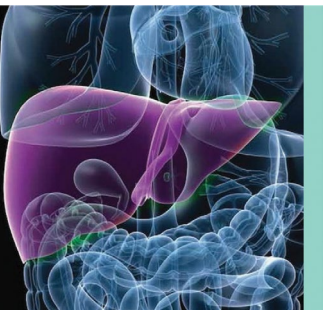

Hepatitis E Virus Infection: Is It Really a Problem in Latin America?

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.

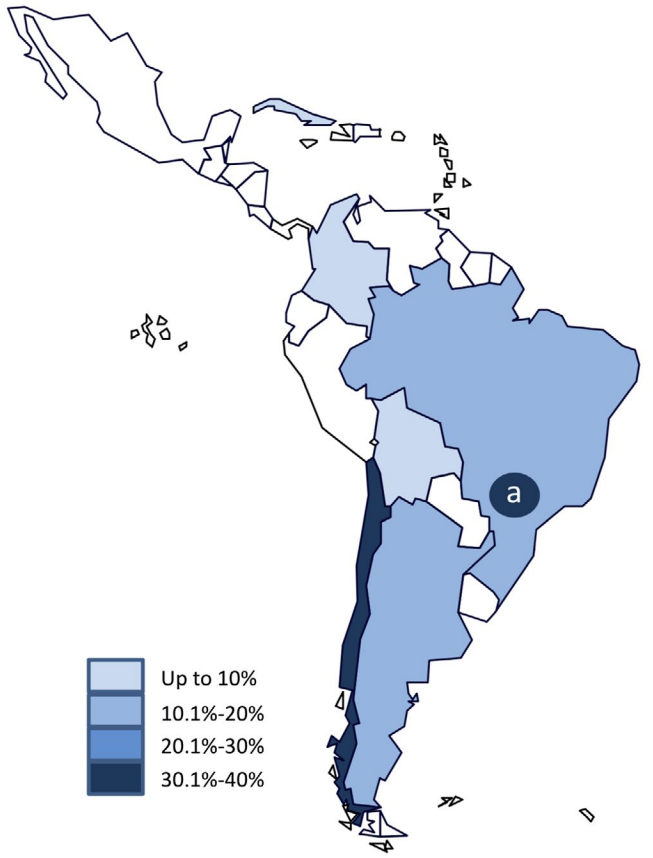

FIG 1 Seroprevalence of HEV IgG in blood donors and the general population reported in Latin America in the last 10 years (2009 to 2019). (*a*) The only seroprevalence study performed with an in-house kit was carried out in Southern Brazil (40.3%).[3]

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

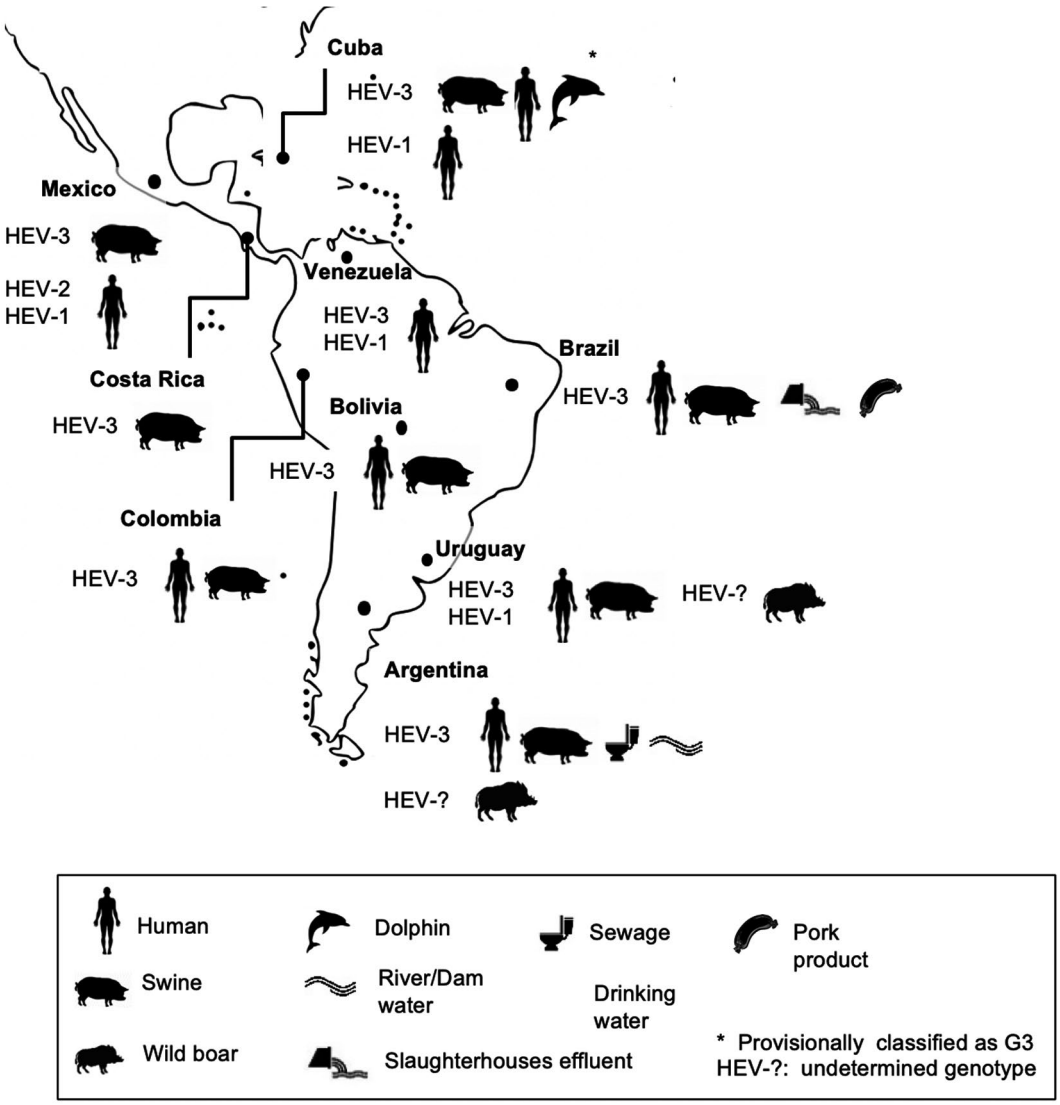

FIG 2 Genotype distribution of HEV in Latin America. HEV genotypes, mammal reservoirs, and environmental detections reported for each country are shown.

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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