# Vaccines as a Control Strategy Against Viral Hepatitis Infections

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## Introduction

Hepatitis is an inflammatory process of the liver, whose etiology may be infectious and also related to toxins such as alcohol, drugs, or autoimmune reactions. Within the sources of infection, viruses are the main etiology.

Currently, viral hepatitis infections are a global health problem despite progress made in the areas of diagnosis, prevention, and treatment. Based on 2015 estimates by the World Health Organization (WHO), this situation translates into 325 million people with chronic hepatitis infections worldwide, 1.34 million deaths a year — similar to the number of deaths by the human immunodeficiency virus[1] (HIV) — and has high morbidity amongst patients and high costs for public health systems, in addition to long-term complications. In 2013, hepatitis viruses were the seventh cause of mortality in the world. For this reason, the WHO has emphasized the importance of generating a comprehensive approach in the fight against these diseases, and helping countries strengthen their strategies against viral hepatitis infections.[2]

The cluster of "viral hepatitis" comprises various hepatotropic viruses, whose transmission route, evolution, treatment, and eventual complications differ based on the types of viruses. These specific characteristics translate into a lack of uniformity in prevalence globally. Despite the fact that several viruses can impair liver function temporarily, currently there are at least five known viruses that primarily infect the liver, with hepatitis as their main clinical manifestation. They comprise hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D or delta (HDV), and hepatitis E (HEV) viruses.[3]

The transmission route for hepatitis A and E is mainly the fecal-oral route through contaminated water and food, hence prevalence increases in places with poor sanitation. The main transmission route for hepatitis B, C, and D is sexual, vertical (mother to child) or through blood and blood products. Hepatitis B, C, and D distribution is heterogeneous based on practices that favor transmission, such as unsafe sexual intercourse, sharing of needles amongst intravenous drug users or unmonitored blood transfusions.

Currently, vaccines are one of the prevention tools used to control these diseases. Monovalent and combined vaccines are available against the hepatitis A and B viruses, while a vaccine against hepatitis E is under development. Further information on hepatitis A, B, and E is presented in this chapter. To date, there are no vaccines against the hepatitis C and D viruses.

# Hepatitis A

The hepatitis A virus is a hepatovirus of the picornaviridae family, of small molecular size, with single-stranded RNA, and is non-enveloped which allows it to survive in low-pH media as well as in mild temperatures for extended periods of time.[4] There are seven genotypes with only one serotype; only four out of the seven genotypes affect humans (genotypes I and III are the most common).[5]

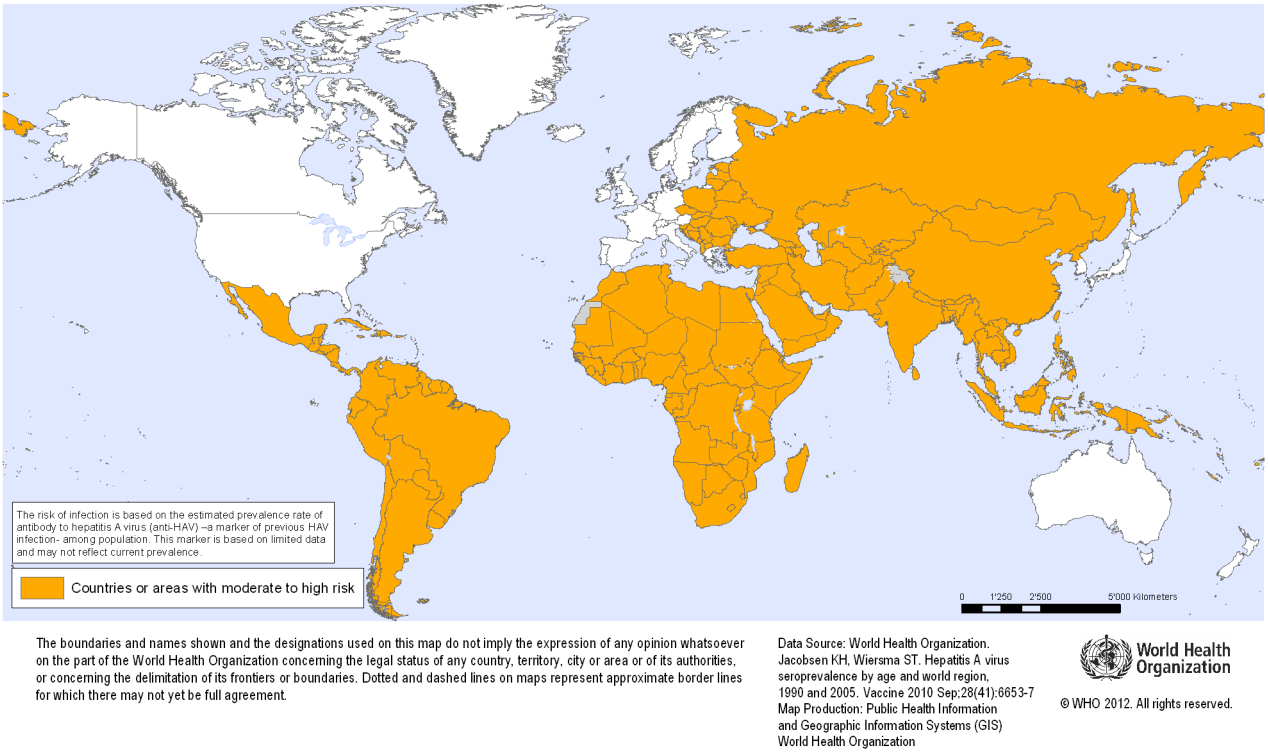
HAV is transmitted primarily via the fecal-oral route along with contaminated food or water. It spreads fast since its viral excretion takes place 10–15 days before the onset of symptoms and up to 7–10 days after the onset of jaundice. Viral excretion in feces prevails in the prodrome of the disease, since the viral load is lower during the symptomatic phase and undetectable for the resolution of symptoms.[4]

Infections due to the hepatitis A virus affect 1.5 million people a year. Estimates indicate that about 70% of the children infected before three years of age suffer from asymptomatic, but productive, infections with the potential to generate outbreaks involving large several cases. These asymptomatic cases in highly-endemic areas result in the underreporting of cases.[6] Fortunately, 99% of the patients spontaneously overcome the condition within 2 to 4 weeks and maintain lifelong immunity against all genotypes. Despite most of the cases often being asymptomatic or having mild gastrointestinal symptoms with or without jaundice, there are acute fulminant manifestations that may require urgent liver transplantation as the sole viable treatment. One percent of cases are estimated to be fulminant hepatitis due to HAV with an incidence rate of 1–3 individuals every 1,000 population, with an 80% mortality rate.[7] Older age is the main risk factor associated with the severity of the infection.[8]

Infection due to HAV has global distribution but its prevalence differs significantly based on the environmental and socioeconomic conditions in every region (Figure 1). Upon introduction of mass vaccination against the HAV infection, the incidence of the infection was significantly reduced all over the world.[9] Therefore, it is extremely important to continuously update information on the estimated risk of disease, as well as national prevention and control strategies such as vaccination coverage, since such interactions translate into permanent shifts in the risk situation.[10]

In most of the countries of the Americas Region and the Caribbean, more than 50% of the population has acquired natural immunity against the hepatitis A virus by 15 years of age. Hepatitis A endemicity is moderate to high and varies between regions, for example with anti-HAV seroprevalence in countries of the Caribbean and the Andean sub-region (Peru, Ecuador, and Bolivia) of 57% and 96% respectively, for individuals aged 15–19.[11] However, endemicity in the Americas Region as well as exposure to the virus are decreasing, thus increasing the risk of outbreaks in older age groups.

**Figure 1.** Global Risk-Level of Hepatitis A




Source: World Health Organization, 2012.

Diagnosis is based on the detection of specific serum antibodies (anti-HAV IgM) two weeks before the onset of symptoms. In cases in which the onset of symptoms has been within the first 5 to 7 days, viral detection and genotyping can be performed using a fecal sample.

Treatment of hepatitis A is supportive and symptomatic. In cases of fulminant liver failure, access to high-complexity centers for liver transplantation will determine the prognosis of the patient.

Prevention and control measures include sanitary and food-safety measures (hand washing, caution around water and food-handling, and hygiene measures) and prevention based on vaccines and immunoglobulin. Gammaglobulin (igG) is indicated as a post-exposure measure for pregnant women and children up to 1 year of age without previous protection.

Starting in the 1990s, various vaccine formulations have been marketed (attenuated live and inactivated) including hepatitis A vaccine formulations and schedules, as mentioned in Table 1 below. The combined formulations for hepatitis A and hepatitis B, as well as hepatitis A and typhoid fever are sometimes used in travelers.[6] Despite the two dose recommendations by manufacturers, in 2012, WHO endorsed the single-dose immunization strategy as of one year of age.

**Table 1.** Availability of Vaccines to Prevent Hepatitis A

| Vaccine | Trade Name (Manufacturer) | Age (Y) | Dose | Route | Schedule | Booster |
|---|---|---|---|---|---|---|
| Hepatitis A vaccine, inactivated | Havrix® (GlaxoSmithKline) | 1–18 | 0.5 mL (720 ELU) | IM | 0, 6–12 mo | None |
| | | ≥19 | 1.0 mL (1,440 ELU) | IM | 0, 6–12 mo | None |
| Hepatitis A vaccine, inactivated | Vaqta® (Merck & Co., Inc.) | 1–18 | 0.5 mL (25 U) | IM | 0, 6–18 mo | None |
| | | ≥19 | 1.0 mL (50 U) | IM | 0, 6–18 mo | None |
| Combined hepatitis A and B vaccine | Twinrix® (GlaxoSmithKline) | ≥18 (primary) | 1.0 mL (720 ELU HAV + 20 µg HBsAg) | IM | 0, 1, 6 mo | None |
| | | ≥18 (accelerated) | same as above | IM | 0, 7, 21–30 d | 12 mo |

Source: Noele P. Nelson, Trudy V. Murphy. "Table 3-02. Vaccines to prevent hepatitis A." Hepatitis A. Chapter 3. Yellow book.

In certain instances, hepatitis A vaccination is recommended for adults, including:[6,12]

- Travelers to sites of intermediate or high endemicity
- Chronic liver disease
- Individuals with clotting disorders
- Men who have sex with men
- Laboratory personnel exposed to the hepatitis A virus
- Food industry personnel
- Childcare personnel in charge of children < 1 year

Morbidity has fallen globally since the licensure of hepatitis A immunization for infants as of 12 months of age. In 2004, the U.S. had an overall rate of 1.9/100,000 population, the lowest rate ever recorded and 79% lower than any previously recorded rate.[13] Similar examples have been observed in countries from various regions such as Argentina, Australia, Israel, Italy and Spain.[14,15] The experience in Argentina is highlighted below, since their vaccination schedule comprises a single dose at 12 months of age.

Similarly, this vaccination strategy has modified the age at which onset of the disease occurs, with an observed increase of incidence amongst adults, as well as higher morbidity. Scientific evidence indicates that these immunization programs may result in a significant reduction of hepatitis A incidence due to acquired immunity. Follow-up of the vaccinated population to assess seroprotection in the long term is key to be able to avoid infection at an older age. National health policies need to include hepatitis A immunization within the framework of public health policies.[16]

## Country Spotlight: Single-Dose Hepatitis A Immunization at One Year of Age in Argentina

As of 2005, the epidemiology of the hepatitis A virus (HAV) in Argentina has shifted due to the introduction of single-dose HAV immunization at 12 months. Local evidence showed a dramatic decline in the number of hepatitis A cases after vaccine introduction and up to the present, as well as a reduction in the number of hospital admissions due to this pathology.[17] Similarly, there has been an impact on cost reduction in the public health sector as determined by medical and social savings resulting from this strategy.[18]

Based on the evidence from Argentina, the WHO recommended the single-dose strategy be implemented by other countries as part of their national immunization schedules in a June 2012 vaccine position paper.[19] Therefore, several countries including Brazil, Colombia, Mexico and Paraguay have implemented this strategy to control the disease. Within this context, Argentina has committed to strengthening surveillance of this pathology as part of the follow-up and assessment of their single-dose strategy.

In 2011, two multicenter studies were performed in Argentina to assess the strategy of a single-dose hepatitis A immunization (HA) at one year of age which was implemented in 2005, in coordination with the National Program for the Control of Vaccine-Preventable Diseases (ProNaCEI), within the National Ministry of Health.[20] In 2011, a seroprevalence study was performed in the short-to-intermediate term to measure anti-HAV antibodies in children four years after immunization with one dose of the hepatitis A vaccine. In the study, 93% (95% CI: 91.7–94.6) of the children maintained protective antibody titers (anti-HAV IgG>10 mUI/ml), indicating that a single-dose HAV vaccine in our environment is highly immunogenic in the intermediate term. In 2013, these studies were repeated and showed 97% seroprevalence of protective anti-HAV antibodies in children vaccinated with a single dose more than seven years prior. In 2016, a new seroprevalence study showed 87% of the children still present protective antibody level, supporting the local strategy. Currently, Argentina is running a study on the "humoral and cellular immune memory response 10 years following single dose vaccination against hepatitis A in Argentinian children," regarding the effective protection of the vaccine in the population.

To date, HAV vaccination coverages at the country level have been satisfactory since the introduction of the vaccine into the National Immunization Schedule. Despite this progress, isolated cases continue to be reported in children under nine years of age without HAV vaccination history, specifically in departments with low coverages. Steadily declining rates have been observed in all age groups and in all regions of the country. A slight increase has been observed in case reporting amongst adults, but no vaccinated children have presented liver failure or the need for transplantation.

# Hepatitis B

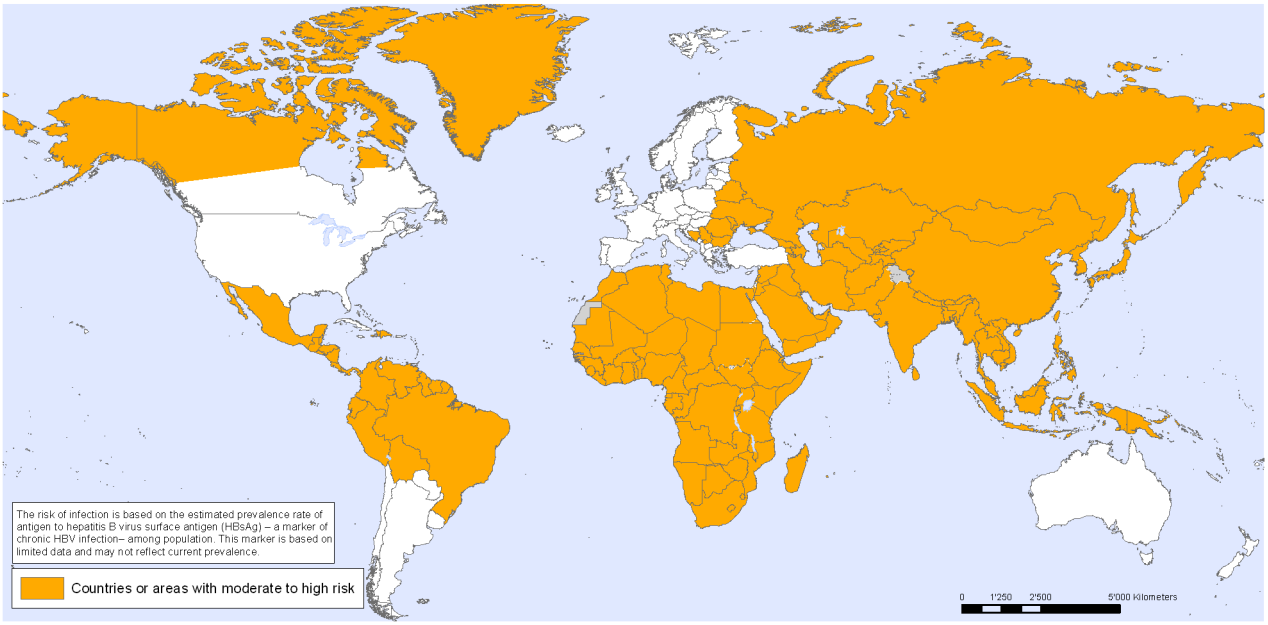
The hepatitis B virus (HBV) infects more than 500 million persons globally. It is the main cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. About 2 billion individuals are estimated to have previous or current HBV infection worldwide, an estimated 257 million people are living with hepatitis B virus infection (defined as hepatitis B surface antigen positive) and more than 240 million are chronic HBV carriers.[21] In 2015, hepatitis B resulted in 887,000 deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma).[22] Acute hepatitis B resulting in fulminant liver failure produces 130,000 deaths a year globally.[23] The high economic cost of this virus is expressed in the years of life lost due to liver pathology accounting for 5% to 10% of liver transplantations.[24,25]

HBV transmission, through the sexual, vertical, and parenteral routes, is very efficacious (10% to 30% if the source is HBsAg positive and 30% to 60% if the source is HBeAg positive). The incubation period is long, between 1 and 4 months. The most common clinical manifestation is acute hepatitis, which is spontaneously resolved within 1 to 3 months. Additionally, there are asymptomatic manifestations that can be observed in up to 60% of cases. Between 6% and 10% of infected individuals will evolve to chronicity. Age is the determining factor for chronicity, and it is common in newborns after an acute infection (90%) and in children < 5 years of age (20%–60%), but it is unusual when the infection is acquired in adulthood (<5%).[26,27]

Due to the virus' human reservoir, it is possible to control, eliminate, and eradicate HBV. Based on studies performed in the United States in 2007, the risk factors to acquire the virus include the use of intravenous drugs (15%), sexual intercourse with persons infected with HBV (6.2%), men who have sex with men, hemodialysis, multiple sexual partners and injuries with sharp elements.

Worldwide prevalence varies by region and within the regions as observed in Figure 2. However, out of the total global population, about half of the population is located in highly-endemic areas.[8]

**Figure 2.** Global Risk-Level of Hepatitis B




Source: World Health Organization, 2012.

Information obtained between 1990 and 2005 shows a prevalence of 2% in the central and tropical regions of Latin America, and ranging between 2% and 4% for the Caribbean and the Andean sub-regions.[28] There is higher prevalence of co-infection with the hepatitis D and B viruses, as observed in the Amazon sub-region.[29,30]

Globally, nine HBV genotypes (A-I) have been identified, with at least an 8% difference in their genomic sequence.[31,32] Higher hepatocarcinoma rates have been observed in patients infected with the C and F

genotypes, and certain A subgenotypes found in Southern Africa. Virus genotyping is extremely important to determine its regional characteristics. In the Americas Region several genotypes co-exist, out of which genotype F is the main one.[33] Antivirals as well as the protection conferred by the licensed vaccines at present have proven to be effective against all genotypes.[34]

There are several supplementary ways to control hepatitis B as detailed by WHO in a 2009 vaccine position paper, including: vaccination of newborns, completion of a 3–4 dose schedule, catch-up vaccination in cohorts of children with low coverage, vaccination of adolescents and adults included in the high-risk groups in countries of low or moderate endemicity, and improvement of coverage in children from highly-endemic countries.[35] The vaccination schedule should have three doses and, for infants, the recommendation is to administer the first dose as soon as possible, preferably within twelve hours after birth.[36]

There are various hepatitis B vaccines, including monovalent or combined with hepatitis A. Vaccines use the recombinant hepatitis B surface antigen (recombinant DNA vaccines), achieving immunogenicity above 90% that decreases in adults older than 40 years, immunosuppressed hosts and tobacco users. Efficacy ranges between 80% and 100%, and its correlate of protection is Anti-HBs >10 UI/L with a recommendation for routine testing solely in special hosts. Several studies have analyzed the vaccine safety profile.

By 2008, 177 of the 193 WHO member states (92%) had incorporated hepatitis B immunization schedules into their national childhood immunization schedules.[37] All of the countries of the Americas have officially introduced the hepatitis B vaccine into their childhood immunization programs.

There are specific indications for the hepatitis B vaccine in adults as shown below:[36]

- Individuals at risk due to sexual exposure: HBsAg-positive sexual partner, individuals with more than one sexual partner over the last 6 months, sexual contact with individuals under follow-up due to sexually-transmitted infections, men who have sex with men.
- Individuals at risk of infection via percutaneous route or mucous exposure to contaminated blood: frequent or recent use of intravenous drugs, close contacts with HBsAg-positive individuals, residents and staff at care centers, health providers, individuals with diabetes mellitus aged 19 to 59.
- Others: travelers to highly-endemic sites for hepatitis B, persons with chronic liver disease, persons living with HIV.

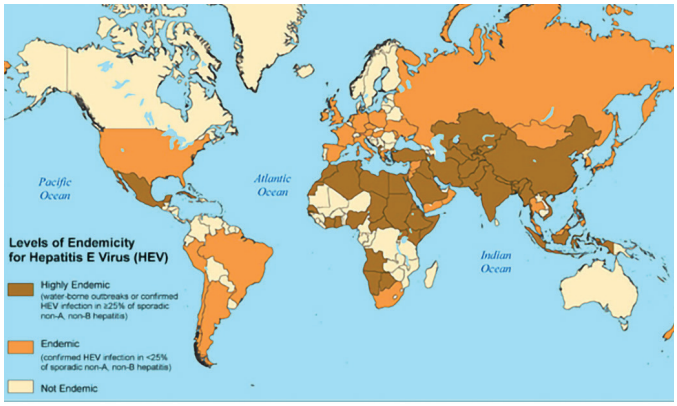
In spite of the known risk factors, epidemiological surveillance in the United States during 2007 has not shown a high percentage of patients with any of the risk factors known for the infection.[38] Overall, 58% of the population did not have a known predisposing factor in this surveillance report.

A multicenter study performed in Argentina has shown that HBV is currently the most frequent cause of fulminant hepatic failure.[39] In this low-endemicity country for HBV, vaccination was implemented as a public health strategy for health personnel in 1992, and a three-dose schedule was implemented for all live births in 2000. Satisfactory and constant coverages were maintained with a steady decline in HBV cases amongst the younger age groups, coinciding with the protection conferred by the vaccine. An increase of reported cases amongst young adults was observed. In 2012, scientific evidence and disease surveillance led to the recommendation of universal hepatitis B immunization for the entire population that had not previously received a complete schedule based on the epidemiological evidence of local and international data. This recommendation was added to the National Immunization Schedule in 2014. Immunization was deemed mandatory and provided free of charge for the whole population, making Argentina the first country to introduce this strategy for the control and elimination of hepatitis B.[40,41]

# Hepatitis E

Every year there are 20 million infections due to the hepatitis E virus, leading to an estimated 3.3 million symptomatic cases.[42,43] WHO estimates that hepatitis E caused approximately 44,000 deaths in 2015 (accounting for 3.3% of the mortality due to viral hepatitis). Three thousand newborns are infected yearly.[44] The route of transmission is fecal-oral with outbreaks involving many cases. Currently, there are four known genotypes, of which 1 and 2 affect mainly humans.[45,46] There is evidence that immuno-suppressed individuals, for example solid-organ transplant recipients, would be more vulnerable to developing a chronic and lethal liver disease due to any of the four genotypes.[47]

Mortality ranges between 0.1% and 4% but the main risk factor for complications is the third trimester of pregnancy when the mortality rate reaches 10% to 50% among pregnant women. Distribution is global, and there are differences by region as observed in Figure 3 below.[48]




Source: Centers for Disease Control and Prevention, 2018.

**Figure 3.** Global Risk-Level of Hepatitis E

The Region of the Americas has low prevalence of the virus but cases and outbreaks have been reported in some countries. Studies conducted in Brazil show prevalence close to 3% in adults, and 1.7% to 16.2% in Bolivia.

To date, only one vaccine against hepatitis E (Hecolin) has been licensed based on the ORF2 239 protein. ORF2 codes for the viral capsid protein, and thus, the neutralizing antibodies. It is derived from a genotype 1 Chinese strain, and it contains aluminum and thimerosal as adjuvants. It is supplied in a pre-filled syringe for a three-dose schedule (0, 1, 6 months) in individuals aged 16 to 65. The vaccine is stable between 2 and 8°C, out of direct sunlight. It has demonstrated 98% (0-6m) immunogenicity versus 100% (0m, 1m, 6m) in a Phase IIa study, and presents a 98.7% seroconversion rate with three doses in Phase III studies (N= 113,000 participants). Its efficacy in Phase II and III studies has shown protection against G4, but evidence is scarce in relation to G1. There is no information regarding G2 and G3. Cross protection has been demonstrated against G4 but there is no evidence in connection with genotypes G1, 2, and 3. Currently, the duration of antibodies is up to 4.5 years. To date, no safety data have been published.[49]

Based on the abovementioned, WHO established in the hepatitis B vaccine position paper that despite HEV being a public health problem, in particular for some countries, there is limited information on global incidence as well as morbidity and mortality. In spite of having a promising vaccine with a good proven response in individuals aged 16 to 65, given the insufficient nature of the data (in particular in individuals <16 years or in connection with cross reaction with G1-2-3), WHO does not recommend routine use in national immunization programmes. However, a country may adopt the most convenient strategy given the local epidemiological situation. Routine use is not recommended in the following populations given insufficient evidence on immunogenicity, effectiveness, and safety profile: pregnant women, individuals <16 years, chronic liver disease patients, patients on organ transplantation lists and travelers. The administration of this vaccine may be considered in outbreak situations, mainly in high risk groups. Studies on immunogenicity, efficacy and safety profile should be performed in groups with limited data.[18]

# Conclusion

Immunization continues to be the most important and cost-effective preventive intervention to reduce morbidity and mortality amongst children. In an era of new vaccines, countries across all regions, including the Americas Region, need to make great efforts to document the epidemiology of these diseases before and after vaccine introduction. Their experiences with the challenge of introducing new vaccines into their national immunization schedules should also be documented. The experience of each country becomes essential and extremely important to spread knowledge locally, regionally, and globally for other countries and regions to benefit from the documented lessons learned and to make evidence-based decisions. Countries also need to decide on the inclusion or exclusion of a specific vaccine based on epidemiological data on disease burden, other available interventions, and the economic cost of the strategy.

Viral hepatitis cases continue to be a great challenge for public health. They demand a joining of public health forces to fight against these viruses with the purpose of improving the quality of life of the population, along with the understanding that vaccines are tools for social equity and equality.

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