2012 Antigen Review for the New Zealand National Immunisation Schedule: Hepatitis B

Auckland UniServices Limited

A wholly owned company of
The University of Auckland

Prepared for:
New Zealand Ministry of Health

Prepared by a scientific team incorporating the
Immunisation Advisory Centre, The University of Auckland
Institute of Environmental Science and Research Ltd.

March 2013

Contact details:

Helen Petousis-Harris
Immunisation Advisory Centre
Tāmaki Innovation Campus
The University of Auckland

Private Bag 92019,
Auckland 1142, New Zealand

Phone: +64 9 923 2078
Fax: +64 9 373 7030
Mobile: +64 27 471 6749
Email: h.petousis-harris@auckland.ac.nz

Executive summary

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family and is responsible for most of the chronic hepatitis burden caused by the five known hepatitis viruses. It is estimated that around 6% of the world's population live with chronic hepatitis B infection and approximately 30% have serologic evidence of HBV infection. The development of recombinant technologies in the early 1980s has led to affordable and effective vaccines, which are now scheduled for prevention strategies in 177 countries. The world's first universal hepatitis B vaccination programme began in Taiwan in 1984 and long term data for the effectiveness of hepatitis B vaccination is now emerging including outcomes for liver cancer.

In New Zealand (NZ), there has been a steady downward trend in the number of hepatitis B notifications which is attributable to the implementation of a universal hepatitis B vaccination programme. The highest notification rate is among Pacific People followed by Asian. The most common risk factor for acute hepatitis B infection is overseas travel and sexual contact. Recent mathematical modelling supports a reproduction number of less than one which indicates eradication is a possibility; however, increased immigration is likely to provide an increasing source of new carriers.

The safety of hepatitis B vaccines is well established and there are few new studies specifically investigating the safety of hepatitis B vaccines. There are no safety signals for use in pregnant women following widespread use; however, the fact that there are few controlled trials in pregnant women using hepatitis B vaccine has been highlighted. Pregnancy outcomes in pregnant women exposed to hepatitis B virus (HBV) are similar to those in the unexposed population. Hepatitis B vaccine is delivered universally as part of multivalent vaccines on infant schedules and these vaccines have been rigorously evaluated for safety.

Hepatitis B vaccination is highly effective with virtually complete protection in persons who seroconvert to the vaccine. Long-term protection of over 20 years has been demonstrated despite a decrease in anti-hepatitis B surface antigen (anti-HBsAg) antibodies over time.

Two-dose schedules have been evaluated in children and adolescents and are generally found to be highly immunogenic and non-inferior to three-dose schedules. Duration of immunity to a two-dose schedule in children has been demonstrated to 10 years, so far. Flexibility in the schedule has also been shown in adults with a third dose given 11 months after the second dose and an accelerated schedule in pregnant women given within four months is immunogenic. Higher antigen doses have been demonstrated to be an effective strategy to improve seroconversion in non-responders to HBV vaccine.

Boosters in the immunocompetent are not required as long as a full course has been adequately administered. However, a booster dose should be considered for immunocompromised patients, based on serological monitoring.

Countries that have introduced universal vaccination against hepatitis B have experienced significant reductions in HBV prevalence and Taiwan has demonstrated a reduction in liver cancer in younger cohorts as a result of over 20 years of hepatitis B vaccination. The effectiveness of HBV vaccination in children born to HBsAg+ mothers indicates that acquisition of infection is relatively rare after post exposure prophylaxis of hepatitis B immunoglobulin (HBIg) and HBV vaccine, and no patients have been documented to acquire infection if they have demonstrated a protective concentration of antibody.

There are two hexavalent vaccines that include hepatitis B antigen for use in routine infant schedules and a range of monovalent and multivalent vaccines for use in other groups. The vaccines can be used in a variety of schedules with one and two dose options. The bivalent hepatitis A and B vaccine, Twinrix®, has been found to increase responses in previous non-responders.

There are no indicators to suggest any changes to the current routine infant schedule are needed. The only factor that requires consideration is the adoption of a universal birth dose, and an important consideration around the potential value of a universal birth dose is the performance of the current screening and neonatal

immunoprophylaxis programme in NZ. Limited regional data from Auckland suggests high uptake of a birth dose in infants born to HBsAg+ mothers, however, gaps have been identified. A national evaluation of the screening and neonatal programmes would be a useful strategy before considering the implementation of a universal birth dose of hepatitis B vaccine.

Global practice around the use of hepatitis B vaccines is varied with respect to vaccines used and schedules. Moves to eliminate hepatitis B infection from the population have prompted recommendations for routine birth doses of vaccine and greater efforts to achieve higher rates of vaccination of both high risk adults as well as non-high risk adults.

This report is one of a series of reports covering the most recent four years of literature for 18 different vaccine preventable diseases. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around hepatitis B vaccines for NZ.

2012 Antigen Review for the New Zealand National Immunisation Schedule: Hepatitis B

Contents

Figures

Tables

Acknowledgements

Abbreviations

ACIP	Advisory Committee for Immunization Practices
AEFI	Adverse Event Following Immunisation
ALT	Alanine aminotransferase
CDC	Centers for Disease Control and Prevention
DTaP-IPV-HepB-HiB	Diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated poliomyelitis and conjugated *Haemophilus Influenzae* type B
GMC	Geometric mean concentration
GMT	Geometric mean titre
GM-CSF	Granulocyte-macrophage colony stimulating factor
HB	Hepatitis B
HBc	Hepatitis B core
HBe	Hepatitis B envelope
HBIg	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
Hib	*Haemophilus influenzae* type B
HIV	Human Immunodeficiency Virus
IgM	Immunoglobulin M
IPV	Inactivated poliovirus
MMR	Measles, mumps and rubella vaccine
MMRV	Measles, mumps, rubella and varicella vaccine
MS	Multiple sclerosis
NACI	National Advisory Committee on Immunization
NHANES	National Health and Nutrition Examination Survey
NP	Nasopharyngeal
NZ	New Zealand
rHBV	recombinant HBV
rHBsAg	recombinant HBsAg
SAE	Serious Adverse Event
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Events Reporting System
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1. Background

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family and is responsible for most of the chronic hepatitis burden caused by the five known hepatitis viruses. The development of recombinant technologies in the early 1980s led to affordable and effective vaccines, which are now scheduled for prevention strategies in 177 countries (1).

It is estimated that 6% of the world's population live with chronic Hepatitis B infection and approximately 30% of the world's population have serologic evidence of HBV infection (2). While highly prevalent around the world, the frequency and burden can vary markedly even within countries. High carrier rates are seen in sub-Saharan Africa, Asia except Japan and India, most of the Middle East, the Amazon basin and Pacific Islands (3, 4). Moderate rates are seen in parts of Eastern Europe, Africa, Central and South America; with low rates in United States (US), northern Europe and Australasia.

Certain subpopulations in areas of low endemicity have high carrier rates, such as New Zealand Māori, Australian Aborigines and Alaskan Native Americans (5). In New Zealand (NZ), the large number of carriers are the source of infection despite good inroads due to vaccination (6).

Since chronic hepatitis is the leading cause of liver cirrhosis, there is significant global morbidity and mortality. Approximately 620,000 HBV-infected people die from chronic liver disease each year. The lifetime risk for developing hepatocellular carcinoma (HCC) in chronic hepatitis patients is 15 to 20 times greater than that for people without HBV infection (2).

In July 1984, Taiwan commenced the world's first universal hepatitis B vaccination program (7). Current hepatitis B vaccines are based on the hepatitis B surface antigen (HBsAg), which is present in abundance on the viral surface. The surface antigen is produced in recombinant yeast or mammalian cells. The currently licenced hepatitis B vaccines are highly immunogenic inducing protective levels of antibody (considered ≥10 IU/L) in over 90% of vaccinees. Around 5 - 10% of vaccines do not respond adequately to vaccination with these vaccines and a variety of strategies have been assessed to improve immune responses in these people.

This review aims to evaluate the literature on vaccination against hepatitis B published from 2009- 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for hepatitis B vaccines as listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around hepatitis B vaccines for NZ.

- General specifications

  - Safety

  - Effectiveness

  - Implementation issues (practicality and possible impact on uptake)

  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination

  - Different options of placement on the schedule, based on international findings and best practice

  - Different vaccine options and comparisons between the options

2.2 New Zealand Epidemiology

The summary of NZ epidemiology has been obtained from the 2011 Annual Surveillance Report from ESR (8).

2.3 Literature search strategy

The points below have formed the focus of the literature search:

- Safety

- Effectiveness in disease control

  - Effect on
    i Indirect effects/herd immunity
    ii. Duration of protection

  - Immunogenicity

- Implementation issues (practicality of and possible impact on uptake)

- Differences that need to be considered for each age group, and groups with particular needs

  - Age

  - High-risk groups – definition of which groups most likely to benefit and which vaccines/s

- Different option for placement on the schedule, based on international findings and best practice

- Different vaccine options and comparison between the options

- Current international research and evidence around use of vaccines

2.3.1 Medline search terms and strategy

MeSH term: Hepatitis B Vaccin*

4298

Limit to Humans, English, 2009 – current

649

NOT Parent, Physician, Survey, Interview, Qualitative

593

NOT Cost and Cost Analysis

564

MeSH term: AND Adverse Effects OR safety

75 (keep and view)

MeSH term: AND Effectiveness OR efficacy

Effect* as a key word

NOT effect, effects, effective

32 (keep and view)

2.3.2 Cochrane Library search terms and strategy

Search term Hepatitis Vaccin*

Limit to Cochrane Reviews, Other Reviews, and Trials 2009-present

8 results (keep and view)

2.3.3 Scopus search terms and strategy

Hepatitis B AND Vaccin* Published 2011 – present

2259

Limit to: Medicine, humans, vaccination, Hepatitis B Vaccine, journals

784

Exclude Letter, Short survey, editorial and erratum

702 (keep and view)

Reject Veterinary, Arts and Humanities, Social science articles.

515

Delete duplicates

Final EndNote library after literature search and revisions 290

2.3.4 Grey literature

Conference abstracts were not sourced one poster was accessed. Two reports were accessed.

2.3.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 28 articles were accessed.

2.3.6 Final library

The final library includes 318 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.
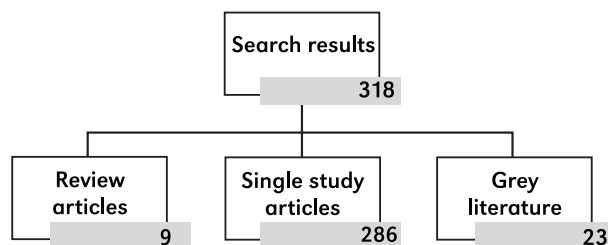
Figure 1. Flow of selection of articles for review

2.4 Participants/populations

Infants and persons considered at high risk for hepatitis B infection.

2.5 Interventions

2.5.1 Monovalent hepatitis B vaccines

2.5.1.1 HBvaxPro®

HBvaxPro® is produced by Merck and Co Inc. each 0.5mL contains 5µg of HBsAg. Each 1mL dose contains 10µg of HBsAg. A 40µg dose has also been produced, but is not available in NZ and is intended for adult predialysis/dialysis patients. This is a sub-unit viral vaccine consisting of surface antigen (HBsAg or Australia antigen) of hepatitis B virus produced in yeast cells. The currently produced vaccine contains no detectable yeast DNA and less than 1% of the protein content is from yeast. The purified protein is treated in phosphate buffer with formaldehyde and then co-precipitated with alum (potassium aluminium sulphate) to form bulk vaccine adjuvanted with amorphous aluminium hydroxyphosphate sulphate (previously referred to as aluminium hydroxide). Each 0.5mL dose contains approximately 0.25mg of aluminium provided as amorphous aluminium hydroxyphosphate sulphate, and 35µg of sodium borate, 4.5mg sodium chloride, and water for injection.

2.5.1.2 Energix-B®

Energix-B® is produced by GlaxoSmithKline Biologicals. Each 0.5ml dose contains 10µg of HBsAg adsorbed to aluminium hydroxide (0.25mg of Al^{3+}) This is a sub-unit viral vaccine consisting of HBsAg of hepatitis B virus produced in yeast cells. A 1ml dose contains twice the 0.5ml dose. Excipients are sodium chloride, sodium phosphate dehydrate, sodium dihydrogen phosphate, water for injections and traces of polysorbate 80.

2.5.2 Combination vaccines that include hepatitis B antigen

2.5.2.1 Twinrix®

Twinrix® is a combination hepatitis A and B vaccine manufactured by GlaxoSmithKline Biologicals. It is available in two formulations administered at 0, 1, and 6 months schedule: adult (720 EL.U of hepatitis A antigen and 20μg of HBsAg for those aged 16 years, and paediatric (360 EL.U of HAV and 10μg of HBsAg for those up to 15 years of age. The adult formulation is also licensed for use as a two-dose schedule (0, 6 months) (Ambirix®) in children and adolescents from one to 15 years of age in many countries. The antigens are separately adsorbed onto aluminium hydroxide and aluminium phosphate. HBsAg is produced by culture of genetically engineered yeast cells in a selective medium.

2.5.2.2 Comvax®

Comvax (Merck Sharp and Dohme) is a *Haemophilus B* Conjugate (Meningococcal Protein Conjugate) and recombinant hepatitis B (Recombinant) Vaccine. Each 5mL dose contains 7.5μg *Haemophilus influenzae* type b purified capsular polysaccharide (PRP), 125μg *Neisseria meningitidis* (OMPC) and 5μg of hepatitis B surface antigen (HBsAg). After conjugation, the aqueous bulk is then adsorbed onto an amorphous aluminium hydroxyphosphate sulphate adjuvant. The vaccine contains no detectable DNA, and 1% or less of the protein is of yeast origin. Each 0.5mL dose contains approximately 225μg of aluminium as amorphous aluminium hydroxyphosphate sulphate, and 35μg sodium borate (decahydrate) as a pH stabiliser, in 0.9% sodium chloride.

2.5.2.3 DTaP-IPV-Hep B/Hib, Infanrix®-hexa

The licenced diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine Infanrix®-hexa, produced by GlaxoSmithKine. Infanrix®-hexa is a combined diphtheria and tetanus toxoids, acellular pertussis, recombinant hepatitis B, inactivated poliomyelitis, and adsorbed conjugated H. influenzae type b vaccine each 5 mL dose contains 10μg H. influenzae type b polysaccharide, 10μg of hepatitis B surface antigen (HBsAg) (9).

2.5.2.4 Hexaxim®

Hexaxim® is a hexavalent vaccine against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b produced by Sanofi Pasteur. One 5ml dose contains 10μg hepatitis B surface antigen produced in *Hansenula polymorpha* yeast cells by recombinant DNA technology and 12μg *H. influenzae* type b polysaccharide.

2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching. Conference abstracts have also been added.

3. Recent New Zealand epidemiology

In NZ, only acute hepatitis B is a notifiable disease, therefore, notification rates do not give an indication of the burden of chronic hepatitis B infection (8). In 2011, 49 cases of hepatitis B were notified, compared with 51 cases in 2010 (Figure 2). There has been a general downward trend in the number of hepatitis B notifications reported between 1984 (over 600 cases) and 2004 (38 cases), with numbers of notifications fluctuating between 38 and 72 in recent years. The general decrease since 1984 is primarily attributed to the introduction of the hepatitis B vaccine to the immunisation schedule between 1985 and 1988.
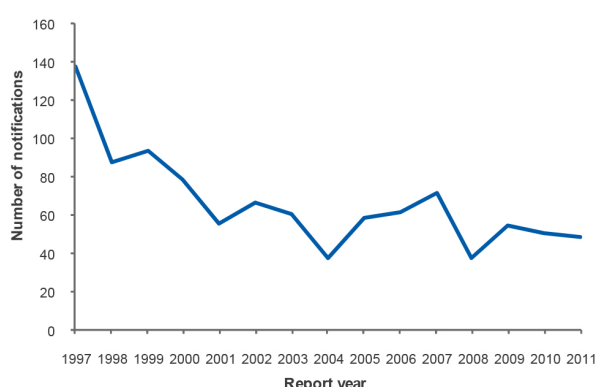
Figure 2. Hepatitis B notifications in NZ by year, 1997–2011 (8)

The national hepatitis B notification rate for 2011 was 1.1 per 100 000 population, similar to the 2010 rate of 1.2 per 100 000.

For the two-year period 2010–2011, the highest annualised rate in district health boards (DHB) with five or more cases was in Tairawhiti (9.7 per 100 000, nine cases), followed by Lakes (2.9 per 100 000, six cases) and Auckland (2.0 per 100 000, 18 cases) DHB.

In 2011, the age specific rate was highest in the 20 – 29 years age group (2.4 per 100 000 population, 15 cases), followed by the 40 – 49 years age group (1.7 per 100 000, 11 cases). The notification rate was higher for males (1.6 per 100 000 population, 34 cases) than females (0.7 per 100 000, 15 cases). Ethnicity was recorded for 46 (93.9%) cases. The highest notification rate was in the Pacific Peoples ethnic group (2.6 per 100 000, seven cases), followed by the Asian (1.7 per 100 000, seven cases), Māori (1.5 per 100 000, 10 cases) and European or Other (0.7 per 100 000, 22 cases) ethnic groups.

Of the 41 (83.7%) cases, where hospitalisation status was recorded, 15 (36.6%) were hospitalised.

The most common risk factors associated with hepatitis B, in 2011, were overseas travel during the incubation period (32.4%), sexual contact with a confirmed case or carrier (22.2%) and household contact with a confirmed case or carrier (10.3%) (Table 1).

Table 1. Exposure to risk factors associated with hepatitis B, 2011 (8)

Risk factor	Yes	No	Unknown	Percentage (%) [a]
Overseas during incubation period	12	25	12	32.4
Sexual contact with confirmed case or carrier	6	21	22	22.2
Household contact with confirmed case or carrier	3	26	20	10.3
Body piercing/tattooing in last 12 months	3	35	11	7.9
Case was child of seropositive mother	1	30	18	3.2
Case is a blood product or tissue recipient	1	36	12	2.7
Occupational exposure to blood	0	36	13	0.0
History of injecting drug use	0	37	12	0.0

[a] Percentage refers to the number of cases that answered "yes" out of the total number of cases for which this information was supplied. Several cases had more than one risk factor recorded.

3.1 Mathematical modelling of hepatitis

Although overall NZ is considered to have low endemicity of hepatitis B, there are areas of medium to high endemicity. There have been many attempts at modelling hepatitis B both in NZ and internationally. To further refine previous work, a model divided the NZ population into age classes and included age-specific vaccination coverage, local data on incidence of infection and vaccination coverage. The basic reproduction number was estimated to be 1.53 and the hepatitis B immunisation programme had reduced this to below one. However, the number of carriers is estimated to continue to provide a source of infection to those who are susceptible until 2100, one of the factors influencing this is increased immigration. Further refinement could help predict the areas for more targeted immunisation (6).

3.2 Chronic hepatitis B infection in New Zealand

Chronic hepatitis B is the leading cause of hepatocellular carcinoma (75%), liver-related mortality (63%) and liver transplantation (32%) in NZ; there are estimated 90,000 individuals with chronic infection. The national hepatitis B screening programme confirmed highest rates in Chinese (9.1%), Pacific Islander (8.5%) and Māori (5.8%){Ishigami, 2011 #651;Tielemans, 2011 #78}. Although Europeans were not specifically targeted in this screening programme, they have an estimated prevalence rate of 1%, which is higher than in Australia, North America and Europe, reflecting the risk of early horizontal transmission (10).

New childhood infections in NZ have been largely eradicated by the introduction of neonatal vaccination. However, as discussed above, increased immigration from countries with high-prevalence throughout the Asia-Pacific region is likely to result in an increase in numbers of chronic infections (11).

3.3 Summary of New Zealand epidemiology

There has been a steady downward trend in the number of hepatitis B notifications since 1984, which is attributable to the implementation of a universal national vaccination programme. The highest notification rate is among Pacific People followed by Asian. The most common risk factor was overseas travel and sexual contact. The most recent mathematical modelling supports a reproduction number of less than one showing the potential for eradication; however, increased immigration is likely to provide an increasing source of new carriers.

4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licenced hepatitis B vaccines. Only Adverse Events Following Immunisation (AEFI) that have been considered subsequent to the pivotal clinical efficacy trials are reviewed here and any major clinical differences between vaccine types.

4.2 Outcomes

Outcomes are vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE). Excluded is reactogenicity (injection site reactions and minor systemic reactions) as these are well established.

4.3 Review

HBV vaccines have a well-documented safety record. There are no conditions of concern that have been found to have an increased risk associated with receipt of hepatitis B vaccines (2).

4.3.1 Safety of hepatitis B vaccine in pregnant women and their infants

HBV vaccine is recommended for pregnant women at higher risk for infection, such as drug users, women with sexually transmitted diseases, multiple sexual partners and infected household contacts, by the Centre of Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynaecologists. NZ recommends not withholding vaccination from these women if they are pregnant.

A 2011 Cochrane review aimed to assess the effectiveness and adverse effects of hepatitis B vaccine when administered to pregnant women for preventing hepatitis B infection in their infants. In order to identify randomised trials they searched the Cochrane Pregnancy and Childbirth Trials Register. They found no randomised trials assessing hepatitis B vaccine with a placebo or no treatment during pregnancy for preventing infant infection, and they excluded other study designs (12).

A 2012 systematic review was more comprehensive in its approach to sourcing studies on the safety of HBV vaccine, as well as pneumococcal and meningococcal vaccines, in pregnancy. There were six studies identified that referred to the HBV vaccine

review. The search also included the Vaccine Adverse Events Reporting System (VAERS) database from June 1990 and identified 88 reports on HBV vaccine for evaluation. Of the six prospective studies, one was an RCT and five were cohort studies in a total of 381 pregnant women. Three studies used a recombinant HBV vaccine while the remaining three used a vaccine containing purified, plasma-derived hepatitis B surface antigen from chronic HB carriers. In the RCT, which compared two versus three doses of HBV vaccine in 100 Indian women in the second or third trimester of pregnancy, investigators stated that ''there were no side effects''. However, in a check of the manuscript, no methods for safety monitoring were described and no specific safety data was presented. One of the cohort studies evaluated the safety of a three-dose schedule of HBV vaccine in 168 pregnant women noting the most common reaction was injection site pain. The observed rates of preterm labour were similar to those seen in the general obstetric population. In another cohort, 16 pregnant women, who were exposed to HBV after *in vitro* fertilisation, received three or four doses of a recombinant vaccine after exposure. One vaccinee had a miscarriage two days post-immunisation and another was lost to follow-up; the remaining delivered healthy infants, who had no developmental problems by the age of 22 months (13).

Data from the VAERS from 1990 to 2011 include 88 evaluable reports of pregnant women vaccinated with the recombinant HBV (rHBV) vaccine. Most of the reports were for women who found they were pregnant after receiving the vaccine and timing of vaccination in relation to the adverse event is uncertain in many cases. Reports included 28 spontaneous abortions, 12 elective abortions, 3 stillbirths, 3 preterm labours, 7 cases of vaginal bleeding, 2 chromosomal abnormalities and 1 case of autism, as well as local and systemic adverse reactions (13).

4.3.2 Safety of hepatitis B in newborn infants of HBsAg positive mothers

A 2009 Cochrane review aimed to assess the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of HBsAg+ mothers. The authors concluded that the vaccine seemed safe, but that few trials reported on adverse events. Reported adverse events were rare and mostly non-serious (14).

4.3.3 Hepatitis B vaccine and autoimmunity

The relationship between hepatitis B vaccination and its potential to trigger autoimmune conditions has been studies (15, 16). The data shows no causal association between hepatitis B vaccine and Guillain-Barré syndrome or demyelinating disorders such as multiple sclerosis. There is also no epidemiologic data supporting a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritic conditions, asthma, sudden infant death syndrome, alopecia, or diabetes (2).

4.3.4 Safety in high risk groups

The immunogenicity of HBV vaccine in adults infected with human immunodeficiency virus (HIV) is lower than healthy persons without HIV infection. A randomised trial compared the safety and immunogenicity of four intramuscular double (40µg) antigen dose and four intradermal (4µg) regimes to the standard hepatitis B regime of zero, four and 24 months. No safety signals were identified for any of the regimes and there was no effect on CD4 cell counts or viral loads (17).

4.3.5 Safety during concomitant administration with other vaccines

Energix-B® was evaluated in a randomised trial given alone or with the HPV vaccine, Cervarix®, in 152 women. There was no difference in reactogenicity observed between the groups and no safety concerns were raised (18). In another study, Twinrix® was evaluated when co-administered with Cervarix® in a randomised trial in 813 girls aged nine - 15 years. The safety and reactogenicity of the two vaccines was similar when co-administered or administered alone (19).

4.3.6 Safety of multivalent infant vaccines including hepatitis B antigen

Detailed reviews of pertussis and tetanus containing multivalent vaccines are included in their respective antigen review reports. Below are some summaries of multivalent vaccines that contain hepatitis B antigen.

A population based case series examined data on 834,740 children in Ontario, Canada. It compared the frequency of emergency room visits and admissions in the three days post the first infant vaccination event at two months in small for gestational aged children (those in the lowest 10th percentile) and very preterm infants compared with term children. When compared with term children, there was a small

non-significant reduction in frequency of emergency room visits and admissions in the three days after the first vaccine event at 2 months of age in small for gestation age near term infants (RR 0.89; 95% CI 0.74-1.07) and more so for very preterm infants (RR 0.67 ; 95% CI 0.49-0.93). The authors speculate that the immune response is attenuated in preterm children resulting in reduced adverse events, but this may be masked because the reduced birth weight results in a comparatively increased dose of vaccine given (20).

Guillain-Barré Syndrome cases were identified from the Kaiser Permanente Northern California databases, from 1995 to 2006, using hospital discharge codes. At total of 550 cases were identified in over 33 million person years. There were no cases of GBS identified as occurring within six weeks of any vaccine (21).

A case of a three month old who developed femoral neuropraxis after vaccination with DTaP-IPV-HPV-Hib vaccine was reported in 2011. Good neurological recovery was made within eight weeks post vaccination (22).

A review of 11 safety studies of the hexavalent combination DTaP-IPV-HepB/Hib (Infanrix®-hexa), conducted over eight years, identified the most commonly reported local reactions in all published studies have been mild and transient pain, redness and/or swelling at the injection site and fever, irritability and/or drowsiness (23). See Table 2.

Table 2. Most frequent adverse events for DTaP-IPV-HepB/Hib (Infanrix®-hexa) from launch up to 2008, spontaneously reported to the GlaxoSmithKline worldwide safety database (OCEANS)

AE	Number of AEs	Frequency per 100,000 doses
Pyrexia	1572	5.9
Injection-site erythema	570	2.1
Injection-site swelling	488	1.8
Crying	465	1.7
Injection-site reaction	294	1.1
Injection-site induration	256	1.0
Hypotonia	218	0.8
Urticaria	210	0.8
Pallor	200	0.8
Erythema	196	0.7

AE: Adverse event; DTaP-IPV-HepB/Hib: Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, hepatitis B/ *Haemophilus influenzae* type b vaccine; OCEANS: Operating Companies Event Accession and Notification System

4.4 Summary vaccine safety

The safety of hepatitis B vaccines is well established and there are few new studies specifically investigating the safety of hepatitis B vaccines.

Although there are few controlled trails in pregnant women using hepatitis B vaccine there are no theoretical safety concerns and no issues have been identified after extensive use. Pregnancy outcomes in pregnant women exposed to HBV vaccine are similar to those in the unexposed population. Hepatitis B vaccine is delivered universally as part of multivalent vaccines on infant schedules and these vaccines have been rigorously evaluated for safety

5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective

The objective of this section is to review the most recent performance data for currently licenced HBV vaccines. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of HBV vaccines and evidence their impact in populations.

5.2 Review

The clinical efficacy of HBV vaccine has been assessed in pre-exposure clinical studies during the 1980s. The studies demonstrated efficacy of 80 - 100% and virtually complete protection against acute and chronic hepatitis B infection in persons who develop anti-HB concentration of 10 mIU/mL or greater after initial vaccination (2).

5.2.1 Immunogenicity

Anti-hepatitis B antibody levels are the only practical and measurable correlate of HBV vaccine protection. An anti- hepatitis B antibody concentration of 10 mIU/mL or more measured one to three months after administration of the last dose of the vaccination series is considered a reliable marker of protection against infection. To illustrate the prolonged duration of protection against hepatitis B, even after disappearance of antibodies, a clear anamnestic response is observed shortly after a booster dose in cohorts of vaccinees up to 23 years after their primary vaccination series (24).

There is evidence to suggest that recombinant HBsAg (rHBsAg) immunogenicity varies when derived from alternative species of yeast, such as *Pichia pastoris*. To compare the immunogenicity of four recombinant hepatitis B vaccines produced in different yeast host strains, 400 healthy adults were randomised and vaccinated in a 0, 1 and 2 month schedule. The vaccines were: Heberbiovac-HB® (Heber Biotec S.A., Cuba), Euvax-B® (LG Chemical Ltd, South Korea), Hepavax-Gene® (Greencross Vaccine Corp., South Korea) and Engerix-B® (GlaxoSmithKline Biologicals, Belgium). Each vaccine dose contained 20µg of antigen. Similar seroprotection rates (anti-HBs ≥10 mIU/mL) about one month after administration of the second and third dose were obtained for Engerix-B®,

Hepavax-Gene®, Euvax-B® and Heberbiovac-HB® vaccines 96.7%, 96.6%, 100%, 100% and 98.8%, 89.5%, 100%, 100%, respectively. Heberbiovac-HB® vaccine achieved significantly higher geometric mean titre (GMT) and rate of hyper-responders at all time-points post-vaccination. The GMT on day 365 after full vaccination was significantly reduced in all groups compared with day 90, although Heberbiovac-HB® continued to show the highest anti- hepatitis B GMT and good-responder rates (25).

5.2.1.1 Two-dose schedule in children

A two-dose regimen of the Twinrix® adult formulation has previously been found immunogenic and safe in children and adolescents in comparison to the established three-dose regimen. A 10 year follow-up assessed the persistence of antibodies to hepatitis A and B in 120 children who were aged one to 11 years at the time they received two doses of the adults formulation at zero and six months. Immune memory was assessed by measuring the anamnestic response to a challenge dose. Ten years after administration of two doses of this vaccine, all subjects remained seropositive for anti-HAV antibodies and 81.7% of subjects continued to have anti-HBV antibody concentrations >10 mIU/mL. All subjects who had HBV antibodies <10 mIU/mL mounted an anamnestic response to a challenge dose. The two-dose regimen, using adult formulation in children aged one to 11 years of age, is highly immunogenic (26).

Two doses of HBV vaccine have been generally demonstrated to be immunogenic in adolescents. However, in a longitudinal study in the US, urban youth had lower antibody responses than previous studies would suggest in this age group. A positive response to hepatitis B antigen (serum antibody 10 mIU/mL) was documented in 41 of 47 Recombivax HB recipients (87.2%; 95% CI 74.3%–95.2%) and in 52 of 55 Twinrix® recipients (94.6%; 95% CI 84.9%–98.9%; p = 0.295). In an adjusted analysis, those identified as Hispanic ethnicity were more likely to have a positive response (OR 7.38, 95% CI 1.56 –34.95; n = 86; p = 0.0018); whereas those who identified as not heterosexual were less likely to respond (OR 0.12; 95% CI 0.02– 0.74; n = 9) (27).

5.2.1.2 Alternative schedules in adults

Two schedules of Twinrix® were assessed in 399 healthy Belgian adults. The vaccine was given at zero, one and 12 months or zero, one and six months. The rate of seroconversion at six months was 70.6% in the group receiving the 0–1–12 and 79.9% in the group receiving 0–1–6; this rate decreased to 55.9% at 12 months in the first group. Seroconversion and seroprotective rates against HBV vaccine, measured at month 13 in group 0–1–12 (98.9% and 95.6%, respectively) and measured at month 7 in group 0–1–6 (99.4% and 97.1%, respectively), were not statistically significantly different. GMT of anti-HBsAg antibodies was more than two fold higher after the 0–1–12 schedule than after 0–1–6 schedule (p < 0.001), indicating that there is flexibility in the vaccination schedule. The seroprotective rates taken at the same study assessment point are similar for both groups and subjects receiving their third dose later that six months will be protected equally (28).

The use of an accelerated schedule given at zero, one and four months was assessed in 200 pregnant women. Seroconversion after one dose, two and three doses was 56% (95% CI 49–63%), 77% (95% CI 71–83%) and 90% (95% CI 85–94%), respectively. Body mass index was inversely associated with seroconversion rates (p < 0.001), but there was no single body mass index above which seroconversion did not occur. This accelerated course was effective, induced protective levels of antibody and can be completed during the course of pregnancy in high-risk women (29).

5.2.2 Anatomical site and immunogenicity

HBV vaccine must be given either intramuscularly or intradermally. Subcutaneous administration results in suboptimal immune responses. There is inconsistency in the evidence around the immunogenicity of HBV vaccine when given to infants in the ventrogluteal as opposed to the anterolateral thigh. A randomised trial in 590 Brazilian infants receiving three doses of HBV vaccine found no immunological difference between the sites and no complications arising from administration into the ventrogluteal site, which is relatively free of major nerves and blood vessels and characterised by the greatest thickness of muscle and the thinnest layer of subcutaneous fat (30).

5.2.2.1 Immunogenicity of hexavalent vaccines

Three formulations of hexavalent vaccines were evaluated for safety and immunogenicity in 756 infants. All formulations included 10µg of HBsAg in 0.5mL.

The three formulations of the hexavalent vaccine used contained either:

- Hib polyribosylribitol phosphate (PRP) conjugate component of tetanus toxoid (PRP-T) 12µg or

- *Neisseria meningitidis* outer membrane protein complex with (PRP-OMPC) 3µg

- *Neisseria meningitidis* outer membrane protein complex with (PRP-OMPC) 6µg

All the above vaccines contained hepatitis B surface antigen (10µg HBsAg (Merck), diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and PRP–T antigens (Sanofi Pasteur), or PRP–OMPC antigen (Merck). The control vaccines were DTaP-IPV/Hib (Pentacel®, Sanofi Pasteur) and HBV vaccine (Recombivax® HB, Merck). Infants received the vaccines at two, four, six and 12 - 14 months of age, except the monovalent hepatitis B vaccine that was administered at two, four and six months. A minimum acceptable post-dose 3 antibody response rate for each antigen was defined by the lower limit of a 95% confidence interval exceeding a pre-specified target. The two formulations containing PRP–OMPC (PRP–OMPC3 and PRP–OMPC6) met the acceptability criteria for the post-dose 3 antibody response for all components tested; whereas the PRP–T containing formulation met the acceptability criteria for all antibody response, except PRP. The post booster antibody titres were high for all formulations (31).

5.2.2.2 Immunogenicity in HIV-infected adults

The immunogenicity of HBV vaccine in adults infected with HIV is lower than healthy persons without HIV infection. A randomised trial compared the safety and immunogenicity of four intramuscular double dose and four intradermal low dose regimes to the standard HBV vaccine regime of zero, four and 24 months. The percentage of responders at week 28 was 65% in the intramuscular three dose group (95% CI 56%-72%; n=91), 82% in the intramuscular four dose group (95% CI 77%-88%; n=119) and 77% in the intradermal group (95% CI 69%-84%; n=108). Both alternative regimes resulted in an improved immune response in HIV infected adults over the standard three-dose regimen (17).

Forty HIV patients in France, who were positive for hepatitis B core (HBc) antigen, negative for both HBsAg and anti-HBs antibodies and who had a CD4 count of >200 cells/μL, were recruited into a study to determine the immune response and optimal schedule for individuals who tested positive for HBc antibodies. All patients had had extensive exposure to highly active antiretroviral therapy (HAART) treatments. An anamnestic response was observed in 32.5% and no baseline factors, including anti-HBe positivity, were predictive of this response. Of the patients, 40.7% did not have an anamnestic response. Follow-up a year later found that only 58.3% of patients who demonstrated an anamnestic response had protective titres one year later. The authors recommend measuring the anti-HBV titre after the first vaccine dose. If no anamnestic response occurs then a full vaccination schedule should be given (up to 6 doses, if necessary), and that this approach should be validated in a larger cohort (32).

The clinical significant of anti-HBc IgG is unclear, but it is thought that it may either represent a "window" phase, that follows acute hepatitis B infection, during which HBsAg is no longer in the bloodstream, but anti-HBsAg antibodies have not yet emerged; a resolved hepatitis B infection with loss of anti-HBs antibodies; an occult chronic HBV infection with undetectable HBsAg; or a false-positive test result (32).

5.2.2.3 Immunogenicity in patients with inflammatory bowel disease

Inflammatory bowel disease (IBD) is frequently treated with immunosuppressive agents and the response to HBV vaccine in these patients is poor. The treatment regimens have resulted in fulminant and fatal infections in patients with IBD who have become infected with hepatitis B. As some high risk immunocompromised groups are recommended to have higher doses of HBV vaccine, a study compared two HBV vaccine protocols using HBV vaccine with different antigen concentrations. A total of 148 IBD patients received either Energix-B® single dose (20μg) at 0, 1 and 6 months (standard protocol) or a double dose accelerated schedule of Energix-B® at 0, 1 and 2 months. Antibodies were measured at one - three months after the last dose. The standard protocol was followed in 46% of patients and the double dose protocol in 54%. The seroconversion rate was higher among patients vaccinated with the double dose

than with the standard dose: 75% versus. 41% (95% CI 65–85%; 29 –54%, respectively, p < 0.001). In the multivariate analysis, vaccination with the double dose was the only factor associated with a better response to the vaccine (OR 4; 95% CI 2 – 8; p < 0.001) (33).

Immunity to hepatitis B and the response to a booster dose were evaluated in 100 children with IBD (mean age of the patients was 17.9 ± 4.0 years) being treated with infliximab in a prospective study. Participants were tested for HBsAg, anti-HBc and anti-HBs antibodies. One booster dose was given to non-immune patients and a serum sample was collected after four weeks to assess the presence of an anamnestic response. None of the patients were positive for HBsAg or anti-HBc. A total of 87 patients were vaccinated against HBV with a booster dose and 49/87 (56%) had immunity to hepatitis B (>10 mIU/mL). The absence of protective antibodies was associated with older age, lower albumin levels and the presence of pancolitis. However, the dose, frequency, duration of infliximab treatment and the concurrent use of immunomodulators were not significantly different between immune and non-immune patients. An anamnestic response was shown in 26/34 (76%) patients who received a single booster immunisation. Non-responders received a higher frequency of infliximab (every 5.9 ± 1.2 weeks versus every 7.1 ± 1.8 weeks, p = 0.01). Overall, of the previously immunised patients, 75/87 (86%) were considered immune against HBV infection following a booster vaccination. However, a significant minority still appeared at risk for hepatitis B infection (34).

5.2.2.4 Immunogenicity in diabetes patients on dialysis

Although diabetic patients are known to have a compromised immune system, the response to HBV vaccine is not known, however, it is known that patients on dialysis often respond poorly to HBV vaccine. A meta-analysis was conducted to evaluate the influence of diabetes on the immune response to HBV vaccine in patients on maintenance dialysis. Twelve studies were identified that involved 1002 patients on long term dialysis. An aggregation of the study results indicated a significant decrease in immunogenicity among the diabetic compared with the non-diabetic patients (pooled odds ratio = 0.52; 95% CI 0.38–0.71). The authors recommended frequent evaluation of immunity in these patients (35).

5.2.2.5 Immunogenicity in patients with chronic kidney disease

As patients with chronic kidney disease are known to have an impaired response to HBV vaccine and these patients often have a compromised nutritional status, a systematic review of the literature with a meta-analysis of clinical studies was undertaken to evaluate the influence of nutrition status on the immune response to HBV vaccine in patients with chronic kidney disease. Seven studies were identified that included 15,172 patients with chronic kidney disease. The rate of seroprotection after a full course of HBV vaccine ranged between 40 and 86%. The aggregation of study results indicated an independent adverse effect of poor nutritional status, usually detected by serum albumin levels, on rates of seroprotection. The summary estimate for adjusted risk ratio was 1.50 (95% CI 1.02 - 2.21). In the subgroup of patients who received HBV recombinant vaccine, the relative risk of impaired serological response after vaccination was 1.63 (95% CI 1.08 - 2.45) for those with poor nutritional parameters at baseline. There appears to be an increased risk for an impaired response to HBV vaccine among patients with poor nutritional status (36).

A meta-analysis was conducted to assess whether adjuvantation of HBV vaccine improved the immunogenicity in patients with chronic kidney disease, which included ten studies involving 1228 patients. The immunogenicity generated by a range of adjuvanted hepatitis B vaccines was not found to be superior to unadjuvanted vaccines. The adjuvants studied included interferon, interleukin-2, GM-CSF, AS02 and AS04 (37).

In contrast to the findings of meta-analysis above, two randomised studies were undertaken to compare HBV vaccine adjuvanted with GlaxoSmithKline's proprietary AS02 adjuvant and a licensed conventional recombinant HBV vaccine (HBvaxPRO™; Sanofi Pasteur MSD) in pre-dialysis, peritoneal dialysis and haemodialysis patients aged ≥18 years, who had either failed to respond to prior vaccination with a conventional HBV vaccine (Study A, n=251) or who had failed to maintain protective antibody concentrations following previous HBV vaccination (Study B, n=181). In Study A, two doses of HB-AS02 given one month apart were superior to two doses of the licensed vaccine in terms of seroprotection rate (76.9% versus 37.6%) and anti-HBs geometric mean antibody concentration (GMC; 139.3 versus 6.9 mIU/ml). In Study B, one month after administration of a single booster dose, seroprotection rates were 89.0%

in the HB-AS02 group and 90.8% in the licensed vaccine group, 81.3% and 60.9% of subjects had antibody concentrations ≥100 mIU/ml, and anti- HBs GMC were 1726.8 and 189.5 mIU/ml, respectively. HB-AS02 was found to be more reactogenic than the licensed vaccine. The investigational HB-AS02 vaccine induced higher seroprotection rates and anti-HBs GMC than a licensed conventional hepatitis B vaccine in patients with uraemia who had failed to respond or to maintain protective antibody titres after prior hepatitis B vaccination (38).

5.2.2.6 Immunogenicity in cirrhotic patients and transplant patients

HBV-positive status has historically been a contraindication for liver transplant due to the high rate of recurrence and rapid progression to liver failure. Treatment with HBIg, to neutralise HBV, and a nucleoside analogue, lamivudine, for the prevention of viral reactivation, has dramatically improved the outcomes for these patients but it is expensive. Transplant recipients who receive their graft from a donor who previously had hepatitis B infection and cleared the infection are still at risk of reactivation. To determine the immunogenicity of HBV vaccination, 15 chronic carriers of HBV and 6 non-HBV carriers who received a graft from an HBcAb-positive donor were vaccinated with a Japanese hepatitis B vaccine. None of the 15 chronic HBV carriers succeeded in maintaining protective titres >100 IU/l. Five of the six non-HBV patients with HBcAb-positive donors achieved HBsAb >100 IU/l without HBIg coadministration. Recipient HBV status (HBV carrier/non-HBV; p=0.001) and recipient age (p=0.006) had a stronger effect on vaccine immunogenicity (39).

Prevention of *de novo* hepatitis B infection after orthotropic liver transplant is an important part of prophylaxis and HBV vaccination is poorly immunogenic in immunocompromised or cirrhotic patients. The rate and factors associated with a response to four intramuscular doses (40μg) of HBV vaccine administered at zero, one, two and six months were evaluated in a cohort of 278 cirrhotic patients awaiting liver transplant, 268 with negative and 10 with positive markers for infection. Of the total, 57 non-responders were revaccinated with the same schedule. The overall response rate was 39.2%; 36% after three doses and 40.7% after four doses. Variables associated with a higher response were: better liver function, absence of diabetes, younger age and presence of anti-HBc positivity (80% versus 37.7%). After multivariate logistic regression analysis, lower liver function (odds ratio [OR] 0.922; p =0 .046),

absence of diabetes (OR 0.359; p =0 .008) and anti-HBc positivity (OR 5.826; p=0 .034) were associated with a higher response. No differences were observed to be associated with gender, weight, body mass index, etiology or tobacco consumption. Among the same patient cohort (n =79), the responses after the third and fourth doses were 36.7% and 51.9%, respectively. The response rate to HBV vaccination in cirrhotic patients evaluated for transplant was greater than 35% among those who received at least 3 doses. It was higher among patients who showed anti-HBc positivity, better liver function, younger age, and non-diabetic status. The fourth dose only increased the response rate by 24% over that obtained after the first three doses, whereas a complete revaccination course achieved a 50% response rate. The authors concluded that vaccination against hepatitis B should be administered in the early stages of disease (40).

To overcome the poor responses to intramuscular administration of hepatitis B vaccine in patients with chronic liver disease, 48 individuals, who had failed to respond to a three dose schedule of 40μg vaccine deliver intramuscularly IM with a booster of either 40 and 80μg, were given 40μg (20μg per arm) intradermally until a response was achieved or three doses had been administered. Twenty-nine of forty-two (69%) individuals had an immunological response, with 15 (51%) of the responders having an optimum response of anti-HBs antibody titre > 100 mIU/ml. No serious dermatological reactions were observed. No differences between those who responded and those who did not were observed with regard to the presence of cirrhosis, diabetes mellitus or chronic kidney disease. The authors recommend this regimen be considered for all such groups (41).

5.2.3 Non responders to hepatitis B vaccination

Patients who have no protective levels of anti-HBs antibody at four to eight weeks after revaccination are either primary non-responders or are infected with HBV. Genetic factors appear to contribute to non-responsiveness to hepatitis B vaccination (42). Vaccine failure has been seen in vertical transmission studies and is thought to be associated with immune tolerance induced by transplacental transfer of HBe antigen (HBeAg) (43). The presence of HBeAg is associated with immunoprophylaxis failure in infants born to HBsAg+ mothers (44).

One study attempted to show an improved rate of response in non-responders by using granulocyte-macrophage colony stimulating factor (GM-CSF) as an adjunct to vaccination in comparison with either 20μg or 40μg antigen doses. Study participants, including 1784 healthy adults and 100 individuals diagnosed as non-responders, were randomised to one of three treatment groups: Group A (n = 34) was given 150 mg of GM-CSF on day 1 then 20μg of the vaccine; Group B (n = 33) was given 40μg of the vaccine only; and group C (n = 33) received 20μg of vaccine per dose. All participants received three doses of vaccine at zero, one and six months. Antibody titres were tested before treatment and at one, two and eight months post first injection. At one month, the seroconversion rate in groups A, B and C was 26.47%, 48.48% and 18.18%, respectively (p=0 .027). At eight months, the seropositive rate of group A (64.71%) and group B (75.76%) was significantly higher than in group C (39.39%) (p =0.011); the GMT for groups A and B was higher than for group C (p=0.0173). The higher antigen dose was an effective strategy to improve seroconversion in non-responders (45).

5.2.4 Effectiveness of hepatitis B vaccine

The last 20 - 30 years have seen an 84% decline in acute hepatitis B incidence in the US as a result of the introduction of hepatitis B vaccines into the immunisation schedule (2). In NZ, hepatitis B notifications have declined from 609 cases in 1984 to 51 cases in 2010 (1.2 per 100,000 population), a reduction of around 92%. Observational studies suggest that that a primary course of HBV vaccine can prevent infection for over 20 years despite diminished or loss of vaccine-induced anti-HBs antibody over time (2).

5.2.4.1 Effectiveness against acute hepatitis B infection and duration of immunity

A study in Taiwan identified the changing incidence of acute hepatitis B infection through notifiable surveillance data collected between 2001 and 2009. The age-specific incidence among vaccination and unvaccinated birth cohorts were compared. A total of 2226 patients with acute hepatitis B infection were identified. Disease rates varied by age; the highest rates occurred among unvaccinated individuals aged 25 – 39 years (2.33/100,000). Due to breakthrough

infection from mother-to-infant transmission, vaccinated infants (0.78/100,000) had higher rates than those aged 1–14 years (0.04/100,000) who had the lowest rates. The incidence in vaccinated birth cohorts was significantly lower than in unvaccinated birth cohorts among patients 15 – 24 years old, with an adjusted-relative risk of 0.42. It was concluded that universal birth HBV immunisation effectively reduced the occurrence of acute hepatitis B infection among adolescents and young adults for over 25 years (46).

It has been observed in Taiwan that a significant proportion of fully vaccinated infants lose immune memory (anamnestic response) to hepatitis B by the age of 15 - 18 years. As of early 2013, it is not known if this is clinically important, boosters have not been needed in Taiwan for at least 20 years (see below). In Taiwan, a booster dose will only be considered when the cohort who have been vaccinated present with clinically significant hepatitis B breakthrough infections. So far these are rare events, see Table 3 (47).

Table 3. Breakthrough hepatitis B virus infections in the vaccinees who received hepatitis B immunisation in childhood (47)

Country/year	Author	No. of subjects studies	No. with HBV infection*	Observation period (years)	Average annual incidence %
Taiwan / 2003	Lin et al	1200	11	7	0.13
UK, Asia / 2004	Boxall et al.	64	1	15.1	0.1
		52	1	11.8	0.16
China, Hong Kong /2004	Yuan et al.	88	3	18	0.19
US, Alaska / 2005	McMahon et al.	1578	16	15	0.08
US, Alaska / 2005	Dentinger et al.	334	6	10	0.18
Italy / 2005	Zanetti et al.	112	1	10.6	0.008

HBV: hepatitis B virus

 * infections were asymptomatic and rarely became chronic.

5.2.4.2 Effectiveness against hepatocellular carcinoma

Taiwan has had a universal HBV vaccine program in place for over 25 years and they have recently been able to demonstrate the impact of the reduction in hepatitis B infection on the prevalence of hepatocellular carcinoma (7). In Taiwan HCC also occurs in children. The annual incidence of HCC in Taiwanese children aged 6–14 years has reduced from 0.52–0.54 per 100,000 children born before July 1984 to 0.13–0.20 per 100,000 children born after the vaccination program.

5.2.4.3 Effectiveness of HBV vaccine in children born to HBsAg-positive mother

Vertical transmission of hepatitis B from infected mother to newborn is 70 - 90% in the absence of prophylaxis. Combined passive and active immunisation of newborns born to hepatitis B positive mothers is 85% to 90% effective at preventing perinatal hepatitis B infections (2).

A retrospective study was conducted in Italy, more than 20 years after HBV vaccine was introduced, to evaluate the effectiveness of post exposure vaccine prophylaxis in 100 infants born to HBsAg$^+$ mothers.

Twenty years after post-exposure prophylaxis of HBIg and HBV vaccine, two subjects (2%) acquired the infection. Of the 98 patients who did not acquire the infection, 62 (63.3%) had an anti-HBs concentration considered protective ($\geq$ 10 mIU/ml). The percentage of protected participants decreased in relation to time from vaccination, with a significant reduction of anti-HBs GMT after five years (p = 0.009) and which reached 10 mIU/ml after approximately 15 years. As of the time of the study, no patients without protective concentration had acquired the infection. In this population, only 12% of the HBsAg-positive mothers were followed in specialised systems after pregnancy, reflecting the limited knowledge of the problem in the general population (48).

A study was conducted in the Netherlands, where babies born to HBsAg$^+$ women receive both passive immunisation with HBIg and at least three doses of HBV vaccine, to evaluate the persistent and transient infections in children born to hepatitis B-infected mothers. All children of HBV-infected mothers, born between January 2003 and July 2007 in the Netherlands, were invited to participate in the serological screening six weeks–four years after completion of their vaccination schedule. The sera were collected when the children were aged between

205 and 1727 days (average = 622; median 482); a total of 1743 serum samples were collected from the estimated 2280 affected children (75.4%). Twelve of these sera contained HBsAg (0.69%). All 12 HBsAg[+] children had completed their HBV-vaccination schedule, which included administration of HBIg within two hours of birth. Five of these 12 children had an anti-HBs antibody titre greater than 1.0 mIU/mL. There were also three older children with high levels of anti-HBc, anti-HBs and anti-HBe antibodies, and HBsAg and HBV DNA negative, which is evidence for a resolved HBV infection. In the group of older children (aged 1.5 – 5 years, n = 728), about half of the HBV-infected children (3 of 7) had already cleared their infection at the time of sampling. The authors advocate for properly evaluating the efficacy of new intervention programmes to prevent vertical HBV transmission and the importance of analysing the HBV markers in serum collected when these children are older than 1.5 years. In a programmatic setting, all children born to HBV-infected mothers should be tested not only for the level of anti-HBs, but also for the absence of HBsAg, since 2 of the 12 HBV-infected children (17%) in this study had a high level of anti-HBs (49).

5.2.4.4 Effectiveness against carriage of hepatitis B virus

The elimination of hepatitis B is a goal that is now being considered. The effectiveness of HBV vaccine in preventing transmission and carriage make this a realistic goal. The effectiveness of HBV vaccine against carriage documented in a number of countries is presented in Table 4 reproduced from Chen et al. (47).

Table 4. Effectiveness of protecting from HBsAg carriage after hepatitis B immunisation (47)

Country	HBsAg (%)		Efficacy (%)
	Before	After	
China, rural	14.6	1.4	90.4
China (Shanghai)	11	0.63	94.3
Egypt (Alexandria)	2.2	0.8	63.6
Gambia	12	0.9	92.5
Indonesia (Lombok)	6.2	1.4	61.1
Italy (Afragola)	13.4	0.9	93.3
Japan (Iwate)	0.9	0.03	96.7
(Shizuoka)	0.3	0.03	90.0
Korea	7.5	0.38	94.9
Malaysia	2.5	0.4	84.0
Micronesia	12	2.9	75.8
Polynesia	6.5	0.7	89.2
Saipan	9	0.5	94.4
Samoa	7	0.5	92.9
Saudi Arabia	6.7	0.3	95.5
Senegal	19	2	89.5
Singapore	4.1	0	100
South Africa	12.8	3.0	76.6
Taiwan (Taipei)	10	0.7	93.0
(Hualien)	9.3	1.9	79.6
(Taichung)	14	1.2	91.4
Thailand	4.3	0.7	83.7
US (Alaska)	16	0	100

5.3 Summary of effectiveness

Hepatitis B vaccination is highly effective with virtually complete protection in persons who seroconvert to the vaccine. Long-term protection of over 20 years has been demonstrated despite a decrease in anti-hepatitis B surface antigen antibodies over time. While the exact mechanism of long-term protection is not yet fully understood, it is mediated largely by the existence of long-term B cell memory cells.

Two dose schedules have been evaluated in children and adolescents and generally found to be highly immunogenic and non-inferior to three-dose schedules. Duration of immunity to a two-dose schedule in children has been so far been demonstrated out to 10 years.

Flexibility in the schedule has also been shown in adults, in which a third dose given 11 months after the second dose and an accelerated schedule in pregnant women given within four months were immunogenic. One of the issues to keep in mind when evaluating and comparing immunogenicity studies is the heterogeneity in the time points for when serology is evaluated.

Higher antigen doses have been demonstrated to be an effective strategy to improve seroconversion in non-responders to HBV vaccine.

There is no need for boosters in the immunocompetent as long as a full course has been adequately administered. However, a booster dose should be considered for immunocompromised patients, based on serological monitoring. After several decades of vaccination against hepatitis B virus in newborns, infants, adolescents, and adults, the question still remains as to whether a booster dose is ever needed.

Countries that have introduced universal vaccination against hepatitis B have experienced significant reductions in HBV prevalence. Taiwan has now been able to show a reduction in HCC in younger cohorts as a result of over 20 years of hepatitis B vaccination.

The effectiveness of HBV vaccination in children born to HBsAg+ mothers indicates that acquisition of infection is relatively rare after post exposure prophylaxis of HBIg and HBV vaccine, and no patients have been documented to acquire infection if they have demonstrated a protective concentration of antibody.

6. Age-specific issues

6.1 Objective

The objective of this section is to consider the evidence for offering the vaccine to different age groups, in particular older age groups.

6.2 Review

There are few age-specific issues of consideration for hepatitis B vaccination. Vaccines appear immunogenic is all age groups targeted for vaccination. Vertical transmission is the primary route of infection therefore the strategies for protecting infants against acquisition of hepatitis B during the neonatal period are most important. NZ currently screen mothers during pregnancy for their hepatitis B status and infants born to mothers who are HBsAg[+] are offered immunoprophylaxis. Ensuring that this programme is robust with systems in place to prevent mothers and infants slipping through is vital.

7.0 Vaccine options

7.1 Objective

The objectives for this section are to consider the different vaccine options available to NZ in terms of available vaccines and schedules.

7.2 Review

7.2.1 Routine infant vaccination

Currently hepatitis B vaccination occurs routinely as a component of a hexavalent vaccine. This is ideal and there are two options for hexavalent vaccines currently available to NZ.

1. Infanrix®-hexa from GSK

2. Hexaxim® from sanofi pasteur

One important consideration for vaccine options is that, although it does not matter which vaccine is used from a hepatitis B perspective, the hexavalent vaccine from sanofi-pasteur contains two rather than three pertussis antigens. As NZ has a significant problem with pertussis, this vaccine is unlikely to be considered.

7.3.2 Catch ups and high risk

There are several monovalent vaccines on the market, and both paediatric and adult formulations are available. There is evidence to show higher antigen vaccines are useful in non-responders and people with immunosuppressive conditions, such as HIV. Also, evidence suggests that the bivalent hepatitis A and B vaccine, Twinrix®, induces superior immune responses in comparison to the monovalent vaccines and can be considered in non-responders. Options for scheduling for several vaccines are presented in Table 5.

Table 5. Vaccine options for hepatitis B.

Vaccine	Manufacturer	Dose μg	Population	Doses and schedule
HBvaxPRO®	Merck & Co	10μg	11 - 15 years	2 (0 and 4 - 6m)
HBvaxPRO®	Merck & Co	5μg	0[1] - 19 years	3
Comvax®	Merck & Co	5μg	All ages	3 doses at 0, 2 and 12 - 15 months
Engerix-B®	GSK	10μg	Over 15 years Neonates, infants and children	0, 1 and 6 months OR 0, 1 and 2 months OR
Engerix-B®	GSK	20μg	Over 15 years And neonates and infants	At least 2 doses OR 0, 1 and 6 months OR 0, 1 and 2 months OR 0, 7 and 21 days (+booster later)
Twinrix®	GSK	10μg	1 - 15 years	3 doses, 0, 1 and 6 months
Twinrix®	GSK	20μg	1 - 15 years 16 years and over	2 doses, 0 and 6 - 12 months 0, 1, 6 months OR 0, 7 and 21 days (+booster later)
Infanrix®-hexa	GSK	10μg		2, 3 and 4 months
Hexaxim®	sanofi pasteur	10μg	6 weeks – 24 months	6, 10, 14 weeks 2, 3, 4 months 3, 4, 5 months 2, 4, 6 months + booster >6months later

[1.] Infants born to HBsAg negative mothers

8. Options for scheduling

8.1 Objective

This section reviews the evidence for different options for placement of HBV vaccine on the childhood immunisation schedule and for special groups.

8.2 Review

8.2.1 Option for routine scheduling

The World Health Organization (WHO) issued a position paper in 2009 updating its strategy for hepatitis B vaccination (1). The following are recommended:

- Universal birth dose for infants within 24 hours of delivery
- Full immunisation of infants by routine immunisation programmes
- Catch-up vaccination of unimmunised cohorts
- Monitoring of progress
- Assessing the impact of immunisation.

There are a variety of schedules used for routine vaccination against hepatitis B internationally; all have been demonstrated to be effective. NZ already routinely immunises all infants and monitors the epidemiology of hepatitis in the population. Catch-ups are offered to high risk populations and professions. NZ offers targeted vaccination at birth.

8.2.1.1 Variations in schedules

8.2.1.1.1 Routine vaccination of infants

Multiple schedules are used successfully including the expanded program of immunisation, schedule of 6, 10 and 14 weeks of age. Programmatically, it is easiest if the three doses of HBV vaccine are delivered in combination vaccines with the diphtheria, tetanus and pertussis vaccination schedule.

8.2.1.1.2 Catch-up schedules

The need for catch-up schedules largely depends on the baseline epidemiology of infection. Where infant programmes are in place, catch-up vaccination of older age groups in not generally warranted.

For adults over 20 years, a full course of hepatitis B is three doses of the adult formulation. The recommendation is for an interval of one to two months after the first dose and the third dose two – five months after the second dose. As with children, the minimum interval between the second and third dose is two months. However, longer intervals between the last two doses result in higher final antibody concentrations but not seroconversion rates. In any age group, disruption of the vaccination schedule does not require restarting the vaccine series (2).

A randomised trial evaluated four different commercially available hepatitis B vaccines in an accelerated schedule in 400 adults. The study demonstrated that three 20µg doses administered at 0, 1 and 2 months are immunogenic. Seroprotection was observed around one month after the second dose in most vaccines (25).

8.2.1.1.3 Booster doses

Booster doses are not recommended by the WHO for immunocompetent individuals. The evidence shows that response to a three dose series provides sufficient protection.

8.2.2 Universal hepatitis B vaccination of newborns

As perinatal and early postnatal transmission are the primary causes of chronic hepatitis B infection, it is globally recommended that the first dose of hepatitis B vaccine be given within 24 hours of birth – regardless of the level of hepatitis B endemicity.

There are four strategy options in order of efficacy for universal hepatitis B vaccination (47).

1. The most straight forward and cheapest approach advocated is to give all newborns a first dose of vaccine, regardless of the hepatitis B status of their mother. This approach does not require maternal screening and HBIg is not administered. Efficacy of the programme may be compromised.

2. To give all infants the first dose of vaccine at birth, screen all mothers for HBeAg and give two doses of HBIg to infants of HBeAg mothers only.

3. To give all infants the first dose of vaccine at birth, screen all mothers for HBsAg and then HBeAg and administer HBIg to infants of HBeAg mothers only

4. To give all newborns the vaccine at birth, screen all mothers for HBsAg and give a dose of HBIg to the infants of HBsAg[+] mothers regardless of HBeAg status. This is expected to be the most efficacious, but is a more expensive option.

8.2.3 Number of doses

The antibody responses to HBV vaccine in adolescents is generally excellent and two-dose schedules have been used successfully (50, 51). In a recent trial, 123 urban youth in the US aged 12 to 17 years were randomised to receive either two doses of Recombivax HB (10µg hepatitis B surface antigen) or Twinrix® (20µg hepatitis B surface antigen and 720 EL.U hepatitis A antigen) at 0 and 24 weeks. Antibody was measured at 0, 28, and 76 weeks. A positive response to hepatitis B antigen occurred in 41 of 47 (87.2%; 95% CI 74.3%–95.2%) Recombivax HB recipients and in 52 of 55 (94.6%; 84.9%–98.9%) Twinrix® recipients (p =0.295). In an adjusted analysis, Hispanic ethnicity was associated with a positive response and identifying as not being heterosexual was associated with being less likely to respond (27).

8.3 Summary of schedule options

There are a variety of schedules that can be used for vaccination against hepatitis B and delivery in combination with diphtheria, tetanus and pertussis-containing vaccines is programmatically the most pragmatic approach as is currently practiced. Universal vaccination of all infants at birth has been recommended by the WHO for all countries regardless of whether they are high, medium or low endemicity. Accelerated catch-up schedules in adults have been demonstrated to be immunogenic as have two dose schedules in adolescents. Booster doses are not recommended.

9. Implementation issues

9.1 Objective

The objective of this section is to consider the issues around implementation of a birth dose of hepatitis B vaccine.

9.2 Review

The current hepatitis B vaccination programme in NZ has had a significant impact on hepatitis B incidence. There are no indicators to suggest any changes to the current practices are needed. The only factor that requires consideration is the adoption of a universal birth dose.

9.2.1 Birth dose

Currently, NZ does not have a routine birth dose of hepatitis B vaccine. As maternal transmission is the main route of hepatitis B transmission interruption of this is an important strategy.

One of the considerations around the potential value of a universal birth dose of hepatitis B vaccine is the performance of the screening programme in NZ. The impact of routine hepatitis B vaccination and routine screening of pregnant mothers has had a significant impact on the reduction in incidence of acute hepatitis

B, and modelling has estimated that the reproduction number is now less than one. If the screening programme is working well, and infants born to HBsAg+ mothers are receiving appropriate prophylaxis, then it may not be necessary to introduce a birth dose of hepatitis B vaccine to all infants.

As of early 2013, the only data about how well NZ is doing in neonatal hepatitis B immunoprophylaxis is some unpublished data from Auckland Regional Public Health Service (presented by S Jury, 2011). A review of ARPHS 2007 data on consent forms for immunoglobulin receipt and a comparison with National Immunisation Register and the New Zealand Blood Service records was undertaken. There were three DHB serving different at risk populations. Table 6 summarises the documentation of immunoprophylaxis, vaccination and subsequent serology for the three Auckland regional district health boards, highlights gaps. These included information not being transferred reliably to the National Immunisation Register, checking of serology and transfer of these to the immunisation register.

A national evaluation of the performances of neonatal hepatitis B prophylaxis programmes would be a useful strategy before considering the implementation of a universal birth dose of hepatitis B vaccine.

Table 6. Documentation of immunoprophylaxis, vaccination and subsequent serology for three regional district health boards (presented by S Jury, 2011)

	DHB 1 n=125 babies (%)	DHB 2 n=188 babies (%)	DHB 3 N=67 babies (%)
ARPHS had details	67 (54%)	97 (51%)	35 (52%)
Registered on the NIR as 'at risk' (all births were registered on the NIR)	57 (46%)	106 (56%)	53/66 (80%)
Known to the Blood Service	122 (98%)	169 (89%)	64 (96%)
Documented anywhere as having received immunoprophylaxis	**100%**	**97%**	**100%**
Of those due: **How many had completed the further 3 vaccination series**	85% (78% on time)*	78%	81% (72% on time)*
How many had serology recorded on the NIR	6/91 **(7%)**	15/188 **(8%)**	7/53 **(13%)**
How many had serology recorded including at community lab	29/91 **(32%)**	30/ 188 **(16%)**	13/53 **(25%)**

* using on-time interval-adjusted vaccination upper limits i.e. upper time interval between imms = 75, 75 and 90 days (as defined p27 of The National Childhood Immunisation Coverage Survey 2005) [4]

9.3 Summary for implementation issues

The current hepatitis B vaccination programme in NZ has had a significant impact on hepatitis B incidence and there are no indicators to suggest any changes to the current practices are needed. The only factor that requires consideration is the adoption of a universal birth dose and an important consideration around the potential value of a universal birth dose is the performance of the current screening and neonatal immunoprophylaxis programme in NZ. Limited regional data from Auckland suggests high uptake of a birth dose in infants born to HBsAg[+] mothers however gaps have been identified. A national evaluation of the screening and neonatal programmes would be a useful strategy before considering the implementation of a universal birth dose of hepatitis B vaccine.

10. International policy and practice

10.1 Objective

The objective of this section is to summarise international practice with regard to the use of hepatitis B vaccines.

10. 2 Review

10.2.1 US recommendations

Foreign-born individuals account for more than 12% of the US population. Authorities have mandated vaccinations for numerous immigrant populations, because many vaccine-preventable disease outbreaks in the US have been correlated with disease importation (52). While part of the medical requirements for immigration into NZ allow for HBsAg screening, there is no requirement for vaccination of new immigrants.

The US has a strategy to eliminate transmission of hepatitis B virus. This includes the universal vaccination of infants starting at birth; prevention of perinatal infection through the routine screening of all pregnant women and immunoprophylaxis for infants born to HBsAg⁺ mothers; routine vaccination of previously unvaccinated children and adolescents and vaccination of previously unvaccinated adults at risk for HBV infection.

Low rates of vaccination against hepatitis B among adults at risk for hepatitis B infection prompted a review of guidelines and new recommendations for improving coverage in the group. Table 7 summarises adults recommended to receive hepatitis B vaccination according to the US advisory committee for immunization practices (ACIP) guidelines. It is also recommended that this should include all adults requesting protection from hepatitis B infection and acknowledgement of a specific risk factor should not be a requirement for vaccination. Since 1996, Centers for Disease Control and Prevention (CDC) has received reports of 29 outbreaks of HBV infection in one or multiple long-term–care facilities (including nursing homes and assisted-living facilities). Of these, 25 involved adults with diabetes who were receiving assisted blood glucose monitoring. After evaluation of risk of HBV infection among adults diagnosed with diabetes - October 2011 ACIP in made the recommendations (2, 53):

- That all previously unvaccinated adults aged 19 through 59 years with diabetes mellitus (type 1 and type 2) be vaccinated against hepatitis B as soon as possible after a diagnosis of diabetes is made.

- Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years however hepatitis B vaccines are less efficacious and less cost-effective among older adults.

Table 7. Adults recommended to receive hepatitis B vaccination in the US (ACIP guidelines)

Persons at risk for infection by sexual exposure	• Sex partners of hepatitis B surface antigen (HBsAg)-positive persons • Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months) • Persons seeking evaluation or treatment for a sexually transmitted disease • Men who have sex with men
Persons at risk for infection by percutaneous or mucosal exposure to blood	• Current or recent injection-drug users • Household contacts of HBsAg-positive persons • Residents and staff of facilities for developmentally disabled-persons • Healthcare and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids • Persons with end-stage renal disease, including predialysis, haemodialysis, peritoneal dialysis and home dialysis patients
Others	• International travellers to regions with high or intermediate of endemic HBV infection (HBsAg prevalence of ≥2%) • Persons with chronic liver disease • Persons with HIV infection • All other persons seeking protection from HBV infection

10.2.2 WHO expanded programme on immunization

Historically, the standard three-dose hepatitis B vaccine series has consisted of two priming doses administered one month apart and a third dose administered six months after the first dose: multiple schedules have been used successfully: at birth and at 1 and 6 months of age; at 2, 4, and 6 months of age; and at 6, 10, and 14 weeks of age as in the WHO's Expanded Programme on Immunization (EPI) schedule. The WHO recommend a minimal interval between doses one and two of four weeks and a minimum interval between doses two and three of four weeks. Schedules with these minimal intervals (e.g. 6, 10, and 14 weeks) have been demonstrated to have seroconversion rates similar to schedules with longer intervals, albeit with lower final anti-HBs concentrations.

10.2.3 Recommended options for adding hepatitis B vaccine to childhood immunisation schedules

Table 8 identifies hepatitis B vaccine schedule options.

Table 8. Recommended options for adding hepatitis B vaccine to childhood immunization schedules, World Health Organization (1)

			Hepatitis B vaccine options*		
			No birth dose		With birth dose
Age	Visit	Other antigens	I	II	III
Birth	0	BCG (OPV0)[†]	-	HepB-birth[‡§]	HepB-birth[‡§]
6 wk	1	OPV1, DTP1	HepB1[¶]	HepB2[§]	HepB2[¶]
10 wk	2	OPV2, DTP 2	HepB2[¶]		HepB3[¶]
14 wk	3	OPV3, DTP3	HepB3[¶]	HepB3[§]	HepB4[¶]
9-12 mo	4	Measles	-	-	-

*Option 1 is recommended in countries that are not yet targeting prevention of perinatal HBV transmission; options II & III are recommended in countries that are targeting prevention of perinatal HBV transmission

† only given in countries where polio is highly endemic

‡ to prevent perinatal HBV transmission, the birth dose should be given as close as possible to the time of delivery, preferably within 12h

§ monovalent vaccine; ¶ monovalent or combination vaccine

BCG – Bacilli Calmette-Guérin; DTP – diphtheria-tetanus-pertussis; OPV – oral poliovirus

10.2.4 Global practices for routine hepatitis B vaccination

Table 9 summarises some of the schedules and vaccines used among and within counties.

Table 9. Global schedules for hepatitis B vaccination

Vaccine brand, formulation and HBsAg content per dose	Age of vaccine recipient	Recommended schedule (dose interval from 1st dose)	Country
Schedule for infants ≤ 12 months			
Comvax 5µg	Infant ≤1 year	2, 4, and 12-15 months not indicated before 6 weeks of age	USA
Engerix®-B (paediatric formulation) 10µg	At Birth (≤7 days)	Single dose at birth (preferable within 24 hours; eligible up to ≤7 days of age)	Australia
Engerix®-B (paediatric formulation) 10 µg	At Birth	0, 1, 6 months or 0, 1, 2, 12 months	Canada
Engerix ®-B (paediatric formulation) 10µg	At Birth	0, 1, 6 months or 0, 2, 4 months or 0, 1, 2, 12 months	USA
H-B-Vax II (paediatric formulation) 5µg	At Birth (≤7 days)	Single dose at birth (preferable within 24 hours; eligible up to ≤7 days of age)	Australia
Infanrix® hexa 10µg	Infant≤1 year	2, 4 and 6 months	Australia
Infanrix® hexa 10 µg	Infants of HB-negative mothers	2, 4, 6, 12-23 months or 2, 4, 6 months or 2, 4, 12-23 months	Canada
Infanrix® hexa 10 µg	Infants of HB-positive mothers	Not indicated before 6 weeks of age	Canada
Recombivax HB® (paediatric formulation) 5µg	At Birth	0, 1, 6 months or 0, 2, 4 months or 0, 1, 2, 12 months	USA
Recombivax HB® 2.5µg	Infants of HB-negative mothers	a schedule of months 0, 1 and at least 2 is approved, the preferred schedule is 0, 1, 6 months	Canada
Recombivax HB® 5 µg	Infants of HB-positive mothers	a schedule of months 0, 1 and at least 2 is approved, the preferred schedule is 0, 1, 6 months	Canada

Monovalent hepatitis B vaccines- standard 3-dose schedule			
Engerix ®-B (paediatric formulation) 10µg	Children (1-10yrs)	0, 1, 6 months or 0, 1, 2, 12 months	Canada
Engerix ®-B (paediatric formulation) 10µg	<20 years	0, 1, 6 months	Australia
Engerix ®-B (paediatric formulation) 10µg	Children (1-10yrs)	0, 1, 6 months or 0, 2, 4 months	USA
Engerix ®-B (paediatric formulation) 10µg	Adolescent (11-19yrs)	0, 1, 6 months or 0, 1, 4 months or 0, 2, 4 months or 0, 12, 24 months	USA
Engerix ®-B (paediatric formulation) 10µg	Adolescent (11-15yrs)	0, 1, 6 months or 0, 12, 24 months	Canada
Engerix®-B (adult formulation) 20µg	≥20 years	0, 1, 6 months	Australia
Engerix®-B (adult formulation) 20µg	≥20 years	0, 1, 6 months or 0, 1, 4 months or 0, 2, 4 months or 0, 1, 2 and 12 months	USA
H-B-Vax II (paediatric formulation) 5µg	<20 years	0, 1, 6 months	Australia
H-B-Vax II (adult formulation) 10µg	≥20 years	0, 1, 6 months	Australia
Infanrix®-hexa 10 µg	12 to 23 months	Months: 1st dose = month 0) 0, 2, 4, 10-21 or 0, 2, 4 or 0, 2, 10-21	Canada
Infanrix®-hexa 10 µg	2 to 7 years	May be given to children aged 24 months to 7 years, if necessary	Canada
Recombivax HB® (adult formulation) 5µg	≥20 years	0, 1, 6 months or 0, 1, 4 months or 0, 2, 4 months	USA
Recombivax HB® (adult formulation) 5µg	11-18 years	a schedule of months 0, 1 and at least 2 is approved, the preferred schedule is 0, 1, 6 months	Canada
Recombivax HB® 2.5 µg	12 to 23 months	a schedule of months 0, 1 and at least 2 is approved, the preferred schedule is 0, 1, 6 months	Canada
Recombivax HB® 2.5 µg	24 months - <11 years	a schedule of months 0, 1 and at least 2 is approved, the preferred schedule is 0, 1, 6 months	Canada

Monovalent hepatitis B vaccines- 2-dose schedule for adolescents aged 11-15 years			
Engerix-B (adult formulation) 20μg	11-15 years	0, 6 months	Australia
Engerix-B (adult formulation) 20μg	11-15 years	0, 6 months	Canada
H-BVax II (adult formulation) 10μg	11- 15 years	0, 4-6 months	Australia
Recombivax- HB (adult formulation) 10μg	11-15 years	0, 4-6 months	USA
Recombivax- HB (adult formulation) 10μg	11-15 years	0, 4-6 months	Canada
Combination hepatitis A/ hepatitis B vaccines			
Twinrix® 20μg	1-15 years	0, 6-12 months (two dose schedule)	Australia
Twinrix® 20μg	1 year <16 years of age	0, 6-12 months (two dose schedule)	Canada
Twinrix® 20μg	≥16 years	0, 1, 6 months	Australia
Twinrix® 20μg	≥20 years	0, 1, 6 months	USA
Twinrix® Junior 10μg	1-15 years	0, 1, 6 months	Australia
Twinrix® Junior 10μg	1 year <16 years of age	0, 1, 6 months	Canada
Accelerated Schedule			
Engerix-B (paediatric formulation) 10μg	<20 years	0, 1, 2, 12 months	Australia
Engerix-B (adult formulation) 20μg	≥20 years	0, 1, 2, 12 months or 0, 7, 21 days, 12 months**	Australia
Twinrix® (720/20) 20μg	≥16 years	0, 7, 21 days, 12 months	Australia

Dialysis Schedule			
Engerix-B Double the dose for health child of same age	<16 years	3 or 4 dose schedule	Canada
Engerix-B 40 µg	≥16 years	0, 1, 2, 6	Canada
H-B-Vax II (dialysis formulation) 40µg	≥20 years	0, 1, 6 months	Australia
Recombivax HB® (dialysis formulation) 40 µg			USA
Recombivax HB® (dialysis formulation) 40 µg	≥20 years	0, 1, 6 months	Canada
Recombivax HB® Double the dose for health child of same age	<19 years	3 or 4 dose schedule	Canada

10.3 Summary of international policy and practice

Global practice around the use of hepatitis B vaccines is varied with respect to vaccines used and schedules. Moves to eliminate hepatitis B infection from the population have prompted recommendations for routine birth doses of vaccine and greater efforts to achieve higher rates of vaccination of both high risk adults as well as non-high risk adults. Routine vaccination of diabetics has recently been added.

References

1.   World Health Organization. WHO position paper on Hepatitis B vaccines. World Health Organization; 2009.

2.   van Damme P, Ward J, Shouval D, Wiersma S, Zanetti A. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 6th ed.2013. p. 205-34.

3.   Luo Z, Xie Y, Deng M, Zhou X, Ruan B. Prevalence of hepatitis B in the southeast of China: a population-based study with a large sample size. European journal of gastroenterology & hepatology. 2011;23(8):695-700.

4.   Bialek SR, Helgenberger L, Fischer GE, Bower WA, Konelios M, Chaine JP, et al. Impact of routine hepatitis B immunization on the prevalence of chronic hepatitis B virus infection in the marshall islands and the federated States of micronesia. The Pediatric infectious disease journal. 2010;29(1):18-22.

5.   Osiowy C, Larke B, Giles E. Distinct geographical and demographic distribution of hepatitis B virus genotypes in the Canadian Arctic as revealed through an extensive molecular epidemiological survey. J Viral Hepat. 2011;18(4):e11-9.

6.   Mann J, Roberts M. Modelling the epidemiology of hepatitis B in New Zealand. J Theor Biol. 2011;269(1):266-72.

7.   Chang MH. Hepatitis B virus and cancer prevention. In: Senn HJ, Otto F, editors. Recent Results in Cancer Research2011. p. 75-84.

8.   The Institute of Environmental Science and Research Ltd. Notifiable and Other Diseases in New Zealand: Annual Report 2011. Porirua, New Zealand; 2011.

9.   Medsafe. Datasheet: Infanrix-hexa [Internet]. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2011. Available from: http://www.medsafe.govt.nz/profs/Datasheet/I/Infanrixhexainj.pdf

10.   Robinson T, Bullen C, Humphries W, Hornell J, Moyes C. The New Zealand Hepatitis B Screening Programme: screening coverage and prevalence of chronic hepatitis B infection. The New Zealand medical journal. 2005;118(1211):U1345.

11.   New Zealand Society of Gastroenterology. Hepatitis B 2007. Available from: http://www.nzsg.org.nz/cms2/research/hepatitis/hepatitis-b/

12.   Sangkomkamhang US, Lumbiganon P, Laopaiboon M. Hepatitis B vaccination during pregnancy for preventing infant infection. The Cochrane database of systematic reviews. 2011(3):CD007879.

13.   Makris MC, Polyzos KA, Mavros MN, Athanasiou S, Rafailidis PI, Falagas ME. Safety of hepatitis B, pneumococcal polysaccharide and meningococcal polysaccharide vaccines in pregnancy: a systematic review. Drug Saf. 2012;35(1):1-14.

14.   Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews. 2009(1).

15.   Muniz Caldas CA, Freire de Carvalho J. The role of environmental factors in the pathogenesis of non-organ-specific autoimmune diseases. Best practice & research Clinical rheumatology. 2012;26(1):5-11.

16.   Zafrir Y, Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y. Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases. Lupus. 2012;21(2):146-52.

17.   Launay O, van der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. Jama. 2011;305(14):1432-40.

18.   Leroux-Roels G, Haelterman E, Maes C, Levy J, De Boever F, Licini L, et al. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. Clin Vaccine Immunol. 2011;18(9):1510-8.

19.   Pedersen C, Breindahl M, Aggarwal N, Berglund J, Oroszlan G, Silfverdal SA, et al. Randomized trial: immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. J Adolesc Health. 2012;50(1):38-46.

20.   Wilson K, Hawken S. Incidence of adverse events in premature children following 2-mo vaccination. Human Vaccines and Immunotherapeutics. 2012;8(5):592-5.

21. Baxter R, Lewis N, Bakshi N, Vellozzi C, Klein NP, Network C. Recurrent Guillain-Barre syndrome following vaccination. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(6):800-4.

22. Papanna MC, Sundararajan S. Femoral neuropraxia after vaccination in a 3-month-old infant: a case report. Journal of pediatric orthopedics Part B. 2011;20(3):162-3.

23. Zepp F, Schmitt HJ, Cleerbout J, Verstraeten T, Schuerman L, Jacquet JM. Review of 8 years of experience with Infanrix hexa (DTPa-HBV-IPV/Hib hexavalent vaccine). Expert Rev Vaccines. 2009;8(6):663-78.

24. Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, et al. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. The Journal of infectious diseases. 2008;197(10):1419-26.

25. Hernandez-Bernal F, Aguilar-Betancourt A, Aljovin V, Arias G, Valenzuela C, de Alejo KP, et al. Comparison of four recombinant hepatitis B vaccines applied on an accelerated schedule in healthy adults. Hum Vaccin. 2011;7(10):1026-36.

26. van Damme P, Kafeja F, Van Der Wielen M, Leyssen M, Jacquet JM. Long-term immunogenicity and immune memory after two doses of the adult formulation of a combined hepatitis A and B vaccine in children 1 to 11 years of age. The Pediatric infectious disease journal. 2011;30(8):703-5.

27. Cunningham CK, Rudy BJ, Xu J, Bethel J, Kapogiannis BG, Ahmad S, et al. Randomized trial to determine safety and immunogenicity of two strategies for hepatitis B vaccination in healthy urban adolescents in the United States. The Pediatric infectious disease journal. 2010;29(6):530-4.

28. De Schryver A, Verstrepen K, Vandersmissen L, Vandermeeren N, Vernaillen I, Vranckx R, et al. Comparative immunogenicity of two vaccination schedules of a combined hepatitis A and B vaccine in healthy volunteers. J Viral Hepat. 2011;18(4):e5-10.

29. Sheffield JS, Hickman A, Tang J, Moss K, Kourosh A, Crawford NM, et al. Efficacy of an accelerated hepatitis B vaccination program during pregnancy. Obstet Gynecol. 2011;117(5):1130-5.

30. Junqueira AL, Tavares VR, Martins RM, Frauzino KV, da Costa e Silva AM, Minamisava R, et al. Safety and immunogenicity of hepatitis B vaccine administered into ventrogluteal vs. anterolateral thigh sites in infants: a randomised controlled trial. Int J Nurs Stud. 2010;47(9):1074-9.

31. Diaz-Mitoma F, Halperin SA, Tapiero B, Hoffenbach A, Zappacosta PS, Radley D, et al. Safety and immunogenicity of three different formulations of a liquid hexavalent diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae b conjugate-hepatitis B vaccine at 2, 4, 6 and 12-14 months of age. Vaccine. 2011;29(6):1324-31.

32. Chakvetadze C, Bani-Sadr F, Le Pendeven C, Lescure FX, Fontaine C, Galperine T, et al. Serologic response to hepatitis B vaccination in HIV-Infected patients with isolated positivity for antibodies to hepatitis B core antigen. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;50(8):1184-6.

33. Gisbert JP, Menchen L, Garcia-Sanchez V, Marin I, Villagrasa JR, Chaparro M. Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2012;35(12):1379-85.

34. Moses J, Alkhouri N, Shannon A, Raig K, Lopez R, Danziger-Isakov L, et al. Hepatitis B immunity and response to booster vaccination in children with inflammatory bowel disease treated with infliximab. The American journal of gastroenterology. 2012;107(1):133-8.

35. Fabrizi F, Dixit V, Martin P, Messa P. Meta-analysis: the impact of diabetes mellitus on the immunological response to hepatitis B virus vaccine in dialysis patients. Alimentary pharmacology & therapeutics. 2011;33(7):815-21.

36. Fabrizi F, Dixit V, Martin P, Jadoul M, Messa P. Meta-analysis: the impact of nutritional status on the immune response to hepatitis B virus vaccine in chronic kidney disease. Dig Dis Sci. 2012;57(5):1366-72.

37. Fabrizi F, Dixit V, Messa P, Martin P. Hepatitis B virus vaccine in chronic kidney disease: improved immunogenicity by adjuvants? A meta-analysis of randomized trials. Vaccine. 2012;30(13):2295-300.

38. Tielemans CL, Vlasak J, Kosa D, Billiouw JM, Verpooten GA, Mezei I, et al. Immunogenicity and safety of an investigational AS02(v)-adjuvanted hepatitis B vaccine in patients with renal insufficiency who failed to respond or to maintain antibody levels after prior vaccination: results of two open, randomized, comparative trials. Vaccine. 2011;29(6):1159-66.

39. Ishigami M, Kamei H, Nakamura T, Katano Y, Ando H, Kiuchi T, et al. Different effect of HBV vaccine after liver transplantation between chronic HBV carriers and non-HBV patients who received HBcAb-positive grafts. J Gastroenterol. 2011;46(3):367-77.

40. Gutierrez Domingo I, Pascasio Acevedo JM, Alcalde Vargas A, Ramos Cuadra A, Ferrer Ríos MT, Sousa Martin JM, et al. Response to vaccination against hepatitis B virus with a schedule of four 40-µg doses in cirrhotic patients evaluated for liver transplantation: Factors associated with a response. Transplantation Proceedings. 2012;44(6):1499-501.

41. Dhillon S, Moore C, Li SD, Aziz A, Kakar A, Dosanjh A, et al. Efficacy of high-dose intra-dermal hepatitis B virus vaccine in previous vaccination non-responders with chronic liver disease. Dig Dis Sci. 2012;57(1):215-20.

42. Lau KC, Lam CW, Law CY, Lai ST, Tsang TY, Siu CW, et al. Non-invasive screening of HLA-DPA1 and HLA-DPB1 alleles for persistent hepatitis B virus infection: susceptibility for vertical transmission and toward a personalized approach for vaccination and treatment. Clinica chimica acta; international journal of clinical chemistry. 2011;412(11-12):952-7.

43. Singh AE, Plitt SS, Osiowy C, Surynicz K, Kouadjo E, Preiksaitis J, et al. Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants. J Viral Hepat. 2011;18(7):468-73.

44. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat. 2012;19(2):e18-25.

45. Lin C, Zhu J, Zheng Y, Chen Y, Wu Z, Chong Y, et al. Effect of GM-CSF in combination with hepatitis B vaccine on revacination of healthy adult non-responders. J Infect. 2010;60(4):264-70.

46. Su WJ, Liu CC, Liu DP, Chen SF, Huang JJ, Chan TC, et al. Effect of age on the incidence of acute hepatitis B after 25 years of a universal newborn hepatitis B immunization program in Taiwan. The Journal of infectious diseases. 2012;205(5):757-62.

47. Chen DS. Hepatitis B vaccination: The key towards elimination and eradication of hepatitis B. Journal of hepatology. 2009;50(4):805-16.

48. Bracciale L, Fabbiani M, Sansoni A, Luzzi L, Bernini L, Zanelli G. Impact of hepatitis B vaccination in children born to HBsAg-positive mothers: a 20-year retrospective study. Infection. 2009;37(4):340-3.

49. Boot HJ, Hahne S, Cremer J, Wong A, Boland G, van Loon AM. Persistent and transient hepatitis B virus (HBV) infections in children born to HBV-infected mothers despite active and passive vaccination. J Viral Hepat. 2010;17(12):872-8.

50. Cassidy WM, Watson B, Ioli VA, Williams K, Bird S, West DJ. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. Pediatrics. 2001;107(4):626-31.

51. Van Der Wielen M, Van Damme P, Collard F. A two dose schedule for combined hepatitis A and hepatitis B vaccination in children ages one to eleven years. The Pediatric infectious disease journal. 2000;19(9):848-53.

52. Nguyen GT, Altshuler M. Vaccine-preventable diseases and foreign-born populations. Primary care. 2011;38(4):633-42, vii-viii.

53. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States, Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: Immunization of Adults MMWR. 2006;55(RR-16).