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REVIEW ARTICLE

Viral hepatitis prevention by immunization

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Abstract

Objective: To present an updated review and criticism of viral hepatitis A and B prevention by immunization.

Sources of data: Review of medical articles obtained from the MEDLINE database. The most recent and representative articles on the subject (2000-2006) were selected. The Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics (AAP), Brazilian Society of Pediatrics and Brazilian Ministry of Health websites were also researched.

Summary of the findings: Viral hepatitis prevention is an enormous challenge to the public health systems of countries and the medical and scientific communities. Hepatitis viruses produce important morbimortality in the world, causing acute and chronic hepatic disease. There are highly efficient vaccines available on the market to prevent new infections by the A and B viruses. However, A and B viruses continue to be among the most commonly notified diseases preventable by vaccines. In this article, we discuss the vaccines used to prevent these infections, with the aim of expanding knowledge and the practice of prevention of these infectious diseases.

Conclusions: Although the vaccines against A and B hepatitis are recommended for various risk groups, estimated vaccine coverage is still modest and many vaccination opportunities are lost. In order to reduce the incidence of A and B hepatitis, which are preventable by vaccines, it is necessary for physicians to encourage their patients to be vaccinated.

J Pediatr (Rio J). 2006;82(3 Suppl):S55-66: Hepatitis A, hepatitis B, vaccines, immunization.

Introduction

Viral hepatitis is an important health problem in Brazil and the world. Notable discoveries and progress have been made over the last three decades, as regards pathogenesis, prevention and treatment. The development of vaccines to prevent these infections, by inducing active immunity against A and B hepatitis viruses, was one of the major scientific conquests. However, morbidity and lethality resulting from these diseases persist. In the USA, in 2003, 61,000 individuals were infected by the viral hepatitis A virus (HAV) and 73,000, by that of hepatitis B.[1] In Brazil, the Ministry of Health estimates that 15% of the population has been in contact with the hepatitis B virus (HBV) and that on an average around 60% of individuals present with anti-HAV antibodies.[2] The Pan American Health Organization (PAHO) estimates that over 90% of the population over the age of 20 years has been exposed to the virus, and assesses infection by HAV in Brazil to be approximately 130 new cases per 100 thousand inhabitants/year.

In 1992, the World Health Organization (WHO) recommended that all countries should introduce hepatitis B vaccine in routine pediatric programs by 1997.[3] Rather than prevent acute hepatitis, the purpose was to reduce chronic infection, frequently not apparent in children, but causing severe sequelae in adult life. About 80 to 90% of the world population live in countries where the prevalence of carriers is moderate (2-7%) or high (> 7%).[4]

The first vaccine available for viral hepatitis prevention was against HBV, developed in the early 1980s, and made with human plasma. Afterwards, it was replaced with vaccines produced by the recombinant DNA technique. Protection against viral hepatitis A (HAV) by vaccines began to be used on a large scale only towards the end of the 1990s. But recently, vaccines against viral hepatitis,

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associated with antigens of HAV and HBV viruses, and vaccines combined with the antigens of other infectious agents, have been made available on the market. The implementation of global immunoprophylaxis programs was efficient and there was significant reduction in infections by HAV and HBV in various regions.[2] At present, hepatitis A and B immunoprophylaxis is done with safe vaccines, available practically all over the world, and the recommendations of the Health agency officials in different countries are well documented.

In Brazil, although the number of notifications does not reflect the true incidence of the infection, studies on seroprevalence for hepatitis A show that the national mean is around 65%.[5] Among the cases of viral hepatitis notified to the health services, approximately half are due to HAV.

In the United States, where home and sexual contact with infected persons was the main HAV transmission mode between 1996 and 2002, there was a reduction in the incidence of the disease, mainly in the group from 5 to 14 years of age. It was observed, however, that the incidence of HAV among persons that travel to endemic areas and men that have sexual relations with men has increased dramatically since 1995.[4,6]

The number of chronic virus B carriers in the world is estimated at 450 million, and at around 2 million in Brazil. In the USA, although there was a large reduction in the incidence of acute hepatitis B, mainly in the group from 15 to 39 years of age, this continues to be the age group most affected by acute infection.[6] Individuals that have multiple sex partners and are drug users continue to be the main transmitters of the disease in that country.[6] It is estimated that the risk of developing hepatocarcinoma is 100 times higher among HBV carriers, in comparison with those that do not have the virus, and that 15-20% of those that have HBV may die prematurely.[3]

The reason for reviewing and expanding current knowledge and the recommendations about these vaccines is based on the high rates of viral hepatitis A and B in some regions of the country, and the persistence of insufficient protection of individuals that become infected and propagate viral infecction.[1,4,6,7] The objective of this article is to review hepatitis A and B prevention by vaccination, describe the properties of the vaccines, review clinical studies and their results and, finally, discuss the impact of introducing these vaccines.

Hepatitis A vaccine

In 1978, Provost & Hillemann,[8] in animal studies, demonstrated the ability of a vaccine inactivated by formalin to produce protective antibodies against HAV. The possibility of cultivating the virus in cell cultures made it possible to manufacture large quantities of the vaccine against HAV, and the use of sensitive immunoassays and antibody neutralizing tests made it feasible to recognize the immunogenic capability of the different vaccines.

Fortunately the HAV virus exists all over the world with one single serotype, with a small degree of antigenic variation.[9] Present evidence has shown that immunity, either acquired naturally or by inactivated vaccines, protects against the different virus A strains.[9] The antibodies resulting from the vaccine, although lower in number, have the same neutralizing capacity as the antibodies naturally produced after infection. Although there is genetic heterogeneity among the different virus A strains, it would appear that there is no significant variation in the conformation of the epitope that determines virus neutralization, as polyclonal antibodies neutralize the virus of all the genotypes.[9,10] As HAV immunity is mainly mediated by antibodies, the vaccine needs to present the epitopic conformation to the individual's immune system in a sufficient dose to induce the formation of neutralizing antibodies. To confer lasting protection, the levels of these antibodies must be considerably higher than those acquired with immunoglobulins.

The following safe and highly efficient vaccines, produced with virus inactivated by formalin, have been available on the market for years: Havrix® (GlaxoSmithKline), Vaqta® (Merck), Avaxim® (Sanofi Pasteur) and Epaxal® (Berna). Their licensure has added an important benefit to the immunoprophylaxis arsenal, and has certainly changed the scenario of hepatitis A prevention.[1] In the public health system, the vaccine is available only in the Special Immunobiology Referral Centers (CRIE – Centros de Referência de Imunobiológicos Especiais) and is distributed for specific groups of individuals. The different vaccines sold in Brazil, with their presentations and doses, are shown in Table 1.[2]

Although the vaccine doses and formulations are different, both the number and the dose intervals are the same: they must be administered in 2 doses, with a 6-month interval between them. Still limited data indicate that if this interval between the 1st and 2nd dose cannot be observed, the antibody concentrations will not be compromised to a major extent. Generally speaking, considering the excellent results obtained with the vaccine, there is no need for post-vaccinal tests.

The HAV vaccine is derived from viruses adapted in cell cultures, afterwards purified and inactivated with formalin and finally adsorbed to an adjuvant, generally aluminum hydroxide.

Clinical studies, based on millions of doses administered to healthy persons, demonstrated the protective efficacy and tolerability of the inactivated vaccines.[11,12] Even vaccination schemes with 1 dose only of the vaccine provide immediate protection.[13] The anti-HAV antibody levels after one single dose of the vaccine are greater than

Table 1 - Preparations and recommended doses of vaccines against hepatitis A

Type of vaccine	Age (years)	Dose	Volume (mL)	Number of doses	Scheme (months)
Havrix® *	1-18	720 ELISA	0.5	2	0 and 6-12
	> 18	1440 ELISA	1.0	2	0 and 6-12
Vaqta® †	1-17	25 U	0.5	2	0 and 6-12
	> 17	50 U	1.0	2	0 and 6
Avaxim® ‡	> 1	160 U	0.5	2	0 and 6-18
Epaxal® §	> 1	500 U	0.5	2	0 and 6
Twinrix® * (Hep A+B)	1-15	360 ELISA + 10 µg of HBsAg (Hep B)	0.5	3	0, 1 and 6
	1-5	720 ELISA + 20 µg of HBsAg (Hep B)	1.0	2	0 and 6-12
	> 16	720 ELISA + 20 µg of HBsAg (Hep B)	1.0	3	0, 1 and 6

* GlaxoSmithKline; † MerckSharp & Dohme; ‡ Sanofi Pasteur; § Berna Biotech.

those produced by immunoglobulin, but are lower than those generated by natural infection.[6,14,15] After 1 month from the first dose > 97% of the children and > 95% the adults developed protective antibody levels (defined as 10 to 20 UI/L).[6,16] In the seventh month, that is, 1 month after the second dose, virtually 100% of the persons presented protective anti-HAV antibody levels. The classical studies of Innis[11] and Werzberger,[12] involving 38,175 children from 1 to 16 years of age, and 1,037 children from 2 to 16 years of age, in Thailand and New York, showed that the vaccines provided protection in 94% and 100%, respectively. The authors demonstrated that the side effects of these vaccines were similar or less intense than those caused by placebo or those caused by hepatitis B vaccine. In addition, the frequency of adverse effects, except fever, diminished with successive doses.[13,17]

Immune response to infection by HAV is complex, but clearly involves cellular and humoral immunity, cellular immunity being necessary in order to develop immunologic memory. Various studies have shown that anti-HAV vaccine induces humoral immunity, with seroconversion levels of up to100%. In accordance with viral kinetic models, protection determined by the inactivated vaccine remains for at least 5 to 10 years, with the possibility of continuing to protect the individuals for up to 20 years after vaccination. Van Herck et al.[18] developed mathematical models to assess the development of anti-HAV antibodies, after administration of 2 inactivated vaccines (Havrix and Avaxim). The two vaccines showed similar results; when the antibody levels were higher than 20 mUI/mL, they remained for at least 10 years after completing the vaccination scheme. It should be remembered that responsive individuals with decreasing and even undetectable titres may continue to be protected through the anamnestic anti-viral response.[11,13] In these vaccinated individuals, antibodies were detected on re-exposure to the antigen, thus confirming the immunologic memory.[19] Although the duration of vaccine induced protection has not been well determined, the mathematical models suggest that protective antibody levels may persist for 24 to 47 years after the second dose, administered 6 to 12 months after the first.[20]

Cederna et al.[19] demonstrated cellular proliferation in response to the vaccine in 10 patients. The vaccine induced an early T cell proliferation response, which persisted for at least 5 months, and was accompanied by gama-interferon production. This virus-specific T cell response suggests that vaccinated individuals present with an early immune reaction (anamnestic) when in the presence of the virus, rapidly producing high levels of neutralizing antibodies. Thus, every time the individual comes into contact with the virus, this may act as a booster dose of the vaccine, suggesting that there is an immunologic memory present in individuals that receive the inactivated vaccine against HAV.[19] It should be remembered that the efficacy of immunoglobulin is

related to the circulating antibodies, and thus only to humoral immunity.[18,19]

Over the last few years the incidence of viral hepatitis A in the United States has shown an important decline with the use of the vaccine, from 12 cases/100,000 individuals in 1995 to 3.1 cases/100,000 in 2002.[4,6,21] This reduction was higher in the states where vaccination of all children over the age of 2 years was recommended by the Advisory Committee for Immunization Practices (ACIP). As from 1999 a decrease of 67% – from 7.2 cases/100,000 to 2.4 cases/100,000 in 2002[4,6] – was observed. This reduction was similar in 6 other North American states, where the vaccine was recommended, although not mandatory – 69% reduction, from 6.4 cases/100,000 to 2 cases/ 100,000 in 2002.[4,6] In the other 33 states, where the HAV vaccine HAV was not established as routine, the reductions in incidence of the disease were much lower – 35%, from 3.4 cases/100,000 in 1999 to 2.2 cases/100,000 in 2002. A great reduction in hepatitis A cases occurred in the age group from 5 to 14 years between 1996 and 2002.[4,6] Recently there was an important change in the recommendations of the ACIP. Both the guidance to vaccinate all children from 12 to 23 months old and the recommendation to include the vaccine against hepatitis A in the routine vaccinal calendar of children and adolescents were approved.[22]

HAV vaccine in special groups

There are various indications for vaccination against hepatitis virus,[2,7] as follows: Chronic liver diseases; individuals with coagulation disturbances; immunodepressed persons; homosexuals of both genders; travelers to endemic zones; family members of hepatitis A patients; day care center workers; health professionals; individuals that are susceptible while there are outbreaks of the infection; residents in orphanages and institutions; illegal drug users; workers in contact with untreated water; children living in areas of intermediate endemicity.

In some groups, as happens with other vaccines, the vaccine against HAV may not result in protective response in all susceptible vaccinated individuals, mainly in immunodepressed patients.[21] Considering that the hepatitis A vaccine is inactivated, no special precaution needs to be taken to vaccinate immunodepressed individuals.[21]

Some studies show that adult individuals infected with HIV present lower seroprotection rates, as well as lower serum levels of anti-HAV antibodies after vaccine application.[23] A Brazilian study demonstrated that the geometric mean of anti-HAV antibody titres did not differ among children infected by HIV and those who were negative.[24]

The prevalence of antibodies against HAV was analyzed by Gouvea et al.,[25] in 352 children and adolescents exposed and/or infected by HIV in São Paulo, with positivity having been observed in only 26%. None of these patients had been vaccinated against hepatitis A. The possibility of infection by HIV being more serious when associated with HAV makes prophylaxis mandatory in this group of patients. Some authors suggest that the vaccine should be offered at an early stage of infection by HIV.[26,27] Other groups of immunodepressed patients, such as chronic renal, dialyzed and hemophilic patients have been studied and presented variable responses, but with good seroconversion rates[28-31] (Table 2).

Table 2 - Seroconversion rates and GMT of HAV vaccine in special groups

Study (application interval)	Group of patients	Age in years (x)	n	% seroconversion (cut-off value)	Final GMT (mUI/mL)
Cañero-Velasco et al.[29] (IM, 1-6 m)	Chronic renal Nephrotic syndrome	2-9 (5.3)	16	100% (≥ 20 mUI/mL)	361
Hess et al.[23] (IM, 0, 1-6 m)	HIV + HIV -	21-60 (33.2)	26 20	76.9% 100% (≥ 20 mUI/mL)	636 1,687
Santagostinho et al.[26] (SC, 1-6 days)	Hemophiliacs HIV + HIV -	1-50 (17)	47 66	85% 100% (≥ 20 mUI/mL)	503 3,199
Ferreira et al.[35] (IM, 0 and 6 m)	Down syndrome	1-11 (3.96)	49	100% (> 33 mUI/mL)	1,719.86

IM = intramuscular; SC = subcutaneous.

The Pediatric Council of the American Liver Foundation[32] recommends the vaccine for children with any type of chronic hepatic disease. The authors consider that HAV may be particularly serious in children with immunodeficiencies and alert to the fact that HAV may serve as a trigger for self-immune hepatic diseases in predisposed individuals.[28,31,32] Although persons with chronic hepatic disease do not present increased risk of contracting HAV, they do appear to have a greater propensity for developing complications and for evolving towards death when they contract the infection.[14,21,23,31] The response of patients with decompensated chronic hepatic disease is known to be lower, with lower antibody levels and lower seroconversion rates, when compared to those with compensated disease.[6,17,33,34]

Response to the vaccine was recently assessed in Porto Alegre, in children with Down syndrome and chronic hepatopathies.[35-37] Satisfactory seroconversion results were obtained, but with lower antibody titres than those in normal children in the same age group. The results are given in Tables 2 and 3.

The seroconversion rates 1 month after the two doses of the vaccine against HAV (0- and 6- month scheme) are similar among healthy adults and individuals with chronic hepatitis B (98.2 vs. 97.7%), with chronic hepatitis C (98.2 vs. 94.3%) or with other hepatopathies (98.2 vs. 95.2%).[6,17,30]

Nebbia et al.[38] studied children and adolescents of up to 16 years of age with cirrhosis and observed an adequate response to HAV vaccine. The results are given in Table 3.

Impact of anti-HAV vaccination

The epidemiologic status of a certain region is not static, it presents changes due to various factors. Among them, perhaps the most important is change in socio-economic and hygiene conditions.[39,40] In some Latin American regions, a decrease in cases in younger age groups has been noted over the last few years, with a shift in the seroprevalence curve of the infection to the adult age group.[41] This basically occurs as a result of the improvement in the populations' sanitary and socio-economic conditions.

The existence of vaccine against HAV makes it feasible to substantially reduce the incidence of the disease, eliminate virus transmission and, eventually, even to eradicate the infection. Reduction in the incidence of the disease will be attained through promoting high levels of immunity in persons who serve as reservoirs of the virus. This highly immunized population will diminish the incidence of HAV and, presumably, virus circulation.

The possibility of implementing anti-HAV vaccine in the public system's calendar demands special considerations. Among others, the following aspects must be taken into account: The local epidemiologic characteristics, cost of the vaccine, the population's health conditions and the vaccinal cover of other infections. For example, a recent seroepidemiologic study of Indian schoolchildren between the ages of 4 – 18 years, showed that at 5 years of age 80% already presented with positive anti-HAV antibodies, thus showing that mass vaccination in this population (even at the age of 5 years) would probably not be cost effective.[42]

It is not easy to define the epidemiologic characteristics of viral hepatitis in countries of continental dimensions, such as Brazil. On the other hand, the high percentage of asymptomatic cases of viral hepatitis A determines that seroprevalence is a better epidemiologic indicator than incidence of the infection. Thus, Costa-Clemens et al.[5] studied the seroprevalence of HAV in four Brazilian capitals and showed a heterogeneous pattern among the different regions. They concluded that children, adolescents and young adults in our country, seronegative for anti-HAV, have a similar risk to that of travelers to highly endemic

Table 3 - Seroconversion rates and GMT of HAV vaccine in children and adolescents who are chronic hepatitis carriers

Study	Group of patients	Age in years (x)	n	Vaccine (months)	% seroconversion (1 m-7 m)	Final GMT (mUI/mL)
Nebbia et al.[38]	HBsAg carriers 24 chronic hep. 0 cirrhosis	2-15 (10.7)	33	Havrix 360 UE (0, 1 and 6)	90,9% 100%	3,776.8
Ferreira et al.[36]	Cirrhosis AVBEH Autoimmune Others	1-14 (4.3) 10-16 (12.4) 2-15 (8.4)	17 7 10	Havrix 720 UE (0 and 6)	94-100% 57-100% 60-90%	1,490.55 506.18 395.44

regions, considering that they are not protected and are under continual risk of exposure.

In Porto Alegre, this heterogeneous pattern was also shown, in accordance with social class, evidencing the need for anti-HAV vaccination. Susceptible children (with negative anti-HAV antibody) live in the same areas where HAV is common[43] (Figure 1). In a similar study conducted in São Luís do Maranhão, the prevalence of IgG anti-HAV in 462 children from state and private schools, with ages ranging between 7 and 14 years, was 71.5% and 36.5% respectively.[44]

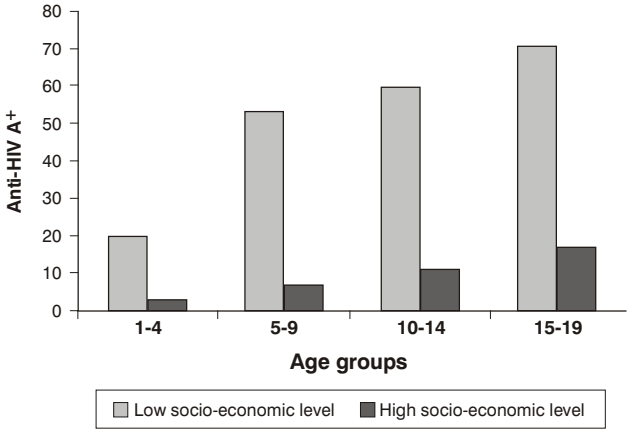


Figure 1 - Prevalence of anti-HAV antibody in two socio-economic levels in Porto Alegre

Up to now no large scale anti-HAV vaccination strategies have been established in Latin American countries. One the one hand, in the highly endemic regions, it is almost impracticable to identify the groups at risk for acquiring the disease; and on the other, the high cost of vaccine makes it difficult to extend this benefit to the entire population.[45-47]

Israel was the first country to adopt universal vaccination for children at 18 and 24 months of age in June 1999, and the results were excellent.[48] A very recent analysis of the impact of this program, 5.5 years after it began, reveals that an important decline has been observed in the incidence of the disease in all age groups, with 90% coverage for the first dose and 85% for the second.[48] The authors suggest that universal immunization programs designed for pre-school children are highly effective and feasible.[48]

Another recent study conducted in Australia also revealed the impact of vaccination in indigenous children (two doses applied at 18 and 24 months).[49] Although the program had been designed to protect the high risk population, there was a rapid and important decline in the notification rates and the benefit was soon extended to other groups in the community.[49]

Children at pre-school age must be the main focus of immunization strategies, because of their critical role in virus transmission.[21,45-47,50] As has been demonstrated by different studies, the efficient way to diminish incidence of the disease and even eradicate the infection is mass vaccination of children. There are, however, many barriers to this measure being adopted, among them: the growing number of vaccinations in childhood, other public health priorities, the cost of vaccine and the reduced number of cost-effectiveness studies of this strategy for our country. Until this happens, the strategy applied in our country will continue to be that of preventing HAV in risk groups, respecting hierarchy as regards the destination of available public resources. While mass vaccination does not occur, we will continue to see patients develop severe hepatitis conditions, including the fulminant form. Recently, in a multi-centric study, we demonstrated that approximately 40% of hepatic insufficiency cases in children in Latin America are due to hepatitis A.[51]

Hepatitis B vaccine

Up to the present time, hepatitis caused by the virus B is one of the main causes of hepatic disease in the world. Epidemiologic studies revealed a strong relation between infection by HBV, cirrhosis and hepatocellular carcinoma and it is calculated that around 1 million people die because of hepatic disease complications every year.[1,4,6,7,51,52] The chronic hepatitis caused by HBV has been revealed as a complex, difficult to manage disease because of, among other factors, peculiarities in the virus-host relationship, the appearance of mutants, viral heterogeneity and the diversity of clinical forms.[53] In the USA it was estimated that in the course of his/her lifetime, an individual has a 5% chance of coming into contact with HBV.[4,21]

The main purposes of vaccination against HBV are to prevent acute disease, prevent hepatopathy from becoming chronic and developing into cirrhosis and/or hepatocarcinoma and, furthermore, to contribute to minimizing viral transmission. The characteristics of HBV transmission make it necessary to implement complex vaccination strategies, in order to protect newborns, adolescent and adults. The strategy used by the WHO, endorsed by practically all the other official organizations for controlling infection by virus B, was to introduce vaccine for all children at birth.[4,54,55]

In the low risk populations, such as the majority of states in Brazil, where transmission primarily occurs in older individuals, immunization of newborns is used to

prevent contamination at the beginning of life and the disease from becoming chronic. It is known that the risk of developing chronic infection is inversely related to age[6,7] (Table 4). By vaccinating children at the beginning of life, horizontal contamination, so frequent in homes where there is an HBV carrier, is also reduced. In addition, when the vaccinal scheme is instituted at this stage of life, there is greater probability of complete series of vaccination being carried out.[52]

Table 4 - Age at infection in relation to possibility of becoming a chronic hepatitis B virus carrier

Child's age (years)	Percentage (%) of children that become chronic carriers
< 1	70-90
2-3	40-70
4-6	10-40
> 7	6-10

The prognosis of chronic hepatitis acquired in childhood remains uncertain. Reactivation of viral replication, or of hepatic disease, may occur much later, at an adult age, and the seroconversion for anti-HBe is not always associated with the disappearance of HBV-DNA and/or with remission of the hepatopathy.

Safe and efficient vaccines against HVB are available all over the world. In global terms, it is estimated that over 1 billion people have already received vaccine against Hepatitis B; in the USA, calculations point towards over 40 million children and 30 million adults already vaccinated.[6,55] The antigen used in the currently available vaccines is a recombinant HBsAg produced by inserting a plasmodium containing the surface antigen gene into the cells of a fungus.[6,55] After purification, HBsAg is adsorved to aluminum hydroxide, and the end product contains over 95% of HBsAg protein, less than 5% of proteins derived from the fungus and no fungus DNA detectable in the vaccine. The Recombivax-HB® vaccines are formulated without preservatives and the Engerix-B® vaccines are considered free of preservatives, although they may contain traces of mercury after the removal of timerosal. These vaccines undergo post-production timerosal removal, which is considered to have no biologic effect.[6] Protection by the vaccine against hepatitis B is, at least partially, derived from the immunologic memory established. The antibody levels derived from the vaccine normally decline with time, but they remain for at least 15 years after the complete series of vaccination, and are reactivated when necessary, by the immunologic memory. For this reason, booster doses are not habitually recommended, unless in some special risk groups.[6,55]

Within the scope of public health, routine assessment of serologic infection markers is not recommended in candidates for vaccination (children and adults), and post-vaccinal anti-HBs research in the serum of immunocompetent individuals is not required.

The vaccines sold in Brazil, with presentations and doses, are shown in Tables 1 and 5.[2] Generally they are administered in 3 doses, the second and third doses being applied 1 and 6 months, respectively, after the first. If the series is interrupted after the first dose, the second must be given as soon as possible and the third at least 2 months after the second. If only the third dose is lacking, it must be administered immediately. Alternative schemes may be used in the following manner:[22]

- Fast vaccination: 1st dose on day 0 and the other doses after 1, 2, and the booster at 12 months;
- Accelerated vaccination: 1st dose on day 0 and the other doses after 7 and 21 days, and the booster at 12 months;
- 2-dose scheme: 1st dose on day 0 and the other 6 – 12 months later (special individuals).

Table 5 - Preparations and recommended doses of vaccines against hepatitis B

Vaccine	Age or group	Dose (µg)	Volume (mL)	Scheme
Engerix-B® *	0-19	10	0,5	0, 1, 6
Euvax® †	> 20	20	1.0	0, 1, 6
	Dialysis	40	2.0	0, 1, 2, 6
Recombivax-HB® ‡	0-19	5	0.5	0, 1, 6
	> 20	10	1.0	0, 1, 6

* GlaxoSmithKline; † Sanofi-Pasteur; ‡ Merck Sharp and Dohme.

Post-vaccination tests are advisable for certain individuals: Children born to infected mothers (must be assessed between 9 and 15 months), health professionals in contact with blood and/or derivatives, hemodialyzed patients (test 1 to 2 months after the last dose of the vaccine) and sexual partners of HBV carriers (test 1 to 2 months after the last dose of the vaccine).

In Brazil, the *Programa Nacional de Imunização* (Brazilian National Immunization Program) recommends that the first dose of the vaccine be administered in the maternity hospital within the first 12 hours of life. If adolescents (11 to 19 years old) have no proof of previous vaccination, the series must be started.[2]

Protection by the vaccine against HVB increases with the number of doses applied. Generally speaking, this is a very efficient vaccine with protection rates of 95%, with variations of 80 to 100% among those individuals that are submitted to the complete vaccination scheme. Protection is considered to exist when the antibody titres to HBsAg (anti-HBs) are higher than 10 mUI/mL.[6] In the pediatric age group, the protection levels attained with the vaccine are 16% to 40% after a single dose, 80% to 95% after two doses and 98 to 100%, after three doses.[6,54] In premature newborns, weighing less than 2 kg, the antibody levels are lower and the seroconversion rates smaller. A recent study conducted by Sadeck & Ramos,[56] about response to vaccination in pre-term newborns, showed a similar response to that in full term babies. However, in 25% of those with birthweight equal to or lower than 1,500 g, the response was not satisfactory. The authors indicated the need to assess seroprotection after the third dose of the vaccine or administer 1 booster dose at 12 months.[56] Among adolescents and adults, the antibody response rates are 20% to 30% after one dose, 75% to 80% following two doses and 90% to 95% after three doses.[6] The assurance of the vaccine's long-term efficiency is due to the anamnestic anti-HBs response.[4,6,7]

The factors that diminish hepatitis B vaccine immunogenicity, in addition to inadequate care of the material (cold chain, for example) include: Age over 40 years, male sex, smoking, obesity and immunologic deficiency.[4,6,7]

Duval et al.,[57] in a 15-year prospective study, compared the immunogenicity of two pediatric vaccines (Engerix-B® and Recombivax-B®) and the effect of the booster dose given 5 years afterwards in a county with low endemicity – Canada. They observed that immunity persisted for 5 years after the primary vaccination in 99% of the vaccinated children from 8 to 10 years of age. There would appear to be long protection (10 to 12 years) in children at greater risk, vaccinated at birth (HBsAg positive and HBeAg positive mothers).

Immunity duration in low risk children born to HBsAg negative mothers, vaccinated soon after birth, is still under discussion.[51] In these individuals, the risk could reappear during adolescence and the beginning of sexual life.

Petersen et al.[52] studied post-vaccination protection duration in high and low risk children of 4 to 13 years of age, vaccinated at birth. They observed that in the majority of cases, anti-HBs disappears at around 5 years of age, although a large number of them showed immunologic memory. In a third of these children, there was failure in the anamnestic response after a booster dose. On the other hand, Gong et al.,[58] in China, assessed vaccination protection 3 to 12 years after vaccination at birth in 2,419 children, and concluded that the protective effects of the recombinant vaccine were significant 12 year later. The authors believe that the vaccine booster is not necessary in these children, since the HBsAg positivity rate in this population did not rise in later years.[58]

Zanetti et al.,[59] in Italy, analyzed immunity duration and the eventual need for a booster dose in 1,212 children and 446 air force recruits, after 10 years of implementing vaccination in nursing infants and adolescents in that country. They concluded that a strong immunologic memory persists for over 10 years after a primary course of immunization, and booster doses of the vaccine are unnecessary.

There is no doubt that immunoprophylaxis has the greatest cost-benefit for global control of infection by the virus B and its complications.[60] Passive immunization by hyper immune immunoglobulin (HBIG), provides temporary immunity at a high cost. Therefore, the most efficient strategy has been universal immunization programs to prevent both perinatal and horizontal transmission of infection by the hepatitis B virus.

The strategies indicated for universal immunization and the risk groups are presented as follows, as well as in Table 6[7,60]: children of HBsAg-positive mothers; home contacts of individuals infected by HBV; workers exposed to blood and/or hemoderivatives; patients having frequent blood and/or hemoderivative transfusions; persons that frequent hemodialysis units; prisoners in correctional institutions; promiscuous men that have sex with men; persons that have more than one sexual partner in a period of 6 months; injectable drug users; immunodepressed patients; lifesavers/firemen; persons originating from high endemicity zones; contacts of immigrants originating from endemic zones.

The strategies depend both on local epidemiologic conditions (high or low prevalence of HBsAg in children) and governmental resources for implementing vaccination. In areas where prevalence of infection by HBV is low, or financial resources are limited, immunization with 3 doses of the vaccine, without pre-natal triage and without the concurrent administration of HBIG, is a reasonable strategy, saves resources and has shown to be efficient in countries such as Thailand and in other Asian countires.[60-62]

Over the last few years some innovations related to vaccines have been assessed. New application routes (intranasal, transcutaneous, aerosol and oral), new devices (microneedle system), purpose of use (prophylactic or therapeutic) and time of vaccine administration are being tested.[63] Thus, Patwardahan et al.[64] recently tested pre-natal vaccination in mothers belonging to high risk populations and the results were encouraging when the mothers were vaccinated in the 20th and 24th weeks of gestation.

In a recently published study, various international agencies, including the WHO and the CDC, affirmed that

Table 6 - Strategies indicated for universal immunization against HVB in accordance with the different endemicity patterns

Regional prevalence	Maternal Screening HbsAg/HBeAg	HBV immunization HBIG/HBV vaccine	Cost
High	Yes/yes	Yes*/yes	High
Low with high risk groups	Yes/no	Yes/yes	High
High	No/no	No/yes	Low
Low	No/no	No/yes	Low

* Children of high risk mothers (HBeAg positive).

up to now there are no data to conclude that the vaccines, particularly hepatitis B, present health risks, and that there are no justifications for changing current immunization practices.[65] However, the "scars" left by irresponsible reports that link severe adverse effects to vaccines may have an important impact on immunization coverage.

HVB vaccine in special groups

It is generally known that the immunogenic capacity of vaccine is lower in certain groups of persons, among them: The elderly, obese, alcoholics, individuals submitted to antiblastic chemotherapy and immunodepressed patients. To improve response to vaccine, some strategies could be implemented. Kappor et al.,[66] for example, used the granulocyte formation stimulating factor with encouraging results.

Premature newborns, weighing less than 2 kg at birth, should receive the first dose of the vaccine when the child is 1 month old.[22] Response to the vaccine, under this circumstance, is comparable to that of full term children, irrespective of the birthweight and gestational age.[22]

Hepatitis B vaccine immunogenicity is low in patients infected with HIV, but the ideal vaccination scheme for these patients is still undefined. There is limited information about the duration of immunologic memory and the most suitable time to start vaccination in severely immunodepressed patients. It is known that the serologic response is directly proportional to the CD4 level. Studies conducted during the 1980s and 1990s, analyzing adults infected by HIV, demonstrated responses between 33% and 56% to recombinant vaccines. North American adolescents infected by HIV, vaccinated against hepatitis B, showed a diminished serologic response, associated with an increase in T cells (CD8+/CD38+). The authors suggested that viral replication continued and activation of the immune system could lead to a reduction in the capacity to respond to the vaccine.[67]

With regard to chronic hepatopathies, when they present light or moderate disease, vaccination results are similar to those of healthy adults, attaining up to 100% seroconversion in some studies.[6,17,33] In patients with cirrhosis due to alcohol, seroconversion rates are low, ranging from 12% to 75% and in patients on liver transplant lists they are even lower, ranging between 7% and 55%.[6]

Vaccine against HBV is recommended at higher doses in patients on hemodialysis. Seroprotection has been documented in 64% of patients with a normal vaccination scheme of three doses, and 86% in those that received an extra dose of vaccine.[4,6] The response basically depends on the doses used and the stage of the renal disease at which the patient was vaccinated. Those that present creatinine over 4 mg/dL, and are on dialysis, respond in a worse manner than those with more moderate renal insufficiency. Chronic nephropathies must be vaccinated as early as possible and it is advisable to institute vaccination before submitting them to dialysis. In these patients, annual antibody level (anti-HBs) monitoring is indicated, as well as a booster dose when these levels are below 10 mUI/mL.[4,6]

Impact of anti-HVB vaccination

Immunization against hepatitis B has always been a successful experience in universal vaccination campaigns in the different countries. It is well known that success is not achieved when the strategy is oriented to vaccinating only risk groups. It is estimated that 25% to 30% of persons with hepatitis B deny having any risk factor whatever for acquiring the infection and therefore, are not identified as vaccination targets. Men that have sex with men, intravenous drug users and promiscuous

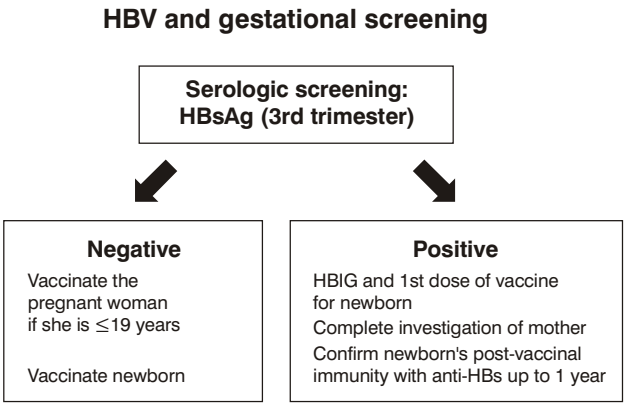
heterosexuals are important risk groups that are not usually reached in vaccinal campaigns. In the United States, only after vaccination was recommended for all newborns in 1991, and in 1996, routine immunization of adolescents from 11 to 12 years of age, was a substantial reduction found in the incidence of hepatitis B.[6]

Another fundamental measure for reducing the incidence of acute virus B hepatitis was the recommendation to test all pregnant women for HBsAg and to protect the newborns of all infected mothers with vaccine and immunoglobulin.[4,6,21]

The Ministry of Health's National Hepatitis Program is undertaking a series of strategic measures to broaden knowledge related to hepatitis in Brazil.[2] One of the aspects that is receiving special attention is serologic screening of HBsAg in pregnant women. The importance of hepatitis B during gestation is mainly because of the high potential of transmission from mother to newborn and the tendency of hepatitis B to become chronic (70-90%) when contact occurs at an early age.

An enquiry recently carried out to assess gynecologists' and obstetricians' knowledge with regard to various aspects of hepatitis B revealed an alarming situation.[68] Approximately half of the 262 professionals interviewed asked for the marker (HBsAg) for mothers in the first trimester of gestation, although it is known that in order to protect the newborn adequately, screening must be done in the third trimester. On the other hand, the large majority of the professionals (group at risk for hepatitis B) had been vaccinated, but only 58% had performed anti-HBs.[68] The scheme proposed by the Ministry of Health is represented in Figure 2.

In the United States, the cumulative effect of the use of the hepatitis B vaccine has shown important reductions in the incidence of acute hepatitis B – from 9.2 cases/100,000 in 1981 to 2.8 cases/100,000 in 2002, the latter rate having been stable since 1999.[4,6]



Brazilian Ministry of Health.

Figure 2 - Hepatitis B triage in pregnant women

In countries where the incidence of hepatitis B is low, universal vaccination may be considered an unsuitable measure from the public health point of view; in these cases, selective immunization would protect the great majority of individuals at risk.

In Formosa, the mortality rate from fulminant hepatitis B in nursing infants, between the years 1974 and 1984, before the universal vaccination era, was 5.36/100,000. This rate fell to 1.71/100,000 between 1985 and 1998, after the vaccination program was launched.[67] At present, fulminant hepatitis occurs almost exclusively in infected nursing infants of mothers that are carriers of HBsAg and HBeAg negative.[69-72] Universal vaccination against hepatitis B in these high endemicity countries effectively reduced both perinatal and horizontal transmission, thus diminishing the rates of chronic hepatitis B.[60,69-71] In Formosa, the incidence of chronic HBsAg carriers diminished from 10% to 1% in children under the age of 15 years.[69] These reductions clearly show that universal vaccination programs are more efficient than vaccination in risk groups.

At present, the development of mutants as a result of vaccination programs is of concern in these high endemicity countries. The prevalence of surface antigen gene mutants, which may cause the vaccine to fail, is the current worry, as it increased gradually 5 to 10 years after the programs were instituted. Reduction in HVB infection rates after the universal vaccination programs started had a dramatic effect on the incidence of hepatocellular carcinoma in children in Formosa. The annual incidence of liver cancer diminished by 75%, from 0.52/100,000 in children born before July 1984 to 0.13/100,000 in those born after 1984.[72] If these rates continue to decline, there should also be a substantial decrease in hepatocellular carcinoma in adults in the near future.

Lastly, it is important to remember that in our country, hepatitis from the Delta virus is still highly prevalent in some areas of Eastern Amazonia. As this concerns a defective virus, the distribution of the infection is superimposed on that of hepatitis B. When protecting individuals against HBV, we are also preventing the specter of serious diseases, both of super-infection and co-infection, determined by the association of B and Delta viruses.

Final considerations

Infections caused by viral hepatitis A and B generate enormous problems related to morbidity and mortality, in addition to costs, not only with the diseases, but also by determining an increase in the number of liver transplants. Instead of us continuing to think of hepatitis A and B as

common diseases that affect our patients, we should perhaps face them now, as infections that can be eradicated from our country. HVB vaccination is already available to all children when they are born, for adolescents up to the age of 19, and for all risk patients in the public health service. HAV vaccine, not yet available in the public health system, should be indicated for patients with financial resources, as these persons form the largest susceptible group and are therefore at greater risk. It should be remembered that for risk groups, this vaccine is available in the public health system at the CRIE in Brazil.

Health professionals, the lay community, above all the parents and the media must be continually informed about the benefits and adequate use of the vaccines available in our country. The actions undertaken by the Evandro Chagas Institute team in Amazonia, since 1953, with regard to viral hepatitis, should serve as inspiration to all of us, as in spite of the great deal that has been done, it is necessary to reflect on the wise words of Bensabath and Soares[73] – "the task has not yet been finished".

Conflict of interest

Cristina Targa Ferreira declares that she has participated in studies on vaccines for Glaxo and Merck Laboratories and currently takes part in a study on hepatitis C (peg-IFN/ribavirin treatment) for Roche. Cristina Targa Ferreira and Themis Reverbel da Silveira declare that they have participated as investigators in studies on viral hepatitis for Roche and GlaxoSmithKline Laboratories.

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