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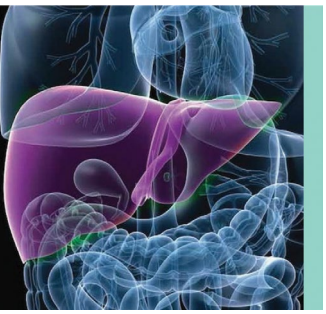

Hepatitis E Virus Infection: Is It Really a Problem in Latin America?

María Belén Pisano, Santiago Mirazo,† and Viviana E. Re**

Hepatitis E virus (HEV) is a positive-strand RNA virus with a 7.2-kb genome (species *Orthohepevirus A*, genus *Orthohepevirus*, family Hepeviridae) that causes 20 million infections every year worldwide, leading to an estimated 3.3 million symptomatic cases of hepatitis E, being the main cause of acute viral hepatitis worldwide.[1,2] The virus is transmitted through the fecal-oral route, principally via contaminated water, although other routes of infection have been described, such as vertical transmission and blood transfusions.[3] Eight genotypes have been described, and four are the most frequent in humans: HEV-1 and HEV-2 infect only human beings, whereas HEV-3 and HEV-4 are zoonotic viruses, which can infect persons by direct contact with animals or ingestion of contaminated food.[2,3]

HEV was first thought to be uncommon in Latin America, because there were no records of epidemics by this agent in the region, with the exception of Mexico and Cuba. The first studies about HEV circulation date from the 1990s, when many countries performed serological studies in different human populations.[3,4] However, only a few countries reported new studies in the last 10 years (approximately), updating and expanding the information about HEV in other epidemiological settings of Latin America, such as detection in animals, environment, and report of clinical cases (acute and chronic diseases). Data from these latest reports evidence a complex scenario regarding HEV epidemiology, mainly because of the heterogeneity in the populations and geographical regions studied (Latin America is a region with more than 620 million inhabitants living in 20 countries). Despite the research progress that has been performed in the last 10 years, several situations are present: (1) lack of updated information on several countries from the region, which yields to the subdiagnosis of hepatitis E; and (2) despite the evidence of viral circulation from many sources in countries that have continued studying HEV over time, there still are subdiagnoses of this disease. Some of the reasons for this could be: (1) hepatitis E is still unknown or neglected by medical practitioners

Abbreviations: HEV, hepatitis E virus; IgG, immunoglobulin G; ND, not determined.

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(due to a lack of access to information); (2) HEV infection is known by the health care team, but there is a lack of access to diagnostic tools; (3) there are clinical cases of hepatitis E, but notifications and publications are not frequent; and (4) hepatitis E is of little relevance to clinicians.

This review aims to gather updated information, and visualize and spread the state of the art regarding HEV in Latin America. For that purpose, we searched published scientific articles by assessment of PubMed/U.S. National Library of Medicine using the following keywords: "HEV/ hepatitis E" and each country of the continent, until November 2019. We also included communications considered relevant from local scientific meetings.

SEROPREVALENCE OF HEV IN LATIN AMERICA

The first reports of immunoglobulin G (IgG) anti-HEV prevalence rate in blood donors and the general population in Latin America (up to the year 2006) varied between 1.5% and 8%.[3,4] In the following years, a gradual increase was observed in the scarce countries studied, probably because of the improvement in the diagnostic kits, showing seroprevalence rates between 4% and 40.3%, depending on the studied region and the differences in the specificity and sensitivity of the serological kits used[3,5,6] (Fig. 1).

In rural populations or individuals who work in pig farms, most of the countries reported higher seroprevalence rates, between 11% and 40%.[3,7-9]

Only in Brazil and Argentina have recent publications about IgG anti-HEV seroprevalence among immunosuppressed subjects been reported, showing discordant results (prevalence rates between 5.8% and 35.7%)[3,10-12]; in individuals with cirrhosis, higher values were found compared with the general population.[13,14]

CLINICAL COURSE OF HEV INFECTIONS OCCURRED IN LATIN AMERICA

Table 1 summarizes acute HEV cases reported in Latin America, which are mainly sporadic cases caused by HEV-3, although HEV-1 has also been detected. Only Mexico and Cuba have documented outbreaks, in which HEV-1, HEV-2, and HEV-3 have been involved (Fig. 2).[4,15] Although HEV-3 is responsible for most clinical cases, HEV-1 should not be discarded (it has been detected in a few indigenous cases in the continent and in one imported case in Argentina),[3] as well as other human genotypes (HEV-4 and HEV-7), because possible new introductions, as a consequence of imported cases, could occur.

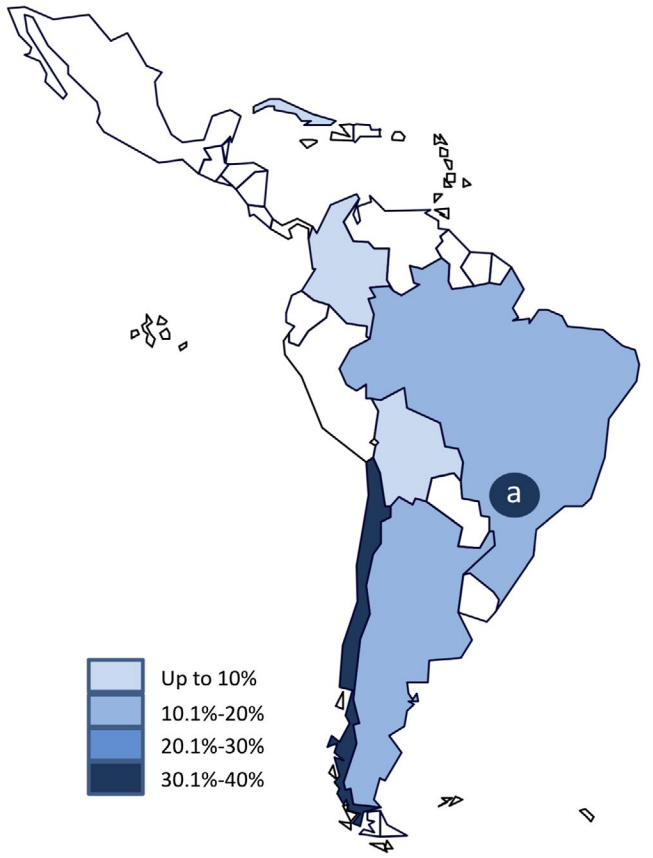

FIG 1 Seroprevalence of HEV IgG in blood donors and the general population reported in Latin America in the last 10 years (2009 to 2019). (*a*) The only seroprevalence study performed with an in-house kit was carried out in Southern Brazil (40.3%).[3]

Chronic cases are scarce (only six have been reported; Table 2), probably because HEV is not an agent taken into account at the time of diagnosis.

Extrahepatic manifestations due to HEV infection are rarely described, and only two cases have been reported (Table 2).[3]

DETECTION OF HEV IN ANIMALS AND THE ENVIRONMENT IN LATIN AMERICA

In the last 10 years (approximately), significant research efforts have been made concerning HEV distribution in animal

TABLE 1. CASES OF ACUTE HEPATITIS E DETERMINED IN LATIN AMERICA BY IGM ANTI-HEV AND/OR RNA-HEV DETECTION

Country	Studied Patients	IgM Anti-HEV	HEV RNA	HEV Genotype (n)	References
Argentina	Not given	ND	2	3i (2)	3
	35	3	3	3i (3)	3
	231	6	9	1a (1)*	3
				3a (5)	
				3a (5)	
				3b (1)	
	143	4	9	3a (7)	3
				3i (2)	
	1	ND	1	ND	25†
	4	ND	2	ND	26†
	1	1	1	3	27†
	1	1	0	ND	28†
Brazil	17	5	ND	ND	3
	64	1	1	3b (1)	3
	96‡	0	3	3 (2)	3
				3i (1)	
	552	6§	6	3b (1)	3
	379	1	0	—	3
Chile	59	1	ND	ND	3
	35	12	ND	ND	3
Colombia	344	6	ND	ND	29
	40	ND	9 stool	3	3
Cuba	146	24	ND	ND	30
	258	53	ND	ND	31
	39	18	ND	ND	31
	58	58	2 sera	1 (11)	15
			18 stool		
Mexico	94	ND	2 stool	2a/3	4
	129	ND	1 stool		
	75	75	13	1 (5)	32
Peru	747	4	ND	ND	3
	2	ND	2	ND	3
Uruguay	Not given	9	9	3 (9)	3
	1	1	1	1	3
Venezuela	74	22	3	1 (2)	3
				3 (1)	

*Imported case from India.
†Personal communications.
‡Renal transplant recipients.
§Two liver transplant recipients.

and environmental reservoirs in Latin America. However, these studies are restricted to a few areas on the continent (Fig. 2).

Serological and molecular detections performed in animals, evidenced by the presence of HEV in domestic pigs, showed elevated seroprevalence rates, ranging from 46% to 100%.[3,16-20] Recently, specific anti-HEV antibodies and RNA have been detected in free-living wild boars from Uruguay and Argentina, where very similar seroprevalence rates were observed (about 22% and 20%, respectively).[19,21] Besides, HEV has also been detected in bottlenose dolphins (Tursiops truncatus), associated with liver disorders.[22] The role of these and other marine mammals in the transmission cycle of HEV in aquatic natural environments is unclear.

All swine HEV strains detected belonged to HEV-3, showing a high degree of genetic heterogeneity among countries and several cocirculating subtypes.[3,16] However, in each particular Latin American country with reported studies on HEV, excepting Bolivia, both human and swine strains were found to be very closely related. Thus, the zoonotic route seems to play a crucial role in the maintenance and transmission of HEV in the region.[3,19,20] This is supported by a recent case of acute hepatitis E in Argentina, in which the sequences of HEV-3 obtained from the patient and pigs from his farm were identical.[27]

Recently, in Uruguay, where the cocirculation of HEV-3 and HEV-1 had been reported, a domestic pig was found to be infected with a human HEV-1 strain. However, the

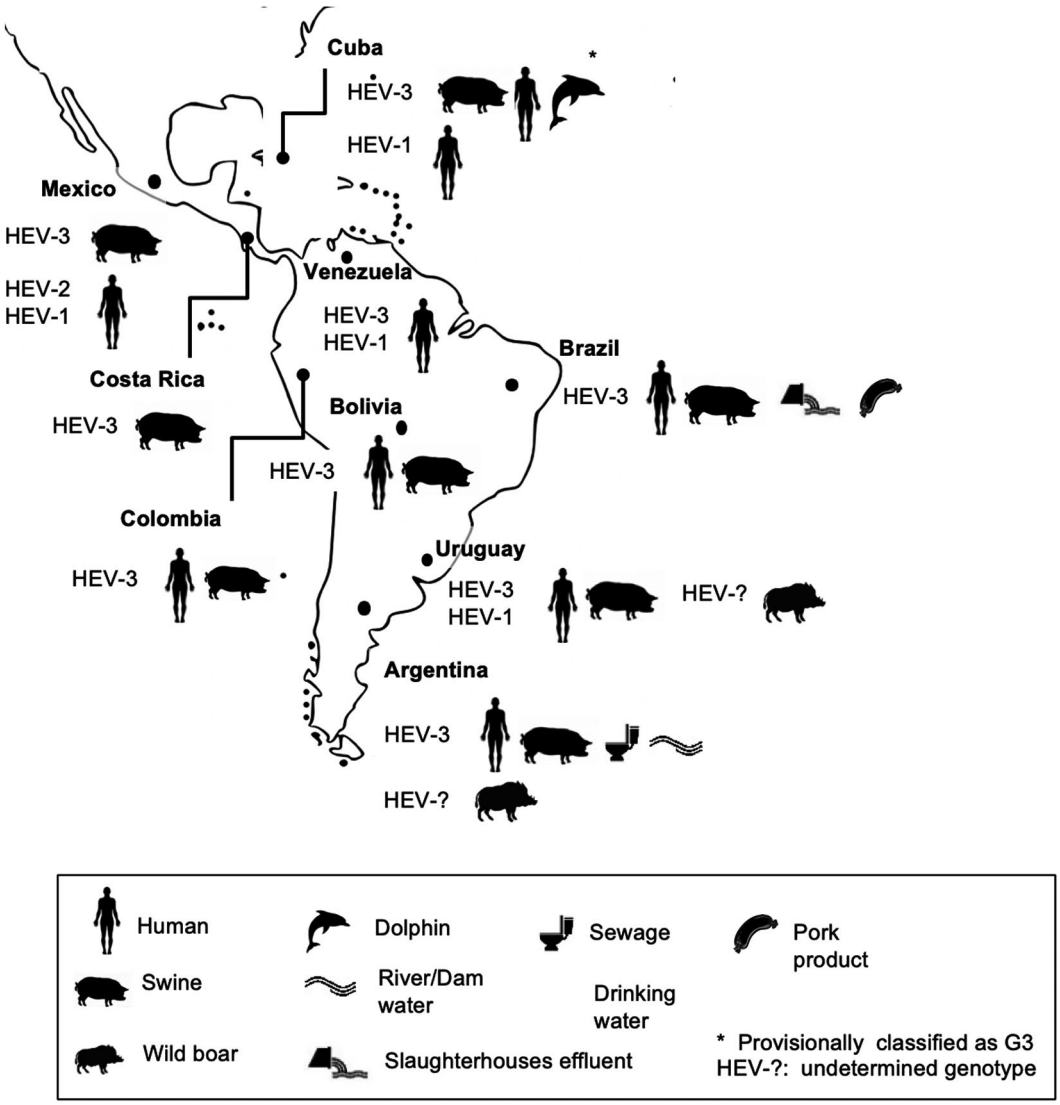

FIG 2 Genotype distribution of HEV in Latin America. HEV genotypes, mammal reservoirs, and environmental detections reported for each country are shown.

TABLE 2. CHRONIC HEPATITIS AND EXTRAHEPATIC MANIFESTATIONS DUE TO HEV IN LATIN AMERICA

Country	Base Clinical Condition	Symptoms of HEV Infection	Treatment	HEV Genotype	Reference
Argentina	Not reported	Subacute thyroiditis	None	3a	3
	Alcohol consumption (~50 g/day)	Aplastic anemia	Cyclosporine, thymoglobulin IV, methylprednisolone and filgrastim Transfusions	3a	3
	Renal transplant	Chronic hepatitis	Ribavirin (16 weeks)	ND	3
	Inflammatory bowel disease	Chronic hepatitis	Ribavirin	ND	26
Brazil	Liver transplant	Chronic hepatitis	Ribavirin (10 weeks)	3b (serum and liver biopsy)	3
	Renal transplant, neurological disorder, co-infection with Epstein-Barr virus	Chronic hepatitis	Without data	3 (serum)	33
Peru	Autoimmune hepatitis	Decompensation with "acute on chronic" hepatitis, which derived in chronic hepatitis	Without data	ND	3
Uruguay	Liver transplant	Chronic hepatitis	Ribavirin (9 weeks)	3 (stool and serum)	34

significance of this finding and the zoonotic potential of this rare case need to be further investigated.[23]

Environmental and food detections of HEV in Latin America have been performed in few countries (Fig. 2). Many strains belonging to HEV-3 have been detected in sewage, river, and dam water from Argentina; drinking water and sewage from Colombia; and slaughterhouse water and sausages from Brazil.[3,24]

Animal and environmental surveillance, together with search of the virus in hosts never explored in Latin America (such as donkey, goat, cow, and sheep), will help to detect early new HEV genotypes for our region.

CONCLUSION

In the last 10 years (approximately), HEV has become an important pathogen responsible for acute and chronic hepatitis in the world, mainly in places where its presence was not well-known or was uncommon. This is not the exception for Latin America, where reports of HEV have increased in the last 10 years, showing viral circulation in many human populations (with the highest prevalence rates in immunosuppressed populations), animal reservoirs, environmental matrices, and food. These findings have allowed the positioning of hepatitis E as a public health problem of increasing concern in Latin America, worthy of being studied, and have partially answered the initial question: HEV infection: is it really a problem in Latin America? However, many gaps in our knowledge are still present, and improvements are required in terms of a complete clinical phenotype characterization and diagnosis, including the harmonization of methods of detection and genotyping. Further efforts on the recognition and awareness of the disease among the health care teams are needed to gain insight into the burden of hepatitis E in our region.

CORRESPONDENCE

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REFERENCES

1) World Health Organization. Fact sheets. Hepatitis E. Available at: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-e. Published July 8, 2019.

2) Webb GW, Dalton HR. Hepatitis E: an underestimated emerging threat. Ther Adv Infect Dis 2019;6:2049936119837162.

3) Pisano MB, Martinez Wassaf MG, Mirazo S, et al. Hepatitis E virus in South America: the current scenario. Liver Int 2018;38: 1536-1546.

4) Echevarría JM, González JE, Lewis-Ximenez LL, et al. Hepatitis E virus infection in Latin America: A review. J Med Virol 2013;85: 1037-1045.

5) Covarrubias N, Naveas P, Miranda J, et al. Hepatitis E virus seroprevalence in blood donors in a university hospital in Chile. Rev Chilena Infectol 2018;35:455-457.

6) Arce LP, Müller MF, Martinez A, et al. A novel in-house enzyme-linked immunosorbent assay for genotype 3 hepatitis E virus reveals high seroprevalence in blood donors in Northern Argentina. Front Microbiol 2019;10:2481.

7) de la Caridad Montalvo Villalba M, Owot JC, Benedito EC, et al. Hepatitis E virus genotype 3 in humans and swine, Cuba. Infect Genet Evol 2013;14:335-339.

8) Alvarado-Esquivel C, Sanchez-Anguiano LF, Hernandez-Tinoco J. Seroepidemiology of hepatitis e virus infection in general population in rural durango, Mexico. Hepat Mon 2014;14:e16876.

9) Campolmi I, Spinicci M, Mayaregua DR, et al. Seroprevalence of hepatitis A virus, hepatitis E virus, and helicobacter pylori in rural communities of the bolivian chaco, 2013. Am J Trop Med Hyg 2018;98:1275-1280.

10) de Oliveira JMNS, Freitas NR, Teles SA, et al. Prevalence of hepatitis E virus RNA and antibodies in a cohort of kidney transplant recipients in Central Brazil. Int J Infect Dis 2018;69:41-43.

11) Ferreira AC, Gomes-Gouvêa MS, Lisboa-Neto G, et al. Serological and molecular markers of hepatitis E virus infection in HIV-infected patients in Brazil. Arch Virol 2018;163:43-49.

12) Bezerra LA, de Oliveira-Filho EF, Silva JVJ, et al. Risk analysis and seroprevalence of HEV in people living with HIV/AIDS in Brazil. Acta Trop 2019;189:65-68.

13) Bricks G, Senise JF, Pott-Jr H, et al. Previous hepatitis E virus infection, cirrhosis and insulin resistance in patients with chronic hepatitis C. Braz J Infect Dis 2019;23:45-52.

14) Fantilli A, Trinks J, Marciano S, et al. Virus de la hepatitis E en pacientes con cirrosis: Inesperada alta prevalencia en pacientes con cirrosis alcohólica. Congreso Hepato 2019;XX/19:O-44.

15) Villalba MDLCM, Lay LDLAR, Chandra V, et al. Hepatitis E virus genotype 1, Cuba. Emerg Infect Dis 2008;14:1320-1322.

16) Kase JA, Correa MT, Luna C, et al. Isolation, detection and characterization of swine hepatitis E virus from herds in Costa Rica. Int J Environ Health Res 2008;18:165-176.

17) Montalvo Villalba M, Owot JC, Benedito EC, et al. Hepatitis E virus genotype 3 in humans and swine, Cuba. Infect Genet Evol 2013;14:335-339.

18) García-Hernández ME, Cruz-Rivera M, Sánchez-Betancourt JI, et al. Seroprevalence of anti-hepatitis E virus antibodies in domestic pigs in Mexico. BMC Vet Res 2017;13:289.

19) Mirazo S, Gardinali NR, Cecilia D, et al. Serological and virological survey of hepatitis E virus (HEV) in animal reservoirs from Uruguay reveals elevated prevalences and a very close phylogenetic relationship between swine and human strains. Vet Microbiol 2018;213:21-27.

20) Marziali F, Acosta J, Bolatti E, et al. Detection of HEV in naturally infected swine from central Argentina by an optimize HEV/MS2 duplex RT-qPCR. Zoonoses Public Health 2019;66:729-738.

21) Pisano MB, Winter M, Raimondo N, et al. New pieces in the transmission cycle of the hepatitis E virus in South America: first viral detection in wild boars from Argentina. Trans R Soc Trop Med Hyg 2019;113:497-499.

22) Montalvo Villalba MC, Cruz Martínez D, Ahmad I, et al. Hepatitis E virus in bottlenose dolphins Tursiops truncatus. Dis Aquat Organ 2017;123:13-18.

23) Mirazo S, Albora C, Quintero Gil D, et al. A case of incidental infection of Hepatitis E virus (HEV) genotype 1 in a domestic pig. Arch Virol 2018;163:3403-3407.

24) Pisano MB, Lugo BC, Poma R, et al. Environmental hepatitis E virus detection supported by serological evidence in the northwest of Argentina. Trans R Soc Trop Med Hyg 2018;112:181-187.

25) Franchi D, Bavdaz B, Pordomingo SM. Virus de hepatitis E. A propósito de un caso. I Congreso Científico Profesional de Bioquímica 2016;1:P104.

26) Bussetti B, Jorge O, Torres Taslakoff A, et al. Hepatitis E: ¿un virus infrecuente o un agente infrecuentemente pensado? Congreso Argentino de Gastroenterología y endoscopía digestiva. Gastro Rosario 2017:TO/P18.

27) Acosta J, Marziali F, Galimberti A, et al. Confirmación de nexo epidemiológico en un caso de hepatitis aguda por virus de hepatitis E. Congreso Argentino Hepato 2019;XX/19:P52.

28) Casenave F, Fernandez Panzardi L, Jemar M, et al. Hepatitis E: hepatitis fulminante en huésped con hepatopatía crónica previa. X Jornadas Infectológicas de Invireno de Córdoba 2019;10:P53.

29) Peláez D, Hoyos MC, Rendón JC, et al. Hepatitis E virus infection in patients with clinical diagnosis of viral hepatitis in Colombia. Biomedica 2014;34:354-365.

30) Lemos G, Jameel S, Panda S, et al. Hepatitis E virus in Cuba. J Clin Virol 2000;16:71-75.

31) Rodríguez Lay Lde L, Quintana A, Villalba MC, et al. Dual infection with hepatitis A and E viruses in outbreaks and in sporadic clinical cases: Cuba 1998-2003. J Med Virol 2008;80:798-802.

32) Realpe-Quintero M, Mirazo S, Viera-Segura O, et al. Hepatitis E virus genotype 1 and hepatitis A virus dual infection in pediatric patients with a low socioeconomic status from Mexico. Intervirology 2018;61:105-110.

33) Mendes De Oliveira J, Rovaris Gardinali N, Rangel Vieira Y, et al. Severe chronic hepatitis in a young immunosuppressed Brazilian patient co-infected with hepatitis E virus (HEV) and Epstein-Barr virus. (EBV). Congreso Argentino de Virologia 2017;12:26-27.

34) Mainardi V, Gerona S, Ardao G, et al. Locally acquired chronic hepatitis E followed by epstein-barr virus reactivation and burkitt lymphoma as a suspected extrahepatic manifestation in a liver transplant recipient. Am J Case Rep 2019;20:1016-1021.