Hepatitis E Virus Seroprevalence Among Hemodialysis and Hemophiliac Patients in Tunisia (North Africa)

Yousr Ben-Ayed,[1]* Hela Hannachi,[1] Nissaf Ben-Alaya-Bouafif,[2] Emna Gouider,[3] Henda Triki,[1] and Olfa Bahri[1]

[1]*Laboratory of Clinical Virology, Institute Pasteur of Tunis, University of Tunis El Manar, Tunis, Tunisia*
[2]*Observatoire National des Maladies Nouvelles et Emergentes, Ministry of Health, Tunis, Tunisia*
[3]*Hematological Unit, Aziza Othmana Hospital, Tunis, Tunisia*

The aims of this study are to determine seroprevalence of Hepatitis E virus (HEV) in Tunisian blood donors and to evaluate its risk of parenteral transmission. Sera collected from 426 blood donors were tested for HEV IgG by indirect ELISA. Individuals were recruited from two national transfusion centers, in the North and the South of the country. Seroprevalence of HEV IgG was then compared with two other groups with increased risk of exposure to parenterally transmitted agents: 80 hemophiliac and 286 hemodialysis patients. Among blood donors, the seroprevalence was estimated to be 4.5%. It was significantly higher in the hemophiliac and hemodialysis groups with 7.5% and 10.2%, respectively, ($P = 0.002$). No significant correlation was observed for this IgG 1 seroprevalence between age and sex among three studied groups. These results suggest that HEV has a high risk of parenteral transmission and confirm that the low endemicity of hepatitis E in Tunisia was observed. ***J. Med. Virol.*** © 2014 Wiley Periodicals, Inc.

KEY WORDS: parenteral risk; hemophilia; dialysis; RNA virus

INTRODUCTION

Hepatitis E virus (HEV) causes a significant public emergent health problem worldwide with approximately 20,000,000 of people infected globally, over 3,000,000 acute cases of hepatitis E, and 57,000 hepatitis E-related deaths (http://www.who.int/mediacentre/factsheets/fs280/fr/). In developing countries, hepatitis E is a water-borne infection associated with large epidemics caused by contaminated drinking water [Mushahwar, 2008; Mansuy et al., 2009; CDCP, 2013]. However, in developed countries, hepatitis E is considered rare, and is commonly linked to imported infection [Worm et al., 2002; Miyamura, 2011]. HEV is transmitted via the fecal-oral route. But, recent studies have shown that the transmission is through the parenteral route [Matsubayashi et al., 2004, 2008; Boxall et al., 2006; Colson et al., 2007]. This hypothesis is supported by the observation that anti-HEV antibodies are more prevalent in patients with history of blood transfusion [Kikuchi et al., 2006]. Nevertheless, the association of transfusion and HEV transmission still remains highly controversial; however, some reports showed a very low prevalence of HEV infection in individuals at risk for parenteral exposure, such as haemophiliacs [Barzilai et al., 1995; Zaaijer et al., 1995]. No association was found between HEV and

Abbreviations: CI, confidence interval; HEV, hepatitis E virus; IgG, immunoglobulin G.

Author contribution: Yousr Ben Ayed and Olfa Bahri designed the study; Yousr Ben Ayed and Hela Hannachi performed the majority of experiments and wrote the manuscript; Nissaf Ben Alaya-Bouafif performed statistical analysis; Emna Gouider provided the collection of all the human material; Hinda Triki and Olfa Bahri were involved in editing the manuscript and provided financial support for this work.

Conflict of interest: None.

Ethical approval: Investigations were approved by Ethics Committee of Tunisian Ministry of Health; Informed consent was obtained for each patient enrolled in the study. All patients gave informed consent for participation and the study was approved by Ethics Committee of Tunisian Ministry of Health.

Grant sponsor: Tunisian Secretariat for Scientific Research and Technology (SERST); Grant number: LR11IPT09.

*Correspondence to: Yousr Ben-Ayed, Laboratory of Clinical Virology, Pasteur Institute of Tunisia, Place Pasteur, Le Belvédère BP 74–1002–Tunis, Tunisia.
E-mail: yousr.benayed@gmail.com

Accepted 28 August 2014

DOI 10.1002/jmv.24082
Published online in Wiley Online Library (wileyonlinelibrary.com).

blood-borne viruses in Italian studies conducted in 1997 [Fabrizi et al., 1997].

HEV is a non-enveloped positive-sense RNA virus belonging to the *Hepeviridae* family and the *Hepevirus* genus [Dalton et al., 2008; Martelli et al., 2008; Aggarwal and Naik, 2009; Forgách et al., 2010]. It has been recognized that HEV has a single serotype and four main genotypes (HEV1–4) [García et al., 2012]. Depending on the infecting genotype, HEV infection is considered a zoonosis [Chang et al., 2009; Song et al., 2014; Van der Poel, 2014]. In fact, Genotypes 1 and 2 have been found to be restricted to human [Yugo and Meng, 2013]. Genotypes 3 and 4 are circulating in both humans and animals [Meng, 2010; Purdy and Khudyakov, 2011].

Despite literature reported that hepatitis E is endemic in North Africa [Miyamura, 2011], no outbreaks have never been reported in Tunisia. However, seroprevalence studies in blood donors are limited. Those published until now targeted different groups of patients. They did not reflect a real epidemiology of the infection in the country and reported discordant results: from 4% to more than 40% of positivity for HEV antibodies [Ben Halima et al., 1998; Rezig et al., 2008; Hannechi et al., 2011a,b].

The aims of this study were to determine the seroprevalence of HEV in Tunisian blood donors and to evaluate the risk of parenteral transmission. For that, seroprevalence of specific IgG in blood donors was estimated and then compared to seroprevalence in hemophiliac and hemodialysis patients.

MATERIALS AND METHODS

Patients

A total of 791 individuals were included in this study enrolled between October 2009 and April 2012. Patients were tested previously for antibodies against other hepatitis viruses (B, C, and D) and HIV. They were confirmed negative for all these infections. Studied population was divided in three distinct groups: (i) 426 blood donors recruited from two transfusion centers, 244 and 182 cases from centers A and B, respectively; (ii) 286 hemodialysis patients from six hemodialysis centers; and (iii) 80 hemophiliac cases enrolled from different regions of the countries and attending the national hemophiliac center for follow-up. Informed consent was obtained for each patient enrolled in the study. Characteristics of these groups are summarized in Table I.

TABLE I. Characteristics of Studied Population

Groups	Number	Mean age (years)	Extremes (years)	Sex-ratio (M/F)
Blood donors				
North	244	27.61	18–54	1.54
South	182	61.63	20–88	10.37
Total	426	42.15	18–88	2.3
Hemodialysis				
Private				
Unit 1	56	56.8	15–90	1.03
Unit 2	61			
Public				
Unit 3	61	51.13	26–87	1.4
Unit 4	66			
Unit 5	29			
Unit 6	13			
Total	286	54.86	15–90	1.2
Hemophiliacs	80	15.62	2–40	—
Total	792	42.33	2–90	2

Serological assays

Serum from all cases was obtained and stored at −20 °C until use. All samples collected from the three groups were tested, in duplicate, for anti-HEV IgG using the same commercial indirect ELISA (Globe Diagnostics Srl, Milan, Italy). The assay was performed according to the manufacturer's instructions. Sera with absorbance greater than the cut-off value were considered positive.

Statistical analysis

Statistical analysis was performed using SPSS statistical software. Proportion comparison was carried out by the Pearson chi-square test or the Fisher's tests. P values <0.05 were considered statistically significant. Ninety five percent confidence intervals were calculated (CI 95%). A standardization of the patients studied by age was performed to restore the age groups distribution.

RESULTS

Anti-HEV IgG was detected in 6.8% (54/791) of studied population. Seroprevalence was 4.5% among blood donors and was significantly higher in hemophiliac and hemodialysis groups with 7.5% and 10.2%, respectively, ($P = 0.002$). The prevalence of anti-HEV IgG remained significantly higher in these two groups compared to blood donors after age adjustment.

No significant difference was observed between hemodialysis and hemophiliac groups. Also, no significant correlation was observed for anti-HEV IgG seroprevalence between age and sex among the three groups (Table II).

For blood donors, IgG was similar between the two recruiting centers, 3.9% (North center) and 4.9% (South center). In the hemodialysis group, the prevalence of IgG varied from 6.1% to 16.4% among hemodialysis units; this difference was not statistically significant (Table III).

DISCUSSION

The epidemiology of HEV in Tunisia is not well known. Previous studies have reported controversial results. Among healthy individuals, the seroprevalence of specific IgG varied significantly 4.3% in young adults [Rezig et al., 2008], 12.1% in pregnant women

TABLE II. Prevalence of IgG Anti-HEV Among Studied Groups

	Blood donors	Hemodialysis	Hemophiliacs
Age			
<20	3 (4.7)	0 (0)	3 (9.1)
[20–40]	8 (4)	3 (7.9)	2 (14.3)
>40	8 (5)	18 (12.2)	—
P	0.214	0.579	0.215
Gender			
M	16 (5)	18 (11.7)	—
F	3 (2.8)	11 (8.27)	—
P	0.427	0.109	—

Numbers (percentages) of patients are shown. No significant difference was observed according to gender and age.

TABLE III. Prevalence and 95% Confidence Interval (CI) for Anti-HEV IgG on Blood Donors and Hemodialysis Patients

Groups	Standardized prevalence (%)	CI 95%	*P*
Blood donors			
North	3.7	[2–6.9]	0.578
South	5.5	[2.3–9.2]	
Hemodialysis			
Private centers			
Unit 1	7.1	[2–17]	0.429
Unit 2	10	[3.7–20.2]	
Public centers			
Unit 3	16.4	[8.1–28.1]	
Unit 4	6.1	[1.9–14.8]	
Unit 5	13.8	[3.9–31.7]	
Unit 6	7.7	[0.2–36]	

No significant difference was observed between blood centers ($P = 0.578$) and dialysis centers ($P = 0.429$) for HEV IgG prevalence.

[Hannechi et al., 2011a,b], and 46% in healthy subjects over 60 years old [Ben Halima et al., 1998]. In blood donors, seroprevalence was 5.4% [Neffati et al., 2012].

The present study was conducted in the two largest blood centers in the country. The serological test used is known to have a good performance confirmed by high specificity and sensitivity of more than 98% (Globe Diagnostics, Milan, Italy). It used, as antigen, a specific polypeptide from ORF2 and ORF3 encoding conservative immunodominant epitopes. These antigens were those targeted to develop efficient HEV serological assays [Khudyakov and Kamili, 2011]. Low prevalence (~3%) was observed in Mediterranean European countries including Italy, Spain, and Greece [Scotto et al., 2012]. Equivalent proportions have also been observed in Netherlands (1.9%) [Verhoef et al., 2012], Japan (3.4%), Brazil (2.3%), and USA (1.2%) [Bortoliero et al., 2006; Takeda et al., 2010]. Conversely, higher rates of HEV infection have been reported in Iran (11.5%) and China (20%). These countries are considered endemic for hepatitis E [Assarehzadegan et al., 2008; Chandra et al., 2008]. Seroprevalence reached 60% in Egypt, especially in rural regions [Delarocque-Astagneau et al., 2012]. These results showed the association of hepatitis E with socio-economic levels. Poor sanitation, most likely, plays a predominant role in the high rate of infection in endemic regions.

Recent studies conducted in some industrialized countries showed large differences between rates of seropositivity. In France, southwestern regions are hyperendemic for HEV, as shown among local blood donors 52.2%. This high prevalence contrasts with the low incidence of autochthonous hepatitis E in France [Mansuy et al., 2008; Mansuy et al., 2011]. These differences may be due to culinary culture of the local community (eating uncooked pork and game products) further supporting zoonotic transmission of HEV infection in the region [Renou et al., 2008]. Similar results have been observed in Japan where prevalence of specific IgG is higher in the East (5.6%) in comparison to the West (1.8%). In these settings, HEV infection is age-dependent and higher in men (3.9%) than in women (2.9%). Differences in dietary patterns (high consumption of pork than beef) may be associated with higher seroprevalence in eastern Japan [Takeda et al., 2010]. In the present study, no correlation was observed between positivity of IgG anti-HEV and age, gender, or origin. This homogenous distribution of HEV prevalence throughout the country can be explained by the absence of specific culinary culture for Tunisian community, particularly the absence of pork consumption. Equivalent distribution of prevalence between socio-demographic variables has also been observed in Muslims communities [Traoré et al., 2012]. Other studies targeting a larger study of patients from specific communities such as Muslims should be done to confirm this hypothesis.

According to literature, this is the first report on epidemiology of hepatitis E in hemophiliac and hemodialysis patients in Tunisia. Higher prevalence (7.5%) of IgG anti-HEV was observed among heamophiliac patients in comparison to blood donors. Similar results have been obtained in France and Japan [Buffet et al., 1996; Toyoda et al., 2008]. These high rates confirmed the risk of HEV parenteral transmission. Thus, transmission by blood transfusion seems to be implicated in hemodialysis patients. Prevalence among hemodialysis varied in Europe from 0% in Ireland to more than 14% in France. In hyperendemic countries, higher rates were observed in hemodialysis patients. In Taiwan, prevalence reaches 31% in this studied patients group [Kamar et al., 2010]. In France, 10.8% of patients under hemodialysis were positive IgG anti-HEV [Buffet et al., 1996]. This rate was estimated to be 19% in Japan [Kikuchi et al., 2006]. In Greece, HEV prevalence among hemodialysis was estimated to be 4.8%, which is higher than that of blood donors (0.26%). The rate varied from one dialysis unit to another (from 1.8% to 9.8%) [Stefanidis et al., 2004] suggesting a possible risk of nosocomial transmission. In the current study, the lack of correlation with hemodialysis center suggests that viral transmission is principally associated to

contaminated blood. Other explanations can be considered for higher proportion of HEV IgG among hemodialysis and hemophiliac patients. It was previously reported that some viral infections such as HIV infection or chronic hepatitis B and C can affect the patient's immunity [Ayoola et al., 2002]. However, for the present study, all these viral infections were previously discarded supporting the real role of parenteral transmission for HEV.

In conclusion, this report confirmed the low endemicity of hepatitis E in Tunisia. The results suggest that the virus had a high risk of parenteral transmission. Preventive measures should be implemented to prevent possible contamination in polytransfused patients and hemodialysis cases.

ACKNOWLEDGMENTS

We thank Pr. Jalel Gargouri, Dr. Mouna Jaballah, and Pr. Najet Mojaat for facilitating blood sampling and data collection from blood donors.

REFERENCES

Aggarwal R, Naik S. 2009. Epidemiology of hepatitis E. J Gastroenterol Hepatol 24:1484–1493.

Assarehzadegan MA, Shakerinejad G, Amini A, Rahim Rezaee SA. 2008. Seroprevalence of hepatitis E virus in blood donors in Khuzestan Province, Southwest Iran. Int J Infect Dis 12:387–390.

Ayoola EA, Want MA, Gadour ME, Al-Hazmi MH, Hamza MK. 2002. Hepatitis E virus infection in haemodialysis patients: A case-controlstudy in Saudi Arabia. J Med Virol 66:329–334.

Barzilai A, Schulman S, Karetnyi YV, Favorov MO, Levin E, Mendelson E, Weiss P, Fields HA, Varon D, Martinowitz U. 1995. Hepatitis E virus infection in hemophiliacs. J Med Virol 46:153–156.

Ben Halima M, Arrouji Z, Slim A, Lakhoua R, Ben Redjeb S. 1998. Epidémiologie de l'hépatite E en Tunisie. Tunis Méd 76:129–131.

Bortoliero AL, Bonametti AM, Morimoto HK. 2006. Seroprevalence for hepatitis E virus (HEV) infection among volunteer blood donors of the Regional Blood of Londrina, State of Paraná, Brazil. Rev Inst Med Trop Sao Paulo 48:87–92.

Boxall E, Herborn A, Kochethu G, Pratt G, Adams D, Ijaz S, Teo CG. 2006. Transfusion-transmitted hepatitis E in a 'nonhyperendemic' country. Transfus Med 16:79–83.

Buffet C, Laurent-Puig P, Chandot S, Laurian Y, Charpentier B, Briantais MJ, Dussaix E. 1996. A high hepatitis E virus seroprevalence among renal transplantation and haemophilia patient populations. J Hepatol 24:122–125.

Centers for Disease Control and Prevention. 2013. Investigation of hepatitis E outbreak among refugees — Upper Nile, South Sudan, 2012–2013. MMWR 62:581–586.

Chandra V, Taneja S, Kalia M, Jameel S. 2008. Molecular biology and pathogenesis of hepatitis E virus. J Biosci 33:451–464.

Chang Y, Wang L, Geng J, Zhu Y, Fu H, Ren F, Li L, Wang X, Zhuang H. 2009. Zoonotic risk of hepatitis E virus (HEV): A study of HEV infection in animals and humans in suburbs of Beijing. Hepatol Res 39:1153–1158.

Colson P, Coze C, Gallian P, Henry M, De Micco P, Tamalet C. 2007. Transfusion-associated hepatitis E, France. Emerg Infect Dis 13:648–649.

Dalton HR, Bendall R, Ijaz S, Banks M. 2008. Hepatitis E: An emerging infection in developed countries. Lancet Infect Dis 8:698–709.

Delarocque-Astagneau E, Abravanel F, Mohsen A, Le Fouler L, Gad RR, El-Daly M, Ibrahim EM, EL-Aidy S, Lashin T, El-Hoseiny M, Izopet J, Mohamed MK, Fontanet A, Abdel Hamid M. 2012. Epidemiological and virological characteristics of symptomatic acute hepatitis E in Greater Cairo, Egypt. Clin Microbiol Infect 18:982–988.

Fabrizi F, Lunghi G, Bacchini G, Corti M, Pagano A, Locatelli F. 1997. Hepatitis E virus infection in haemodialysis patients: A seroepidemiological survey. Nephrol Dial Transplant 12:133–136.

Forgách P, Nowotny N, Erdélyi K, Boncz A, Zentai J, Szucs G, Reuter G, Bakonyi T. 2010. Detection of hepatitis E virus in samples of animal origin collected in Hungary. Vet Microbiol 143:106–116.

García CG, Sánchez D, Villalba MC, Pujol FH, de Los Ángeles Rodríguez Lay L, Pinto B, Chacón EP, Guzmán MG. 2012. Molecular characterization of hepatitis E virus in patients with acute hepatitis in Venezuela. J Med Virol 84:1025–1029.

Hannechi N, Boughammoura L, Marzouk M, Tfifha M, Khlif A, Soussi S, Skouri H, Boukadida J. 2011a. Viral infection risk in polytransfused adults: Seroprevalence of seven viruses in central Tunisia. Bull Soc Pathol Exot 104:220–225.

Hannechi N, Hidar S, Harrabi I, Mhalla S, Marzouk M, Ghzel H, Ghannem H, Khairi H, Boukadida J. 2011b. Seroprevalence and risk factors of hepatitis E among pregnant women in central Tunisia. Pathol Biol 59:115–118.

Kamar N, Abravanel F, Mansuy JM, Peron JM, Izopet J, Rostaing L. 2010. Hepatitis E infection in dialysis and after transplantation. Nephrol Ther 6:83–87.

Khudyakov Y, Kamili S. 2011. Serological diagnostics of hepatitis E virus infection. Virus Res 161:84–92.

Kikuchi K, Yoshida T, Kimata N, Sato C, Akiba T. 2006. Prevalence of hepatitis E virus infection in regular hemodialysis patients. Ther Apher Dial 10:193–197.

Mansuy JM, Legrand-Abravanel F, Calot JP, Peron JM, Alric L, Agudo S, Rech H, Destruel F, Izopet J. 2008. High prevalence of anti-hepatitis E virus antibodies in blood donors from South West France. J Med Virol 80:289–293.

Mansuy JM, Mengelle C, Miédougé M, Abravanel F, Izopet J. 2009. Viral hepatitis E. Arch Pediatr 16:717–720.

Mansuy JM, Bendall R, Legrand-Abravanel F, Sauné K, Miédouge M, Ellis V, Rech H, Destruel F, Kamar N, Dalton HR, Izopet J. 2011. Hepatitis E virus antibodies in blood donors, France. Emerg Infect Dis 17:2309–2312.

Martelli F, Caprioli A, Zengarini M, Marata A, Fiegna C, Di Bartolo I, Ruggeri FM, Delogu M, Ostanello F. 2008. Detection of hepatitis E virus (HEV) in a demographic managed wild boar (Sus scrofa scrofa) population in Italy. Vet Microbiol 126:74–81.

Matsubayashi K, Nagaoka Y, Sakata H, Sato S, Fukai K, Kato T, Takahashi K, Mishiro S, Imai M, Takeda N, Ikeda H. 2004. Transfusion-transmitted hepatitis E caused by apparently indigenous hepatitis E virus strain in Hokkaido, Japan. Transfusion 44:934–940.

Matsubayashi K, Kang JH, Sakata H, Takahashi K, Shindo M, Kato M, Sato S, Kato T, Nishimori H, Tsuji K, Maguchi H, Yoshida J, Maekubo H, Mishiro S, Ikeda H. 2008. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route. Transfusion 48:1368–1375.

Meng XJ. 2010. Recent advances in hepatitis E virus. J Viral Hepat 17:153–161.

Miyamura T. 2011. Hepatitis E virus infection in developed countries. Virus Res 161:40–46.

Mushahwar IK. 2008. Hepatitis E virus: Molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention. J Med Virol 80:646–658.

Neffati H, Ritter J, Feki S, Dron AG, Slim A, Hassine M, Braham H, Ramiere C, Andre P, Aouni M, Scholtes C. 2012. Seroprevalence of hepatitis E virus infection in rural and urban populations, Tunisia 2012. Clin Microbiol Infect 18:119–121.

Purdy MA, Khudyakov YE. 2011. The molecular epidemiology of hepatitis E infection. Virus Res 161:31–39.

Renou C, Moreau X, Pariente A, Cadranel JF, Maringe E, Morin T, Causse X, Payen JL, Izopet J, Nicand E, Bourliere M, Penaranda G, Hardwigsen J, Gerolami R, Peron JM, Pavio N. 2008. A national survey of acute hepatitis E in France. Aliment Pharmacol 27:1086–1093.

Rezig D, Ouneissa R, Mhiri L, Mejri S, Haddad-Boubaker S, Ben Alaya N, Triki H. 2008. Seroprevalences of hepatitis A and E infections in Tunisia. Pathol Biol 56:148–153.

Scotto G, Giammario A, Centra M, Francesco V, Martinelli D, Fazio V. 2012. Seroprevalence of hepatitis E among blood donors in a district of Southern Italy. Blood Transfus 10:565–566.

Song YJ, Park WJ, Park BJ, Lee JB, Park SY, Song CS, Lee NH, Seo KH, Kang YS, Choi IS. 2014. Hepatitis E virus in humans and animals. Clin Exp Vaccine Res 3:29–36.

Stefanidis I, Zervou EK, Rizos C, Syrganis C, Patsidis E, Kyriakopoulos G, Sdrakas L, Tsianas N, Rigopoulou EI, Liakopoulos V, Dalekos GN. 2004. Hepatitis E virus antibodies in hemodialysis patients: An epidemiological survey in central Greece. Int J Artif Organs 27:842–847.

Takeda H, Matsubayashi K, Sakata H, Sato S, Kato T, Hino S, Tadokoro k, Ikeda H. 2010. A nationwide survey for prevalence of hepatitis E virus antibody in qualified blood donors in Japan. Vox Sang 99:307–313.

Toyoda H, Honda T, Hayashi K, Katano Y, Goto H, Kumada T, Takahashi K, Abe N, Mishiro S, Takamatsu J. 2008. Prevalence of hepatitis E virus IgG antibody in Japanese patients with hemophilia. Intervirology 51:21–25.

Traoré KA, Rouamba H, Nébié Y, Sanou M, Traoré AS, Barro N, Roques P. 2012. Seroprevalence of fecal-oral transmitted hepatitis A and E virus antibodies in Burkina Faso. PLoS ONE 7: e48125.

Van der Poel WH. 2014. Food and environmental routes of Hepatitis E virus transmission. Curr Opin Virol 4:91–96.

Verhoef L, Koopmans M, Duizer E, Bakker J, Reimerink J, Van Pelt W. 2012. Seroprevalence of hepatitis E antibodies and risk profile of HEV seropositivity in The Netherlands, 2006–2007. Epidemiol Infect 24:1–10.

Worm HC, Van der Poel WHM, Brandstätter G. 2002. Hepatitis E: An overview. Microbes Infect 4:657–666.

Yugo DM, Meng XJ. 2013. Hepatitis E virus: Foodborne, waterborne and zoonotic transmission. Int J Environ Res Public Health 10:4507–4533.

Zaaijer HL, Mauser-Bunschoten EP, Tne Veen JH, Kapprell HP, Kok M, van den Berg HM, Lelie PN. 1995. Hepatitis E virus antibodies among patients with hemophilia, blood donors, and hepatitis patients. J Med Virol 46:244–246.