this risk group can lead to chronic liver infection, cirrhosis, and even death [8]. According to WHO, the mortality rate in HEV-infected cases was approximately 3.3% in the general population. In comparison, a significantly higher mortality rate of 20 to 25% was observed among HEV1 infected pregnant women, especially in their third trimester of gestation which was not observed among HEV3 or HEV4 infected pregnant women [4,9].

The first case of transfusion-transmitted HEV (TT-HEV) was reported from Japan in a 67-year-old Japanese man in 2004 by Mitsubayashi *et al.* from Hokkaido. Since then, there has been a steady rise in the detection of TT-HEV cases reported from different parts of the world [7,10,11]. Only a few nations have conducted research and implemented screening strategies to prevent HEV spread through blood transfusion [12]. Healthy blood donors with asymptomatic HEV infection may be at risk of transmitting HEV through blood donations because of its high prevalence in endemic regions and the rise in sporadic cases reported from industrialized countries. It can also be more dangerous to immunocompromised transfusion recipients or in high-risk groups [8]. There are reports of HEV infection among immunocompromised individuals and patients receiving multiple blood transfusions that resulted in acute hepatitis, chronic hepatitis, and cirrhosis [1,7,13].

Knowing the prevalence, risk of transmission, and burden of TT-HEV infections could assist in improving the blood donor selection strategies and provision of safe blood transfusion. However, the paucity of literature on TT-HEV from geographically distinct countries and its consequences in blood transfusion recipients is probably causing an obligatory remark on screening HEV among blood donors. These obligations were also due to the difference in findings and suggestions of epidemiological studies among blood donors in each respective country. A review of HEV morbidity and the economic burden of the disease due to TT-HEV cases may indirectly strengthen the enforcement strategies for HEV screening among blood donors. There were few reports on the prevalence and incidence of HEV among blood donors and TT-HEV infections among blood recipients. However, circumscribed studies have reported their findings through molecular diagnostics [14,15]. Therefore, this review is to elucidate the existing literature on the prevalence of HEV among blood donors and transfusion-transmitted HEV-infected cases to process a remarkable judgment on the screening of HEV among blood donors.

Methodology

The review identified the recent literature on TT-HEV infections among blood transfusion recipients and donors and scrutinized the recent progress on establishing HEV screening strategy among blood donors. This study summarizes the reported cases of TT-HEV infection among recipients and the prevalence of HEV among blood donors from multiple databases and bibliographic screening.

Search strategy

Scientific databases such as PubMed, Scopus, Web of Science, Embase, and CINAHL were searched for articles, reports, reviews, and short communications related to the subject topic between 2000 to 2022 AD. Open access report and institutionally subscribe journal article with full access were selected for the review. The information that includes serological screening and molecular screening of HEV among blood donors was thoroughly scrutinized to extract the prevalence and incidence data. Accordingly, TT-HEV cases were also examined through evidence of HEV infection before and after blood transfusion The genotype of the donors and recipients were matched to confirm the status of transfusion-transmitted infection, which helps to limit the errors in TT-HEV diagnosis.

Result

From the different databases and bibliographic screening, we found 121 manuscripts that report the prevalence and incidence of HEV among blood donors and cases of confirmed TT-HEV infection among recipients. Twenty-six articles reported TT-HEV

infections, and 101 research articles reported the prevalence or incidence of HEV among blood donors.

This review exclusively incorporated data on the prevalence and incidence of HEV among blood donors published between 2011 and 2022 to understand the recent trends in this context. To increase the accuracy of the results, we considered the publications for the review that had a sample size of more than 1000 participants. There was a total of 56 reports on HEV among blood donors meeting the inclusion criteria of the present review process.

Transfusion transmitted Hepatitis E Virus infection

The findings on TT-HEV infections reported during the study period are shown in Table 1. It was observed that there were 41 patients confirmed to have TT-HEV infection, wherein most of them had either chronic underlying diseases or immunosuppression. However, there were also reports of TT-HEV infection in immunocompetent individuals [13,29].

Most of the patients infected with transfusion-transmitted HEV received the infection through the transfusion of red blood cell (RBC) components. And all the TT-HEV confirmed cases found in this review were caused by either HEV3 or HEV4 genotype, mostly from industrialized countries such as France, Germany, Japan, Spain, and the United Kingdom. Interestingly, no reports of HEV1 and HEV2 transfusion-transmitted HEV infections were found among the recipients of blood transfusions. Further, the risk of transmission varied with the implicated blood component transfused (Table 1).

Anti-HEV antibody prevalence among blood donors

The prevalence of anti-HEV antibodies exhibits variation among different countries, with a higher reported prevalence of anti-HEV IgM and IgG antibodies in endemic regions and developing countries (Table 2). It was observed that the prevalence was high among blood donors in the endemic countries such as in Asian, African and South Americans. Overall, we observed that anti-HEV IgM antibody prevalence was in the range from 0% to 4.78% as shown in Supplementary table S1 and Table S2.

In addition to that the seroprevalence (anti-HEV IgG antibody) was exclusively very high in Poland (43.5%) among the developed countries which is comparable to that of the developing and endemic countries. We noted that the overall seroprevalence ranged from as low as 1.3% in Italy and 60.5% in India [66,67]. Supplementary table S1 contains a summary of studies reported before 2010 and studies with fewer than 1000 participants. The finding shows that there were significant numbers of blood donors exposed to HEV in the recent past.

HEV RNA among blood donors

A mini-pool Nucleic acid amplification test (NAT) or Individual NAT (ID-NAT) was the most common molecular screening technique reported from Western countries. Universal HEV RNA screening with NAT among blood donors is routinely practised in few developed countries such as in Europe [68]. In contrast, there were very few reports from developing countries on the use of molecular techniques for screening HEV RNA. It was observed that none of the HEV endemic countries implemented HEV screening among blood donors. Table 3 illustrates various studies on HEV RNA screening among blood donors. HEV3 was the predominant genotype identified among blood donors and the most prevalent genotype identified among TT-HEV-infected individuals. At the same time, HEV1 was observed to be the single genotype identified among the blood donors in developing countries. Procleix HEV assay (Grifols, S.A) and RealStar® HEV Real-time RT-PCR test kit (Altona Diagnostics GmbH) were the most commonly used techniques for screening HEV among blood donors and that the limit of detection (LOD) could be 7.9 IU/ml and 4.7 IU/ml respectively [57,69]. This LOD could increase with the increase in the pool size in mini-pool NAT.

Also in the supplementary table S2, a study with a sample size fewer than 1000 and a report published prior to 2010 was summarize in order to minimize the content requirement of table.

Discussion

The rising trend of HEV infection among blood donors and transfusion recipients globally indicates Hepatitis E is an emerging infectious disease and is of concern to transfusion medicine [69]. There were several reports of TT-HEV, and confirmation of HEV transmission through blood transfusion was based on examining the pre- and post-transfusion HEV status of the transfusion recipient and comparing the genotype similarity with that of the intended blood donors, which was also termed as trace back in blood transfusion services [92]. In contrast to TT-HEV documented in industrialized countries, it was rarely reported from developing countries, however outbreaks and epidemics in most of the developing countries were mainly related to the natural route of transmission [5].

Blood donation and HEV transmission

Studying the HEV seroprevalence and viremia among healthy blood donors in different countries provides

Table 1. Reported cases with transfusion transmitted hepatitis E virus infection.

			Recipient (serology and PCR result)								Blood donor (serology and PCR result)				
Year	Country	Age/ Sex	Primary Diagnosis	Detection HEV after blood transfusion	HEV IgM	HEV IgG	HEV RNA PCR	Genotype identified	Component transfused	Outcome of the disease	HEV IgM	HEV IgG	HEV RNA PCR	Genotype identified	Sequence region
2004	Japan [7]	67/M	Open Heart Surgery	37 days	+	+	+	4	FFP	On day 130 of post-transfusion, the patient had no sign of Hepatitis	-	-	+	4	ORF1
2004	Japan [16]	31/M	Haemodialysis	21 days	-	-	+	3	RBC	Sub-clinical infection without any raise in ALT enzyme	-	-	+	3	ORF2
2006	UK [17]	65/M	B Cell Lymphoma	34 days	-	-	+	3	RBC	The patients remain asymptomatic with mild jaundice and anti-HEV IgG undetectable till day 132 of post-transfusion	+	+	+	3	ORF2
2007	France [10]	7/M	Rhabdoid Tumour in Kidney	NA	+	NA	+	3f	RBC	NA	-	-	+	3f	ORF2
2007	Japan [18]	21/M	T-Cell Lymphoma	NA	-	-	+	3	RBC	The patient died, and poor immune response	NA	NA	+	3	Whole gene
2008	Japan [19]	64/M	Non-Hodgkin's Lymphoma, ASCTP	22 days	NA	NA	+	4	Platelet	Spontaneous resolution	+	+	+	4	ORF2
2012	France [20]	81/M	Chronic Autoimmune thrombocytopenia	Five months post blood transfusion (~164 days)	+	+	+	3f	Platelet	The patient died	-	-	+	3f	ORF1 & ORF2
2013	France [21]	55/M	Liver Transplant due to HCC (of HBV)	17 days	-	-	+	3c	RBC	Resolved with Ribavirin therapy	-	-	+	3c	ORF1 & ORF2
2014	France [11]	36/M	Chronic renal failure, renal transplant	~4 months	+	-	+	3f	FFP	Chronic HEV infection, therefore, Ribavirin therapy was initiated	NA	NA	+	3f	ORF1
2014	France [11]	61/M	Liver Transplant	~6 months	-	-	+	3f	FFP	The patient remained viremic even after two months. Therefore, Ribavirin treatment was given	NA	NA	+	3f	ORF1
2014	Japan [22]	70/M	Myelodysplastic syndrome	21 days	-	-	+	3	RBC	The patient died of a lung abscess	-	-	+	3	ORF2
2014	Germany [23]	47/M	Immunocompromised, Chronic HEV	20 days	+	+	+	3f	Platelet	Chronic HEV infection	-	-	+	3f	ORF1
2015	Japan [24]	70s/M	Myocardial Infarction	10 days	+	+	+	3	Platelet	Spontaneous resolution, HEV RNA undetectable at day 115 of post transfusion	NA	NA	+	3	ORF2
2016	France [25]	48/F	Kidney Transplant	14 months	-	+	+	3f	FFP	Chronic Hepatitis E virus infection	NA	NA	+	3f	ORF1
2016	Japan [26]	41/M	Living donor liver transplant	3 days	+	+	+	3b	Platelet	Chronic HEV infection, HEV RNA becomes negative on day 417 of POD	NA	NA	+	3b	ORF1 & ORF2
2016	Japan [27]	37/F	Burkitt's Lymphoma	NA	-	-	+	3	Platelet	Chronic HEV infection, no viral RNA clearance even after eight months of ribavirin therapy	NA	NA	+	3	ORF1 & ORF2
2016	Germany [28]	33/M	Stem cell transplant	NA	NA	NA	+	3	RBC	Chronic HEV infection, there is a relapse of HEV after ribavirin treatment was stopped	NA	+NA	+	3	NA
2016	Germany [28]	71/M	Heart Transplant	54 days	NA	NA	+	3	Plasma	ALT normalized within three months; however, no antiviral treatment could be the reason that fluctuates the viral load without HEV RNA clearance	NA	NA	+	3	NA
2016	Germany [28]	61/F	Acute Myeloid Leukaemia	49 days	NA	+	NA	3	Platelet	NA	NA	NA	+	3	NA
2017	Spain [29]	61/M	Axillofemoral bypass surgery	>1 month of transfusion	+	NA	+	3f	RBC	Spontaneous resolution after one month of diagnosis	-	-	+	3f	ORF2
2017	France [13]	M	Splenectomy due to splenic injury	35 days	-	-	+	3f	Platelet	After two months of ribavirin treatment, the viral load decreased but continued till day 135 of post-trauma	NA	NA	+	3f	ORF2
2017	France [30]	56/M	Heart Transplant	68 days	+	+	+	3	RBC	The patient died of multi-organ failure on day 153 of POD	-	-	+	3	ORF2

(*Continued*)

Table 1. (Continued).

			Recipient (serology and PCR result)								Blood donor (serology and PCR result)				
Year	Country	Age/ Sex	Primary Diagnosis	Detection HEV after blood transfusion	HEV IgM	HEV IgG	HEV RNA PCR	Genotype identified	Component transfused	Outcome of the disease	HEV IgM	HEV IgG	HEV RNA PCR	Genotype identified	Sequence region
2017	Australia [31]	6/M	Liver Transplant	More than two months after transfusion	NA	NA	+	3	FFP	Resolved after three months of ribavirin therapy	NA	NA	+	3	ORF2
2017	France [32]	34/F	Liver transplant	~4 months	-	-	+	3	RBC	NA	-	-	+	3	ORF2
2017	France [32]	42/F	Liver transplant	~4 months	-	-	+	3f	ATP	NA	-	-	+	3f	ORF2
2018	Greece [33]	50/M	Thalassaemia	2 months	+	NA	+	3	RBC	Self-limiting, recovered within a month, all biochemical test normalized	+	NA	+	3	ORF2
2018	Spain [34]	48/M	Thrombocytopenic Purpura	2 months	+	+	+	3f	Cryo#	After 12 weeks of ribavirin treatment, the ALT, and platelet become normal, and HEV RNA is undetectable	+	-	+	3f	ORF2
2019	Japan [35]	64/F	Acute Myeloid Leukaemia*	112 days	-	-	+	3b	Platelet	Progress to Chronic infections, HEV RNA and IgM undetectable at day 321 post transfusion	NA	NA	+	3b	ORF2
2020	France [36]	50-59/M	Thrombotic Microangiopathy	45 days	+	+	+	3f	Plasma	NA	NA	NA	+	3f	ORF1 & ORF2
2020	France [36]	50-59/M	Liver Transplant	3 months post-transplant	+	-	+	3f	Plasma	Chronic infection successfully treated with Ribavirin therapy	NA	NA	+	3f	ORF1 & ORF2
	France [37]	57/M	Thyrotoxicosis and drug-induced thrombotic microangiopathy	Within two months after transfusion	NA	NA	+	3f	SD-plasma	No therapy, spontaneous resolution	NA	NA	+	3f	ORF1 & ORF2
	France [37]	55/M	Kidney transplant	Within two months after transfusion	NA	NA	+	3f	SD-plasma	Chronic Infection, ribavirin treatment resolved the infection after three months	NA	NA	+	3f	ORF-2
	France [37]	58/M	Liver Cirrhosis and Transplantation	Within three months after transfusion	NA	NA	+	3f	SD-plasma	Chronic infection, resolved after six months of ribavirin treatment	NA	NA	+	3f	ORF-1
	France [37]	42/F	Acute Myeloid Leukaemia	Within a month after transfusion	NA	NA	+	3f	WBPC	Chronic infection, resolved after seven months of ribavirin treatment	NA	NA	+	3f	ORF-2
	France [37]	67/F	Non-Hodgkin Lymphoma	Within three months after transfusion	NA	NA	+	3f	RBC	Chronic infection, resolved after a month and a half treatment with ribavirin	NA	NA	+	3f	ORF-2
	France [37]	64/M	Allogenic Hematopoietic stem cell transplantation	After six months of transfusion	NA	NA	+	3f	RBC	Chronic infection, spontaneous resolution	NA	NA	+	3f	ORF-2
	France [37]	88/M	Chronic Lymphoid Leukaemia	Within a month after blood transfusion	NA	NA	+	3c	RBC	Chronic infection, spontaneous resolution	NA	NA	+	3f	ORF-1
	France [37]	36/M	Hemolytic Uremic Syndrome/ Kidney Transplant	Within six months after transfusion	NA	NA	+	3f	SD-plasma	Chronic infection, resolved after five months of ribavirin therapy	NA	NA	+	3f	ORF-2
	France [37]	44/F	Chronic renal failure/Kidney Transplant	After six months of transfusion	NA	NA	+	3f	RBC	Chronic infection, treatment associated resolution of three-month ribavirin therapy	NA	NA	+	3f	ORF-1
	France [37]	50/M	Hodgkin Lymphoma/allogenic HSC transplantation	After six months of transfusion	NA	NA	+	3c	APC	Chronic infection, spontaneous resolution at allogenic HSC transplantation, i.e. in the context of reduced immunosuppression	NA	NA	+	3c	ORF-1 & ORF-2

(*Continued*)

Table 1. (Continued).

			Recipient (serology and PCR result)								Blood donor (serology and PCR result)				
Year	Country	Age/ Sex	Primary Diagnosis	Detection HEV after blood transfusion	HEV IgM	HEV IgG	HEV RNA PCR	Genotype identified	Component transfused	Outcome of the disease	HEV IgM	HEV IgG	HEV RNA PCR	Genotype identified	Sequence region
	France [37]	55/F	Hodgkin Lymphoma/allogenic HSC transplantation	Within a month after transfusion	NA	NA	+	4d	APC	Chronic infection, spontaneous resolution at allogenic HSC transplantation, i.e. in the context of reduced immunosuppression	NA	NA	+	4d	ORF-1
	France [37]	46/F	Acute Myeloid Leukaemia	Within three months of transfusion	NA	NA	+	3a	WBPC	Spontaneous resolution	NA	NA	+	3a	ORF-2
	France [37]	60/M	Acute Myeloid Leukaemia/ allogenic HSC transplantation	Within a month after transfusion	NA	NA	+	3f	WBPC	Treatment-associated resolution after three months of ribavirin therapy	NA	NA	+	3f	ORF-2
	France [37]	18/M	Acute Lymphoid Leukaemia	Within a month after transfusion	NA	NA	+	3c	WBPC	Ribavirin treatment associated resolution	NA	NA	+	3c	ORF-2
	France [37]	47/M	Bilateral Lung Infection	Within three months after transfusion	NA	NA	+	3f	APC	Spontaneous resolution	NA	NA	+	3f	ORF-2

[#]cryosupernatant plasma, FFP; Fresh frozen Plasma, SD-plasma; Solvent or detergent treated plasma, RBC; Red blood concentrate, WBPC; Whole blood pooled platelet concentrate, APC; Apheresis platelet concentrate, ASCTP; autologous peripheral stem cell transplant, ALT; Alanine transaminase, NA; Not available, POD; post operative day.

Table 2. Prevalence of HEV antibodies among blood donors**.

Continent	Country	Author, Year of Publication	Sample size(N)	IgM reactive(n)	Prevalence (%)	IgG reactive(n)	Prevalence (%)	Screening kit used for HEV IgM antibody	Screening Kit used for HEV IgG antibody	Ref.
Africa	Burkina Faso	Traore et al., 2016	1497	13	1.9	584	39	Wantai	DiaPro	[38]
Asia	China	Ren et al., 2014	10741	109	1.02	2945	27.4	Wantai	Wantai	[39]
	Nepal	Shrestha et al., 2016	1845	55	2.98	773	41.89	Wantai	Wantai	[40]
	Qatar	Nasrallah et al., 2017	5854	34	0.58	1198	20.5	Wantai	Wantai	[41]
	China	Wang et al., 2017	9069	131	1.44	2682	29.5	Wantai	Wantai	[42]
	China	Wen et al., 2018	5345	38	0.71	1227	22.96	Wantai	Wantai	[43]
	India	Tripathy et al., 2019	2447	5	0.2	433	17.7	Inhouse Prep	Inhouse Prep	[44]
	China	Cheng X et al., 2019	4044	43	1.1	799	19.8	Wantai	Wantai	[45]
	China (H.K)	Tsoi et al., 2020	2000	16	0.08	315	15.8	Wantai	Wantai	[46]
	Saudi Arabia	Alhatlani et al., 2021	1078	-	-	61	5.7	-	Fortress Diagnostics, Antrim, UK	[47]
	China	P. Fu et al., 2021	1864	21	1.13	249	13.36	Inhouse Prep	Inhouse Prep	[48]
Europe	Scotland (UK)	Cleland et al., 2013	1559	0	0	73	4.7	Wantai	Wantai	[49]
	Netherland	Slot et al., 2013	1401	49	3.5	-	-	Wantai	-	[50]
			5239	-	-	1401	26.7	-	Wantai	
	Germany	Juhl D et al., 2014	1019	-	-	69	6.8	-	recomline	[51]
	Spain	Sauleda et al., 2015	1082	-	-	216	19.96	-	Wantai &, recomline	[52]
						116	10.72			
	Austria	Fischer et al., 2015	1203	-		163	13.55	-	Wantai	[53]
	Ireland	O'Riordan et al., 2016	1076	-	-	57	5.3	-	Wantai	[54]
	Scotland (UK)	Thom et al., 2018	1714	-	-	104	6.1	-	Wantai	[55]
	Netherland	Mooij et al., 2018	2100	-		648	31	-	Wantai	[56]
	Poland	Grabarczyk et al., 2018	3079	39	1.27	1340	43.52	Wantai	Wantai	[57]
	Italy	Spada et al., 2018	10011	46	0.4	869	8.7	Wantai	Wantai	[58]
	Switzerland	Niederhauser et al., 2018	3609	-	-	737	20.4	-	Wantai	[59]
	Croatia	Miletic et al., 2019	1036	46	4.44	209	20.17	DiaPro and recomline	DiaPro and recomline	[60]
	Italy	Spada et al., 2022	1816	33	1.8	-	-	Wantai	-	[61]
			7172	-	-	597	8.3	-	Wantai	
North America	United States of America	Xu et al., 2013	1939	8	0.4	364	18.8	Wantai	Wantai	[62]
	United States of America	Stramer et al., 2016	4499	26	0.58	329	7.3	MP Diagnostic	MP Diagnostic	[63]
	United States of America	Zafrullah et al., 2018	5040	146	2.9	569	11.29	DSI	DSI	[64]
			5040	93	1.85	537	10.65	MP Diagnostic	MP Diagnostic	
			5040	34	0.67	619	12.28	Wantai	Wantai	
Oceania	New Zealand	Hewitt J et al., 2018	1013	-	-	98	9.7	-	Wantai and MP Diagnostics	[65]

** The table was prepared inclusively for articles published before 2010 and sample size less than 1000 numbers in order to limit number of reference allotted for the publication, Inhouse prep; Inhouse preparation, DSI; Diagnostic System Incorporated (DSI S.r.l., Milan, Italy), H.K; Hong Kong.

Table 3. Prevalence and incidence of HEV RNA among blood donors (sample size more than 1000).

Continent	Country	Author, Year of publication	Sample size (N)	Reactive (n)	Incidence rate (or ratio)	genotype	HEV RNA screening kit used	Ref.
Africa	South Africa	Maponga et al., 2020	10000	1	1:10000	3	Procleix HEV assay	[70]
Asia	Japan	Minagi et al., 2016	620140	36	1:15075	3	Inhouse preparation	[71]
	China	Wang et al., 2017	9069	6	1:1511	NA	Inhouse preparation	[42]
	India	Katiyar et al., 2018	1799	0	0	NA	Inhouse preparation	[67]
	China	Wen et al., 2018	11747	24	1:489	4	Inhouse preparation	[43]
	China	Tsoi et al., 2019	10000	2	1:5000	4	Procleix HEV assay	[46]
	Thailand	Intharasongkroh et al., 2019	30115	26	1:1158	3	Inhouse preparation	[72]
	China	P. Fu et al., 2021	1864	0	0	NA	Inhouse preparation	[48]
	India	Mishra K et al., 2021	13050	7	1:1864	NA	RealStar HEV RT-PCR Kit 1.0	[2]
	Japan	Sakata et al., 2021	4018435	886	1:4535	3	Inhouse and Procleix HEV assay	[73]
Europe	Germany	Vollmer et al., 2012	16125	13	1:1240	3a, 3c & 3e	RealStar HEV RT-PCR kit	[74]
	Germany	Baylis et al., 2012	18100	4	1:4525	3	Inhouse preparation	[75]
	Sweden	Baylis et al., 2012	95835	12	1:7986	3	Inhouse preparation	[75]
	Scotland (UK)	Cleland et al., 2013	43560	3	1:14520	3	Inhouse preparation	[49]
	Netherland	Slot et al., 2013	45414	17	1:2671	3	Inhouse preparation	[50]
	Germany	Corman et al., 2013	93955	14	1:6711	3	Inhouse preparation	[76]
	France	Gallian et al., 2014	53234	24	1:2218	3	RealStar HEV RT-PCR kit	[77]
	England	P Hewitt et al., 2014	225000	79	1:2848	3	Inhouse preparation	[78]
	Spain	Sauleda et al., 2015	9998	3	1:3332	3f	Procleix HEV assay	[52]
	Austria	Fischer et al., 2015	58915	7	1:8416	3	RealStar HEV RT- PCR kit version 1.0	[53]
	Ireland	O'Riordan et al., 2016	24985	5	1:4997	3	Procleix HEV assay	[54]
	Denmark	Harritshoj et al., 2016	25637	11	1:2330	3	Procleix HEV assay	[79]
	Netherland	Hogema et al., 2016	59474	41	1:1450	3	Inhouse preparation	[80]
	Italy	Spada et al., 2018	10011	0	0	NA	RealStar HEV RT-PCR kit 1.0	[58]
	Poland	Grabarczyk et al., 2018	12664	10	1:1266	3i and 3c	Procleix HEV assay	[57]
	Germany	Westholter et al., 2018	18737	23	1:814	3	Cobas HEV Assay	[81]
	Scotland (UK)	Thom et al., 2018	94302	38	1:2481	3	Cobas HEV Assay	[55]
	Germany	Dreier et al., 2018	235534	182	1:1294	3	RealStar HEV RT-PCR kit	[69]
	Spain	Rivero et al., 2019	11313	4	1:2828	3	Inhouse preparation	[82]
	Belgium	Vercouter et al., 2019	38137	7	1:5448	NA	Cobas HEV Assay	[83]
	United Kingdom	Harvala et al., 2019	1838747	480	1:3830	3	Cobas HEV Assay	[12]
	Italy	Spreafico et al., 2020	9726	1	1:9726	NA	Procleix HEV assay	[84]
	UK	Smith et al., 2021	848612	411	1:2064	3	NA	[85]
	Italy	Spada et al., 2022	7172	0	0	NA	Procleix HEV assay	[61]
	Portugal	Healy et al., 2022	20393	4	1:5098	NA	Inhouse preparation	[86]
	Germany	Healy et al., 2022	167122	167	1:1000	NA	Inhouse preparation	
	Spain	Bes et al., 2022	655523	151	1:4341	3	Procleix HEV assay	[87]
North America	USA	Baylis et al., 2012	51075	0	0	NA	Inhouse preparation	[75]
	USA	Stramer et al., 2016	18829	2	1:9414	NA	Procleix HEV assay	[63]
	USA	Roth et al., 2017	128021	4	1:32005	3a	Cobas HEV Assay	[88]
	Canada	Delage et al., 2019	50765	11	1:4615	3	Cobas HEV assay	[89]
	USA	Delage et al., 2019	50724	3	1:16908	3a, 3b	Cobas HEV assay	
Oceania	Australia	Shrestha et al., 2016	14799	1	1:14799	3	Procleix HEV assay	[90]
	Australia	Hoad et al., 2017	74131	1	1:74131	NA	Procleix HEV assay	[91]
	New Zealand	Hewitt J et al., 2018	5000	0	0	NA	RealStar HEV RT- PCR kit version 1.0	[65]

*HEV sub-genotype – 3a, 3b, 3e, 3f, 3c, 3uc, 4b, 4c, 4 g. USA; United States of America, UK; United Kingdom, NA; Not available

alarming data for the transfusion medicine speciality. As each HEV reactive blood component unit might be able to transmit HEV to a maximum of up to three prospective blood recipients. The infectivity of HEV also depends on the blood component infused and the infective dose, which may differ from one component to another [8,78]. Though the pathogen inactivation technology allows pooled plasma to prevent transmission of infectious agents, there had been reports of ineffective towards HEV where the viral RNA is detected in the pooled blood component or pooled plasma [11,36,93]. Therefore, this part of pooling and inactivation through pathogen inactivation technology has to be further emphasized.

We perceived that HEV had been transmitted through different blood components, such as packed red cells, platelets, pooled granulocytes, and fresh-frozen plasma. Patricia *et al.* state that HEV transmission depends on factors like the type of blood component transfused and implicated viral RNA concentration in blood donors [78]. Tedder *et al.*, estimate a minimum infectious dose of $2X10^4$ IU of HEV RNA could cause infections in 55% of the HEV contaminated blood transfusion transmitted recipient, while there were also report of 951 IU and 6660 IU infectious dose for RBC and platelet donations [94,95]. Patients of solid-organ transplant, stem cell transplant, dialysis, pregnant women, immunocompromised, malignancy, and other hematological disorders were considered high-risk groups for HEV infection. Their status in acquiring HEV infection is owing to their long-term blood transfusion

dependent condition and immunosuppression status [16,96]. Due to immunosuppression in these patients are prone to develop obstructive liver diseases and chronic liver infections without viral clearance. Asymptomatic or undetectable HEV infection among organ and blood donors makes up the risk of transmitting the infection to organ transplant patients and transfusion recipients [1]. Transfusion-transmitted HEV infection could be a dreadful disease as 20 viremic donors have been detected in Japan and have transmitted HEV to the patients [97]. And, also in England, out of 43 HEV-infected blood recipients from viremic blood donors, 18 of them had HEV infection and developed the disease [98].

Risk of transmission through blood transfusion

The evidence of HEV transmission through blood transfusion was elaborated comprehensively for genotype-3 and genotype-4 through a trace-back algorithm. It has been shown that PBMCs and other blood components can replicate HEV1. Furthermore, the introduction of blood-derived HEV-1 into humanized mice resulted in a productive infection [99,100]. This could be in vitro evidence in establishing the infectivity of HEV in blood components. However, the evidence for HEV1 and HEV2 as the causative agent of TT-HEV is still lacking in blood transfused patients. This is probably because these genotypes were highly prevalent in developing countries with limited resources to perform an extensive investigation on cases with post-transfusion hepatitis. Further, as genotype determination does not change the underlying disease status, there is a reluctance to perform genomic analysis. However, unlike HEV transmission through the oral route, where the stomach's acidic environment offers a protective effect to some extent, blood transfusion is associated with an almost 50% definite risk of transmission of infection [69,97].

A systematic review of HEV seroprevalence among healthy blood donors globally has reported the seroprevalence proportion of 0.058 (0.049 to 0.068). Even while the total concentration of HEV RNA is quite low, it varies greatly within and between similar geographic regions [101,102]. The incidence of HEV viremia in donors varies from 1 in 157 in Italy to 1 in 15,075 in Japan (Tables 2 and 3). Several reports are available on HEV prevalence and viremia detected among blood donors, as shown in supplementary table S1 and S2, mostly from Asian and European countries.

The instances like the absence of HEV antibodies and high viral load in the blood component could increase the transmission risk of HEV in recipients. HEV seroconversion can be delayed among immunosuppressed patients, thereby prolonging the viremia and expanding the clinical significance of the disease acquired [98]. HEV RNA is detectable in the blood during the incubation period and persists up to 4 weeks while the anti-HEV IgM antibody could be detected during the incubation period and even up to 5 to 6 months of post infection [103,104].

The laboratory screening and diagnostic methods, specificity and sensitivity of the test also influence the incidence (or prevalence) of HEV within and across populations. In this review, we observed that the blood centers commonly use serological testing methods such as Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescence assay for detecting IgM and IgG antibodies against HEV and NAT-based polymerase chain reaction (PCR) to detect HEV RNA. It was known that PCR is still considered the most dependable technique for laboratory confirmation of HEV infection in blood and stool samples [105]. Additionally, there is considerable variability in the sensitivity and specificity of commercially available serological test kits for screening and diagnosis of HEV infection [106]. ID-NAT and mini-pool NAT with different pool sizes also have an impact on the detection rate and incidence of HEV among blood donors [105]. Apart from blood components, HEV RNA reactivity was also reported in plasma fractionation pools [107].

Clinical outcome of TT-HEV infection

Acute Hepatitis E is usually a self-limiting infection with symptoms lasting for 4 to 6 weeks among the general population, wherein 40% of HEV infection leads to the development of jaundice. However, chronic illness was recorded among the immunocompromised patients with HEV3 or HEV4 genotype infections [4,5]. Symptoms of HEV infection include muscle and joint pain, fatigue, and vomiting. Laboratory testing parameters, such as liver enzymes Alanine-aminotransferase (ALT), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP), and bilirubin were elevated among the cases. There was also a late onset of illness among the TT-HEV-infected patients, leading to chronic hepatitis. A similar pattern of clinical outcomes has been recognized among eight cases of TT-HEV infections in this review, predominantly with their underlying immunosuppressed condition. And there was a persistent increase in the liver enzyme levels in addition to the presence of HEV-RNA in the serum even up to least six months or more among these patients [27,35].

The current review did not identify any reports of transfusion-transmitted HEV in cases in pregnant women. However, HEV1 infected pregnant women and patients with chronic hepatitis E were known to be a vulnerable group to develop severe clinical

complications such as coagulation disorders, jaundice, hepatic encephalopathy, ascites, and sometimes even fulminant hepatic failure [9,108]. Extrahepatic manifestations such as neurological symptoms, kidney injuries, and hematological disorders are rarely identified [5,37]. In this review, except for a few, most TT-HEV-infected patients progressed to chronic HEV infection (Table 1, outcome of the disease) [7,19–21,35]. The disease burden and outcome of chronic HEV infection could be considerably different from the general course of the disease.

The strategy to manage HEV infection irrespective of natural infection of TT-HEV is based on the clinical presentation. Generally, the acute infection should be treated conservatively corresponding to the viral load clearance by the immune system or a short-term Ribavirin therapy could be effective. In the case of chronic HEV infection particularly among the immunocompromised patients, dose reduction or discontinuation of the immunosuppressant should be considered as primary concern. As the immunosuppressant drugs could elevate the HEV replication, administering this type of drugs is not suggestive, otherwise, ribavirin and (or) pegylated interferon-alpha (peg-IFN) could be used for treatment [109].

HEV among blood donors in developed countries

It was notably observed that NAT screening was commonly used in developed countries, wherein routine HEV screening reported HEV3 genotype among the blood donors which is highly infectious among immunocompromised patients [69]. Moreover, cases of HEV3 and HEV4 infections were reported particularly through the consumption of undercooked pork and its products. Therefore, other than zoonotic concerns, improved hygiene and sanitation in the current decades could be a reason for lower incidence of HEV in many industrialized countries [110].

Some of the economically advanced countries, namely Germany, France, the Netherlands, Ireland, the United Kingdom, Spain, Austria, Luxembourg, and Japan, have implemented HEV screening strategies for the blood units [15,68,111]. The United Kingdom, Ireland, France, Germany, Spain, Austria, Luxembourg, and the Netherlands have adopted universal screening of blood donors for HEV. In contrast, other countries have implemented selective screening of blood units intended to be administered to patients of high-risk groups [68,112]. Factors influencing the decision of different screening strategy approaches include risk assessment, resource availability, health economics, reputational, political, and other influences. Among European countries, Greece, Italy, Portugal, Poland, Belgium, and Malta are still evaluating their research finding for mandatory screening of HEV among blood donors; however, it is not compulsory for screening of HEV in most endemic countries [68,69]. Implementation of selective screening is yet a debate in European countries as the infection risk from dietary sources might not be ruled out or could be more common [15,98]. Selective screening of HEV for blood units to be transfused to high-risk patients could prevent comorbidities due to TT-HEV infection. However, cost-effectiveness analysis of screening methodologies, either serological, ID-NAT, or Mini-pool NAT should be an important concept to consider. Antigen capture-based ELISA is simple faster and suitable for laboratories lacking molecular diagnostic equipment [98].

Some of the European medicine agencies recommended mini-pool NAT screening in HEV in plasma-derived products [113]. Drier *et al.*, suggest a mini-pool NAT screening of 96 samples of blood donations should be adequate as a routine screening assay to rule out viremic donors and to cover at least a large part of the viremic phase, in contrast Laperche *et al.*, from France suggest that less than 12 samples should be pooled to minimize the potential risk associated with blood component with higher plasma volume [69,112].

HEV among blood donors in developing countries

There are several disease patterns of HEV in developing countries which are determined by the geographical distribution of genotypes, socioeconomic status, access to potable water, sanitation, the regional occurrence of HEV genotypes, etc [110]. HEV1 and HEV2 genotypes of HEVs are reported mostly from developing and hyperendemic countries, and the same genotypes were reported from blood donors in countries like India and Nepal etc [40,44]. It was also revealed that more than one-third of the donors had evidence of past infections [38,40,67]. However, there were no reports on the molecular confirmation of TT-HEV infections among transfusion recipients from developing countries. Therefore, rigorous research should be carried out to mitigate a possible risk of HEV transmission through blood transfusion. Based on the latest literature, if TT-HEV infections are identified in the future, it would be a steppingstone and an impressive concept to include HEV as an important TTIs in developing countries.

Recommendations and future perspectives

It is recommended to define transfusion safety protocols specifically tailored for the high-risk group, including selective screening of blood components. This targeted approach can potentially decrease the incidence of HEV infection among this vulnerable

population. It is crucial to identify and document the incidence of transfusion-transmitted HEV (TT-HEV). This data is essential to determine the importance of screening for HEV among blood donors. Additionally, deliberate efforts should be made to determine the prevalent genotype and its natural route of infections, providing valuable insights into how different genotypes may influence disease outcomes.

Prioritizing the study of HEV among blood donors in countries endemic and hyperendemic for HEV1 and HEV2 genotypes is essential. This research is crucial for making informed decisions on whether mandatory screening for HEV among blood donors should be implemented. The implementation of such screening requires a well-considered policy that takes into account the economic implications for the country. Achieving this necessitates raising awareness and sensitizing key stakeholders, including blood transfusion centers and implementing bodies.

Implementing a standardized protocol for serology and molecular testing could substantially enhance the detection rate of HEV and reduce the residual risk of infection. However, assessing the cost-effectiveness of routinely screening blood donors for HEV will be essential to guide future best practices.

Conclusion

The transmission of HEV among recipients of various blood products is evident and has a significant impact, especially among immunocompromised patients. The risk of infections, disease progression, and severity varies from immunocompetent to immunosuppressed patients. Further study on the infused component, viral load, and genotype-specific disease outcomes of HEV infections in transfusion recipients might be necessary to predict outcomes among the at-risk group. Considering HEV as an emerging threat to transfusion safety, formulating guidelines on screening blood units in endemic countries is the need of the hour.

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