

# Hepatitis B and the Need for a Booster Dose

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**After several decades of vaccination against hepatitis B virus in newborns, infants, adolescents, and adults, the question remains whether a booster dose is ever needed. Long-term protection is most commonly measured through 4 methods: the anamnestic response after administration of a booster dose, infection rate in vaccinated populations, in vitro B and T cell activity testing, and seroepidemiological studies. Long-term protection is present despite a decrease in anti-hepatitis B surface antibodies over time. The exact mechanism of long-term protection, however, is not yet fully understood. There is no need for boosters in immunologically potent persons as long as a full course was adequately administered that respected the recommended timelines, as evidenced by studies conducted up to 20 years after the original immunization course. However, a booster dose should be planned for immunocompromised patients, based on serological monitoring.**

Over 2 billion people worldwide have been exposed to hepatitis B virus (HBV) infection, and at least 378 million are chronically infected and are at risk for severe disease and death [1]. Different degrees of endemicity are recognized. If seroprevalence of hepatitis B surface antigen (HBsAg) is >8%, the region is considered to be of high endemicity; if HBsAg seroprevalence is 2%–8%, the region is considered to be of intermediate endemicity; and if HBsAg seroprevalence is <2%, the region is considered to be of low endemicity. Hepatitis B is a bloodborne and sexually transmitted infection. Perinatal and horizontal transmission is evident in countries where the disease is highly endemic and within households containing HBsAg carriers, but administering the vaccine at birth adequately controls perinatal transmission.

Currently, the therapeutic options for treating chronic HBV infection are difficult to implement and are not yet fully effective, leaving room for further

improvements. Vaccination is an easy and cost-effective measure to prevent disease and infection. Additionally, vaccination eliminates the incidences of persistent HBV infection and chronic liver disease and diminishes the pool of chronic carriers, thus limiting transmission of infection to susceptible contacts [2].

A complete standard vaccination schedule exists in 3 doses that are most commonly administered as a 0-, 1-, and 6-month schedule. A 3-dose course induces protective antibody concentrations in >95% of healthy infants, children, and adolescents and in >90% of healthy adults [3, 4]. The minimum spacing of doses is 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3 [5]. The primary hepatitis B immunization series, starting at birth, consists of at least 3 doses of vaccine (1 monovalent at-birth dose followed by 2 monovalent or combined vaccine doses). Four doses may be given for programmatic reasons, administered according to the schedules of national routine immunization programs [1].

The term “booster” refers to a vaccination given some time after a primary vaccination series and with the aim of providing rapid protective immunity against a significant breakthrough infection (ie, infection resulting in serological test results positive for HBV and/or clinical disease) [1].

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## METHODS

Starting from the article by Banatvala et al [6], we examined literature and insights regarding the need for booster doses against hepatitis B published since 2002. A Medline search was conducted using the National Library of Medicine's PubMed online search engine. Keywords included "hepatitis B," "booster," and "vaccination." The starting year was not defined, and the end date was July 2010. Any "related article" hyperlinks were followed for each retrieved article. The reference list of the retrieved articles was also used to identify related literature. No language priority was chosen. In the Cochrane library, no review was encountered on hepatitis B booster doses, with the exception of a review related to the vaccination of health care workers (HCWs).

## PRESENT EVIDENCE

Even at the beginning of the HBV vaccination program, the most evident way to investigate the duration of protection was via the measurement of hepatitis B surface antibodies (anti-HBs). In 1989, Jilg et al [7] compared 3 different schedules in young healthy adults (range, 22–26 years of age). With an enlarging interval between dose 2 and dose 3, a higher geometric mean concentration (GMC) of anti-HBs was induced after the complete series. For the first time, a correlation was demonstrated between the peak titer 1 month after a complete series and the duration of the presence of antibodies: the higher peak value, the longer the persistence of anti-HBs [7]. This finding was subsequently confirmed in several different studies [8, 9]. The protective cutoff level was set at  $\geq 10$  mIU/mL anti-HBs, based on vaccine efficacy studies [10–12]. Additionally, data from The Gambia supported the use of peak antibody response as the best indicator of protection against carriage [12].

Among children who respond to the complete primary 3-dose vaccination series with anti-HBs concentrations of  $> 10$  mIU/mL, 15%–50% have low or undetectable concentrations of anti-HBs 5–15 years after the start of the vaccination series [13]. In adults, anti-HBs concentrations decrease rapidly within the first year after primary vaccination and more slowly thereafter. A decrease was noticed to a level of  $< 10$  mIU/mL in 7%–50% of vaccinated adults within 5 years after vaccination and in 30%–60% within 9–11 years after vaccination [13].

In 1989, Wismans measured the anamnestic response to a booster vaccine in vivo, after anti-HBs levels had decreased to below the seroprotective level [14]. Excellent humoral responses were shown, indicating immune memory for HBsAg. Despite low or undetectable antibody levels years after vaccination, the acquisition of HBsAg seemed to be rare. Immune memory was confirmed in studies following challenge with HBV vaccine (Table 1) and in vitro production of anti-HBs in circulating B cells [28].

Based on those studies that confirmed immune memory [29], the Centers for Disease Control and Prevention (CDC) and the Canadian National Advisory Committee on Immunization advised, in 1991 and 1992, respectively, that a booster dose no longer be administered to fully vaccinated healthy subjects [30, 31]. Tilzey highlighted the discordance between the recommendations in the United Kingdom and the United States, because the former still recommended booster doses in 1995 for HCWs if anti-HBs levels had waned [32]. Finally, on the basis of the literature and available follow-up data, a European consensus group stated in the *Lancet* in 2000 that there was no recognized need for booster doses in healthy, fully vaccinated infants, adolescents, and adults [33].

These reports meant tremendous cost savings, especially in developing countries with high HBV endemicity [33]. Immunocompromised people (eg, human immunodeficiency virus-positive and chronic renal failure), however, have slower primary and secondary immune responses and a lower peak after vaccination. All recommendations advise that these specific groups undergo serological monitoring and receive a booster dose if anti-HBs levels decrease below 10 mIU/mL. Intravenous drug users, persons with risky sexual behavior, travelers, residents in mental institutions, those who have close contact with carriers, and immigrants do not need boosters [1].

Over the years, data for longer post-vaccination follow-up periods have become available. Banatvala et al [6] described accumulated data from long-term follow-up studies among infants, children, and adults. In Tables 1 and 2, information published in the last 10 years is added to that mentioned in the paper of Van Damme and Banatvala [40]. To date, no compelling evidence has been found to suggest that a booster dose is needed, even after more than 20 years of follow-up data acquisition.

For adolescents (11–15 years of age), a 2-dose schedule at 0 and 4–6 months with an adult dosage is an effective alternative for a 3-dose (pediatric dosage) schedule [41]. After 10 years of follow-up in the Czech Republic, 85.9% of the adolescents (aged 12–15 years) vaccinated with the 2-dose schedule had anti-HBs levels of  $\geq 10$  mIU/mL, as did 85.1% of those who received 3 pediatric doses [41]. However, the adolescents who were vaccinated with the 2-dose schedule had slightly lower GMC 10 years after receiving the doses. In Belgium, a 5-year follow-up study showed fewer adolescents (aged 11–15 years) had anti-HBs levels of  $\geq 10$  mIU/mL if vaccinated via the 2-dose schedule (79.5%, compared with 91.4% of those vaccinated with 3 doses), but after a challenge dose, all subjects mounted a rapid anamnestic response, indicating immune memory [42].

In this article, four main methods are used to approach the concept of long-term protection: the anamnestic response to booster vaccinations, the measurement of infections in vaccinated populations (HBsAg/hepatitis B core antibody [anti-HBc]

**Table 1. Studies in Different Populations in Regions With Different Endemicity During the Past Decade, Using Anamnestic Response to a Booster Dose as a Measure for Immune Memory if Anti-HBs Decreased <10 mIU/mL**

Reference	Year of publication	Vaccinated population	No. of subjects	Country	No. of doses or schedule in months	Duration of follow-up, years	Anamnestic response
[15]	2003	Infants	70 + 41	Samoa	3 doses; 0.1.6 starting at birth, booster at 5 or 9 years	5 or 9	100% after 5 years, 93% after 9 years
[16]	2004	Infants of carrier mothers	116	UK	3–4 doses, starting at birth	10	86%
[17]	2004	Infants of carrier mothers + infants from noncarrier mothers	78 + 113	China	4 doses, starting at birth	15	97.3–96.7%
[18]	2007	Adolescents	620, 11 lost anti-HBs	Italy	3 doses	11	91.7%
[19]	2005	Adolescents	550	Canada	3 doses	5	99%
[20]	2005	Infants and recruits	1212 children, 446 recruits	Italy	3 doses: 3.5.11 months and 0.1.6 for recruits	10	97% children and 96% recruits
[21]	2006	Infants	94	Iran	3 doses starting at birth	10	95.8%
[22]	2007	Adolescents	255	The Gambia	3 doses	15	92.3%
[23]	2007	Infants; recombinant vaccine	166	Alaska	3 doses starting at birth	5–7	99%
Adolescents; recombinant vaccine		138	Alaska	3 doses starting at birth	10–15	88%	
Adolescents; plasma derived		74	Alaska	3 doses starting at birth	12–15	71%	
[24]	2007	Infants of carrier mothers	37	Alaska	3 doses starting at birth	15	51% after 2 weeks, 62% after 1 month
[25]	2008	Infants	872	Taiwan	3 doses starting at birth	15–21	70.3%
[26]	2009	Young adults	127	Taiwan	3 doses starting at birth	18–23	75.6% after 1 month; 20% after 1 week
[27]	2009	Children	186	Germany	3 doses + 1	7–9	98.9%

**NOTE.** Anti-HBcs, anti-hepatitis B surface antibody.

seroconversion), and in vitro testing for T and B cell activation. Additionally, seroepidemiological research gives an idea of the changes in the carrier rate in vaccinated populations and the impact of immunization programs.

The definition of a breakthrough infection with HBV found most often in the literature is an infection characterized by the development of anti-HBc, without clinical features and without carrier state development. Infection with acquisition of HBsAg, a significant breakthrough infection, has been reported in infants of carrier mothers, related to the maternal viral load, as well as in one HCW [36, 43].

#### **Anamnestic Response to Booster Dose as a Way to Demonstrate Long-term Protection**

Cohorts of vaccinated people are followed up around the world; the current longest duration of follow-up is 23 years after primary vaccination [26, 44]. Regardless of the endemicity in the country [20, 45] and regardless of natural boosting [17], anamnestic responses measured shortly after vaccine-induced

boosting illustrate the prolonged duration of protection against hepatitis B, even after the disappearance of vaccine-induced serological anti-HBs (Table 1).

Instead of testing 1 month after booster administration, some investigators have been testing immune responses earlier. Fifteen years after immunization, in Alaskan children who received 3 doses starting at birth, only 51% showed an anamnestic response 2 weeks after a 5- $\mu$ g booster dose, whereas 62% showed a response after 1 month [24]. Jan et al [26] also measured early anamnestic responses in Taiwanese students vaccinated at birth, 18–23 years earlier. A low percentage of anamnestic responses were encountered after 1 week (20.5%). However, titers equaled those in other studies after 1 month (75%), revealing that anamnestic immune responses need time. Nevertheless, those who had the earliest anamnestic response in the study of Jan et al [26] were those who ended up with the highest levels of anti-HBs 1–6 months after the booster dose. As the incubation time is, on average, 90 days from exposure to onset of jaundice and 60 days from exposure to onset of abnormal alanine transaminase levels, the stimulation of

memory cells should trigger anti-HBs production rapidly enough so that subjects reach the appropriate level for protection within 2 months and can therefore be considered protected against infection, or at least against the clinical consequences of infection. In addition, even an absent anamnestic response following such a booster vaccination may not necessarily mean that individuals are susceptible to HBV infection [24].

Some authors suggest that other factors influence long-term protection. Boxall et al [16] report the influence of hepatitis B immunoglobulins (HBIG) co-administered with the hepatitis B vaccine at birth on immunological memory induction in countries where the disease has low endemicity; the study suggests that early administration of HBIG could lead to a more rapid loss of memory. The potential influence by the type, number and composition of candidate vaccines administered is another issue. Samandari et al [23] reported that 31% of adolescents who, 12 to 15 years earlier, had been vaccinated with the plasma-derived vaccine (3 doses) at birth did not respond to a booster dose, compared with only 17% of adolescents vaccinated at birth with the recombinant vaccine (3 doses).

#### **Measurement of Infections as a Way to Measure Long-term Protection**

Table 2 gives an overview of follow-up studies using anti-HBc, HBsAg, or HBV DNA to measure infections and protection in vaccine recipients.

Breakthrough infections occur in 0%–17.7% of the general population [22] and in up to 33.3% in children of carrier mothers [25] after 15 years of follow-up (Table 2). In long-term follow-up studies, breakthrough infections do occur, illustrated by the seroconversion of anti-HBc antibodies, but few clinically significant infections are diagnosed and few new carriers are reported [34, 37, 46].

From a public health point of view, the likelihood of becoming a hepatitis B carrier is even more important. Viviani et al [47] recently published the evaluation of 24 years of a hepatitis B vaccination program in The Gambia: 67% vaccine efficacy against development of anti-HBc and 96.6% vaccine efficacy against carriage was reported. The impact on hepatocellular cancer had already been seen: the risk of hepatocellular carcinoma attributable to HBV at age <50 years was 70%–80% lower than that for historical cohorts.

#### **T- and B-Cell Activity as a Way to Measure Long-term Protection**

Memory B lymphocytes are elicited through vaccination and involved in long-term immunity and protection against hepatitis B [11]. The response of an increase in antibodies to a booster dose is a result of triggering memory B lymphocytes, sensitized through an initial exposure to antigen, which remain capable of rapid proliferation, differentiation, and production of specific antibodies upon a subsequent encounter with the same antigen.

Bauer et al [28] analyzed B cell memory by co-cultivation of isolated B cells with CD4+ T cells and the identification of anti-HBs-secreting cells by enzyme-linked immunospot assay (ELI spot). Their results showed significant numbers of HBsAg-specific memory T and B cells present in all vaccine recipients despite the absence of specific antibodies. Lu et al [17, 25] conducted a 15- to 18-year follow-up in infants; 63% had no anti-HBs in the long term. A booster dose was administered to seronegative children, and 28.7% showed no anamnestic response (10% of the total population). In this last group, HBsAg-specific interferon (IFN)  $\gamma$  and interleukin 5-secreting peripheral blood mononuclear cells remained negative in 27.2% of subjects after booster administration (enzyme-linked immunospot assay). The timing of the enzyme-linked immunospot assay test was different (after 28 days) compared with that in study by Bauer et al [28] (after 10 days). There is a possibility that the latter measurement resulted in an underestimation of the cellular immunity.

Chinchai et al [48] reported long-term follow-up in both humoral and cellular immune parameters in Thailand, and 69.9% of participants showed a seroprotective titer after 18–20 years. In addition, 81.8% of participants who displayed IFN- $\gamma$ -producing cells were also positive for anti-HBs, but only 50% of participants who displayed anti-HBs were positive for IFN- $\gamma$ -producing cells. However, the results are difficult to compare with those of other studies because of the methods used.

To summarize, the exact immunological mechanism of long-term protection is not well understood, and recent studies raise even more questions.

#### **Seroepidemiology as a Way to Measure Long-term Protection**

The results of effective implementation of universal hepatitis B programs have become apparent in terms of a reduction not only in the incidence of acute HBV infection but also in the carrier rate in immunized populations. Seroepidemiological studies have been performed to measure the effect of hepatitis B vaccination programs in vaccinated populations, including the long-term protection the vaccination programs can give. Epidemiological research in Thailand in the population of those 0–60 years old showed a significant decrease in the carrier rate in the younger population (ie, in the subset of the population that was vaccinated) [49]. Several epidemiological studies have been performed in Taiwan. One such study, in a cohort of university students, revealed the major impact of vaccination on the carrier rate, which decreased from 9.8% before vaccination to 0.8% in the vaccinated cohort after 23 years [50, 51]. The average annual incidence of hepatocellular carcinoma among children 6–14 years of age during 1981–1986 was 0.7 cases per 100,000 population, whereas during 1990–1994, it was 0.36 cases per 100,000 population [52]. Ni YH et al [53] stated that, after a 20 year follow-up period, no booster administration is needed, based on

**Table 2. Data on Studies in Different Populations in Regions With Different Endemicity During the Last Decade, Using Measurement of Hepatitis B Markers as Markers for Breakthrough Infection in Vaccinated Populations**

Reference	Year of publication	Vaccinated population	No. of subjects	Country	No. of doses or schedule	Duration of follow-up, years	Method	Breakthrough infections: anti-HBc antibody positive and/or HBsAg positive	Increase in anti-HBs antibodies, %
[34]	2001	Adolescents	334	Alaska	3 Doses: birth (0–8 d), 24–103 d, 146–286 d	16	2 Consecutive anti-HBc OR 1 anti-HBc and 1HBV DNA PCR	1.8% anti-HBc; 0.9% HBV DNA positive	
[35]	2001	Infants of carrier mothers	522	Italy	Birth + 3 doses	5–14	HBsAg, anti-HBc	3.3% anti-HBc; 3 infants carrier HBsAg	
[36]	2003	Infants of carrier mothers	112	China	3 Doses: 0, 1, and 6 months or 0, 2, and 8 months or 0, 1, and 2 months	16	2 Consecutive anti-HBc; HBsAg	3.5% Infants HBsAg; 8.9% anti-HBc	21.1
[16]	2004	Infants of carrier mothers	116	UK	3–4 Doses starting at birth	15	HBsAg, anti-HBc	1.7% anti-HBc	
[17]	2004	Infants of carrier mothers	191	China	4 Doses starting at birth	15	HBsAg, anti-HBc	33.3% anti-HBc; 1 infant HBsAg	
[37]	2005	General population	1578	Alaska	3 Doses: 0, 1, and 6 months	15	2 Consecutive anti-HBc OR 1 anti-HBc + 1HBV DNA PCR OR HBsAg	1% anti-HBc, 3 infants HBsAg, 3 infants HBV DNA positive	5.4
[21]	2006	Infants	146	Iran	3 Doses starting at birth	10	HBsAg, anti-HBc	7.5% anti-HBc	
[38]	2006	Adolescents	1350	The Gambia	3 Doses	15	HBsAg, anti-HBc	13.8% anti-HBc, 0.7% HBsAg	
[25]	2008	Young adults	6156	Taiwan	4 Doses	15–21	HBsAg, anti-HBc	4.1% anti-HBc	
[39]	2009	Infants of carrier and noncarrier mothers	204	Thailand	3 or 4 Doses: 0, 1, and 6 months or 0, 1, 2, and 12 months	15–17	HBsAg, anti-HBc	2.9% (6 of 204) HBsAg, acquired in the first year of life; 26% (53 of 204) anti-HBc	

**NOTE.** Anti-HBc, anti-hepatitis B core antibody; d, days; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.

seroepidemiological findings, because no new carriers received a diagnosis in the different vaccinated birth cohorts. In The Gambia, childhood HBsAg prevalence decreased from 10% to 0.6% after the introduction of the universal infant immunization program [54, 55]. In Malaysia, HBsAg seroprevalence in 7- to 12-year-old children decreased from 1.6% in 1997 to 0.3% in 2003 after implementation of a universal infant program in 1990 [56]. Recent data from Hawaii show a reduction of 97% in the prevalence of HBsAg after the initiation of the infant hepatitis B vaccination program in 1991. The incidence of new acute hepatitis B infection in children and adults was reduced from 4.5 cases per 100,000 population in 1990 to 0 cases in the period from 2002 through 2004 [57]. In Bristol Bay, Alaska, 3.2% of children were HBsAg positive before universal hepatitis B vaccination; 10 years after introduction of a universal program, no child under 10 years of age was HBsAg positive [46]. Although most studies were conducted in regions with high endemicity, data from countries with low endemicity also show beneficial impact on disease incidence. For example, in Catalonia, Spain, the HBsAg carrier rate decreased from 1.5% to 0.7% and the anti-HBc antibody prevalence decreased from 15.6% to 8.7% at 15 years after introduction of preadolescent HBV vaccination and vaccination of infants of carrier mothers [58]. Likewise, in Italy, where a universal vaccination program was started in 1991 for infants as well as for adolescents, surveillance data have shown a clear overall decrease in the incidence of acute hepatitis B cases, from 11 cases per 100,000 in 1987 to 3 cases per 100,000 population in 2000 and 1.6 cases per 100,000 population in 2006 [59, 60]. This decrease was even more striking for people between the ages of 15 and 24 years, in whom the incidence decreased from 17 cases per 100,000 population in 1990 to less than 1 case per 100,000 population in 2003 [20].

## CONCLUSIONS

Vaccine efficacy studies have demonstrated virtually complete protection against acute and chronic hepatitis B in immunocompetent people, with post-immunization anti-HBs levels of  $\geq 10$  mIU/mL. Therefore, seroprotection against HBV infection was defined as having an anti-HBs level of  $\geq 10$  mIU/mL after having received a complete immunization schedule.

Immunity against HBV provides protection against infection as well as against disease. Protection against infection is associated with antibody persistence, which is directly related to the peak production of anti-HBs after primary vaccination. Protection against disease (ie, acute hepatitis, prolonged viremia, carriage, and chronic infection) is associated with immune memory, which persists beyond the time at which anti-HBs disappear.

The evidence on the duration of immunity after a complete primary series of vaccinations has increased as the time since the

first vaccination series were implemented has increased. We have data for  $>20$  years, which demonstrate that, in healthy individuals, the specific immune memory for HBsAg can outlast the presence of vaccine-induced antibodies, conferring effective protection against acute disease and the development of a HBsAg carrier state, even in those showing waning or disappearance of anti-HBs [2, 6, 9, 11, 61]. Persistence of anti-HBs at a concentration of  $\geq 10$  mIU/mL is not necessary for protection, because it is immune memory that matters.

Based on current scientific evidence, booster vaccination against hepatitis B for immunocompetent children and adults is not recommended for long-term protection [20, 26]. Immunocompromised patients, however, should be monitored and receive a booster vaccination if their anti-HBs levels decrease below 10 mIU/mL [33].

The question that remains to be answered is how long immune memory will last. Early evidence suggests that the answer will come from the power of the initial immune response and from the time since primary vaccination [17, 23]. Long-term follow-up studies during the third decade after vaccination administration are needed to confirm the duration and persistence of immune memory. In addition, studies that follow-up birth cohorts vaccinated  $>20$  years ago are needed as those individuals become sexually active and potentially exposed to HBV infection.

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