Hepatitis delta is caused by the hepatitis delta virus (HDV). HDV is unique among pathogens that cause disease in humans because it needs the support of the hepatitis B virus (HBV) to induce liver disease.

HDV infection can occur only if the virus is either transmitted concomitantly with HBV or it superinfects patients with HBV. The first case, coinfection, usually consists of self-limited acute HBV and HDV, which tends to be more severe than acute HBV. Although most patients progress to spontaneous healing, 5% to 10% of these cases evolve into chronic infection.¹

The second scenario, superinfection, may present as classic acute hepatitis in previously asymptomatic patients with HBV or rapidly progressive liver disease in patients with chronic HBV liver infection.

HDV is present on all continents; however, it is a public health problem in several areas of the world, including the western Amazon, Eastern Europe, and Africa. In Amazonia, HDV is endemic among indigenous and isolated riverside populations. Compared with the rest of the world, HDV-related disease is unique in this region because of two unusual HBV and HDV genotypes: genotype F and genotype 3, respectively.² These are the most divergent genotypes, and they are believed to cause more aggressive disease, as well as unusual forms of hepatitis.

An atypical form of delta hepatitis was initially described in Brazil, where it was named “Lábrea fever” because it predominated in the city of Lábrea in the Alto Purus region. Subsequently, Lábrea fever was described in areas of the Amazon rainforest located in Peru.
Colombia (Santa Marta), and Venezuela. First described in young individuals, this peculiar fulminant hepatitis has a high fatality rate and unique histological picture, with moderate hepatocellular necrosis, hepatocellular ballooning, and enlarged hepatocytes containing cytoplasmic drops of fat surrounding the nucleus. These cells are called *morula cells* because of their morphological aspect.

There is scientific evidence implicating the HDV genotype 3, prevalent in the Brazilian Amazon, in the worst pathogenesis and, consequently, the greater aggressiveness of HDV in this region.

Because of these unique features, Amazonia is a research field for HDV infection. This article reviews the epidemiological aspects of HBV and HDV infections, as well as the impact of control measures through vaccination in the Peruvian and Brazilian Amazon.

**HBV AND HDV INFECTION IN PERUVIAN AMAZONIA**

Peru is a multicultural and multilingual country, as expressed in the coexistence of 72 ethnic groups—in the Andes and 65 in the Amazon region, which are called *native communities*. Currently, some of these communities share spaces with emigrants or settlers from other regions of the country. In these Amazonian populations, viral HBV and HDV since previous decades have been characterized as hyperendemic and induce a greater presence of fulminant hepatitis, cirrhosis, and hepatocarcinoma. As a result, immunization programs against HBV have been implemented for both native and mestizo residents in areas of the Amazon, as well as in countries that share the Amazon region with Peru.

**Epidemiology**

In 1996, a cross-sectional study was conducted by random sampling in 870 inhabitants of 37 native communities distributed in 12 hydrographic basins of the Peruvian Amazon. The study obtained epidemiological information on viral HBV and HDV and determined the presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), total hepatitis B core antibody (anti-HBc), immunoglobulin M, hepatitis B core antigen antibody, and anti-delta using the enzyme-linked immunosorbent assay. The average age was 22.7 years (range: 1-94 years), and 50.7% were male. Previous HBV infection was determined in 59.7% and recent infection in 1.8%. Of 82 (9.4%) chronic carriers of HBsAg, 21.9% had positive HBeAg. In 44.2% of children younger than 10 years, a history of infection was evidenced. HDV infection was present in 39% of chronic HBV carriers. The prevalence of HBV was higher in natives (64.3%) than in mestizos (50.6%) and in the northern jungle basins (73%) than in the central and southern basins (42%). HBV infection was associated with the consumption of “masato” (a drink made with prechewed yucca consumed by children and adults) (odds ratio [OR], 4.9; 95% confidence interval [CI], 3.4-7.4) and bat bites (OR, 1.7; 95% CI, 1.2-2.4). No significant differences were found in relation to sex. This 1996 study showed the hyperendemicity of HBV and HDV in the indigenous and mestizo populations of the different basins of the Peruvian Amazon (Fig. 1A).

**Control**

Knowing the efficacy and importance of vaccination and the vulnerability of indigenous peoples to HBV, since 1996 the HBV vaccine has been incorporated into the expanded immunization program for children younger than 1 year of age and residents of areas of intermediate and high endemicity in Peru, and since 2003 the vaccine for children younger than 1 year has been universalized nationwide. In particular, in the Amazonian towns of Candoshi and Chapra, the United Nations Children’s Fund coordinated with the Ministry of Health of Peru and local authorities to allow the entry of health personnel to administer vaccinations in the population.

After the immunization against HBV began, cross-sectional studies of prevalence in different native communities were conducted. One study was in three river basins (Pastaza, Morona, and Bajo Urubamba rivers) where six indigenous peoples live (Chapra, Candoshi, Machiguengas, Yine, Asháninka, and Nanti). A total of 742 children younger than 5 years were included in whom HBsAg, total anti-HBc, and hepatitis B surface antibody (anti-HBs) were determined. Of these children, 51.2% were male and 22.9% younger than 1 year, no cases with HBsAg were detected, and there was a history of infection in 2%. Although vaccination demonstrated with a card was 58.5% of the respondents, 85% showed anti-HBs protective antibodies (Fig. 1B and Table 1). Similar results have been reported in other communities, such as the Matsés.

The hyperendemicity of HBV in the indigenous population of the Amazon region puts the survival of these
populations at risk, as shown in the study conducted in Peru in 1996, as well as others carried out in different areas of the Amazon.\(^7\,^8\)

Previous studies in the Andean region of Peru showed the impact of immunization against HBV in children, which allowed it to be extended to other areas, such as the Amazon, where the hyperendemicity for HBV and HDV is greater. Studies conducted in the Amazon years after the start of immunization show a significant reduction in the rate of HBV infection in children younger than 5 years,\(^6\) which makes it possible to reduce the complications of chronic infection, such as cirrhosis and hepatocarcinoma, in these communities. In other studies conducted in Amazonian communities in the region, such as Colombia, less than 1% of chronic HBsAg carriers are reported compared with 2% of carriers 8 years before the introduction of the HBV vaccine;\(^5\) however, in African rural areas with poor access to health services, there are still high prevalence rates despite vaccination programs that have been initiated.\(^10\)

As expected after vaccination against HBV, the reduction of this infection and the near elimination of HDV are shown; however, considering the geographical difficulties of transport and maintenance of the cold chain, a pending task is the sustainability of high vaccination coverage in these populations. Although the vaccine is effective and safe for prevention and is achieving the goal of preventing infection, amidst the dispersion of the native communities of the Amazon, the limitations on access to health services, and intercultural aspects, it remains an important challenge in the treatment of chronic carriers of HBV who did not have the opportunity to be immunized.

**HEPATITIS B INFECTION IN THE JAVARI VALLEY, WESTERN BRAZILIAN AMAZON: EPIDEMIOLOGY OVER A 30-YEAR PERIOD**

Considering the indigenous population and communities who live in the Amazon basin, the Amazon region, although presenting a very heterogenous distribution in
HBV prevalence, is highly endemic even after 30 years of the universal vaccination program.\textsuperscript{11-13}

The indigenous reserve of Javari is an area of 32,900 square miles on the border between Brazil and Peru and home of the Matis, Mayoruna, Marubo, Kanamari, Kulynan, and Korubo groups. It also has the largest concentration of people in voluntary isolation, characterized in the 1990s as hyperendemic for HBV and HDV.

**BACKGROUND AND EPIDEMIOLOGICAL DATA**

From 1989 to 2003, official epidemiological surveillance investigated outbreaks of hemorrhagic syndromes in the region, diagnosed as severe malaria and/or hepatitis B and D. Finally, in 2007 the Ministry of Health decided to sponsor a serological survey.

Here we explore results of the 2007 survey using conventional serology and subsequent surveys with rapid tests implemented from 2015, evaluating possible changes in the last 10 years.

The first survey included 80% of the valley’s population—approximately 2,700 individuals from different indigenous ethnic groups. Half of them (51%) had previous contact with HBV (immunoglobulin G anti-Hbc) but also showed a 61% protection pattern (anti-HBs-positive). Almost 10% were chronic carriers—mostly young individuals with an average age of 19 years—and 40% of them also carried HDV (Fig. 2).

The introduction in 2015 of rapid tests allowed operationalization of the survey without the complexity of handling biological samples (Fig. 3).

The overall carrier rate today is possibly 3.5%, ranging from 8.8% among the Kulina community to 1.2% among the Kanamary community, with no recent carriers among the Korubo community. The mean age of positives was 35 years (range: 18-75 years) (Table 2).

The first survey revealed carrier rates of greater than 10% and perhaps the highest prevalence of HDV ever described. Surprisingly, HBV was not found in individuals with recent contact.

![FIG 2](image_url) HBsAg prevalence distribution by ethnic group and geographic localization, 2007.
These viruses were possibly introduced in the region by the groups from the former rubber extraction in the State of Acre and disseminated broadly, facilitated by socio-cultural aspects. The fulminant hepatitis outbreaks, such as Lábrea fever, now belong to the past with the effective introduction of universal vaccination in the region.

However, the seriousness of high prevalence, extended transmission, and evidence of vertical transmission has added to the presence of the large number of individuals with chronic active hepatitis and liver cirrhosis (HBV and HDV). Intervention measures should focus on three fronts: surveillance, vaccination, and treatment.

The rapid tests allow us to assess possible changes associated with mass immunization and monitoring of carrier mothers, ensuring the first dose and immunoglobulin at birth.

The reduction in prevalence rates and the blockade of transmission among children is evident. Factors such as high mortality in chronic decompensated and antiviral treatment have probably had the greatest impact on reducing these rates. Despite the progress made, the problem remains, because most carriers are of reproductive age.

The Javari Valley still houses unspoiled culture and nature. The preservation of the forest implies the protection of the “Forest People.” We believe the continuity of the program must address the challenge of implementing new

**TABLE 1. PREVALENCE OF ANTI-HBS ACCORDING TO DOSES OF VACCINES RECEIVED* BY AREA AND BY INDIGENOUS PEOPLE OF THE ALTO AMAZON AND BAJO URBAMBA, PERU, 2009**

| Dose Received | Shapras | Candidi | Mashigengas | Yine | Asháninka | Nanti | Total |
|---------------|---------|---------|-------------|------|-----------|-------|-------|
| N            | %       | N       | %           | N    | %         | N     | %     |
| Three doses  | 93      | 90.3    | 94          | 66.2 | 118       | 99.2  | 13    | 92.9  | 29    | 100   | 0     | 0     | 347   | 85.3  |
| Two doses    | 11      | 100     | 4           | 66.7 | 47        | 97.9  | 11    | 100   | 7     | 100   | 6     | 100   | 86    | 96.9  |
| One dose     | 1       | 33.3    | 6           | 100  | 15        | 93.8  | 5     | 100   | 2     | 100   | 1     | 100   | 30    | 90.9  |
| Not precise  | 17      | 94.4    | 21          | 67.7 | 55        | 98.2  | 33    | 100   | 4     | 100   | 36    | 97.3  | 166   | 92.7  |

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*According to vaccination card available at the time of the survey.

**TABLE 2. HBsAg PREVALENCE DISTRIBUTION BY ETHNIC GROUP: RESULTS OF THE RECENT SURVEY WITH RAPID TESTS, 2015-2018**

| Ethnic Group | 2015 | 2016 | 2017 | 2018 | Total |
|--------------|------|------|------|------|-------|
| N            | %    | N    | %    | N    | %     |
| NA           | 898  | 11   | NA   | NA   | 898   |
| NA           | 68   | 6    | NA   | NA   | 68    |
| NA           | 77   | 0    | NA   | NA   | 77    |
| NA           | 263  | 6    | NA   | NA   | 263   |
| NA           | 698  | 31   | NA   | NA   | 698   |
| NA           | 435  | 16   | 229  | 5    | 664   |
| NA           | 2,668 | 75   | 75 (3.5) |

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lines of care that ensure immediate actions toward the carrier and susceptible individual in their place of residence. However, the new technologies used must preserve the environmental and cultural uniqueness.

In conclusion, although HBV and HDV infections are public health problems in the Amazon region, vaccination intervention measures are having a positive impact and should be strengthened in indigenous communities. In addition, the levels of protection should continue to be assessed.

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