

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Update on the recommended use of Hepatitis B
vaccine

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



Public Health
Agency of Canada

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publique du Canada

Canada

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP,
INNOVATION AND ACTION IN PUBLIC HEALTH.**

—Public Health Agency of Canada

Également disponible en français sous le titre :
Mise à jour des recommandations concernant l'utilisation du vaccin contre l'hépatite B

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following table highlights key information for immunization providers. Please refer to the remainder of the Statement for details

1. What

Hepatitis B virus (HBV) causes liver infection. Although the majority of individuals will spontaneously clear the infection, the risk of becoming a chronic carrier in unvaccinated individuals varies with age at which the infection occurs: up to 95% of infants, 50% of children less than 5 years of age and 10% of adolescents and adults will develop chronic infection.

Infant and adolescent immunization programs have been successfully implemented in all Canadian provinces and territories since 1990s. Duration of protection following a completed primary schedule is believed to be long lasting and no routine booster doses are currently indicated for immunocompetent individuals.

2. Who

This Statement addresses whether there is a need for HB re-immunization of adolescents who have received routine immunization in infancy, risk of HB infection in people with diabetes and timing of re-vaccination of people with immunocompromising conditions.

3. How

Although decline of antibody levels may be observed over time, long-term protection and prevention of chronic infection is dependent on the presence of T- and B-cell memory. Anamnestic response to a HB vaccine challenge dose is considered to be a reliable measure of preserved immunologic memory and a correlate of protection in previously immunized individuals.

4. Why

The majority of acute cases occur in unimmunized household contacts of a HB carrier and in people 30 years of age and older who acquire infection through unprotected sexual activity, sharing injection drug equipment or procedures with percutaneous exposure.

Healthy, immunocompetent, individuals who received HB vaccine according to recommended schedules are considered to be immune to HB infection. Presence of anamnestic response in the majority of individuals vaccinated in infancy is indicative of long-term protection.

I. INTRODUCTION

This statement will supplement previous NACI statements on hepatitis B (HB) by:

- Providing an overview of current HB epidemiology in Canada and national sources of HB-related surveillance
- Reviewing evidence pertaining to primary and booster immunization in those vaccinated as infants and in individuals with diabetes and immunocompromising conditions
- Reviewing evidence pertaining to indications for HB immunoglobulin (HBIG) administration
- Making recommendations regarding existing HB immunization schedules, serological testing of immunocompromised persons, and surveillance and research priorities

The primary goal of the statement is to provide further guidance on the need for re-immunization of adolescents who have received routine immunization with a HB containing vaccine in infancy.

II. METHODS

The NACI Hepatitis Working Group (HWG) reviewed such considerations as the epidemiology, target populations, the safety, immunogenicity, efficacy, effectiveness of the vaccines, vaccine schedules, and other aspects of the overall immunization strategy. Evidence search, review and synthesis were performed by PHAC medical advisors under the supervision of the HWG. Following the critical appraisal of relevant studies, summary tables with ratings of the quality of the evidence were prepared using NACI's methodological hierarchy (Tables [4](#) and [5](#)).

HB infection has been a nationally notifiable disease since 1969. Clinically and laboratory diagnosed cases are reported to provincial and territorial (P/T) health authorities, which in turn provide aggregate data to the Public Health Agency of Canada (PHAC) Canadian Notifiable Disease Surveillance System (CNDSS). National surveillance data obtained from P/T health authorities include age, sex, jurisdiction and year of reported cases.

Evidence on vaccine effectiveness and long-term immunogenicity, including immune memory and anamnestic response following the administration of a HB booster dose, was obtained through a literature review of published and unpublished studies. The broad literature search of primary studies using key words “hepatitis B” AND “vaccine OR vaccination OR immunization” published in English and French was conducted using Medline, EMBASE and Cochrane Library of Clinical Trials. Immunogenicity studies were included if results contained data on children and adolescents vaccinated at less than one year of age with a hepatitis B vaccine and provided with a vaccine booster at least 10 years following the completion of a primary immunization series; studies that reported results from cohorts in which individuals received booster immunization at shorter intervals were not considered by the HWG due to the potential selection bias. The initial search was conducted in April 2015 and an updated search was completed in April 2016. Two independent reviewers also hand searched reference lists of articles identified through the literature search. A total of 41 relevant articles were reviewed and critically appraised by HWG members and NACI ([Table 1](#)). HWG also took note of the results of a Cochrane library review of studies published in June 2016 ⁽¹⁾ that reviewed benefits and harms of a booster dose of HB vaccine when provided at more than five years after the completion of the recommended primary immunization schedule. The review did not identify any randomised clinical trials that

would provide evidence for supporting or rejecting the need for a HB booster dose in healthy individuals with antibody levels below 10 IU/L.

HWG Chair presented the evidence and proposed recommendations to NACI on August 1, 2016. Following the review of the evidence and consultation at the NACI meeting on October 5 2016, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text of this update.

III. EPIDEMIOLOGY OF HEPATITIS B

HB virus (HBV) causes acute and chronic infection of the liver. Typical symptoms of acute infection include nausea, abdominal pain, fever and signs of liver dysfunction such as jaundice, dark urine, changes in stool colour and hepatomegaly. Acute HBV infection may be asymptomatic in up to 50% of adults and 90% of children, and fulminant hepatitis may occur in 1% to 2% of cases. Although the majority of individuals spontaneously clear the infection after 4 to 8 weeks, the risk of becoming a chronic carrier, potentially leading to cirrhosis and hepatocellular carcinoma, varies inversely with the age at which the infection occurs. Infants have a 90% to 95% chance, children over one year and less than 5 years of age 25% to 50% chance, and adolescents and adults 3% to 10% chance of developing chronic infection. Adults with diabetes may be at greater risk of progression to chronic infection and more severe disease.⁽²⁻⁵⁾

Following immunization, the duration of seroprotection (commonly accepted to be anti-HBs ≥ 10 IU/L) and the presence of anamnestic response have been associated with maternal infection status,⁽⁶⁾ the age of primary series initiation and the potency of doses used in the primary vaccine schedule.⁽⁷⁻⁹⁾ While the level of HB surface antigen antibodies (anti-HBs) is thought to be important for preventing acute infection, presence of immunologic memory is required for long-term protection.⁽¹⁰⁻¹⁵⁾ Due to a long incubation period of 60–90 days on average, even in the absence of protective antibody levels, stimulation of memory cells by immunization following exposure to HBV is believed to result in an antibody response which is adequate for the prevention of acute infection. Evidence also suggests that, in previously immunized individuals with preserved T- and B-cell memory, breakthrough infection (i.e. detection of HB core antigen antibodies [anti-HBc], HB surface antigen [HBsAg] or HBV DNA) does not lead to the development of chronic disease.⁽¹⁶⁻¹⁸⁾

Over the decade preceding the introduction of routine adolescent and infant HB immunization programs in the 1990s, all P/Ts experienced an incremental increase in acute HB infection rates, with the peak of 13/100,000 reported in 1989.⁽¹⁹⁾⁽²⁰⁾⁽²¹⁾ Since then, CNDSS data have demonstrated a continuous downward trend in HB disease incidence across Canada. A recently released analysis⁽²²⁾ confirmed this trend, noting a decrease in reported rates of acute HB cases from 1.0/100,000 in 2005 to 0.5/100,000 in 2013 and chronic HB cases from 13.6/100,000 to 12.0/100,000 between 2009 and 2013. Since 2005, rates of reported cases of acute HB infection have remained below 1.0/100,000 in individuals under 20 years of age, who would have been eligible for routine HB immunization as infants or adolescents. Substantial reductions in rates of reported acute HB have been noted also among those aged 30 to 39, whose eligibility for vaccine would have increased over that time period.⁽²³⁾ The rates for acute and chronic HB infection are observed to be higher in males than females. However, a more detailed analysis using CNDSS has been limited by the lack of explanatory data (e.g. risk factors or

immunization status information), variation in reporting practices across P/Ts, reporting delay and the overall low number of acute HB cases.

Information used for the estimate of national HB infection prevalence based on blood samples is also collected through the Canadian Health Measures Survey (CHMS).⁽²⁴⁾ Data collected between 2007 and 2011 for the population aged 14 to 79 indicate a prevalence of current HB infection of 0.4% (95% CI: 0.2-0.8), with the highest infection reported in the non-white (1.8%, 95% CI: 0.9-3.4) and the foreign-born populations (1.6%, 95% CI: 0.9-2.9).⁽²⁵⁾

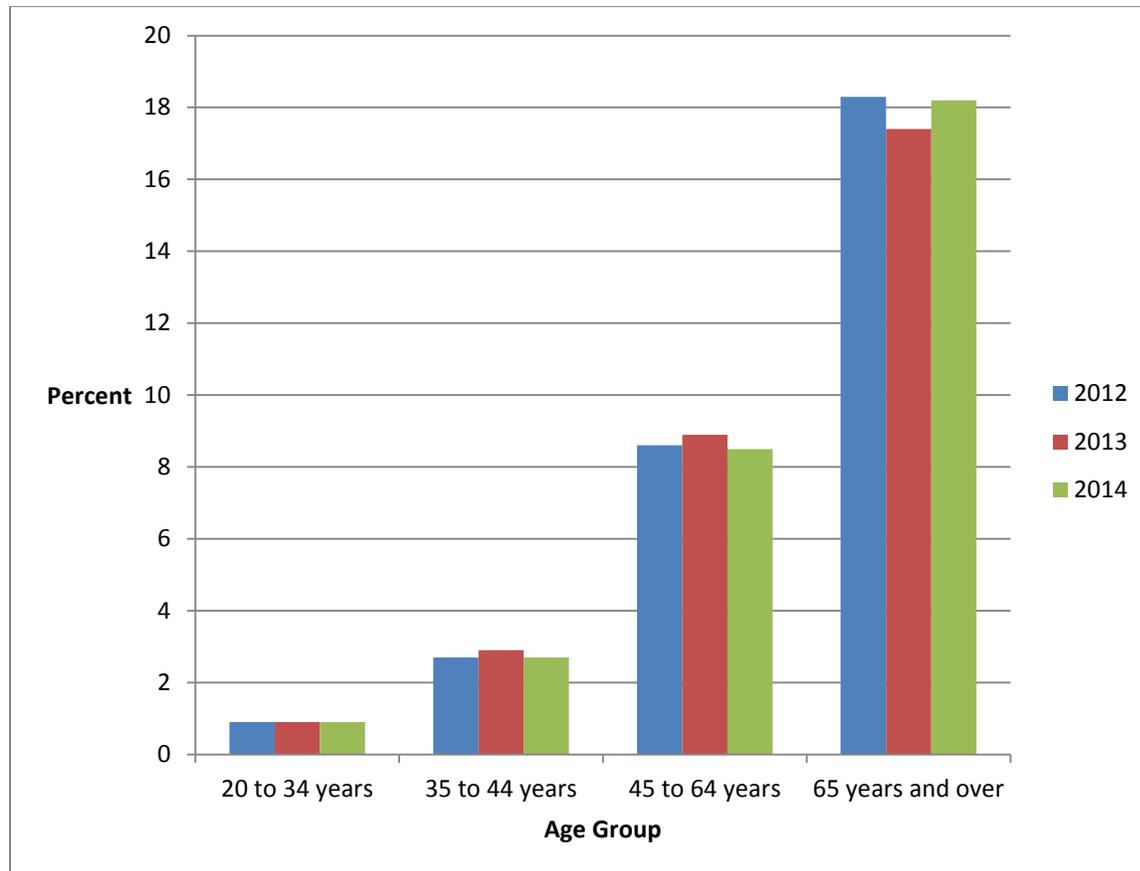
Since 1994, the Public Health Agency of Canada (PHAC) has routinely monitored immunization coverage through the National Immunization Coverage Survey (NICS). In P/Ts with universal infant immunization programs, the 2013 NICS survey estimated HB vaccine coverage with at least 3 doses among children 7 years of age to be 74.5% (95%CI: 70.8, 77.9) and coverage with at least one dose among adolescents 17 years of age to be 87.9% (95%CI: 86.6, 89.1).⁽²⁶⁾

Detailed information about routine P/T immunization programs and vaccination schedules is available on the Government of Canada website (<http://healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/schedule-calendrier/infants-children-vaccination-enfants-nourrissons-eng.php>) and in the Canadian Immunization Guide (CIG).⁽⁴⁾

HB infection in adults with diabetes

The proportion of adults with diagnosed diabetes increases with age, with the sharpest increase in prevalence occurring after the age of 45 years. In 2014, 6.7% of Canadians aged 12 or older (approximately 2 million people) reported that they had diabetes.⁽²⁷⁾ On average, between 2012 and 2014, there were approximately 65,000 individuals age 20-34, 130,000 individuals age 35-44, 845,000 individuals age 35-64 and 915,000 individuals age 65 and over living with diabetes in Canada.⁽²⁸⁾ Due to the implementation of universal infant and adolescent immunization programs, the majority of individuals under the age of 30 born in Canada are likely to have been vaccinated against HB.

Figure 1: Prevalence of diabetes among adults by age group, 2012/14 (Population who reported that they have been diagnosed by a health professional as having Type 1 or Type 2 diabetes, CCHS)



In 2011, the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC) published data on the risk of HB infection among adults with diabetes.⁽²⁹⁾ The population risk for HB infection among these individuals was estimated from 865 confirmed cases of acute HBV infection reported during 2009–2010 from eight Emerging Infections Program (EIP) sites constituting approximately 17% of the U.S. population. A multivariate analyses found adults 23 to 59 years of age with diabetes to have 2.1 (95% CI: 1.6–2.8) times the odds of developing acute HB compared to adults of the same age without diabetes. The odds were 1.5 (95% CI: 0.9–2.5) times as likely for persons aged 60 years and older.⁽³⁰⁾ Additional ACIP analysis of National Health and Nutrition Examination Survey (NHANES) data for the period 1999 to 2010 indicated a 60% ($p < 0.001$) higher seroprevalence of antibody to HB core antigen among adults with diagnosed diabetes compared with those without diabetes. In the US, the reported coverage of adults 19 years of age and older with at least 3 doses of HB vaccine was 24.5% (32.2% among adults aged 19–49 years and 15.7% among adults aged ≥ 50 years).⁽³¹⁾

Similar epidemiological data that would allow an estimate of the HB disease burden and risk of infection among individuals with diabetes is not currently available in Canada.

IV. VACCINES

Additional details about the types and contents of HB-containing vaccines available for use in Canada are provided in CIG.⁽⁴⁾

IV.1 Efficacy and effectiveness

Pre-exposure

HWG's assessment of evidence on long-term efficacy and effectiveness of HB vaccines in immunocompetent individuals, with particular focus on individuals immunized as infants and HCWs, was based on the findings of a joint Viral Hepatitis Prevention Board/World Health Organization (VHPB/WHO) conference, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization updated review of evidence on long-term protection of HBV vaccination,⁽³²⁻³⁴⁾ as well as the results of a meta-analysis conducted by Poorolajal et al. A supplementary literature search of studies published since November 2011 and a request for additional data from HB vaccine manufacturers did not identify any evidence that would suggest reduced long-term vaccine efficacy following immunization in infancy or among HCWs.

In November 2011 and October 2015, a comprehensive review of studies with up to 30 years of follow-up data was presented to WHO. Data on vaccination failures demonstrated that these events were rare and did not result in new clinical cases amongst the vaccinated population. The review did not find evidence for the need for a HB vaccine booster dose in routine immunization programmes.

A meta-analysis of long-term protective effects of HB immunization in over 9,300 individuals that was published in 2010 reported similar findings. Conducted by Poorolajal et al⁽³⁵⁾, the study found that overall cumulative incidence of breakthrough infection (using anti-HBc as a marker of infection) up to 20 years following the receipt of 3 vaccine doses was 0.007 [95% CI: 0.005 to 0.010]. Variation among studies included in the meta-analysis ranged from 0 to 0.094 (cumulative incidence 0.006 [95% CI: 0.002 to 0.010] after 11-15 years and 0.010 [95% CI: 0 to 0.019] after 16-20 years). Cumulative incidence of infection was determined to be 0.009 [95% CI: 0 to 0.019] among participants receiving the recombinant vaccine and 0.020 [95% CI: 0.010 to 0.030] among participants receiving the plasma-derived vaccine ($p = 0.003$). In studies covering a 20 year period, only eight transient HBsAg seroconversions were recorded, with no individuals becoming chronic carriers. Cumulative incidence of infection was 0.001 [95% CI: 0.000 to 0.005] for regions with low endemicity, 0.061 [95% CI: 0.000 to 0.177] for regions with intermediate endemicity and 0.017 [95% CI: 0.008 to 0.025] for regions with high endemicity ($p < 0.001$).

Post-exposure

Immunization with HBIG and HB vaccine within 24 hours after birth is estimated to be 85% to 95% effective in preventing HB infection in exposed neonates.^(2, 4, 36, 37) Prophylaxis with HB vaccine provided within one week of percutaneous or mucosal exposure to HB-positive blood and within two weeks of sexual exposure to HB-positive persons, has been demonstrated to be highly effective in preventing HB infection.⁽⁴⁾ A literature search, review of recommendations from other jurisdictions and a request for unpublished data from vaccine manufacturers did not provide any new evidence concerning the efficacy of post-exposure prophylaxis (PEP) with HB vaccine and immune globulin (HBIG).

IV.2 Immunogenicity

In total, HWG reviewed 39 publications that reported data on the immune response following the administration of a HB booster dose in individuals who were immunized as infants. In the majority of these studies, prior to booster vaccination, seroprotection (defined as anti-HBs titer ≥ 10 IU/L) was present in approximately 60-85% of individuals at 10 years and 30-40% of individuals at 15 years subsequent to primary immunization in infancy. Following booster vaccination, anamnestic response was present in 95-100% of individuals at 10 years, and 65-100% of individuals at 15 years after the completion of a HB primary immunization series. Based on the presence of anti-HBs ≥ 10 IU/L, protection against HB infection can be expected to range from 95-100% at 10 years and 85-100% at 15 years post HB immunization in infancy. Among adults who received primary immunization as infants, seroprotective antibody levels were found in approximately one third of individuals prior to, and 75-90% following the receipt of booster immunization. In all studies, virtually all individuals who did not reach seroprotective titres following the receipt of a booster dose were without detectable antibody levels at baseline. It should be noted that, although some of the reviewed studies did report a seroprotection cut-off at 12 IU/L, it was commonly perceived by NACI members that these levels were due to differences in used laboratory assays and were not relevant to the overall conclusions pertaining to vaccine immunogenicity.

An analysis of data from 21 studies⁽³⁸⁻⁵⁸⁾ in which anamnestic response was measured 10 to 23 years following primary immunization in infancy that was conducted by Hu et al. (unpublished)⁽⁵⁹⁾ for the British Columbia Ministry of Health was presented to the HWG. The study authors found that, in the majority of reviewed studies, anamnestic response (defined as anti-HBs titer ≥ 10 IU/L one to four weeks post booster vaccination) was present in more than 95% of individuals at 10 years and among approximately 75% of individuals at 20 years following primary immunization. Similar declining trends in antibody levels following booster immunization have also been reported in a meta-analysis of 29 studies involving more than 2,600 individuals.^(12, 39, 40, 42-44, 48, 49, 53-55, 57, 58, 60-75) conducted by Shonberger et al⁽⁸⁾. Based on the analysed data, study authors developed a prognostic model for estimating protection against HB infection up to 17 years post HB immunization in infancy. According to the model, when provided with three doses of at least 5 μg of HBsAg (last and preceding dose provided at least 6 months apart), anti-HBs level of ≥ 10 IU/L is observed in 92% (95% CI: 82-100) of individuals at 15 years following primary immunization. The proportion of individuals likely to be protected would slightly be reduced (90%, 95% CI: 78-100) in case of a shorter gap (less than 6 months) between last and preceding dose, and considerably reduced (61%, 95% CI: 33-88) in individuals who received doses containing less than 5 μg of HBsAg. The study did not find any association between the age of first dose and booster immunization antibody levels. In addition to these findings, HWG also considered results from subsequently (since September 2011) published studies that reported on post-booster immune response following immunization in infancy as well as unpublished data from a relevant Canadian trial.

Unpublished results⁽⁷⁶⁾ of a trial conducted in British Columbia that tested immune response persistence among adolescents 10 to 16 years of age following immunization in infancy using a 2, 4, 6 month schedule were also shared with the HWG. Among 215 adolescents 15 to 16 years of age who received a 5 μg dose series of Recombivax HB vaccine, 64% (138/215) were identified as being seronegative (anti-HBs titre < 12 IU/L) and challenged with a vaccine dose to assess immune memory. In this age group 1.4% (3/215) of individuals were found to be primary non-responders and 4.2% (9/215) required two additional vaccine doses to achieve seroprotection. In the 10 to 11 year age group that received a 2.5 μg dose series of Recombivax

HB vaccine in infancy, 78.6% (107/136) of individuals were seronegative and challenged with a vaccine dose. In this group, 97.1% (133/136) responded to a challenge dose. The remaining 2.9% (3/136) of individuals achieved seroprotective titres following the receipt of two additional vaccine doses. No primary non-responders were observed in this cohort. The investigators concluded that infant HB vaccination provides adequate protection throughout childhood but protection continuing well into adulthood is less certain than following adolescent immunization.

A study by Middleman A. et al.⁽⁷⁷⁾ reported antibody response to booster vaccination in 420 individuals 16 to 19 years who previously received 3 doses (2.5µg/dose) of recombinant vaccine by 12 months of age. Despite low (24%) prevalence of seroprotection, 92% exhibited protective antibody levels independent of the challenge dose used (10 µg or 20 µg dose). Although seroprotection was similar between individuals whose primary series was initiated within 7 days of age and those immunized at 4 weeks or older, older age at first dose was associated with significantly higher GMT levels (487.84 [CI: 319.65; 744.54] vs. 1745.77 [CI: 1065.45; 2860.49]).

In another study, Bagheri-Jamebozorgi et al.⁽⁷⁸⁾ measured immune responses in 300 individuals 20 years following the receipt of 3 doses of Engerix®-B vaccine (10 µg) provided at birth, 1.5 and 9 months of age. From 189 (63%) individuals who did not have protective antibody levels (anti-HBs <10 IU/L) at baseline, 138 received a booster dose that resulted in a 97% response rate (134/138).

Anamnestic response among adolescents 12 to 13 years of age who previously received three doses (0, 1, 6 months) of Engerix®-B vaccine (10 µg) before 18 months of age was also assessed by Behre et al.⁽⁷⁹⁾. Study authors found seroprotective titres to be present in 78.3% (95% CI: 73.1, 83) of study participants, with the proportion of those with seroprotective titres rising to 98.9% (95% CI: 96.9, 99.8) following the receipt of a booster dose. In the same population, Van Der Meeren et al.⁽⁸⁰⁾ reported anti-HBs titre of ≥10 IU/L to be present among 65% of individuals at 15 to 16 years following primary immunization. After receiving a 10 µg booster dose, protective titres were found in all but 6% of these individuals.

Hudu et al.⁽⁸¹⁾ evaluated immunity against HB among 402 undergraduate students 23 years after receiving one to three doses of HB vaccine at birth, 1 and 5 months of age. The study reported a presence of seroprotective titres in 252 individuals, of whom 68% received three, 19% two, and 13% one dose of vaccine. Although the majority of seronegative individuals (85/150) received only one vaccine dose in infancy, following the receipt of a booster, 94% (141/150) achieved protective antibody level of ≥10IU/L. Similarly, Chan et al.⁽⁸²⁾ evaluated immune response to booster immunization in a cohort of 212 students, 80% of whom lacked seroprotection 19 years following primary immunization with three doses (0,1,6) of plasma-derived vaccine. Of 69 students who received the booster immunization, 10 (14.5%) remained seronegative one month following the first booster dose. After receiving three booster doses, all students achieved seroprotective titres.

Chen et al.⁽⁸³⁾ measured immune response in 1142 individuals following the administration of two different booster doses at 10 to 15 years after primary immunization (0,1,6). Although approximately 50% of individuals had undetectable (anti-HBs < 1IU/L) antibody titres in both groups, after administering the first booster dose, seroprotection was observed in 86.7% (449/518) of the group receiving a 5 µg vaccine dose, and 91.2% (569/624) of the group receiving a 10 µg vaccine dose. In both groups, following the administration of 3 booster doses, more than 99% of individuals achieved seroprotective titres. A smaller European study conducted by Teoharov et al. found a 100% response rate to a booster dose of HB vaccine in 30 children between 10 and 15 years of age who received 3 doses of HB vaccine by 6 months

of age.⁽⁸⁴⁾ In another study conducted by Chen et al.⁽⁸³⁾ that used a combined Hepatitis A and B (HAHB) vaccine for booster immunization, similar seroresponse rates were reported as in children who received a HB vaccine booster. Following the first HAB booster dose, 75% of children achieved seroprotective titres, and following dose 3 seroprotective titres were observed in 98% of vaccinated individuals.

In another study conducted in Taiwan by Chang et al.,⁽⁸⁵⁾ 92.5% of seronegative adolescents who received immunization in infancy and were provided with a booster dose of HB vaccine at 15 years of age achieved seroprotective titres 6 weeks post vaccination. In a similar population-based cohort study conducted by Katoonizadeh et al.,⁽⁸⁶⁾ a booster dose was provided to 275 children aged 10 to 18 years who were born to a family with at least one HBsAg positive parent and immunized in infancy with three doses of HB vaccine. Anamnestic immune response was observed in 96% of individuals 10-11 years of age, 86% of individuals 12-14 years of age and 75% of individuals 15-18 years of age.

In addition to these studies, HWG also reviewed data on long term immunity following the use of a combination vaccine (Infanrix hexa; DTaP-HB-IPV-Hib) administered in infancy. An assessment report published by the European Medicines Agency⁽⁸⁷⁾ provided data on vaccine immunogenicity following the receipt of a single 10 µg dose of HB vaccine at 12 to 13 years of age in individuals who received three doses of DTaP-HB-IPV-Hib vaccine by 9 months of age and one dose of DTaP-HB-IPV-Hib between 11 and 18 months of age. Four weeks after the receipt of the HB vaccine booster, 97.6% (95% CI: 95.1, 99) achieved seroprotective antibody levels (anti-HBs ≥ 10IU/L) and 94% (95% CI: 90.7, 96.5) achieved anti-HBs concentration of more than 100 IU/L. Anti-HBs GMC increased 160 fold to 3502.6 IU/L (95% CI: 2672, 4591.5) following immunization with HB vaccine. Another study by Avdicova et al. reported on the persistence of antibody and immune memory 10 to 11 years following primary vaccination in infancy with DTPa-HBV-IPV-Hib or monovalent HB vaccine co-administered with DTPa-IPV-Hib. After the HB challenge dose, 97% of DTPa-HBV-IPV-Hib group recipients and 99% of children in the co-administration group achieved seroprotective titres. Anti-HBs levels equal to or over 100 IU/L were present in over 93.5% of individuals in both groups. Anti-HBs GMCs increased by at least 180 fold following the HB vaccine booster.⁽⁸⁸⁾

Two studies^(89, 90) providing information about seroprotection in immunocompromised individuals were reviewed by the HWG. A study by Inaba et al. measured long-term antibody levels in 141 children who received HB vaccine according to a three dose schedule at 12, 15 and 18 months following allogeneic hematopoietic stem cell transplantation (HSCT). Prior to immunization, only 51.8% of study participants had seroprotective levels (anti-HBs ≥10IU/L); this increased to 77.1% after the receipt of 3 doses of HB vaccine post-transplant. At more than 5 years following post-HSCT immunization, 72.9% of study participants retained seroprotective titres (43/59). Another meta-analysis of 12 studies measuring long-term immune responses to vaccination in HIV-infected patients (follow-up ranging from 12 to 115 months) was conducted by Kerneis et al. The meta-analysis reported a decrease of protection over time with 71% of primary responders maintaining seroprotective titers at year one, 33%-61% at year two, and 40% at year five following the receipt of three vaccine doses each containing 40 µg of HBsAg. In children born to HBsAg positive HIV-infected mothers, maintenance of seroprotective antibody titres was found to be 24% after 5.5 years. The meta-analysis found that, among primary responders, 38% (95%CI: 23%-54%) of adults and 61% (95%CI: 27%-90%) of children maintained protective antibody titers two years after immunization, and 8% (95%CI: 2%-19%) of adults and 30% (95%CI: 0%-76%) of children five years after immunization.

Information pertaining to the immunogenicity of HB vaccine in individuals with diabetes was also reviewed by the HWG. A systematic review of the literature^(29, 91, 92) conducted by Schillie et al. reported a similar age-dependent response among individuals with and without diabetes, when HB vaccine was administered in accordance with the recommended schedules. The proportion protected was generally greatest among children, ranging from 54.2–100.0% (median, 93.9%) in those with diabetes and 98.0–100.0% (median 100.0%) in children without diabetes. In adults, particularly those who were older, median seroprotection was lower among individuals with diabetes (31.3–94.4% [median, 88.2%]) compared to those without (35.2–96.9% [median, 93.6%]). Similar to healthy adults, lowest seroprotection rates in these studies were reported among diabetic adults with chronic kidney disease (ranging 41.8–85.3% [median, 60.1%]).

IV.3 Safety

HB containing vaccines are well tolerated, with adverse reactions such as irritability, headache, fatigue and injection site reactions (e.g., pain and redness) commonly being mild and transient.⁽⁴⁾

In October 2011, for the purpose of assessing safety outcomes in individuals with diabetes following HB vaccine administration, ACIP published a review of 12 studies.⁽⁹³⁾ None of the reviewed studies reported serious vaccine-related adverse events, although ACIP did note the very rare occurrence of anaphylaxis in yeast-sensitive individuals that was reported by the Institute of Medicine (IOM).⁽⁹⁴⁾

V. RECOMMENDATIONS

Please refer to [Table 6](#) for an explanation of NACI grading of evidence.

Recommendation 1: NACI does not recommend routine booster doses of HB vaccine for immunocompetent individuals following the completion of a recommended HB immunization schedule given in infancy. (NACI Evidence Grade B Recommendation)

NACI concludes that there is fair evidence to make this recommendation, based on the limited information available through epidemiological and literature reviews summarized in this statement. Continuous, long-term, assessment of enhanced epidemiological data for the appearance of acute disease or the HBsAg carrier state in immunized populations (general population and groups-at-risk) is required before revising current recommendations. National enhanced surveillance systems should as a minimum include information on: age, sex, comorbidities, vaccination and immigration status.

Recommendation 2: NACI recommends that adults with diabetes need not be considered as a separate high risk group for immunization with HB vaccine. (NACI Evidence Grade I Recommendation)

NACI recommends HB vaccine for all individuals without contraindications who wish to decrease their risk of HB, including individuals with Type 1 and Type 2 diabetes. American data suggest a higher prevalence of previous or current HB infection among adults with diabetes compared to adults without diabetes, but similar Canadian epidemiological data are lacking. As there are notable differences between health care systems in the USA and Canada, and there is no current indication of higher risk of infection for individuals with diabetes in the general

Canadian population, NACI does not have sufficient evidence to consider these individuals a separate high risk group for immunization with HB containing vaccine. NACI will continue to monitor the evidence as it evolves.

Recommendation 3: For immunocompromised individuals, initial annual monitoring of HB antibody levels following HB immunization may be considered. (NACI Evidence Grade B Recommendation)

Optimal timing and frequency of further serological testing should be based on the severity of the immunocompromised state and whether the risk of HB is still present. In immunocompromised persons who initially responded to HB vaccine, booster immunization is required if anti-HBs titres fall below 10 IU/L. This recommendation is in line with similar recommendations made by the US Advisory Committee on Immunization Practices (ACIP), World Health Organization (WHO) and Australia's national immunisation technical advisory group. For individuals with chronic kidney disease and on dialysis who are known to respond sub-optimally to HB vaccination and in whom anti-HBs concentrations decline rapidly, NACI has previously recommended annual evaluation of HB antibody levels.

Recommendation 4: Immunization with HB-containing vaccine should be provided according to determined provincial and territorial (P/T) schedules. (NACI Evidence Grade I Recommendation)

There are several authorized schedules for HB vaccines in Canada. Over the last 2 decades, all P/Ts have effectively implemented prenatal HB screening and at-risk infant immunization programs. With marked reductions in HB incidence that have been observed across Canada and no data demonstrating an obvious advantage of any of the used schedules, optimal timing of primary HB vaccination remains to be contingent on existing P/T epidemiology and specific programmatic considerations. Epidemiological information demonstrating failure of universal prenatal screening and routine immunization programs (i.e. detection of HBV infection in infants and children awaiting immunization) should be collected and analysed on an ongoing basis, so that appropriate changes can be made to existing HB immunization programs as needed.

VI. SURVEILLANCE AND RESEARCH PRIORITIES

- Continuous monitoring of HB epidemiology in Canada including incidence and trends of acute and chronic disease
- Development and maintenance of enhanced surveillance systems that have the ability to capture cases of vaccine failure and breakthrough infection, particularly in high risk individuals
- Studies that aim to determine the duration of immunity and long-term correlates of protection, with particular focus on countries with low HB incidence
- Studies to determine the level of humoral, cellular anamnestic or both responses that are required for preventing chronic infection, and the timing of booster doses according to preserved anamnestic response
- Studies for evaluating the efficacy and effectiveness of Hepatitis B programs in long-term care facilities

TABLES

Table 1: Summary of evidence on long-term immunogenicity and effectiveness of HB vaccination in infancy

| STUDY DETAILS | | | | | SUMMARY | |
|--|---|--|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Samandari T, Fiore AE, Negus S, et al. Differences in response to a hepatitis B vaccine booster dose among Alaska children and adolescents vaccinated during infancy. <i>Pediatrics</i> 2007; 120: e373-381. ⁽⁴⁶⁾ | <p>Primary immunization: Three doses of recombinant (2.5-, 5-, or 10 µg dose formulation) or plasma-derived vaccine (10 µg dose)</p> <p>Booster immunization: Recombivax; Merck & Co, 5 µg dose</p> | <p>US, Alaska</p> <p>Nonrandomized comparison study</p> <p>Anamnestic response defined as: fourfold or higher rise in anti-HBs if at baseline antibody levels ≥10 IU/L or anti-HBs ≥10 IU/L if at baseline <10 IU/L.</p> <p>Serology at 4 weeks post booster dose</p> | <p>N=212</p> <p>Alaska Native peoples</p> <p>Group 1: 138 children 10-14.7 years of age previously immunized with recombinant vaccine</p> <p>Group 2: 74 children 11.7-14.9 years of age previously immunized with plasma-derived vaccine</p> | <p>Group 1:</p> <ul style="list-style-type: none"> 14% (20/138) with anti-HBs ≥10 IU/L at baseline; 59% (87/138) with anti-HBs <0.1 IU/L 88% (120/137) with anamnestic response after booster dose; 81% (71/87) of children with anti-HBs <0.1 IU/L with anamnestic response Mean anti-HBs GMC (95% CI): <ul style="list-style-type: none"> At baseline: 4.6 IU/L At 4 weeks post booster: 145 IU/L (89.1–237.0) <p>Group 2:</p> <ul style="list-style-type: none"> 21% (16/74) with anti-HBs ≥10 IU/L at baseline; 51% (38/74) with anti-HBs <0.1 IU/L 71% (53/74) with anamnestic response after booster dose; 50% (19/38) of children with anti-HBs <0.1 IU/L with anamnestic response Mean anti-HBs GMC (95% CI): <ul style="list-style-type: none"> At baseline: 3.2 IU/L At 4 weeks post booster: 29.8 IU/L (12.4–71.8) <p>No study participant with evidence of chronic hepatitis B virus infection.</p> | II-1 | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|--|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Hammit LL, Hennessy TW, Fiore AE, et al. Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: a follow-up study at 15 years. <i>Vaccine</i> , 2007; 25(39-40): 6958-64. ⁽⁵⁸⁾ | Primary immunization: Recombivax, Merck & Co, 2.5 µg dose at birth, 1-3 and 6-9 months of life Booster immunization: Recombivax, Merck & Co, 5 µg dose | US, Alaska Serological study Serology 10-14 days and one month after booster dose Anamnestic response defined as antibody increase within 15 days of booster dose in those with anti-HBs <10 IU/L or, for children with anti-HBs ≥5 IU/L, a 4-fold rise in antibody | N=37 Individuals median 14.6 years of age (range 13.7–15.6) born to seronegative mothers; all individuals with anti-HBs ≥10 IU/L at 18 months of age | 5% (2/37) of children with anti-HBs ≥10 at study enrollment; all children anti-HBcAg(-) 51% (18/35) participants with anamnestic response two weeks post booster; 60% (21/35) with protective antibody levels on one month after booster dose 16 and 23-fold increase in GMC observed 13 and 28 days post booster, respectively | III | Poor |
| Petersen KM, Bulkow LR, McMahon BJ, Zanis C, Getty M, Peters H, Parkinson AJ. Duration of hepatitis B immunity in low risk children receiving hepatitis B vaccinations from birth. <i>Pediatr Infect Dis J</i> . 2004 Jul;23(7):650-5. ⁽⁷³⁾ | Primary series: 10 µg dose of plasma-derived vaccine (Heptavax-B, Merck Sharp & Dohme) provided within first 7 days of life, at 4–6 weeks and 6 months of age. | US, Alaska Serological study | Group 1: 17 children, mean age 12.6 years, born to HBsAg(-) mothers and immunized with plasma-derived vaccine; all with anti-HBs titers of ≥10 IU/L following primary immunization | Group 1: <ul style="list-style-type: none"> 24% (4/17) with anti-HBs ≥10 IU/L at baseline 67% (8/12) with anti-HBs ≥10 IU/L at 6 weeks post vaccination Group 2: <ul style="list-style-type: none"> 31% (5/16) with anti-HBs ≥10 IU/L at baseline 90% (9/10) with anti-HBs ≥10 IU/L | II | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|---|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | Booster dose: Recombivax (5 µg dose) | | Group 2: 16 children, mean age 12.1 years, born to HBsAg(+) mothers and immunized with plasma-derived vaccine; all with anti-HBs titers of ≥10 IU/L following primary immunization | at 6 weeks post vaccination | | |
| West DJ, Watson B, Lichtman J, Hesley TM, Hedberg K. Persistence of immunologic memory for twelve years in children given hepatitis B vaccine in infancy. <i>Pediatr Infect Dis J.</i> 1994 Aug;13(8):745-7 ⁽⁹⁵⁾ | Primary immunization: Two 5 µg doses of plasma-derived vaccine (Heptavax-B, Merck and Co) provided at 3 and 11 months of age Booster immunization: Recombivax, Merck and Co, 5 µg dose | US Serological study Serology 7 days and one month after booster dose Anamnestic response defined as two-fold antibody increase within 7 days or antibody titre ≥10 IU/L in individuals with anti-HBs <10 IU/L | N=14 Children 12 years following completion of primary immunization in infancy who were initially recruited to participate in a Heptavax-B safety/immunogenicity study | No children HBsAg(+) or Anti HBc(+); all children with anti-HBs titre ≥10 IU/L One week following booster administration, all exhibited 2 to 42 fold rise in titre; all with titres exceeding those achieved following primary immunization at 4 weeks after booster immunization | II | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Middleman A. et al. Duration of Protection After Infant Hepatitis B Vaccination Series. Pediatrics 2014; 133:6 e1500 -e1507 ⁽⁷⁷⁾ | Primary immunization: Three 5 µg doses; primary immunization completed by 12 months of age Booster immunization: ENGERIX®-B, GlaxoSmithKline, 10 or 20 µg dose | US Non-randomized comparison serological study | N=420 Group 1: 240 individuals 16 to 19 years old in whom immunization was initiated within 7 days of birth Group 2: 180 individuals 16 to 19 years old in whom immunization initiated at 4 or more weeks of age | Group 1: <ul style="list-style-type: none"> 16.7% with anti-HBs≥10 IU/L at baseline 90.4% with anti-HBs≥10 IU/L post booster Group 2: <ul style="list-style-type: none"> 33.9% with anti-HBs≥10 IU/L at baseline 93.9% with anti-HBs≥10 IU/L post booster <p>GMTs in response to a challenge dose significantly higher among those in Group 2 versus Group 1 and among those who received the 20 µg versus 10 µg dose; no differences observed between groups in the proportion of participants achieving seroprotection</p> | II | Good |
| Bialek SR, Bower WA, Novak R, et al. Persistence of protection against hepatitis B virus infection among adolescents vaccinated with recombinant hepatitis B vaccine beginning at birth: a 15-year follow-up study. Pediatr Infect Dis J, 2008; 27(10): 881-5. ⁽⁴⁸⁾ | Primary immunization: Recombivax, Merck and Co, 5 µg dose at birth, 2.5µg at 2 and 6 months of age Booster immunization: Recombivax; Merck & Co, 5 µg | Micronesia Serological study Anamnestic response defined as: anti-HBs ≥10 IU/L if at baseline <10 IU/L. Serology at 2 | N=105 Individuals immunized in infancy median 15.1 years prior to study enrolment (median age of study participants 15.8 years) and with no evidence of HB infection at 2-3 | 60%(63/105) of study participants with protective antibody levels at 35 months following initial immunization 7% (7/97) with anti-HBs≥10 IU/L and anti-HBc (-) at baseline; none HBsAg(+); 7.6% (8/105) anti-HBcAg(+); 3/8 anti-HBc (+) individuals with anti-HBs≥10 IU/L Following booster administration, 48% (46/97) of study participants achieved | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | dose | weeks post booster dose | years of age | seroprotective titres after booster dose; higher proportion of seroprotection (64.3% vs. 35.2%) among individuals who had seroprotective titres at 35 months following primary immunization | | |
| Chaves SS, Groeger J, Helgenberger L, et al. Improved anamnestic response among adolescents boosted with a higher dose of the hepatitis B vaccine. <i>Vaccine</i> , 2010; 28(16): 2860-4. ⁽⁵⁷⁾ | Primary immunization: Recombivax, Merck and Co, 5µg dose at birth and 2.5µg dose at 2 and 6 months of age Booster immunization: Recombivax, Merck and Co, 5 or 10 µg dose | Micronesia Serological, non-randomized, comparison study Serology 14 days after booster dose Antibody titre ≥10 IU/L considered protective Anamnestic response defined as 4 fold increase in anti-HBs and titre ≥10 IU/L | Group 1: 89 individuals median 17.7 (95% CI: 16.7, 18.7) years of age provided with 10 µg dose Group 2: 105 adolescents median 15.7 (95% CI: 14.9, 16.8) years of age provided with 5 µg dose | None of study participants HBsAg(+) Group 1: <ul style="list-style-type: none"> 16% (14/89) anti-HBcAg(+) Among anti-HBcAg(-) individuals, 9% (7/74) with anti-HBs≥10 prior to booster dose 60.0% (36/60) with anamnestic response following booster dose; in total, 65% (44/68; 95% CI: 52, 76) of individuals with anti-HBs≥10 after booster dose Group 2: <ul style="list-style-type: none"> 7.6% (8/105) anti-HBcAg(+) Among anti-HBcAg(-) individuals 7% (7/96) with anti-HBs≥10 prior to booster dose 44% (39/89) with anamnestic response following booster dose; in total, 48% (46/96) of individuals with anti-HBs≥10 after booster dose | III | Poor |
| Chaves SS, Fischer G, Groeger J, Patel PR, Thompson ND, Teshale | Primary immunization: Recombivax, | Palau Serological, non- | Group 1: 172 individuals median 11 (95% CI: 10.3, | 5% (9/190) anti-HBcAg(+) Group 1: | III | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|--|---|---|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| EH, Stevenson K, Yano VM, Armstrong GL, Samandari T, Kamili S, Drobeniuc J, Hu DJ. Persistence of long-term immunity to hepatitis B among adolescents immunized at birth. Vaccine. 2012 Feb 21;30(9): 1644-9. ⁽⁹⁶⁾ | Merck and Co, 5µg dose at birth and 2.5µg dose at 2 and 6 months of age (first dose before 7 days after birth and third dose before 1 year of age) Booster immunization: Recombivax, Merck and Co, 5 or 10 µg dose | randomized, comparison study Serology 14 days after booster dose Antibody titre ≥10 IU/L considered protective Anamnestic response defined as 4 fold increase in anti-HBs and titre ≥10 mIU | 11.7) years of age Group 2: 60 adolescents median 15.8 (95% CI: 15.1, 16.5) years of age All participants HBsAg/anti-HBc(-) and with Protective anti-HBs titers at 12 months of age; more than 70% with anti-HBs ≥100 IU/L at 12 months of age | <ul style="list-style-type: none"> 79% (59/75) without protective titres prior to booster dose 81% (48/59) with anamnestic response following booster dose Group 2: <ul style="list-style-type: none"> 8% (49/53) with anti-HBs≥10 prior to booster dose 71% (35/49) with anamnestic response following booster dose | | |
| Salama II, Sami SM, Salama SI, Rabah TM, El Etreby LA, Abdel Hamid AT, Elmosalami D, El Hariri H, Said ZN. Immune response to second vaccination series of hepatitis B virus among booster dose non-responders. Vaccine. 2016 Feb 27 ⁽⁹⁷⁾ | Primary immunization: not stated Booster immunization: 10 µg dose of Euvax rHB vaccine | Egypt Serological, non-randomized, comparison study Antibody titre ≥10 IU/L considered protective Anamnestic response defined as anti-HBs titre ≥10 IU/L 4 weeks after receipt of booster dose | Group 1: 1026 individuals between 10 and 15 years of age Group 2: 821 individuals ≥15 years of age All study participants received 3 vaccine doses in infancy | Group 1: <ul style="list-style-type: none"> 41% (420/1026) individuals with anti-HBs≥10 at baseline 90% (420/468) individuals with anti-HBs≥10 after booster dose Group 2: <ul style="list-style-type: none"> 30% (250/821) individuals with anti-HBs≥10 at baseline 87% (303/350) individuals with anti-HBs≥10 after booster dose | III | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|--|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Boxall, EH, A Sira J, El-Shuhkri N, et al. Long-term persistence of immunity to hepatitis B after vaccination during infancy in a country where endemicity is low. <i>J Infect Dis</i> , 2004; 190(7): 1264-9 ⁽⁵¹⁾ | <p>Primary immunization: 10 µg dose⁽⁹⁸⁾ of recombinant (HBVax, Merck Sharp and Dohme) vaccine provided at birth, 1, 2 and 6 months of age; some children also received HBIg at birth</p> <p>Booster immunization: recombinant HBVax II, Aventis Pasteur, 5 µg dose</p> | <p>UK</p> <p>Serological study</p> <p>Serology at 4 weeks post booster dose</p> <p>Antibody titre ≥10 IU/L considered protective</p> | <p>N=116</p> <p>Children who received 3 doses of HB vaccine with or without HBIg at birth</p> <p>Group 1: 64 children mean age 14.5 years (7.7–17.3) born to HBsAg(+) mothers previously recruited to participate in a HB vaccine efficacy study</p> <p>Group 2: 52 siblings of initially recruited children, mean age 11.7 years (6.0–18.4)</p> | <p>None of the children in either group HBsAg(+); 1 child in each group anti-HBcAg(+)</p> <p>Group 1:</p> <ul style="list-style-type: none"> 50% (32/64) with anti-HBs≥10 IU/L at baseline 89% (57/64) with anti-HBs≥10 after booster dose; 3 children, although with seroprotective titres, were considered to be primary responders due to low antibody levels 11-fold increase in mean anti-HBs GMC pre/post booster Majority (5/7) of children that did not respond to booster dose received HBIg at birth; of 29 children given vaccine plus HBIg, 8 (27%) did not respond to the booster dose vs. 2/35 (6%) of children given vaccine alone (p=0.034). <p>Group 2:</p> <ul style="list-style-type: none"> 54% (28/52) with anti-HBs≥10 IU/L at baseline 77% (40/52) with anti-HBs≥10 after booster dose; one child, although with seroprotective titres, was considered to be a primary responder due to low antibody | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|---|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | | | | <p>levels</p> <ul style="list-style-type: none"> • 37-fold increase in mean anti-HBs GMC pre/post booster • Of 13 nonresponders and primary responders, 2 are likely to have received vaccine plus HBIg, and 11 only the vaccine <p>Levels of antibody in children born to HBeAg(+) and HBeAg(-) mothers similar</p> | | |
| Behre U, Bleckmann G, Crasta PD, Leyssen M, Messier M, Jacquet JM, Hardt K. Long-term anti-HBs antibody persistence and immune memory in children and adolescents who received routine childhood hepatitis B vaccination. Hum Vaccin Immunother. 2012 Jun;8(6):813-8. ⁽⁷⁹⁾ | <p>Primary series: Three-dose schedule (0, 1 and 6 months) with ENGERIX®-B, GlaxoSmithKline (10 µg dose); first two doses provided before 9 months of age and third dose provided at before 18 months of age</p> <p>Booster dose: ENGERIX®-B, GlaxoSmithKline (10 µg dose)</p> | <p>Germany</p> <p>Serological study</p> <p>Serology 4 weeks after booster dose</p> <p>Anamnestic response defined as anti-HBs ≥10 IU/L in pre-booster seronegative individuals or at least a 4-fold increase in anti-HBs level in those who were seropositive prior to booster immunization</p> | <p>N=282</p> <p>Children mean age 12.4 years (SD: 0.48) immunized at birth</p> | <p>78% (220/282; 95% CI: 73.1–83) with anti-HBs ≥ 10 IU/L prior to booster immunization; 8% (23/282) of children without detectable antibody (<3.3 IU/mL) levels</p> <p>97.2% (95% CI: 94.5–98.8) of children with anamnestic response to the challenge dose; 98.9% (95% CI: 96.9–99.8) seropositive following booster immunization</p> <p>91.3% (95% CI: 72.0–98.9) children without detectable antibody titres achieved anti-HBs ≥ 10 IU/L post booster; 93.6% (95% CI: 90.1-96.2) with anti-HBs ≥100 IU/L</p> | III | Good |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Van Der Meeren O, Behre U, Crasta P. Immunity to hepatitis B persists in adolescents 15-16 years of age vaccinated in infancy with three doses of hepatitis B vaccine. 2016 Apr 16. pii: S0264-410X(16)30142-6. ⁽⁸⁰⁾ | <p>Primary series: Three-dose schedule (0, 1 and 6 months) with ENGERIX®-B, GlaxoSmithKline (10 µg dose); first two doses provided before 9 months of age and third dose provided at before 18 months of age</p> <p>Booster dose: ENGERIX®-B, GlaxoSmithKline (10 µg dose)</p> | <p>Germany</p> <p>Serological study</p> <p>Serology 4 weeks after booster dose</p> <p>Seropositivity defined as anti-HBs from 6.2-10 IU/L and seroprotection as anti-HBs ≥10 IU/L. Anamnestic response defined as anti-HBs ≥10 IU/L in pre-booster seronegative individuals or at least a 4-fold increase in anti-HBs level in those who were seropositive prior to booster immunization</p> | <p>N= 292</p> <p>Children mean age 15.3 (SD: 0.5) years immunized at birth</p> | <p>65% (190/292; 95% CI: 59.6–70.9) with anti-HBs ≥ 10 IU/L prior to booster immunization</p> <p>97.9% (95% CI: 95.6–99.2) with anti-HBs ≥ 10 IU/L following booster dose; 90.8% (95% CI: 86.8–93.8) with anti-HBs ≥ 100 IU/L</p> <p>6% (6/102) of individuals with antibody levels <10 IU/L remained without seroprotection following booster dose; all seropositive individuals achieved seroprotection, resulting in an overall observed anamnestic response in 96.9% (95% CI: 94.2-98.6) of study participants</p> <p>Median increase in GMC post booster immunization 150 fold (4134.9 IU/L; 95% CI: 3114.2–5490.1)</p> | III | Good |
| Kao JT, Wang JH, Hung CH, et al. Long-term efficacy of plasma-derived and recombinant | Primary immunization: 5 ug plasma-derived (HEVAC- | <p>Taiwan</p> <p>Serological study</p> | Group 1: 437 children 12-15 years of age born to HBsAg(+) and | <p>Group 1:</p> <ul style="list-style-type: none"> 65% (286/437) with anti-HBs≥10 prior to booster dose; mean anti-HBs GMT 240.6±330.4 IU/L; | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|---|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| hepatitis B vaccines in a rural township of Central Taiwan. Vaccine, 2009; 27(12): 1858-62. ⁽⁵⁶⁾ | <p>B®; Pasteur Institut, Marnes-la-Coquette, France. or LGVAC-B®; Lifeguard Pharmaceutical Inc., Taipei, Taiwan) or 2.5 µg dose of recombinant vaccine (Recombivax HB®; Merck Sharp & Dohme)</p> <p>Booster immunization: ENGERIX®-B, GlaxoSmithKline, 2.5 µg dose</p> | <p>Antibody titre ≥10 IU/L considered protective; anamnestic response defined as increase in anti-HBs to ≥10 IU/L</p> <p>Serology 3 weeks after booster dose</p> | <p>previously immunized with plasma-derived vaccine at 0, 1, 2 and 12 months of age</p> <p>Group 2: 1101 children 12-15 years of age previously immunized with plasma-derived vaccine at 0, 1, 2 and 12 months of age</p> <p>Group 3: 250 children 12-15 years of age immunized with recombinant vaccine at 0, 1, and 6 months of age</p> <p>Infants born to HBeAg(+) mothers also received HBIg at birth</p> <p>Booster dose administered to</p> | <p>11.4% (50/437) HBsAg(+) and 29.5% (129/437) anti-HBcAg(+)</p> <ul style="list-style-type: none"> 66% (70/105) of seronegative individuals with anti-HBs≥10 after booster dose; mean anti-HBs GMT 370.2±422.5 IU/L <p>Group 2:</p> <ul style="list-style-type: none"> 44% (484/1101) with anti-HBs≥10 prior to booster dose; mean anti-HBs GMT 92.3±220.9 IU/L; 5.4% (59/1101) HBsAg(+) and 12.5% (138/1101) anti-HBcAg(+) 75% (318/544) of seronegative individuals with anti-HBs≥10 after booster dose; mean anti-HBs GMT 395.6±414.2 IU/L <p>Group 3:</p> <ul style="list-style-type: none"> 36% (90/250) with anti-HBs≥10 prior to booster dose; mean anti-HBs GMT 41.9±123.8 IU/L; 1.2% (3/250) HBsAg(+) and 4.4% (11/250) anti-HBcAg(+) 93% (146/157) of seronegative individuals with anti-HBs≥10 after booster dose; mean anti-HBs GMT 610.6±401.7 IU/L | | |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | | | individuals with antibody titre <10 IU/L | | | |
| Chang YC, Wang JH, Chen YS, Lin JS, Cheng CF, Chu CH. Hepatitis B virus vaccination booster does not provide additional protection in adolescents: a cross-sectional school-based study. BMC Public Health. 2014 Sep 23;14:991. ⁽⁸⁵⁾ | Primary immunization: 5 ug plasma-derived (HEVAC-B®; Pasteur Institut, Marnes-la-Coquette, France. or LGVAC-B®; Lifeguard Pharmaceutical Inc., Taipei, Taiwan) or 5 or 20 ug dose of recombinant vaccine (Recombivax HB®; Merck Sharp & Dohme or ENGERIX®; GlaxoSmithKline) Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | Taiwan Serological study Antibody titre ≥10 IU/L considered protective; anamnestic response defined as increase in anti-HBs to ≥10 IU/L Serology 6 weeks after booster dose | N=1054 Adolescents 15 years of age who received immunization in infancy | <ul style="list-style-type: none"> • 397/1054 (37.7%) with anti-HBs ≥10 prior to booster dose • 529/570 (92.5%) of individuals that received a booster dose with anti-HBs ≥10 • Median anti-HBs titres before and after booster dose were 1.1 and 545.5 IU/L, respectively • An analysis of HBsAg prevalence that was conducted as a part of a larger longitudinal study (N= 6950; individuals from 6 to 18 years of age) did not show any statistical significance (p = 0.154) with aging | III | Fair |
| Su FH, Cheng SH, Li CY, et al. Hepatitis B seroprevalence and anamnestic response | Primary immunization: 5 µg dose of plasma-derived | Taiwan Serological study | N=843 Students mean age | 34% (283/843) with seroprotective titres at baseline; 44% of seronegative individuals without detectable titres (anti-HBsAg <0.1 IU/L) | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|---|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| amongst Taiwanese young adults with full vaccination in infancy, 20 years subsequent to national hepatitis B vaccination. Vaccine, 2007; 25(47): 8085-90. ⁽⁴³⁾ | (Havac B, Pasteur-Merieux, or Lifeguard, Hsin-Chu) vaccine provided at birth, 1, 2, and 12 months of age Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | Serology 4 weeks after booster dose Antibody titre between 10 and 100 IU/L considered borderline protective; ≥ 100 IU/L considered protective; anamnestic response defined as increase in anti-HBs titre ≥10 IU/L | 18.7±0.4 years immunized in infancy | 2.7% (23/843) anti-HBcAg(+)/HBsAg negative and 1.4% (12/843) anti-HBcAg(+)/HBsAg positive; 75% (8/12) anti-HBcAg(+)/HBsAg(+) individuals received HBIg at birth 75% (238/316) of individuals achieved anti-HBs≥10 IU/L after receiving booster dose 81.3% (70/78) of individuals who failed to exhibit anamnestic response with pre booster serum anti-HBs level <0.1 IU/L | | |
| Jan CF, Huang KC, Chien YC, et al. Determination of immune memory to hepatitis B vaccination through early booster response in college students. Hepatology, 2010; 51(5): 1547-54. ⁽⁴⁴⁾ | Primary immunization: At least three 5 µg doses of plasma-derived vaccine (first dose provided at birth) Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | Taiwan Serological study Serology at 7 to 10 days and 4 weeks after booster dose Seroprotective titer defined as anti-HBs≥10 IU/L | N= 127 HBsAg(-), anti-HBc(-) and anti-HBs(-) students 18-23 years of age immunized in infancy | 76% (96/127) with anti-HBs≥10 IU/L at 4 weeks after booster dose; protective antibody levels achieved by 20.5% (26/127) at 7 to 10 days post booster From 101 study participants who were seronegative at 7 to 10 days post booster dose, 70% (70/101) developed protective antibody titres at 4 weeks after immunization | II-3 | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|---|---|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Lin CC, Yang CY, Shih CT, Chen BH, Huang YL. Waning immunity and booster responses in nursing and medical technology students who had received plasma-derived or recombinant hepatitis B vaccine during infancy. <i>Am J Infect Control</i> . 2011 Jun;39(5):408-14. ⁽⁷⁴⁾ | Primary series: 5 µg dose of plasma-derived vaccine (HavacB; Pasteur-Merieux, Lyon, France, or Lifeguard hepatitis B vaccine, Hsin-Chu, Taiwan) at 0, 1, 2, and 12 months of age or recombinant vaccine at 0, 1, and 6 months of age Booster dose: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | Taiwan Serological study Seroprotection defined as anti-HBs≥10 IU/L. | Group 1: 1,133 students 16 years of age who received plasma-derived vaccine in infancy Group 2: 674 students 16 years of age who received recombinant vaccine in infancy Majority (93%) of study participants female | Group 1: <ul style="list-style-type: none"> 43% (490/1133) with protective titres at baseline; 1% (9/1133) HBsAg(+) 92.9% (39/42) with anti-HBs≥10 IU/L post booster immunization Group 2: <ul style="list-style-type: none"> 33% (226/674) with protective titres at baseline; 1% (5/674) HBsAg(+) 96% (326/340) with anti-HBs≥10 IU/L post booster immunization | III | Fair |
| Wang LU and Lin HH. Ethnicity, substance use, and response to booster hepatitis B vaccination in anti-HBs-seronegative adolescents who had received primary infantile vaccination. <i>J Hepatol</i> , 2007; 46(6): 1018-25 ⁽⁴¹⁾ | Primary immunization: plasma-derived hepatitis vaccine, 5 µg dose ⁽⁹⁹⁾ at birth, 1, 2 and 12 months of age Booster immunization: ENGERIX®-B, | Taiwan Serological study Responders defined as booster recipients with postbooster anti-HBs titer ≥10 IU/L. | N=386 Adolescents mean 15.9 ± 0.5 years of age with anti-HBs titers <10 IU/L immunized in infancy | 49% (190/386) with undetectable (<0.1 IU/L) antibody levels at baseline 77.2% (298/386) of study participants achieved seroprotection 4 weeks after booster dose; 59% (112/190) of individuals with undetectable antibody levels and 95% (186/196) of those with antibody levels between 0.1 and 9.9 IU/L responded to booster immunization (OR 13.97; 95%CI: | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|---|---|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | GlaxoSmithKline, 20 µg dose | | | 6.63,29.44) | | |
| Lu CY, Ni YH, Chiang BL, et al. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. <i>J Infect Dis</i> , 2008; 197(10): 1419-26. ⁽⁴⁰⁾ | Primary immunization: Four 10 µg doses of plasma-derived (Hevac B; Pasteur-Mérieux) Vaccine provided at birth, 1, 2 and 12 months of age; infants born to HBeAg(+) mothers also received HBIG Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | Taiwan Serological study Serology at 4 weeks post booster Anti-HBs concentrations ≥10 IU/L defined as protective. Booster provided only to individuals in Group 2 | Group 1: 175 individuals 18-21 years of age immunized as infants and born to HBsAg(+) mothers Group 2: 5,981 individuals 15-17 years of age immunized as infants | Group 1: <ul style="list-style-type: none"> 62.3% (109/175) anti-HBsAg(+) at baseline 6.3% (11/175) HBsAg(+) and 11.4% (20/175) HBcAg(+) Group 2: <ul style="list-style-type: none"> 37% (2215/5981) anti-HBsAg(+) at baseline 1.6% (96/5981) HBsAg(+) and 4.1% (247/5981) HBcAg(+) 71% (617/872) of participants who received a booster dose achieved seroprotection; no significant difference (p=0.7, Chi2 test) observed between individuals ≥16 years of age (28.9% [161/581]) and <16 years of age (29.7% [79/273]). | III | Good |
| Lu SN, Chen CH, Chen TM, et al. Hepatitis B virus infection in adolescents in a rural township--15 years subsequent to mass hepatitis B vaccination in Taiwan. <i>Vaccine</i> , 2006; 24(6): 759-65. ⁽³⁸⁾ | Primary immunization: plasma-derived (Hevac B; Pasteur-Mérieux) vaccine, 10 µg dose at birth, 1, 2 and 12 months of age; infants born to HBeAg(+) | Taiwan Serological study Serology at 4 weeks post booster Anamnestic response defined | Group 1: 440 individuals 14-15 years of age born to to HBsAg(+) mothers Group 2: 1,014 individuals 13-15 years of age immunized as | Group 1: <ul style="list-style-type: none"> 64% (281/440) with anti-HBs≥10 ml.U./mL at baseline 18% (80/440) anti-HBsAg and anti-HBcAg positive; 11% (50/441) HBsAg positive 65% (68/105) with anamnestic response following booster dose Group 2: | III | Good |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | <p>mothers also received HB immunoglobulin</p> <p>Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose</p> | <p>as development of anti-HBs titer ≥10 ml.U./mL</p> | <p>infants</p> | <ul style="list-style-type: none"> 44% (440/1014) with anti-HBs≥10 ml.U./mL at baseline 15% (65/440) anti-HBsAg and anti-HBcAg positive 7.6% anti-HBcAg(+); 5% (52/1014) HBsAg positive 65% (365/496) with anamnestic response following booster dose | | |
| <p>Lu CY, Chiang BL, Chi WK, et al. Waning immunity to plasma-derived hepatitis B vaccine and the need for boosters 15 years after neonatal vaccination. <i>Hepatology</i>, 2004; 40(6): 1415-20.⁽³⁹⁾</p> | <p>Primary immunization: plasma-derived (Hevac B; Pasteur-Mérieux) vaccine, 5 µg dose at birth, 1, 2 and 12 months of age; infants born to HBeAg(+) mothers also received HB immunoglobulin</p> <p>Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose</p> | <p>Taiwan</p> <p>Serological study</p> <p>Serology at 4 weeks post booster</p> <p>Response defined as development of anti-HBs titer ≥10 ml.U./mL</p> | <p>Group 1: 78 adolescents 15 years of age born to HBsAg(+)/HBeAg(+) mothers and immunized in infancy; all individuals HBsAg(-)/anti-HBs(+) at 18 months of age</p> <p>Group 2: 113 adolescents 15 years of age immunized in infancy</p> | <p>Group 1:</p> <ul style="list-style-type: none"> 70% (54/77) with anti-HBs≥10 ml.U./mL at baseline; 33% (26/78) anti-HBc(+) 1 HBsAg(+) individual previously with anti-HBs=21 IU/L at 18 months of age and HBsAg(-) at 7 years of age 91% (21/23) responded to booster dose; 97% (75/77) with seroprotective titres following booster 15-fold increase in antibody titres following booster; 7-fold in those with titer <10 IU/L.) <p>Group 2:</p> <ul style="list-style-type: none"> 38% (41/109) with protective titres at baseline 3.5% (4/113) HBsAg(+) and 4.4% (5/113) anti-HBc (+) 97% (61/63) with anti-HBs≥10 ml.U./mL after booster dose | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|--|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Wang LY, Lin HH. Short-term response to a booster dose of hepatitis B vaccine in anti-HBs negative adolescents who had received primary vaccination 16 years ago. <i>Vaccine</i> . 2007 Oct 10;25(41):7160-7 ⁽⁶⁴⁾ | <p>Primary series: 5 µg dose of plasma-derived vaccine (HavacB; Pasteur-Merieux, Lyon, France, or its equivalent derivative, Lifeguard hepatitis B vaccine, Hsin-Chu, Taiwan) provided at 0, 1, 2, and 12 months of age</p> <p>Booster dose: ENGERIX®-B, GlaxoSmithKline, 20 µg dose</p> | Taiwan sero-epidemiological study | <p>N=395</p> <p>Seronegative adolescents (mean 15.9±0.6 years of age) immunized in infancy</p> <p>Seropositive rate for the cohort from which the subgroup was selected was 45%</p> | <p>Two months post booster immunization, 77% (298/386) of individuals achieved seroprotective titres</p> <p>Among individuals who had undetectable prebooster titers (<0.1 IU/L) approximately 35% had postbooster titers ≥10 IU/L; among adolescents who had prebooster titers between 0.1 and 9.9 IU/L, 95% developed protective titres post booster</p> <p>Among 283 students with titer ≥10 IU/L at two months following booster immunization, more than 25% lost protection at 12 months</p> <p>For the principle cohort from which seronegative subject were selected for booster immunization, 87% of individuals were estimated to have seroprotective titres following the receipt of booster</p> | II | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|--|---|---|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Teoharov P, Kevorkyan A, Petrova N, Baltadzhiev I, Van Damme P. Immune memory and immune response in children from Bulgaria 5-15 years after primary hepatitis B vaccination. <i>Pediatr Infect Dis J.</i> 2013 Jan;32(1):51-3. | Primary series: ENGERIX®-B, GlaxoSmithKline Booster dose: ENGERIX®-B, GlaxoSmithKline | Bulgaria sero-epidemiological study | Group 1: 52 children mean 10.46 (± 1.21) years of age previously immunized at birth, 1 and 6 months of age Group 2: 36 children mean 14.91 (± 1.29) years of age previously immunized at birth, 1 and 6 months of age | Group 1: <ul style="list-style-type: none"> 56% (29/52) with anti-HBsAg ≥ 10 IU/L at baseline Group 2: <ul style="list-style-type: none"> 61% (22/36) with anti-HBsAg ≥ 10 IU/L at baseline All 11 Group 1 and 9 Group 2 seronegative study participants who received a booster dose achieved anti-HBsAg ≥ 10 IU/L | III | Poor |
| Avdicova M, Crasta PD, Hardt K, Kovac M. Lasting immune memory against hepatitis B following challenge 10-11 years after primary vaccination with either three doses of hexavalent DTPa-HBV-IPV/Hib or monovalent hepatitis B vaccine at 3, 5 and 11-12 months of age. <i>Vaccine.</i> 2015 May 28;33(23):2727-33. | Primary series: DTPa-HBV-IPV/Hib (Infanrix-hexa, GlaxoSmithKline) containing 10 μ g of HBsAg provided at 3, 5, 11 months of age ENGERIX®-B, GlaxoSmithKline, 10 μ g dose Booster dose: ENGERIX®-B, GlaxoSmithKline, | Slovakia Follow-up to previously conducted RCT trial | Group 1: 95 children mean 11.3 years of age who previously received three doses of combined hexavalent vaccine in infancy Group 2: 89 children 10-11 years of age who previously received three doses of monovalent HB vaccine co-administered with a | Group 1: <ul style="list-style-type: none"> 48.4% (46/95; 95% CI 38.0; 58.9) with anti-HBsAg ≥ 10 IU/L pre challenge dose 96.8% (91/95; 95% CI 91.0; 99.3) with anti-HBsAg ≥ 10 IU/L post challenge dose 93.6% (88/95; 95% CI 86.6; 97.6) with anti-HBs ≥ 100 IU/L after challenge dose GMC pre/post: 13.5 (95% CI 9.7; 18.7) / 2528.6 (95% CI 1572.1; 4067.1) Group 2: <ul style="list-style-type: none"> 58.4% (52/89; 95% CI 47.5; 68.8) with anti-HBsAg ≥ 10 IU/L | II | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|-------------------------------------|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | 10 µg dose | | pentavalent vaccine | <p>pre challenge dose</p> <ul style="list-style-type: none"> 98.9% (88/89; 95% CI 93.9; 100) with anti-HBsAg ≥10 IU/L post challenge dose 94.4% (84/89; 95% CI 87.4; 98.2) with anti-HBs ≥100 IU/L after challenge dose GMC pre/post: 17.8 (95% CI 12.4; 25.4) / 3815.1 (95% CI 2442.3; 5959.5) | | |
| Da Villa G, Peluso F, Picciotto L, Bencivenga M, Elia S, Pelliccia MG. Persistence of anti-HBs in children vaccinated against viral hepatitis B in the first year of life: follow-up at 5 and 10 years. <i>Vaccine</i> . 1996 Nov; 14(16):1503-5. ⁽⁴⁹⁾ | <p>Primary series: 5 µg dose of plasma-derived (Pasteur-Merieux Hevac B) vaccine</p> <p>Booster dose: 20 µg dose of recombinant vaccine ENGERIX®-B, SmithKline</p> | Italy Serological study | <p>Group 1: 214 children who received three doses of plasma-derived vaccine at 3, 5 and 11 months of age 10 years prior to the study</p> <p>Group 2: 260 children who received four doses of plasma-derived vaccine at 1, 2, 3 and 12 months of age 10 years prior to the study</p> | <p>Group 1:</p> <ul style="list-style-type: none"> 58% (123/214) with anti-HBsAg ≥10 IU/L, 41.1% (88/214) seronegative and 1.4% (3/214) anti-HBcAg(+)/anti-HBs(-) 97% (85/88) with protective titres following booster immunization <p>Group 2:</p> <ul style="list-style-type: none"> 77% (200/260) with anti-HBsAg ≥10 IU/L, 22.7% (59/260) seronegative and 0.4% (1/260) anti-HBcAg(+)/anti-HBs(-) 95% (56/59) with protective titres following booster immunization | II | Fair |
| Da Villa G, Pelliccia MG, Peluso F, Ricciardi E, Sepe A. Anti-HBs responses in children | Primary series: 5 µg dose ⁽¹⁰⁰⁾ plasma-derived (Pasteur-Merieux | Italy Non-randomized serological | Group 1: 69 children immunized with 3 doses in infancy (month 1, 2 | <p>Group 1:</p> <ul style="list-style-type: none"> 60% (39/65) with anti-HBsAg ≥10 IU/L prior to booster 92% (24/26) achieved | II | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|---|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| vaccinated with different schedules of either plasma-derived or HBV DNA recombinant vaccine. Res Virol. 1997 Mar-Apr; 148(2):109-14. ⁽⁷⁰⁾ | Hevac B) vaccine Booster dose: 20 µg dose of ENGERIX®-B, SmithKline | comparison study | and 3) 10 years prior to study enrolment Group 2: 53 children immunized with 3 doses in infancy (month 3, 5 and 11) 10 years prior to study enrolment Group 3: 50 children immunized with 2 doses in infancy (month 3 and 5) 10 years prior to study enrolment | seroprotective levels following booster Group 2: <ul style="list-style-type: none"> 66% (35/53) with anti-HBsAg ≥10 IU/L 94% (17/18) achieved seroprotective levels following booster Group 3: <ul style="list-style-type: none"> 56% (28/50) with anti-HBsAg ≥10 IU/L 2% (1/50) Anti-HBcAg(+)/Anti-HBs negative 86% (18/21) achieved seroprotective levels following booster | | |
| Resti M, Azzari C, Mannelli F, et al. Ten-year follow-up study of neonatal hepatitis B immunization: are booster injections indicated? Vaccine, 1997; 15(12-13): 1338-40. ⁽⁵⁴⁾ | Primary immunization: plasma-derived Hevac B vaccine (Pasteur), 5µg dose; all received HBIG at birth, 2 and 12 months of age Booster immunization: ENGERIX®-B, | Italy Serological study Seroprotection: anti-HBs ≥10 mIU/ml | N=53 Children born to HBs(+)mothers 10 years after primary immunization | 68% (36/53) with protective titres at 10 years of age; 26% (14/53) with undetectable antibody levels 100% (17/17) of study participants achieved seroprotection after booster dose Markers of HB infection negative in all children | II-3 | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | GlaxoSmithKline, 10 µg dose | | | | | |
| Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC, Cuccia M, Mangione R, Marrone F, Negrone FS, Parlato A, Zamparo E, Zotti C, Stroffolini T, Mele A; Study Group. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. <i>Lancet</i> . 2005 Oct 15-21; 366(9494): 1379-84 ⁽⁶⁷⁾ | Primary series: ENGERIX®-B, GlaxoSmithKline (10 µg dose) at 3, 5, and 11 months of age Booster immunization: ENGERIX®-B, GlaxoSmithKline (10 µg dose) | Italy Serological study Seroprotection: anti-HBs ≥10 mIU/ml Serologic testing conducted 2 weeks post booster administration | N=1,212 Children immunized 10.6 ± 0.3 years prior to study recruitment | 64% (779/1212; 95% CI: 61.6, 67) seropositive; antibody undetectable (<1IU/L) in 9% (106/1212; 95% CI: 7.2,10.3) 97% (332/342) seropositive following booster immunization; 11% (10/88) of individuals with undetectable antibody prior to booster immunization remained seronegative following booster administration (7% [6/88] with undetectable antibody levels) | II | Good |
| Chan PK, Ngai KL, Lao TT, Wong MC, Cheung T, Yeung AC, Chan MC, Luk SW. Response to booster doses of hepatitis B vaccine among young adults who had received neonatal vaccination. <i>PLoS One</i> . 2014 Sep 8;9(9):e107163. ⁽⁸²⁾ | Primary series: plasma-derived vaccine at 0,1 and 6 months of age Booster dose: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | China (Hong Kong) Serologic testing conducted 4 weeks post booster administration | N=212 Medical and nursing students enrolled who previously (mean age 19 years) received primary immunization in infancy | 19% (40/212) Anti-HBsAg(+),80% (170/212) Anti-HBsAg(-); 1% (2/212) HBsAg(+) 86% (59/69) with anti-HBs≥10 mIU/ml after first booster dose; in the remaining individuals anti-HBs levels ranged from 0.11 to 6.29 IU/L; after receiving three doses of booster vaccination all students with seroprotective titres | III | Fair |
| Chen Y, Lv H, Gu H, Cui F, Wang F, Yao J, Xia S, Liang X. The effects of | Primary series: recombinant vaccine (5µg) | China | Individuals 10-15 years of age immunized as | Group 1: • 49% (255/518) with undetectable titres (< 1IU/L) prior to booster | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|---|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| different dosage levels of hepatitis B vaccine as booster on anti-HBs-negative children 5-15 y after primary immunization; China, 2009-2010. Hum Vaccin Immunother. 2014;10(2):498-504 ⁽¹⁰¹⁾ | provided at 0,1 and 6 months of age Booster dose: three-doses of (0,1 and 6 months) of 5 µg (ShenzhenKangtai Biotechnology Co) or 10 µg (Dalianhanxin Biotechnology Co) recombinant vaccine | | infants with antiHBs< 10IU/L Group 1: 518 individuals who received 5 ug booster dose Group 2: 624 individuals who received 10 ug booster dose | immunization <ul style="list-style-type: none"> 87% (449/518) with seroprotective titres after dose 1 and 99.4% (515/518) after dose 3 Group 2: <ul style="list-style-type: none"> 51% (317/624) with undetectable titres (< 1IU/L) prior to booster immunization 91% (569/624) with seroprotective titres after dose 1 and 99.5% (621/624) after dose 3 | | |
| Zhu CL, Liu P, Chen T, Ni Z, Lu LL, Huang F, Lu J, Sun Z, Qu C. Presence of immune memory and immunity to hepatitis B virus in adults after neonatal hepatitis B vaccination. Vaccine. 2011 Oct 13;29(44): 7835-41. ⁽⁶⁹⁾ | Primary series: plasma-derived Hep-B Vax (5µg) provided at 0,1 and 6 months of age Booster immunization: 10µg dose of Vecon recombinant vaccine (Shenzhen Kangtai Biological Products Co.) | China Serological study Seroprotection: anti-HBs ≥10 mIU/ml Serology at 2 and 4 weeks and 6 months post booster immunization Anamnestic response defined | N= 404 24-year old adults previously immunized in infancy | 30% (121/404) with seroprotective titres; 1% (4/404) HBsAg positive, 7% (27/404) HBsAg(-)anti-HBcAg(+) 84% (87/103) of seronegative individuals with protective titres 4 weeks after first booster dose; 65% (68/103) with anamnestic response 6% (6/103) of seronegative individuals remained seronegative 6 months after the second booster dose 80% (32/40)of individuals who did not have protective titres when previously tested at 5 years of age achieved | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|---|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | provided at 0 and 1 months | as seroprotective levels 2 weeks post booster administration | | seroprotection one month post booster | | |
| Yao J, Ren J, Shen L, Chen Y, Liang X, Cui F, Li Q, Jiang Z, Wang F. The effects of booster vaccination of hepatitis B vaccine on anti-HBV surface antigen negative children 11-15 years after primary vaccination. Hum Vaccin. 2011 Oct; 7(10):1055-9. ⁽⁶⁶⁾ | Primary series: recombinant vaccine (5µg) provided at 0,1 and 6 months of age Booster dose: three 20 µg doses of recombinant vaccine (NCPC GeneTech Biotechnology Pharmaceutical Co) provided at 0,1 and 6 months | China Serological study Seropositivity defined as anti-HBsAg ≥10 IU/L | N=841 Children 11 to 15 years of age (mean 13 ± 1.5 years of age) | 47% (393/841) seropositive at study enrolment 85% (378/444) of children developed protective antibody titers following first booster immunization. Following administration of two additional booster doses (children who remained seronegative after first booster), 1.5% (6/429) identified as primary non responders and 13.5% (57/426) as secondary non responders (loss of immune memory) | II | Good |
| Chen Y, Gu H, Cheng S, Shen L, Cui F, Wang F, Yao J, Xia S, Lv H, Liang X. The effects of booster vaccination on combined hepatitis A and hepatitis B vaccine in both anti-HBs and anti- | Primary series: recombinant vaccine (5µg) provided at 0,1 and 6 months of age Booster dose: | China | N=151 Individuals with HB antibody titre <10IU/L immunized 10-15 years prior to study recruitment | 75.5% (114/151) children achieved seroprotective titres after dose 1, and 98% (148/151) after dose 3 of booster immunization | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|--|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| HAV negative children 5-15 years after hepatitis B vaccine primary immunization. Hum Vaccin Immunother. 2013 Apr;9(4):898-902. ⁽⁸³⁾ | three-doses of of combined Hepatitis A and Hepatitis B vaccine provided at 0,1 and 6 months | | | | | |
| van der Sande MA, Waight PA, Mendy M, Zaman S, Kaye S, Sam O, Kahn A, Jeffries D, Akum AA, Hall AJ, Bah E, McConkey SJ, Hainaut P, Whittle HC. Long-term protection against HBV chronic carriage of Gambian adolescents vaccinated in infancy and immune response in HBV booster trial in adolescence. PLoS One. 2007 Aug 15;2(8):e753 ⁽¹⁰²⁾ | Primary immunization: ⁽¹⁰³⁾ Four 5µg doses of plasma-derived hepatitis B vaccine (HBVvaxH; Merck, Sharpe & Dohme) provided at birth, 1, 4 and 9 months of age. Booster immunization: EuvaxH | Gambia Seropositivity defined as anti-HBs ≥10 IU/L Anamnestic response defined as four fold or greater rise in anti-HBs antibody within two weeks of booster dose, or anti-HBs antibody level ≥10 IU/L within two weeks of the booster dose if seronegative prior to booster immunization. 60% randomly selected from Groups 1 and 2 to | Participants of the Gambia Hepatitis Intervention Study (GHIS) with documented at least 2 doses of vaccine in infancy Group 1: 492 15-year old children immunized with 3 or 4 doses Group 2: 84 15-year old children immunized with 1 or 2 doses Group 3: 424 unimmunized 15-year old children | Group 1: <ul style="list-style-type: none"> • VE against chronic infection estimated at 96.6% (95%CI: 91.5,100) • 34% (154/382) seropositive at baseline • 0.4% (2/492; 95%CI: 0.4,1.5) HBsAg(+); 17.7% (87/492; 95%CI: 14.4,21.3) anti-HBcAg(+) Group 2: <ul style="list-style-type: none"> • VE against chronic infection estimated at 90.1% (95%CI: 69.9,100) • 37% (23/62) seropositive at baseline • 1.2% (1/84; 95%CI: 0.03,6.5) HBsAg(+); 22.6% (19/84; 95%CI: 14.2,33) anti-HBcAg(+) Group 3: <ul style="list-style-type: none"> • 13.2% (51/420; 95%CI: 10.1, 16.8) HBsAg(+); 53.3% (226/424; 95%CI: 48.4, 58.1) anti-HBcAg(+) | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|--|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | | receive booster immunization | | 97% (210/217) seropositive at 2 weeks and 78% (207/264) one year post booster immunization (Group 1 and 2 participants); all 7 seronegative individuals with anti-HBs antibody level <10 IU/L at baseline | | |
| Saffar MJ and Rezai MS. Long-term antibody response and immunologic memory in children immunized with hepatitis B vaccine at birth. <i>Indian Pediatr</i> , 2004; 41(12): 1232-7 ⁽⁵⁵⁾ | <p>Primary immunization: recombinant vaccine ENGERIX®-B, GlaxoSmithKline, 10 µg dose</p> <p>Booster immunization: recombinant vaccine, 10µg (IM), 5µg (IM), or 2.5µg (ID) dose</p> | <p>Iran</p> <p>Serological, non-randomized, comparison study</p> <p>Serology 10-14 days after booster dose</p> <p>Antibody titre ≥10 IU/L considered protective; anamnestic response defined as increase in anti-HBs to ≥10 IU/L</p> | <p>N=453</p> <p>All infants 10 to 11 years of age</p> <p>Children who received primary immunization at birth, 1.5 and 9 months of age</p> <p>Group 1: 57 children provided with 10µg booster dose IM</p> <p>Group 2: 52 children provided with 5µg booster dose IM</p> <p>Group 3: 56 children provided with 2.5 µg dose ID</p> | <p>58% (262/453) with seroprotective antibody levels at baseline; 18.6% (84/453) with undetectable antibody titres (<2 IU/L)</p> <p>Group 1:</p> <ul style="list-style-type: none"> 95% (54/57) with anti-HBs≥10 after booster dose Mean anti-HBs GMC 166.76 ± 105.61 IU/L <p>Group 2:</p> <ul style="list-style-type: none"> 89% (46/52) with anti-HBs≥10 after booster dose Mean anti-HBs GMC 130.91 ± 107.18 IU/L <p>Group 3:</p> <ul style="list-style-type: none"> 79% (44/56) with anti-HBs≥10 after booster dose Mean anti-HBs GMC 103.2 ± 89.3 IU/L <p>No children in the study HBs-Ag(+) or anti-HBcAg(+)</p> | III | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|--|--|--|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Jafarzadeh A, Montazerifar SJ. Persistence of anti-HBs antibody and immunological memory in children vaccinated with hepatitis B vaccine at birth. J Ayub Med Coll Abbottabad. 2006 Oct-Dec;18(4):4-9 ⁽⁶⁰⁾ | Primary series: ENGERIX®-B, GlaxoSmithKline (10 µg dose) at birth, 1.5 and 9 months of age Booster dose: ENGERIX®-B, GlaxoSmithKline (10 µg dose) | Iran Seroprotection defined as anti-HBs ≥10 IU/L | N=146 Healthy 10-11 year old children immunized in infancy | 48% (70/146) study participants with protective anti-HBs antibody titres; all children HbsAg(-) and 7.5% (11/146) anti-HBcAg(+) (+) 95% (72/76) seropositive following booster immunization | III | Fair |
| Katoonizadeh A, Sharafkhah M, Ostovaneh MR, Norouzi A, Khoshbakht N, Mohamadkhani A, Eslami L, Gharravi A, Shayanrad A, Khoshnia M, Esmaili S, George J, Poustchi H, Malekzadeh R. Immune responses to hepatitis B immunization 10-18 years after primary vaccination: a population-based cohort study. J Viral Hepat. 2016 Apr 29 ⁽⁸⁶⁾ | Primary series: Recombinant HBV 10 µg dose) at birth, 1 and 6 months of age; HB immunoglobulin (HBIG) was provided immediately after birth to children born to HBs positive mothers. Booster dose: not stated | Iran Seroprotection defined as anti-HBs ≥10 IU/L ; anamnestic response defined as anti-HBs to ≥10 IU/L 4 weeks following administration of booster dose | N=275 Group 1: 25 children 10–11 years of age Group 2: 85 children 12–14 years of age Group 3: 163 children 15–18 years of age | Group 1: <ul style="list-style-type: none"> 96% (24/25) with anti-HBs ≥10 after booster dose Mean anti-HBs 376 IU/L Group 2: <ul style="list-style-type: none"> 86% (73/85) with anti-HBs ≥10 after booster dose Mean anti-HBs 372 IU/L Group 3: <ul style="list-style-type: none"> 75% (122/163) with anti-HBs ≥10 after booster dose Mean anti-HBs 250 IU/L Of 56 non-responders, 41 received a second vaccine booster; 76% (31/41) achieved anti-HBs ≥10 IU/mL. One study participant (2% 1/41) had no response following the receipt of 3 booster doses | III | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|---|---|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Bagheri-Jamebozorgi M, Keshavarz J, Nemati M, Mohammadi-Hossainabad S, Rezayati MT, Nejad-Ghaderi M, Jamalizadeh A, Shokri F, Jafarzadeh A. The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination with recombinant hepatitis B vaccine at infancy. Hum Vaccin Immunother. 2014;10(12):3731-6. ⁽⁷⁸⁾ | Primary series: ENGERIX®-B, GlaxoSmithKline (10 µg dose) provided at birth, 1.5 and 9 months of life Booster dose: Heberbiovac, Heberbiotec Co, Cuba (20 µg dose) | Iran Serologic study Anamnestic response defined as anti-HBs ≥10 IU/L in pre-booster seronegative individuals or at least a 4-fold increase in anti-HBs level in those who were seropositive prior to booster immunization Seropositivity and seroprotection defined as anti-HBs antibody concentrations ≥ 1.0 IU/L and ≥ 10 IU/L, respectively. | N=300 Healthy individuals who completed primary immunization 20 years prior to study recruitment | 37% (111/300) with seroprotective titres; all individuals negative for HBsAg and anti-HBcAg; 12% (35/300) seronegative Post booster 97% (134/138) with seroprotective titres; 91% (125/138) demonstrated anamnestic response | III | Poor |
| Hudu SA, Malik YA, Niazlin MT, Harmal NS, Adnan A, Alshrari AS, Sekawi Z. Antibody and immune | Primary series: three doses of recombinant vaccine provided at birth, 1 month, | Malaysia | N=402 Individuals who received three doses (240, 60%), | 63% (252/402) with seroprotective antibody levels at baseline; among those with seroprotective titres, 71% [171/240] received three doses, 68% [47/69] received two doses, and 37% | II | Poor |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| memory persistence post infant hepatitis B vaccination. Patient Prefer Adherence. 2013 Sep 27;7:981-6. doi: 10.2147/PPA.S49776. eCollection 2013. ⁽⁸¹⁾ | and 5 months of age Booster dose: recombinant hepatitis B vaccine, Euvax B; Sanofi S.A., Paris, France (20 µg) | | two doses (69, 17%) or one dose (93, 23%) of recombinant HB vaccine 23 years after the receipt of primary series | (34/93) received one dose of HA vaccine 5% (20/402) anti-HBc(+); none HBsAg(+) Majority (85/150) of seronegative individuals received only one vaccine dose 94% (141/150) of vaccinated individuals with anamnestic response 4 weeks post booster | | |
| Poovorawan Y, Chongsrisawat V, Theamboonlers A, et al. Persistence of antibodies and immune memory to hepatitis B vaccine 20 years after infant vaccination in Thailand. Vaccine, 2010; 28(3): 730-6. ⁽⁴²⁾ | Primary immunization: ENGERIX®-B, 10 µg dose at birth, 1, 2 and 12 months of age Booster immunization: ENGERIX®-B, GlaxoSmithKline, 20 µg dose | Thailand Non randomized, serological comparison study Anamnestic response defined as HBs titre ≥10 IU/L in individuals with a titre <3.3 IU/L or a 4-fold increase in individuals with a titre ≥3.3 IU/L | N=36 Individuals who received neonatal immunization 20 years prior to study; majority born to HBsAg(+) mothers (half also HBeAg(+)) | 60.5% (95% CI: 43.4, 76) with antibody titre ≥10 IU/L and 86.8% (95% CI: 71.9, 95.6) with antibody titre ≥3.3 IU/L 4 weeks following booster all participants (95%CI: 90.3, 100) achieved antibody titre ≥10 IU/L Similar anamnestic responses were also observed in a second group of study participants (n=36) who received an additional vaccine dose at 5 years of age | III | Fair |

Table 2: Summary of evidence on duration of immunity in immunocompromised individuals

| STUDY DETAILS | | | | | SUMMARY | |
|---|------------------------------------|--|--|--|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Inaba H. et al, Longitudinal analysis of antibody response to immunization in paediatric survivors after allogeneic haematopoietic stem cell transplantation. Br J Haematol. 2012 Jan;156(1):109-17 ⁽⁸⁹⁾ | ENGERIX®-B, GlaxoSmithKline | Prospective long-term follow-up study Immunization at 12, 15 and 18 months after HSCT Serology conducted for at least 10 years after allo-HSCT or until 18 years of age, whichever period was longer Seroprotection defined as anti-HBs \geq 10IU/L | N=141 (n=59 after year 5) survivors one year after receiving allo-HSCT median age at allo-HSCT 8.5 years (range, 0.1–21.6 years) median age at time of immunization 9.5 years (range 1.6–25.1 years) | 51.8% individuals with seroprotection prior to immunization 77.1% with seroprotection 2 years after immunization 72.9% with protective antibody levels at more than 5 years Negative titres were significantly associated with lower CD4 counts (P=0.005) and history of grade 2–4 acute GVHD (P=0.036); older age at immunization marginally associated with negative titres (P=0.053). Persistently negative titres seen in 11% and loss of protective antibody levels observed in 20% of study participants | III | Fair |
| Kerneis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boelle PY: Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. Clin Infect Dis 2014, 58(8):1130–1139. ⁽⁹⁰⁾ | HB vaccine, 10 and 40 μ g dose | Twelve studies included in meta-analysis, with follow-up ranging from 12 to 115 months. | | Seroprotection typically decreased over time: after 3 doses of 40 μ g HBsAg, 71% of primary responders maintained protective antibody titers at year one, 33%-61% at year two, and 40% at year five; seroprotection particularly poor in children born to Ag HBs+ HIV-infected mothers after 3 doses of 10 μ g HBsAg (24% with protective antibody level after 5.5 years). | II-2 | Fair |

| STUDY DETAILS | | | | | SUMMARY | |
|---------------|---------|--------------|--------------|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| | | | | <p>Less than one half of primary responders maintained protective antibody titers two years after immunization (38% (95% CI 95% = 23%; 54%) in adults and 61% (27%; 90%) in children), and only 17% (95% CI95%: 3%; 36%) after five years.</p> <p>Vaccine schemes with double-dosed schemes compared to standard dose did not improve maintenance of seroprotection after 2 years (respectively 41% [CI95%: 14- 71] and 50% [CI95%: 24-77%])</p> <p>Protective anti-HBs titer most rapidly waned in individuals with anti-HBs between 10 and 100 IU/L</p> | | |

Table 3: Summary of evidence on immunity of individuals with diabetes

| STUDY DETAILS | | | | | SUMMARY | |
|---|--|--|--|---|-------------------|---------|
| Study | Vaccine | Study Design | Participants | Summary of Key Findings and Outcome Data | Level of Evidence | Quality |
| Schillie SF, Spradling PR, Murphy TV. Immune response of hepatitis B vaccine among persons with diabetes: a systematic review of the literature. <i>Diabetes Care</i> 2012; 35:2690 - 7 ⁽⁹²⁾ | Recombinant (16 studies) and plasma-derived (2 studies) vaccine, HBs-antigen dose range from 3 to 40µg | Systematic review Peer-reviewed, published RCT or observational studies assessing response to HB vaccine among persons with diabetes type 1 or 2 17 studies included: 2 RCT, 12 prospective, and 3 retrospective studies published between 1989 and 2012 | Seroprotection against HB virus infection assessed in 1,764 subject 8.4 to 79.5 years of age (633 with diabetes) | Seroprotection proportions ranged from 31.3–100.0% (median, 73.4%) among persons with diabetes and 35.2–100.0% (median, 87.1%) for those without diabetes. The proportion protected was generally greatest among children: 54.2–100.0% (median, 93.9%) in those with diabetes and 98.0–100.0% in individuals without diabetes; in adults, median seroprotection lower among individuals with diabetes (31.3–94.4% [median, 88.2%]) compared to those without (35.2–96.9% [median, 93.6%]). Lowest seroprotection rates reported among diabetic adults with chronic kidney disease (41.8–85.3% [median, 60.1%]). | II-2 | Good |

Table 4. Levels of Evidence Based on Research Design

| Level | Description |
|-------|--|
| I | Evidence from randomized controlled trial(s). |
| II-1 | Evidence from controlled trial(s) without randomization. |
| II-2 | Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy. |
| II-3 | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence. |
| III | Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees. |

Table 5. Quality (internal validity) Rating of Evidence

| Quality Rating | Description |
|----------------|--|
| Good | A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well. |
| Fair | A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw". |
| Poor | A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations. |

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Table 6. NACI Recommendation for Immunization -- Grades

| Grade | Recommendation |
|-------|--|
| A | NACI concludes that there is good evidence to recommend immunization. |
| B | NACI concludes that there is fair evidence to recommend immunization. |
| C | NACI concludes that the existing evidence is conflicting and does not allow making a recommendation for or against immunization; however other factors may influence decision-making. |
| D | NACI concludes that there is fair evidence to recommend against immunization. |
| E | NACI concludes that there is good evidence to recommend against immunization. |
| I | NACI concludes that there is insufficient evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making. |

LIST OF ABBREVIATIONS

| <i>Abbreviation</i> | <i>Term</i> |
|----------------------------|---|
| anti-HBc | Antibody to HB core antigen |
| anti-HBs | Antibody to HB surface antigen |
| HBsAg | HB surface antigen |
| ACIP | Advisory Committee on Immunization Practices |
| CDC | U.S. Centers for Disease Control and Prevention |
| CHMS | Canadian Health Measures Survey |
| CIG | Canadian Immunization Guide |
| CNDSS | Canadian Notifiable Disease Surveillance System |
| CSR | Clinical Study Report |
| EIP | Emerging Infections Program |
| HAHB | Hepatitis A and B |
| HB | Hepatitis B |
| HBV | Hepatitis B virus |
| HBIG | Hepatitis B immune globulin |
| HSCT | Hematopoietic Stem Cell Transplant |
| HWG | NACI Hepatitis Working Group |
| GMC | Geometric mean antibody concentration |
| GMT | Geometric mean titres |
| NACI | National Advisory Committee for Immunization |
| NICS | National Immunization Coverage Survey |
| NHANES | U.S. National Health and Nutrition Examination Survey |
| SAGE | Strategic Advisory Group of Experts on Immunization |
| P/T | Provincial and Territorial |
| PHAC | Public Health Agency of Canada |
| VHPB | Viral Hepatitis Prevention Board |
| WHO | World Health Organization |

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