

Introduction of hepatitis B vaccine into childhood immunization services

**Management guidelines, including
information for health workers and
parents**



**DEPARTMENT OF VACCINES
AND BIOLOGICALS**



*World Health Organization
Geneva
2001*

**The Department of Vaccines and Biologicals
thanks the donors whose unspecified financial support
has made the production of this document possible.**

This document was produced by the
Expanded Programme on Immunization
of the Department of Vaccines and Biologicals

*Ordering code: WHO/V&B/01.31
Printed: November 2001*

This document is available on the Internet at:
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Abbreviations

AD	auto-disable (injection devices)
AEFI	adverse events following immunization
BCG	bacillus Calmette-Guérin (vaccine)
DTP	diphtheria-tetanus-pertussis (vaccine)
EPI	Expanded Programme on Immunization
FIC	fully immunized child
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HepB	hepatitis B (vaccine)
Hib	<i>Haemophilus influenzae</i> type b (vaccine)
HIV	human immunodeficiency virus
IPV	injectable polio vaccine
OPV	oral polio vaccine
SIGN	Safe Injections Global Network
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VVM	vaccine vial monitor

Glossary

Acute hepatitis B: new symptomatic HBV infection.

Antibody to HBsAg (anti-HBs): the protective antibody that develops following recovery from HBV infection and after vaccination.

Antibody to hepatitis B core antigen (anti-HBc): antibody produced in all HBV infections (indicating infection at sometime in the past).

Combination vaccine: a vaccine made by combining antigens that prevent different diseases (e.g. DTP).

Chronic HBV infection: persistent (long-term) infection with HBV.

Cirrhosis: permanent liver damage (scarring).

Formulation: the form in which a vaccine is presented (e.g. liquid or lyophilized, monovalent or in combination).

Hepatitis B e antigen (HBeAg): a marker of increased infectivity in persons who are infected with HBV.

Hepatitis B surface antigen (HBsAg): a marker present in persons who are currently infected with HBV (i.e. persons with both recent infection and chronic infection).

IgM class antibody to hepatitis B core antigen (IgM anti-HBc): antibody detectable for four to six months after infection with HBV, indicating recent infection.

Monovalent vaccine: a vaccine containing antigen for protection against a single disease.

1. Introduction

Hepatitis B is a major public health problem. Approximately 30% of the world's population, i.e. about 2 billion people, have serological evidence of infection with hepatitis B virus (HBV) (1). It is estimated that 350 million of them have chronic HBV infection, about a million of whom die each year from chronic liver disease, including cirrhosis and liver cancer. HBV is second only to tobacco as a known human carcinogen.

A safe and effective vaccine against hepatitis B has been available since 1982. WHO recommends that hepatitis B vaccine be included in routine immunization schedules for all children in all countries (2). The present manual provides management guidelines for the introduction of hepatitis B vaccine into childhood immunization services, with particular reference to developing countries.

2. Hepatitis B virus infection

2.1 Clinical features

Persons infected with HBV have both short-term and long-term outcomes. On becoming infected a person can have either symptomatic disease, i.e. acute hepatitis B, or an asymptomatic infection with no signs or symptoms of disease. In either case the person may either recover from the infection and develop lifelong immunity or develop a chronic infection that usually lasts throughout life.

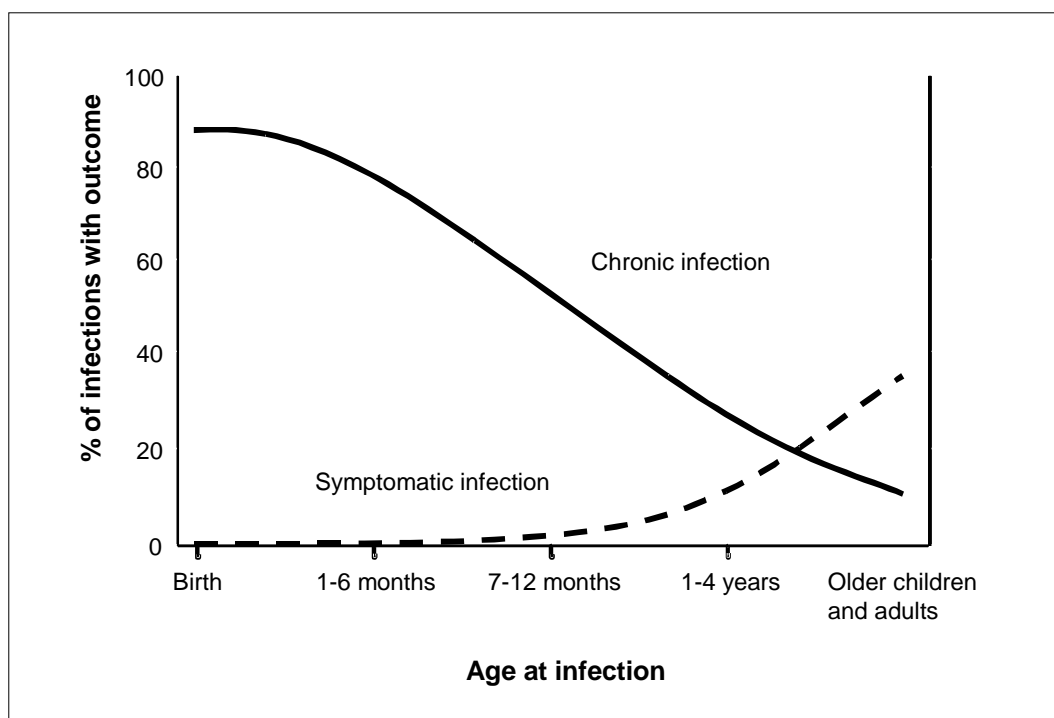
Acute hepatitis B. In persons with acute hepatitis B the incubation period after becoming infected is usually 3-4 months, with a range of 6 weeks to 6 months. Symptoms and signs of disease usually last for several weeks and include loss of appetite, weakness, nausea, vomiting, abdominal pain, jaundice (yellow skin or eyes), dark urine, skin rashes and joint pain. About 1-2% of persons with acute hepatitis B die from fulminant hepatitis.

Chronic HBV infection. Most of the disease burden associated with HBV infection is in persons who develop the chronic condition. Such persons often do not feel sick for decades after becoming infected. However, about 25% and 15% respectively of those who become chronically infected during childhood and at older ages die of liver cancer or cirrhosis (3).

2.2 Age distribution

The age at which a person becomes infected with HBV is the main factor determining the outcome (Fig. 1). Among children under 5 years of age who become infected, fewer than 10% are symptomatic, whereas 80-90% of infants infected during the first year of life and 30-50% of children infected between 1 and 4 years of age develop the chronic condition (4). However, 30-50% of adults are symptomatic when first infected but only 2-5% become chronically infected.

Figure 1. Outcome of hepatitis B virus infection by age at infection



2.3 Transmission

HBV is spread by either skin puncture or mucous membrane contact with infected blood or other body fluids. The highest concentrations of the virus occur in blood and wound secretions. Moderate concentrations of HBV are found in semen and vaginal fluid, and lower concentrations occur in saliva (5). HBV is not spread by air, food or water.

The primary routes of spread are:

- from mother to baby (perinatal);
- from child to child;
- through unsafe injections and blood transfusions;
- through sexual contact.

Perinatal transmission. Perinatal transmission from mothers infected with HBV, i.e. positive for hepatitis B surface antigen (HbsAg), to their newborn infants is a major source of HBV infections in many countries (6-12). Perinatal transmission usually happens at the time of birth; *in utero* transmission is relatively rare, accounting for under 2% of perinatal infections in most studies (8, 10-12). There is no evidence that HBV can be spread by breastfeeding (13). The risk of perinatal transmission depends on the presence of hepatitis B e antigen (HBeAg) in the blood of mothers infected with HBV. The risk of chronic HBV infection is in the approximate range 70-90% from such mothers who are HBeAg-positive, and about 5-20% from those who are HBeAg-negative (5, 6, 14).

Child-to-child transmission. The spread of HBV from child to child accounts for most HBV infections (16-31). Transmission usually happens in household settings but may also occur in child day care centres and in schools (32-37). The most probable mechanisms of child to child spread involve contact of skin sores, small breaks in the skin, or mucous membranes with blood or skin sore secretions (5). HBV may also spread because of contact with saliva through bites or other breaks in the skin, and as a consequence of the pre-mastication of food (19, 38-41). In addition the virus may spread from inanimate objects such as shared towels or toothbrushes, since it can survive for at least seven days outside the body and can be found in high titres on objects, even in the absence of visible blood (31, 42, 43).

Transmission associated with injection and blood transfusion. Unsafe injection practices are a major source of transmission of HBV and other bloodborne pathogens (e.g. hepatitis C virus, HIV) in many countries (44, 45). Blood transfusion is a major source of HBV transmission in countries where the blood supply is not screened for HBsAg.

In many developing countries, up to 50% of injections are administered with needles and syringes that are reused without sterilization. Moreover, a substantial proportion of therapeutic injections, accounting for approximately 90% of the estimated 12 billion injections administered each year throughout the world, are unnecessary. Injectable medications are often inappropriately used, and most medications given in primary care settings can be administered orally (46).

Unsatisfactory infection control practices, including the reuse of contaminated medical or dental equipment, failure to use appropriate disinfection and sterilization practices for equipment and environmental surfaces, and improper use of multidose medication vials, can also result in the transmission of HBV and other bloodborne pathogens. In addition, the injection of illicit drugs is a common mode of HBV transmission in many countries.

Sexual transmission. HBV is efficiently transmitted by sexual contact, which can account for a high proportion of new hepatitis B infections among adolescents and adults in countries with low and intermediate endemicity of chronic HBV infection (47). In countries where HBV infection is highly endemic, sexual transmission does not account for a high percentage of cases because most persons are already infected during childhood.

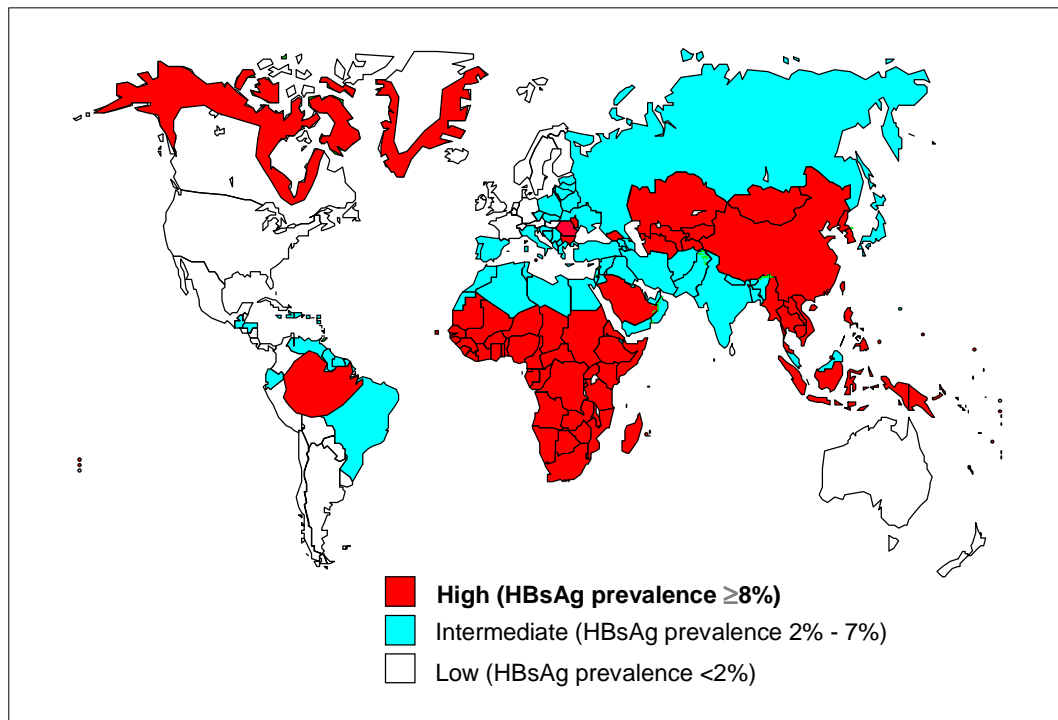
2.4 Global distribution

Approximately 45% of the world population live in areas where chronic HBV infection is highly endemic ($\geq 8\%$ of the population are HBsAg-positive); 43% live in areas of intermediate endemicity (2-7% HBsAg-positive); and 12% live in areas of low endemicity ($<2\%$ HBsAg-positive) (Fig. 2).

- In areas of high endemicity the lifetime risk of HBV infection is more than 60% and most infections are acquired from perinatal and child-to-child transmission, when the risk of developing chronic infection is greatest. In these areas, acute hepatitis B is uncommon because most perinatal and early childhood infections are asymptomatic. However, rates of liver cancer and cirrhosis in adults are very high.

- In areas of intermediate endemicity the lifetime risk of HBV infection is 20-60% and infections occur in all age groups. Acute hepatitis B is common in these areas because many infections occur in adolescents and adults. However, high rates of chronic infection are maintained mainly because of infections occurring in infants and children.
- In areas of low endemicity the lifetime risk of HBV infection is less than 20%. Most HBV infections in these areas occur in adults in relatively well-defined risk groups, but a high proportion of chronic infections may occur as a consequence of perinatal and child-to-child transmission

Figure 2. Geographical distribution of HBV endemicity



3. Hepatitis B immunization strategies

Most of the serious consequences of HBV infection (i.e. liver cancer and cirrhosis) occur among persons who are chronically infected and serve as the main reservoir for the transmission of new infections. The principal objective of hepatitis B immunization strategies is, therefore, to prevent chronic HBV infections.

Hepatitis B immunization strategies include:

- routine infant vaccination;
- prevention of perinatal HBV transmission;
- catch-up vaccination of older age groups.

3.1 Routine infant vaccination

The routine vaccination of all infants as an integral part of national immunization schedules should be given high priority.

In countries of intermediate and high endemicity of HBV infection, routine infant hepatitis B vaccination is a high priority because the majority of chronic infections are acquired during early childhood.

The routine vaccination of infants is also a high priority in countries of low endemicity because this is the only strategy that can prevent HBV infections acquired in all age groups (children, adolescents and adults). In these countries the majority of chronic infections are acquired among adolescents and adults but early childhood infections are important in maintaining the burden of chronic infection. Furthermore, many children who are infected have mothers who are NOT infected with HBV. These infections would not be prevented by identifying infants born to HBsAg-positive women and giving them a birth dose of hepatitis B vaccine (see section 3.2) that screen pregnant women for HBsAg (22, 27, 29, 48). Routine childhood immunization is also required in order to achieve optimal prevention of HBV infections acquired by adolescents and adults, because strategies targeting adolescent and adult risk groups have failed to control hepatitis B adequately. These immunization strategies for high-risk groups have not been very successful because of the difficulty of immunizing persons in many risk groups before they initiate high-risk behaviours and because of infections occurring among persons with no identified risk factor.

3.2 Prevention of perinatal HBV transmission

In order to prevent perinatal HBV transmission the first dose of hepatitis B vaccine should be given as soon as possible after birth, preferably within 24 hours. In most countries the most feasible strategy for preventing perinatal HBV transmission involves giving a dose of hepatitis B vaccine to all infants at birth. An alternative strategy is to screen all pregnant women for HBsAg and to provide immunization at birth to infants of HBV-infected mothers. However, extensive resources are required in order to screen pregnant women and track infants of infected mothers. Moreover, few countries have implemented services that have been successful in optimally identifying infants of HBV-infected mothers and in tracking these infants in order to assure completion of the hepatitis B vaccine series.

When considering the incorporation of strategies to prevent perinatal HBV transmission in a particular country it is necessary to take into account the relative contribution of perinatal transmission to the overall hepatitis B disease burden and the feasibility of delivering the first dose of hepatitis B vaccine at birth. In general it is most feasible to deliver the vaccine at birth to infants who are born in health facilities. In addition, the availability of monovalent hepatitis B vaccine in prefilled single-dose injection devices (e.g. Uniject™) can facilitate the administration of the vaccine by birth attendants to infants delivered at home (49, 50).

Consideration should be given to the following priorities for incorporating a dose at birth.

- *In all countries.* Achieving a high level of completion of the hepatitis B vaccine series among all infants should be the highest priority. This has the greatest overall impact on the prevalence of chronic HBV infection in children, regardless of whether it is feasible to administer a birth dose (see Section 4.11).
- *In countries where a high proportion of chronic HBV infections is acquired perinatally (e.g. in south-east Asia).* A birth dose should be given to infants who are delivered in hospitals when hepatitis B vaccine is introduced. Efforts should also be made in these countries to give hepatitis B vaccine as soon as possible after birth to infants delivered at home (see Sections 5.3 and 8).
- *In countries where a lower proportion of chronic HBV infections is acquired perinatally (e.g. in Africa).* The administration of a birth dose may be considered after evaluating:
 - the relative contribution of perinatal HBV infections to the overall disease burden;
 - the feasibility and cost-effectiveness of providing a birth dose.

3.3 Catch-up vaccination of older persons

When hepatitis B vaccine is incorporated into routine childhood vaccination schedules the need for catch-up vaccination in age groups older than one year should be assessed. In particular it should be noted that health care workers exposed to blood are likely to be at high risk of becoming infected with HBV. The need for catch-up vaccination of older persons in other groups varies, depending on the endemicity of HBV infection in particular countries.

In countries where chronic HBV infection is highly endemic, most such infections are acquired among young children. The routine vaccination of infants rapidly reduces the transmission of HBV in this circumstance, and catch-up vaccination of older children is not usually required. It is particularly important that catch-up vaccination for older age groups should not hinder efforts to achieve a high level of completion of the vaccination series among infants and to prevent the spread of the virus from mothers to babies by means of a birth dose.

In countries of intermediate and low endemicity there may be a substantial disease burden from chronic infections acquired by older children, adolescents and adults. In these countries, vaccinating infants alone may not substantially lower the incidence of the disease for decades, and catch-up strategies targeted on these older age groups, in addition to routine infant vaccination, may be desirable.

Possible target groups for catch-up immunization include age-specific cohorts (e.g. routine immunization of young adolescents) and persons with risk factors for acquiring HBV infection. The establishment of surveillance for acute hepatitis B and the performance of seroprevalence studies on HBV infection can assist in determining the groups at highest risk of acquiring HBV infection, e.g. clients and staff of institutions for the developmentally disabled, injecting drug users, men who have sex with men, and persons with multiple sex partners. Vaccination and other prevention efforts may be targeted at these groups (see Section 7).

4. Hepatitis B vaccine

Two types of hepatitis B vaccine are available.

- Recombinant or genetically engineered vaccines are made using HBsAg synthesized in yeast or mammalian cells into which the HBsAg gene has been inserted.
- Plasma-derived vaccines are prepared from purified HBsAg from the plasma of persons with chronic HBV infection.

The two types are similar with respect to safety, immunogenicity and efficacy.

4.1 Formulations

Hepatitis B vaccines are available in monovalent formulations that protect only against hepatitis B, and in combination formulations that protect against hepatitis B and other diseases (e.g. DTP-HepB, DTP-HepB+Hib, Hib-HepB).

- Monovalent hepatitis B vaccine **MUST BE USED** for the birth dose.
- Combination vaccines that include hepatitis B vaccine **MUST NOT BE USED** to give the birth dose of hepatitis B vaccine because DTP and Hib vaccines should not be administered at birth.
- Either monovalent hepatitis B vaccine or combination vaccines may be used for later doses in the hepatitis B vaccine schedule. Combination vaccines can be given whenever all the antigens in the vaccines are indicated.

4.2 Immunogenicity and efficacy in children

Pre-exposure immunization. A course of three doses of hepatitis B vaccine induces protective levels of antibody to HBsAg (anti-HBs) in over 95% of healthy infants and children when given in a variety of schedules, including the following: at 6 weeks, 10 weeks and 14 weeks; at 2 months, 4 months and 6 months; at birth, 1 month and 6 months (51-55). Children who respond to hepatitis B vaccine are protected against acute hepatitis B and chronic infection.

Post-exposure immunization. Post-exposure immunization, beginning at birth with either hepatitis B vaccine alone or with hepatitis B vaccine and hepatitis B immune globulin (HBIG), can prevent the spread of more than 90% of HBV infections from mother to baby (56). The efficacy of giving recombinant hepatitis B vaccines alone is similar to that of giving hepatitis B vaccine with HBIG (56). Thus the use of HBIG is not necessary, particularly in countries where pregnant women are not screened

for HBsAg. Optimum efficacy in preventing perinatal HBV infections is achieved when hepatitis B vaccine is given within 24 hours after birth. There is no evidence of protection against perinatal transmission if the first dose of vaccine is given more than seven days after birth.

4.3 Interchangeability

The types and formulations of hepatitis B vaccines can be interchanged. Vaccines of different types and from different manufacturers can be used for each dose that a child receives.

4.4 Presentation

Hepatitis B vaccines are available in liquid single-dose and multidose glass vials, and in prefilled single-dose injection devices (e.g. Uniject™). Multidose vials generally contain 2, 6 or 10 doses.

4.5 Dosage

The standard paediatric dose is 0.5 ml. The quantity of HBsAg protein per dose that induces a protective immune response in infants and children varies with the manufacturer, ranging from 1.5 µg to 10 µg, because of differences in hepatitis B vaccine production processes. For this reason there is no international standard of vaccine potency expressed in µg HBsAg protein, and the relative efficacy of different vaccines cannot be assessed on the basis of differences in HBsAg content.

4.6 Administration

Hepatitis B vaccine is given by intramuscular injection in the anterolateral aspect of the thigh (infants) or deltoid muscle (older children). It can safely be given on the same day as other vaccines (e.g. DTP, OPV, Hib, measles, BCG, and yellow fever vaccine). In addition, it can be given at any time before or after a different inactivated or live vaccine because inactivated vaccines such as hepatitis B vaccine generally do not interfere with the immune response to other inactivated or live vaccines (57).

If hepatitis B vaccine is administered on the same day as another injectable vaccine, it is preferable to give the two vaccines in different limbs. If more than one injection has to be given in the same limb, the thigh is the preferred site of injection because of the greater muscle mass, and the injection sites should be 2.5 cm to 5 cm apart so that any local reactions are unlikely to overlap (57).

The injection equipment used for hepatitis B vaccine is of the same type as that used for all other EPI vaccines except BCG.

Sterile injection equipment is essential for all injections (see Section 6.8).

- 0.5-ml auto-disable (AD) injection devices are recommended as the first choice (see WHO-UNICEF-UNFPA joint statement on the use of AD syringes in immunization services [[WHO/V&B/99.25](#)]).
- In immunization services where sterilizable syringes are still used, a 0.5-ml sterilized syringe should be used.

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- If neither AD nor sterilizable syringes are available, standard disposable syringes (1.0 ml or 2.0 ml) can be employed but must be used **ONCE ONLY** and safely disposed of after use.
 - Whichever type of syringe is used, a 25-mm, 22- or 23-gauge needle is recommended.

The following practices should be avoided when giving hepatitis B vaccine.

- Hepatitis B vaccine **SHOULD NOT** be given in the buttock as this route of administration has been associated with decreased protective antibody levels, probably because of inadvertent subcutaneous injection or injection into deep fat tissue. In addition there may be a risk of injury to the sciatic nerve.
- Hepatitis B vaccine **SHOULD NOT** be administered intradermally because this route of administration does not produce an adequate antibody response in children.
- Hepatitis B vaccine **SHOULD NOT** be mixed in the same syringe with other vaccines unless specifically recommended by the manufacturer. (Note: pentavalent DTP-HepB+Hib vaccine is supplied in two separate vials, one containing DTP-HepB vaccine (liquid), the other containing Hib vaccine (lyophilized). The manufacturer recommends mixing the contents of the two vials and giving DTP-HepB+Hib vaccine in the same syringe.)

4.7 Storage temperature and shelf-life

The storage temperature for hepatitis B vaccine is the same as for DTP vaccine, i.e. between 2 °C and 8 °C. The vaccine is generally stable for at least four years from the date of manufacture if stored in this temperature range. Most hepatitis B vaccines are relatively heat stable and have only a small loss of potency when stored between 20 °C and 26 °C for up to a year and at 37 °C for two to six months (58, 59). However, there may be considerable variations in heat stability between hepatitis B vaccines from different manufacturers. The package insert should therefore be consulted in order to know the manufacturer's recommended shelf-life for each specific vaccine.

Hepatitis B vaccine and combination vaccines that contain hepatitis B vaccine **MUST NOT BE FROZEN**. The freezing of hepatitis B vaccine causes the HBsAg protein to dissociate from the alum adjuvant and thus to lose its immunogenicity/potency (see Section 6.3 for precautions against the freezing of hepatitis B vaccine). The freezing point of hepatitis B vaccine is about -0.5 °C.

The pentavalent DTP-HepB+Hib formulation is supplied in two separate vials (liquid DTP-HepB and lyophilized Hib) that are not packaged together. Lyophilized Hib vaccine can be stored either frozen at -20 °C or refrigerated between 2 °C and 8 °C; however, liquid DTP-HepB vaccine **MUST NOT BE FROZEN**. To ensure that Hib is correctly reconstituted with DTP-HepB it is recommended that both vials of the pentavalent DTP-HepB+Hib formulation are stored together between 2 °C and 8 °C, and both vials should be shipped and distributed together.

Further information on the storage temperature and shelf-life of hepatitis B vaccine can be found in the following documents.

- Galazka A, Milstien J, Zaffran M. *Thermostability of vaccines* (WHO/GPV/98.07).
- Proper handling and reconstitution of vaccines avoids programme errors. *Vaccines and Biologicals Update*, 2000, 34: 1-4.

4.8 Indications

All infants aged under 1 year should receive a full series of hepatitis B vaccine.

The need for catch-up immunization of older age groups and for targeted risk groups varies between countries (see Section 3.3).

4.9 Contraindications

There are very few reasons to withhold or postpone the administration of hepatitis B vaccine. Immunizations are too often delayed or denied because of conditions falsely believed by health care workers to be contraindications for the administration of vaccine.

A child with a history of a severe allergic reaction (e.g. generalized urticaria, difficulty in breathing, swelling of the mouth and throat, hypertension, shock) to a previous dose of hepatitis B vaccine should not receive another dose.

The following are NOT contraindications:

- minor illness, such as respiratory tract infection or diarrhoea with temperature below 38.5°C;
- allergy or asthma;
- family history of convulsions;
- treatment with antibiotics;
- infection with HIV;
- breastfeeding;
- history of seizures (convulsions, fits);
- chronic illnesses such as chronic diseases of the heart, lung, kidney or liver;
- stable neurological conditions such as cerebral palsy and Down syndrome;
- prematurity or low birth weight;
- history of jaundice at birth.

4.10 Limitations

Hepatitis B vaccine protects only against hepatitis B; it does not protect against other types of hepatitis or jaundice.

More than 95% of infants develop protective antibodies after three doses of hepatitis B vaccine. However, a small percentage are not protected after vaccination.

4.11 Schedule

Hepatitis B immunization should be introduced as an integral part of the existing childhood immunization schedule. Hepatitis B vaccine schedules are very flexible and there are multiple options for adding the vaccine to existing national immunization schedules without requiring additional visits for immunization (Table 1).

Table 1. Options for adding hepatitis B vaccine to childhood immunization schedules

						Hepatitis B vaccine options		
						No birth dose	With birth dose	
Age	Visit		Other antigens			I	II	III
Birth	0	BCG [OPV0] ¹				HepB -birth ²	HepB -birth ²	
6 weeks	1		OPV1	DTP1		HepB1 ³	HepB2 ²	DTP-HepB1 ⁴
10 weeks	2		OPV2	DTP2		HepB2 ³		DTP-HepB2 ⁴
14 weeks	3		OPV3	DTP3		HepB3 ³	HepB3 ²	DTP-HepB3 ⁴
9–12 months	4				Measles			

¹ Only given in high polio endemic countries

² Monovalent vaccine

³ Monovalent or combination vaccine

⁴ Combination vaccine

Programmatically, it is usually easiest if the three doses of hepatitis B vaccine are given at the same time as the three doses of DTP (See Table 1, Option I). This schedule prevents infections acquired during early childhood, which account for most of the HBV-related disease burden in countries of high endemicity. It also prevents infections acquired later in life. However, this schedule does not prevent perinatal HBV infections because it does not include a dose of hepatitis B vaccine at birth.

Two schedule options can be used to prevent perinatal HBV infections: a three-dose schedule of monovalent hepatitis B vaccine, the first dose being given at birth and the second and third being given at the same time as the first and third doses of DTP vaccine (Table 1, Option II); or a four-dose schedule in which a birth dose of monovalent hepatitis B vaccine is followed by three doses of a combination vaccine (e.g. DTP-HepB) (Table 1, Option III).

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- The three-dose schedule (Table 1, Option II) is less expensive but may be more complicated to administer because infants receive different vaccines at the second immunization visit than at the first and third visits. Moreover, it may be difficult to achieve a high level of completion of the three-dose vaccine series with this schedule in countries where a high percentage of children are not born in hospitals.
 - The four-dose schedule (Table 1, Option III) may be easier to administer programmatically but is more costly.
 - Other factors to consider in deciding which hepatitis B vaccine schedule to use in a particular country include the following.
 - The minimum interval between dose 1 and dose 2 is four weeks, and the minimum interval between dose 2 and dose 3 is four weeks.
 - Schedules should optimize the percentage of children completing the hepatitis B vaccine series; higher vaccine coverage is usually achieved with earlier administration of vaccines.
 - If a dose is missed it should be given as soon as possible. There is no need to start the schedule again.

4.12 Long-term protection and booster doses

Many studies have shown that infants, children and adults who have responded to a three-dose hepatitis B immunization series are protected from the disease for as long as 15 years, even if they lose protective antibodies over time (55, 60). Long-term protection relies on immunological memory, which allows a protective anamnestic antibody response after exposure to HBV (61). Booster doses of vaccine are not, therefore, recommended (62, 63).

4.13 Safety

Hepatitis B vaccine is very safe. Mild transient side-effects that may occur after immunization include soreness at the injection site (3-9%); fatigue, headache and irritability (8-18%); and fever higher than 37.7°C (0.4-8%). These transient side-effects usually start within a day after the vaccine has been given and last from one to three days. When hepatitis B vaccine is given at the same time as DTP vaccine the rate of fever and/or irritability is no higher than when DTP is given alone.

Serious allergic reactions to the vaccine, i.e. hives, difficulty in breathing and shock are rare, affecting about one child per 600 000 vaccinated (64).

Allegations have been made on the basis of case reports that hepatitis B vaccine causes chronic illnesses, including multiple sclerosis, chronic fatigue syndrome, diabetes, rheumatoid arthritis and autoimmune disorders. However, no investigations have yet found any association between hepatitis B vaccination and these diseases (65, 66).

Additional information on the safety of hepatitis B vaccine can be found in the following document.

- [*Supplementary information on vaccine safety. Part 2: Background rates of adverse events following immunization \(WHO/V&B/00.36\).*](#)

5. Management decisions

5.1 Are monovalent or combination vaccines more suitable?

When choosing a suitable hepatitis B vaccine or vaccines for national immunization schedules the following issues should be considered.

- *Cost.* The cost of combination vaccines, may be higher than that of some monovalent products. However, other programme costs may be lower with combination vaccines than with monovalent vaccines (e.g. personnel, cold chain, injection equipment).
- *Local vaccine production.* The use of DTP-containing combination vaccines in countries with local DTP production may lead to the displacement of the locally produced product. Options for these countries may include monovalent hepatitis B vaccines or a combination product that does not incorporate DTP.
- *Number of injections.* The use of combination vaccines decreases the number of injections required in a single visit and the quantity of needles and syringes required.
- *Impact on personnel.* The introduction of combination vaccines requires less time for vaccination per child and simplifies record-keeping.
- *Flexibility in adding to national immunization schedules.* The use of monovalent vaccines enables more flexibility in introducing hepatitis B vaccine into existing immunization schedules. This arises because monovalent hepatitis B vaccine can be administered at any age, whereas DTP-containing combination vaccines must be given in accordance with the DTP schedule and cannot be used for the birth dose of hepatitis B vaccine.
- *Impact on cold chain capacity.* The impact of monovalent and combination vaccines on cold chain storage requirements will vary depending on the type of vaccine used (See Section 6.3).
- *Vaccine security.* Theft is more likely with monovalent vaccines than with combination vaccines that incorporate DTP because of DTP reactogenicity and because DTP is not recommended for children over 5 years of age.
- *Vaccine supply.* Quantities of DTP-HepB vaccine that are sufficient to meet demand may not be available until at least 2004-2005.

5.2 How should hepatitis B vaccine be phased into existing infant immunization services?

The highest priority when hepatitis B immunization is initiated is to achieve high levels of completion of the vaccine series among infants for whom it begins at birth or with the first dose of DTP vaccine. Achieving high vaccine coverage among these infants has the greatest overall impact on the prevalence of chronic HBV infection in children.

It is usually most feasible to phase in hepatitis B vaccine by giving the vaccine to infants who have not yet completed the DTP vaccine series. Children who have started, but not completed, the DTP vaccine series when hepatitis B vaccine is introduced may receive only one or two doses of hepatitis B vaccine and may not be fully protected against HBV infection. However, it may be logistically difficult to complete the hepatitis B vaccine series for these infants because additional visits may be required.

5.3 What strategies can be used for delivery of hepatitis B vaccine at birth?

In countries where a birth dose of hepatitis B vaccine is used to prevent perinatal HBV transmission (see Section 3.2), effective strategies have to be designed and implemented in order to deliver the vaccine. Hepatitis B vaccine can be administered at the same time as other vaccines that may be given close to the time of birth, including BCG and OPV. However, in order to prevent the spread of HBV from mother to baby, hepatitis B vaccine must be given as close as possible to the time of delivery, preferably within 24 hours. The design of strategies for administering the birth dose must therefore consider the roles of both obstetric staff (e.g. obstetricians, midwives and birth attendants) and immunization programme staff. In addition, record-keeping systems need to be developed in order to facilitate the transfer of information on the administration of the birth dose between these two categories of personnel.

Strategies that can be considered for delivery of the birth dose of hepatitis B vaccine include the following.

Immunization of neonates delivered in health facilities. The immunization of neonates while they are in health facilities presents an opportunity that should not be missed. Immunization can be offered at a fixed time each day so as to cover all deliveries that have occurred within the previous 24 hours.

Immunization of neonates delivered at home. The immunization of neonates who are not born in hospital presents additional challenges to the immunization delivery system. Hepatitis B vaccine may be given to these infants in immunization clinics or during home visits as close as possible to the time of birth. Some of the prerequisites for providing hepatitis B vaccine for infants delivered at home may include:

- motivated health staff;
- receptive communities;
- timely notification of births;

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- adequate transport allowances;
 - attention to cold chain issues (see Sections 6.3 and 8);
 - availability of single-dose vials of hepatitis B vaccine (e.g. UNIJECT™);
 - ensuring that injections can be safely administered.

5.4 How can costs of hepatitis B vaccine introduction be estimated?

When planning for the introduction of hepatitis B vaccine, capital and recurrent costs related to its delivery should be estimated and included in the annual budget of the immunization programme. Among the additional capital costs there might be those of investment in cold chain equipment and information campaigns targeted at the general public. Additional recurrent cost items include vaccines, AD syringes, training, safe disposal of waste, and evaluation of the impact of the programme.

Further information on calculating the costs of introducing hepatitis B vaccine is available in the forthcoming document entitled “Guidelines for estimating costs of introducing new vaccines into the national immunization system”.

5.5 How can the addition of hepatitis B vaccine be used to strengthen routine immunization services?

The introduction of hepatitis B vaccine should be used as an opportunity to strengthen existing routine immunization services. When hepatitis B vaccine is introduced, plans should be made regarding specific elements of the immunization service which need to be improved. Measurable indicators should be established in order to monitor progress towards strengthening these elements. Those requiring particular attention include:

- vaccine stock management;
- reducing vaccine wastage (see Section 6.5);
- injection safety (see Section 6.8).

6. Operations

When introducing hepatitis B vaccine into the routine childhood immunization schedule, systems need to be adapted or set up for ordering and storage of the vaccine, monitoring vaccine use and wastage, monitoring vaccine coverage, preparation and training of staff, and advocacy and communication about hepatitis B and hepatitis B vaccine.

6.1 Vaccine procurement

Estimating vaccine needs. The number of hepatitis B vaccine doses required is estimated using the size of the birth cohort, the coverage rate for DTP and the number of doses in the immunization schedule. These calculations should also include wastage and the size of the reserve stock. For economic or logistical reasons, some countries may choose to phase in hepatitis B immunization over time. For example, during the first year or years there may be targeting on infants in regions where the prevalence of chronic HBV infection is high relative to that in other regions of the country in question, or on infants in urban areas. In such cases, vaccine requirements depend on the size of the target group.

Vial size. Both single-dose and multidose vials may be needed to accommodate hepatitis B immunization in various settings. Multidose vials are generally used for all scheduled immunization sessions in fixed facilities and outreach sessions, and for the immunization of neonates delivered in hospitals. Single-dose vials may be appropriate in hospitals where only one or two infants are born each day and for the immunization at birth of infants delivered at home.

The use of single-dose vials can decrease vaccine wastage. However, single-dose vials cost more per dose than multidose vials. Moreover, single-dose vials add to the requirements for cold chain storage and transportation space. Careful calculations need to be made of requirements for single-dose and multidose vials at each level of the cold chain. Orders at each level should specify separately the number of single-dose and multidose vials required.

Further information on vaccine procurement can be found in the following documents.

- [Procurement of vaccines for public sector programmes – a reference manual \(WHO/V&B/99.12\)](#).
- [Guidelines for the international procurement of vaccines and sera \(WHO/VSQ/98.05\)](#).
- [Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies \(WHO/VSQ/97.06\)](#).

6.2 Packaging and shipping of vaccine

For the packaging and shipping of hepatitis B vaccine the following procedures need particular attention.

- Because hepatitis B vaccine **CANNOT BE FROZEN**:
 - every box used to pack and ship vaccine should be labelled “REFRIGERATE AT 2 °C TO 8 °C - DO NOT FREEZE”;
 - Freezeguard indicators must accompany all international shipments of hepatitis B vaccine, and, ideally, all in-country shipments.
- Vaccine cold chain monitor cards must be included with each shipping box.
- To discourage the theft of hepatitis B vaccine, packaging and shipping boxes can be labelled “Paediatric Vaccine” and “Property of the Ministry of Health”.

Further information on the packaging and shipping of vaccines can be found in the following document.

- [Guidelines on international packaging and shipping of vaccines \(WHO/V&B/01.05\)](#).

6.3 Cold chain issues

Adding hepatitis B vaccine to a national immunization schedule requires:

- an assessment of cold chain storage capacity and cold chain procedures at all administrative levels;
- the development and implementation of plans to modify cold chain storage capacity and cold chain procedures, if needed.
- *Cold chain capacity.* The impact of introducing hepatitis B vaccine on cold chain storage capacity should be carefully considered. It varies in accordance with the following factors.
- *Use of monovalent versus combination vaccines.* The type of vaccine selected may have considerable impact on cold chain storage capacity. For example, the storage requirements for multidose vials of DTP-HepB vaccine are the same as those for multidose vials of DTP vaccine (Table 2). However, if monovalent hepatitis B vaccine or DTP-HepB+Hib vaccine are used, storage requirements will increase (Table 2).

- *Hepatitis B vaccine storage and shipping volumes.* The storage volumes for hepatitis B vaccines supplied through UNICEF are shown in Table 2. The WHO recommended standard storage volume for DTP vaccine is 2.5 cm³ per dose in 20-dose vials (3.0 cm³ per dose in 10-dose vials); and the total storage volume for other EPI vaccines (BCG, DTP, measles, OPV, TT) is about 11.0 cm³ per dose.

Table 2. Hepatitis B vaccine storage volumes (cm³ per dose)¹

Vaccine	1-dose vials	2-dose vials	6-dose vials	10-dose vials
HepB monovalent	9.7/14.9/33.80 ⁵	4.8	2.72	2.3
HepB (Uniject [®]) ²	24.6	—	—	—
DTP + HepB ³	—	—	—	8.2
DTP-HepB (combined)	9.7	4.84	—	3.0
DTP-HepB + Hib ⁴	—	9.7	—	—

¹ Net storage volume only includes primary packaging. It does not include secondary packaging, insulated packaging, or air circulation space needed to refrigerate vaccines.

² Monovalent HepB (liquid) in prefilled single-dose injection device.

³ One vial DTP (liquid) plus one vial HepB (liquid) packaged together.

⁴ One vial DTP-HepB (liquid) packaged together with one vial Hib (freeze-dried). Hib is reconstituted with DTP-HepB.

⁵ Multiple values represent products from different manufacturers.

- *Use of single-dose vs. multi-dose vials.* The use of single-dose vials increases the need for storage space. For example, if single-dose vials are used instead of ten-dose vials, three to four times more storage and transportation space is necessary (Table 2).
- *The administrative level of the cold chain.* Both the cold chain equipment used and the extra storage capacity available may vary at each administrative level of the cold chain. Increased vaccine storage requirements at a particular administrative level may be handled by either increasing the amount of storage capacity and/or by increasing the frequency of vaccine shipments.

A vaccine volume calculator is available from WHO headquarters to assist countries in planning for space requirements when introducing new vaccines. This tool can be used to calculate the net storage volume per child fully immunized in accordance with various vaccine schedules and the percentage change in storage volume required when introducing a new vaccine ([WHO/V&B/01.24](#)).

Precautions to prevent freezing of vaccine. Because hepatitis B vaccine is inactivated by freezing, storage and shipping procedures for the prevention of freezing should be assessed at all levels of the cold chain. This is particularly important at higher levels, where chest freezers are capable of freezing to -20 °C or below, and where greater numbers of vials could be affected. The risk of lost potency attributable to freezing may also increase at the lower levels of the cold chain when vaccine is transported in cold boxes and may come into contact with ice packs. Vaccine should not be used if the possibility exists that it has been frozen. The shake test can be used to assess whether this has happened ([WHO/EPI/LHIS/98.02](#)).

The precautions against the freezing of hepatitis B vaccine are the same as for DTP and TT. They include the following.

- At each level of vaccine distribution, ice packs taken from a freezer should be kept at room temperature for 5 to 10 minutes (until beads of water are present on the ice packs) before putting them in a vaccine carrier or cold box.
- A barrier of insulating material should be placed between the ice packs and the vaccine, both along the sides of the container and over the top.

Additional information on cold chain management issues can be found in the following documents.

- Safe vaccine handling, cold chain and immunizations. A manual for the Newly Independent States ([WHO/EPI/LHIS/98.02](#)).
- Immunization in practice. Module 3: The cold chain ([WHO/TRAM/98.01-11 REV.1](#)).
- Temperature monitors for vaccines and the cold chain ([WHO/V&B/99.15](#)).
- Product Information Sheets, 2000 edition ([WHO/V&B/00.13](#)).

6.4 Vaccine security

There is a possibility of theft of vaccine supplies because there may be a demand for hepatitis B vaccine for older children and adults. Procedures that can be used to secure vaccine stocks and prevent theft include:

- using refrigerators with locks and keys, or putting refrigerators in locked rooms;
- comparing inventories frequently against ledgers in order to detect discrepancies.

6.5 Reducing vaccine wastage

Since hepatitis B vaccines are more expensive than other EPI vaccines it is important to monitor wastage and develop and implement strategies for reducing it.

Monitoring vaccine wastage. This can reduce wastage by providing reliable data for estimating the number and size of vials to be ordered. The wastage rate during a certain period is calculated as:

$$\frac{(\text{number of doses supplied}^* - \text{number of immunizations given})}{\text{number of vaccine doses supplied}}$$

For example, let us assume that 1000 vaccine doses are supplied and 750 immunizations are given from January to March.

$$\text{The wastage rate for this period is: } \frac{(1000 - 750)}{1000} = 0.25 \text{ or } 25\%.$$

* Number of doses supplied may be determined as follows: (number of doses present at beginning of period)+(number of doses received)-(number of doses present at end of period).

The wastage of hepatitis B vaccine should be routinely monitored and reported (e.g. quarterly). If routine reporting is not feasible, consideration should be given to reporting wastage for a short period (e.g. a year), in order to establish a history, and then reporting intermittently.

Strategies for reducing vaccine wastage. Assessing the causes of vaccine wastage is an important way to reduce it because they vary between settings. The possible causes include breakdown of the cold chain, freezing of vaccine, labels becoming detached from vials, outdated vaccine, theft and the discarding of partly used vials after immunization sessions.

Strategies for reducing vaccine wastage include:

- careful planning of vaccine ordering and distribution;
- implementation of the WHO multidose vial policy;
- appropriate use of single-dose and multidose vials;
- careful maintenance of the cold chain;
- attention to vaccine security; and
- raising demand for immunization services.

Additional information on monitoring and reducing vaccine wastage can be found in the following documents.

- Quality of the cold chain: WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services ([WHO/V&B/99.18](#)).
- WHO policy statement: the use of opened multidose vials of vaccine in subsequent immunization sessions ([WHO/V&B/00.09](#)).

6.6 Implementing the multidose vial policy

According to the WHO multidose vial policy ([WHO/V&B/00.09](#)), opened multidose vials of hepatitis B vaccine may be reused in subsequent immunization sessions for up to four weeks in fixed health facilities if all the following conditions are met.

- The expiry date has not passed.
- The vial has been stored under appropriate cold chain conditions (i.e. refrigerated between 2 °C and 8 °C).
- The vaccine vial septum (where the needle is put in to withdraw doses) has not been submerged in water (to prevent this from happening, well-sealed ice packs should be used in vaccine carriers and water should not be allowed to accumulate where the vials are stored).
- An aseptic technique has been used to withdraw all doses.
- The vaccine vial monitor (VVM), if attached, has not reached the discard point.

In outreach sessions, opened multidose vials of hepatitis B vaccine may be reused in subsequent immunization sessions for up to four weeks if:

- all the conditions for reuse of multidose vials in fixed health facilities are met;
- a VVM is attached to the vial.

Note: the pentavalent DTP-HepB+Hib formulation is supplied in two separate vials (liquid DTP-HepB and lyophilized Hib). Since this vaccine contains a preservative, it can be reused safely over an extended period after reconstitution. However, the application of the multidose vial policy with DTP-HepB+Hib vaccine is recommended only if specific supervision and training activities are conducted in order to ensure appropriate implementation.

6.7 Estimating requirements for injection equipment

Managers at each level are responsible for ensuring that adequate supplies are available at all times so that each injection can be given with a sterile needle and a sterile syringe. The following points are of particular importance.

- If AD or disposable needles and syringes are used, clinics should have at least one month's supply of injection equipment at all times.
- If sterilizable equipment is used a stock of reusable syringes and needles should be maintained. This should be equal in number to 10% more than the largest number of injections given in a single session, and there should be sufficient fuel for sterilization and adequate spare parts for the maintenance of steam sterilizers. In addition, policies and procedures should exist for the regular replacement of reusable syringes and needles.

Estimates must also be made of requirements for:

- storage for syringes and needles;
- sterilization equipment for sterilizable syringes and needles;
- waste disposal boxes (sharps boxes) for used syringes and needles;
- incinerator capacity for destroying used syringes and needles.

Further information on estimating needs for injection equipment can be found in the following documents.

- [Immunization in practice. Module 4: Ensuring safe injections \(WHO/EPI/TRAM/98.04\).](#)
- [Immunization in practice. Module 5: Organizing immunization sessions \(WHO/EPI/TRAM/98.05\).](#)

6.8 Maintaining injection safety

Unsafe injection practices can put patients, health care workers and the community at risk of bloodborne infections (e.g. HBV, hepatitis C virus, HIV). Furthermore, in countries in which monovalent hepatitis B vaccine is used, three additional injections are required and there is an increased requirement for the disposal of waste syringes. The introduction of hepatitis B vaccine offers a good opportunity to review,

update and reinforce policies and procedures for the safe and appropriate use of injections. If possible, policies and plans for safe and appropriate use of injections should apply both to injections given for immunization and to therapeutic injections, because approximately 10 therapeutic injections are given for each immunization injection.

Elements of safe injection policies and procedures include the following:

- assuring the availability of sterile injection equipment and safety boxes, including the use of AD syringes for all injectable immunizations ([WHO/V&B/99.25](#));
- appropriate disposal of sharps waste;
- initiatives to promote behaviour change among patients and health care workers in order to decrease the overuse of injections and encourage safe injection practices.

The development of safe injection policies and procedures may be achieved with increased effect and reduced cost if an initial assessment of injection practices is conducted. A tool for assessing injection safety in immunization services (tool C) is available from WHO/HQ at <http://www.injectionsafety.org/html/resources.html>.

Additional information on safe injection practices can be found in the following documents.

- [Report of the first meeting of the Steering Committee on Immunization Safety \(WHO/V&B/00.17\)](#).
- [WHO-recommended policy: safety of injections in immunization programmes \(WHO/EPI/LHIS/96.05 Rev.1\)](#).
- [Immunization in practice. Module 4: Ensuring safe injections \(WHO/TRAM/98.01-11\)](#).
- [Unsafe injection practices and transmission of bloodborne pathogens \(WHO/DCT/99.1\)](#).
- *Aide-memoire for a national strategy for the safe and appropriate use of injections* (available at the SIGN Internet site: <http://www.injectionsafety.org>).
- *Toolbox to assess and evaluate injection practices* (available at the SIGN Internet site: <http://www.injectionsafety.org>).

6.9 Monitoring vaccine coverage

The monitoring of hepatitis B vaccine coverage should be incorporated into routine immunization monitoring systems as soon as the vaccine is introduced. Staff at all levels should monitor progress in vaccine coverage particularly closely during the first several years after introduction.

With the addition of hepatitis B vaccine to the routine childhood immunization schedule, a fully immunized child (FIC) is defined as one completing HepB3 in addition to other vaccines already in the routine schedule. The definition of HepB3 completion depends on the immunization schedule used in a particular country.

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- If a three-dose hepatitis B vaccine schedule is used (Table 2, Options I and II), HepB3 completion should be defined as completion of the third hepatitis B vaccine dose.
 - If a four-dose hepatitis B vaccine schedule is used, with a birth dose of monovalent vaccine and three doses of a combination vaccine (Table 2, Option III), HepB3 completion should be defined as completion of the third dose of the combination vaccine.

Hepatitis B vaccine coverage can be monitored using both routine service statistics and special coverage surveys. Service statistics should be monitored for each district on at least a quarterly basis. The EPI vaccine coverage monitoring chart (WHO/EPI/TRAM/98.01) can be used to monitor these indicators graphically and provide feedback to other administrative levels. Immunization coverage surveys are useful for obtaining additional information relating to the assessment and improvement of immunization coverage. Such surveys can be done using either 30-cluster surveys or the lot quality technique. Standard questionnaires used for EPI surveys have to be modified to include hepatitis B vaccine doses.

The following are examples of statistics that can be used to monitor hepatitis B vaccine coverage.

- *HepB3*. This measures the proportion of infants who complete the hepatitis B immunization series. Monitoring should include the number and estimated proportion of children who complete the hepatitis B vaccine series (using the birth cohort as the denominator).
- *HepB1 vs. HepB3* [(HepB1 - HepB3)/HepB1]. This monitors the drop-out rate (the proportion of children that are incompletely vaccinated), which should not be higher than drop-out rates for DTP and polio vaccines.
- *HepB3 vs. DTP3* [(HepB 3 - DTP3)/HepB3]. This monitors completion of the hepatitis B vaccine series in comparison with that of the DTP series. By the time the child has completed the DTP series it should have received the last (third or fourth) dose of hepatitis B vaccine. If combination vaccines are used (e.g. DTP-HepB), comparisons with historical DTP3 coverage may be useful. If HepB3 coverage is more than 5% less than DTP3 coverage an investigation should be conducted to assess missed opportunities for administering hepatitis B vaccine.
- *HepB-birth coverage*. Measuring the percentage of children receiving hepatitis B vaccine within 1-2 days after birth provides an indicator of the success of the programme in preventing perinatal HBV infections.
- Additional information on monitoring and increasing vaccine coverage can be found in the following documents.
- [WHO-recommended standards for surveillance of selected vaccine-preventable diseases \(WHO/EPI/GEN/98.01 Rev. 1\)](#).
- [Information for action - developing a computer-based information system for the surveillance of EPI and other diseases \(IFA manual\) \(WHO/EPI/GEN/98.15\)](#).
- [WHO vaccine-preventable diseases monitoring system: 2000 global summary \(WHO/V&B/00.32\)](#).

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- [Immunization in practice. Module 11: Monitoring immunization coverage \(WHO/EPI/TRAM/98.01-11 REV.1\).](#)
 - *EPI coverage survey (WHO/EPI/MLM/91.10).*
 - *Facilitator guide for the EPI coverage survey (WHO/EPI/MLM/91.11).*
 - [Imaginative ways of raising immunization coverage \(EPI update 32, November 1997\).](#)
 - *Monitoring immunization services using the lot quality technique (WHO/VRD/TRAM/96.01).*
 - *Monitoring immunization services using the lot quality technique – answer sheets (WHO/VRD/TRAM/96.01, Suppl. 1).*

6.10 Monitoring immunization safety

Hepatitis B immunization is extremely safe. See Section 4.13 for a full discussion of possible adverse events following hepatitis B immunization. All serious adverse events suspected by health workers or the public to be associated with hepatitis B immunization should be reported, including abscesses, hospitalizations, deaths and any other severe or unusual medical incidents. All serious adverse events should be reported to the district health authorities and then to national immunization staff in the health ministry of the country in question.

Additional information on immunization safety monitoring can be found in the following documents.

- [Supplementary information on vaccine safety. Part 1: Field issues \(WHO/V&B/00.24\).](#)
- [Supplementary information on vaccine safety. Part 2: Background rates of adverse events following immunization \(WHO/V&B/00.36\).](#)
- [Surveillance of adverse events following immunization: field guide for managers of immunization programmes \(WHO/EPI/TRAM/93.02 REV.1\).](#)

6.11 Revision of EPI forms and materials

When hepatitis B vaccine is integrated into national immunization services, the following training and informational materials and forms used in the monitoring and evaluation of the programme have to be revised;

- immunization schedules;
- immunization cards;
- vaccine stock forms and cards;
- immunization tally sheets;
- reports of doses delivered;
- immunization registers;
- informational material for parents;
- training material for health care workers;

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- immunization coverage surveys;
 - country EPI evaluations;
 - computer programmes.

It is recommended that revised materials be distributed before hepatitis B vaccine is introduced. Alternatively, health workers may add hepatitis B vaccine data by hand to existing forms and use these as long as they last. However, errors and omissions are more likely to occur if the latter course is chosen.

6.12 Training of health care staff

Training for health care staff in both the public and private sectors is essential in connection with the introduction of hepatitis B vaccine into national immunization schedules. These people are responsible for handling and administering the vaccine and they are a major source of information for parents and other members of the public. The extra burden of new training can be minimized if the delivery of information on hepatitis B is integrated into existing training programmes.

Health care staff who need training include EPI personnel, physicians, nurses, midwives, traditional birth attendants, community health workers and administrators.

The following issues are among those that should be considered when training programmes for health care staff are being developed and implemented.

- Training should be given before the immunization programme begins and before public information campaigns are undertaken.
- All training materials relating to immunization should be updated as soon as possible to include information about hepatitis B and hepatitis B vaccine.
- Training may take place through the distribution of supplements to immunization training manuals, regular staff meetings, in-service training workshops, newsletters and professional journals.
- Every opportunity should be used to reach health care staff, even if this means that some individuals may receive the same information more than once.
- Curricula for health care staff training programmes and schools should be updated to include information about hepatitis B and hepatitis B vaccine.

Among the key messages for health care staff are those relating to:

- hepatitis B and its consequences;
- modes of HBV transmission;
- who is at risk of becoming infected;
- the efficacy of hepatitis B immunization;
- limitations of hepatitis B vaccine;
- why and how the vaccine is being added to national immunization schedules;
- the target group or groups for immunization and why they are chosen;

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- how to use the addition of hepatitis B vaccine to strengthen national immunization services;
 - how to handle the vaccine, including cold chain requirements;
 - how to administer the vaccine;
 - the importance of administering the first dose as soon as possible after birth to prevent perinatal HBV transmission (if applicable to the national immunization schedule);
 - the revised immunization schedule, including the importance of administering the complete vaccine series in order to provide long-term protection;
 - the side-effects and safety of hepatitis B vaccine;
 - safe injection practices;
 - how to respond to parents' questions about the vaccine;
 - methods for monitoring and evaluating the impact of hepatitis B immunization.

Sample training material for health care staff is presented in Annex 1.

Additional information on the training of health care staff can be found in the following documents.

- *Guidelines for planning training activities for immunization and disease control activities (WHO/EPI/TRAM/95.02).*
- *Training evaluation: a guide to the evaluation of training courses on immunization and other disease control activities (WHO/EPI/TRAM/95.03).*

6.13 Advocacy and communication

When introducing hepatitis B vaccine into national immunization schedules, advocacy and communication are important in order to generate support and commitment for the new vaccine. In addition, preparations should be made to dispel misconceptions about hepatitis B and hepatitis B vaccine that could undermine public confidence in vaccines.

The primary target audiences for advocacy and communication are decision-makers/opinion leaders and the general public, including parents. The following issues should be considered when strategies for reaching these groups are being designed and implemented.

Decision-makers/opinion leaders. Advocacy efforts among decision-makers and opinion leaders are important in generating commitment for adding hepatitis B vaccine to national immunization schedules. The decision-makers and opinion leaders who should be considered in this connection include:

- health ministry officials;
- other government officials (e.g. finance ministry officials);
- clinicians in the private sector;
- donor agencies;

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- nongovernmental organizations;
 - community leaders and decision-makers;
 - religious leaders;
 - teachers.

Among the key messages for these groups are ones on:

- the disease burden associated with HBV-related cirrhosis and liver cancer in the country concerned;
- modes of HBV transmission;
- who is at risk of becoming infected;
- the efficacy and cost-effectiveness of hepatitis B immunization;
- the safety of hepatitis B vaccine;
- the importance of safe injection practices;
- the target group or groups for immunization and how they were chosen;
- the importance of using the addition of hepatitis B vaccine to strengthen national immunization services;
- the importance of their role as advocates for the successful introduction of hepatitis B vaccine;
- the need for financial support to ensure the sustainability of hepatitis B immunization.

Additional information on the design and implementation of advocacy efforts can be found in the following document.

- [Advocacy: a practical guide with polio eradication as a case study \(WHO/V&B/99.20\)](#).

Parents and the general public. Advocacy and communication efforts for parents and the general public give them the opportunity to understand the disease burden associated with hepatitis B (liver cancer and cirrhosis) and to learn how to protect their children against the disease. However, mass media campaigns should not generate a demand for new vaccines in excess of supply.

Among the key messages for parents and the general public are those relating to:

- hepatitis B and its consequences;
- modes of HBV transmission;
- who is at risk of becoming infected;
- efficacy of hepatitis B immunization;
- limitations of hepatitis B vaccine;
- why the vaccine is being added to the national immunization programme;

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- the target group or groups for immunization, and an explanation of why older children are not being immunized with hepatitis B vaccine (if applicable to the national programme);
 - how many times and when babies should be immunized in order to achieve full protection against hepatitis B;
 - the safety of hepatitis B vaccine, and what side-effects to expect.

An example of informational material for parents is provided in Annex 2.

Additional information on advocacy and communication efforts for parents and the general public can be found in the following document.

- [*Immunization in practice. Module 10: Communicating with parents and involving communities \(WHO/EPI/TRAM/98.01-11 REV.1\).*](#)

Managing public relations issues linked to vaccine safety. Preparations should be made to respond in a timely manner to misconceptions about hepatitis B and hepatitis B vaccine that could undermine public confidence in the immunization programme. Misconceptions about the disease may occur because most people who die from liver cancer and cirrhosis of the liver attributable to HBV became infected as children but did not become ill at that time (see Section 3.2). Misconceptions about the safety of hepatitis B vaccine may occur because of case reports of adverse reactions after immunization (see Section 4.13).

Additional information on how to manage public relations issues related to vaccine safety can be found in the following document.

- [*Supplementary information on vaccine safety. Part 1: Field issues \(WHO/V&B/00.36\).*](#)

7. Assessing hepatitis B disease burden and the impact of hepatitis B immunization

7.1 Assessment of hepatitis B disease burden

The primary methods of assessing the disease burden associated with HBV infection involve:

- conducting serosurveys to determine the prevalence of HBsAg (serological marker of chronic HBV infection) and total antibodies to hepatitis B core antigen (total anti-HBc) (serological marker of acute, chronic or resolved infection);
- conducting surveillance for new (acute) hepatitis B cases;
- measuring deaths from cirrhosis and liver cancer.

The assessment of disease burden varies between countries in relation to data requirements, the availability of resources and the feasibility of conducting studies. This section provides an overview of the strengths and limitations of various methods of assessing disease burden.

The serological markers of HBV vary according to whether the infection is acute or chronic.

- *Acute hepatitis B.* A diagnosis of acute hepatitis B can be made by detecting IgM class antibody to hepatitis B core antigen (IgM anti-HBc) in serum; IgM anti-HBc is generally detectable at the time of clinical onset and declines to undetectable levels within six months. Total anti-HBc persists indefinitely as a marker of past infection. Anti-HBs becomes detectable in patients who resolve their infection. The presence of anti-HBs after acute infection generally indicates recovery and immunity from reinfection.
- *Chronic HBV infection.* In patients with chronic HBV infection, both HBsAg and total anti-HBc are persistently detectable, generally for life. In addition, a negative test for IgM anti-HBc together with a positive test for HBsAg in a single serum specimen usually indicates that an individual has chronic HBV infection.

Seroprevalence of HBV infection. Adequate seroprevalence data for assessing the disease burden associated with HBV infection are generally available in particular countries or in countries adjacent to them where HBV endemicity is similar. Consequently, additional seroprevalence studies are not usually needed before hepatitis B immunization is implemented. Sources of HBV seroprevalence data include papers published in international, regional and national journals and unpublished reports of research projects and evaluations conducted by health ministries,

university and academic physicians, United Nations agencies and nongovernmental organizations. Where possible, multiple sources of data can be used to account for possible differences in seroprevalence between geographical areas (e.g. regional, urban vs. rural), socioeconomic categories and ethnicities.

Seroprevalence data relating to hepatitis B among children can provide useful baseline information in advance of the implementation of universal immunization of infants against the disease.. Serological surveys of pregnant women and first-time unpaid blood donors generally offer the most useful means of estimating the prevalence of HBV infection among adults in the general population. Groups that are not representative of the general population and usually have a higher prevalence of HBV infection include repeat and paid blood donors, prostitutes, injecting drug users, patients attending sexually transmitted disease clinics, and hospitalized patients.

Additional sources of information on HBV seroprevalence data include the following.

- *Protocol for assessing prevalence of hepatitis B infection in antenatal patients* (WHO/EPI/GEN/90.6).
- The United States National Library of Medicine MEDLINE database (<http://www.nlm.nih.gov/databases/freemedl.html>).

Acute hepatitis B surveillance. Surveillance for acute hepatitis B cases, i.e. new symptomatic infections, can be used to assess disease burden, monitor trends in the incidence of new infections and assess risk factors for becoming infected with HBV. Among the issues that need to be considered in conducting such surveillance and interpreting surveillance data are the following.

- HBV is one of five viruses known to cause hepatitis in humans. Because acute disease caused by all of these viruses is similar, specific diagnostic tests are required to determine the cause in a person with signs and/or symptoms of acute hepatitis (e.g. jaundice). Preferably, all cases of suspected acute viral hepatitis should be classified by serological testing for at least HBsAg, IgM anti-HBc, and IgM antibody to hepatitis A virus (IgM anti-HAV). Patients who are positive for IgM anti-HBc are confirmed as having acute hepatitis B. Patients who are not tested for IgM anti-HBc, are HBsAg-positive and are negative for IgM anti-HAV are suspected of having acute hepatitis B.
- Acute hepatitis B surveillance can be integrated into existing disease surveillance systems, such as those for infectious and vaccine-preventable diseases. In countries that do not have sufficient resources to routinely perform appropriate diagnostic testing for acute viral hepatitis, serological testing of patients in selected (sentinel) sites can assist in determining the disease burden caused by different hepatitis viruses.
- Children do not usually become ill on acquiring HBV infection but they are most likely to develop chronic infection. Consequently, reported cases of hepatitis B greatly underestimate the magnitude of the disease burden, particularly in countries where HBV infection is highly endemic and the majority of chronic infections are acquired during childhood.

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- Because a higher proportion of older children, adolescents and adults are symptomatic, monitoring the incidence of acute hepatitis B in these older age groups can give a more accurate estimate of the disease burden. However, the disease burden in older age groups is also underestimated because of underreporting and asymptomatic infections.

A tool allowing acute hepatitis B surveillance to be used in the measurement of risk factors for HBV infection, including the association with unsafe injections, is available at the SIGN Internet site (<http://www.injectionsafety.org>).

Cirrhosis and liver cancer deaths. Deaths from chronic liver disease (cirrhosis and liver cancer) are the ultimate measure of disease burden associated with HBV infection. In many countries, chronic liver disease deaths can be ascertained from national vital statistics records or from a systematic review of death certificates. However, issues that need to be considered in interpreting the data include the following.

- In some countries, vital statistics do not accurately reflect deaths from chronic liver diseases because of difficulties in making diagnoses and because many persons with these diseases die at home rather than in hospital.
- Because there are many etiologies of chronic liver disease (e.g. hepatitis B, hepatitis C, alcohol) the proportion of deaths attributable to chronic liver disease that are HBV-related have to be estimated from seroprevalence studies among patients with cirrhosis and liver cancer.

7.2 Evaluating the impact of hepatitis B immunization

In addition to vaccine coverage, the most reliable way to measure the impact of hepatitis B immunization is to assess the prevalence of chronic HBV infections among young children. The effectiveness of routine immunization of infants against hepatitis B in significantly reducing or eliminating the prevalence of chronic HBV infection has been demonstrated in a variety of countries and settings (Table 3). In addition, such vaccination has been effective in reducing the incidence of liver cancer in children (67).

Table 3. Effectiveness of routine immunization of infants against hepatitis B immunization in reducing the prevalence of chronic HBV infection in children

Study site (reference)	No. tested ¹	Follow-up (years)	Vaccine coverage	% chronic infection	
				Before	After
Alaska (60)	268	1-10	96%	16	0.0
FSM ² (68)	364	3-4	82%	NA ³	1.1
FSM ² (68)	544	2	37%	12	2.9
Gambia (69)	675	9	100%	10	0.6
Indonesia (70)	2519	4	>90%	6.2	1.9
Saipan (71)	200	3-4	94%	9	0.5
Samoa (68)	435	7-8	87%	7	0.5
Saudi Arabia (72)	4791	1-8	85%	6.7	0.3
Taiwan (73)	424	7-10	73%	10	1.1

¹ Number of subjects tested in follow-up serosurveys after implementation of programme.

² Federated States of Micronesia.

³ Not available.

8. Future directions

8.1 Use of hepatitis B vaccine outside the cold chain

Hepatitis B vaccine is relatively heat-stable for several months (see Section 4.7). Furthermore, no significant differences were found in seroconversion rates and levels of protective antibody between infants who received a first dose that had been stored in the cold chain and those who received a first dose stored for up to a month at tropical temperatures (50).

The use of hepatitis B vaccine in prefilled single-use injection devices (e.g. Uniject™) outside the cold chain has been reported to simplify logistics, minimize vaccine wastage and facilitate the speed and efficiency of immunization during home visits (49). The use of such devices outside the cold chain could, therefore, greatly enhance vaccine delivery in outreach services. This is particularly true of the first dose of hepatitis B vaccine given at birth in order to prevent perinatal HBV transmission. However, experience in using hepatitis B vaccine outside the cold chain is limited. Large-scale demonstration projects, covering, for instance, entire countries, are needed to evaluate cost, cost-effectiveness, logistics (e.g. storage, transport, administration, waste disposal), vaccine coverage and safety issues before use outside the cold chain can be recommended.

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Annex 1:

Information for health care staff

What is hepatitis B?

Hepatitis B is a serious liver disease caused by the hepatitis B virus (HBV), which is present in the blood and body fluids of infected individuals.

After a person is first infected, HBV can cause a short-term (acute) illness that leads to:

- loss of appetite;
- nausea;
- tiredness;
- pain in muscles, joints or stomach;
- diarrhoea and vomiting;
- jaundice (yellow skin or eyes);
- dark urine.

HBV can also cause a long-term (chronic) infection that can stay undetected in the body for decades before it leads to:

- permanent liver damage (cirrhosis);
- liver cancer;
- death.

**Hepatitis B is NOT the same as Hib disease.
To prevent both hepatitis B and Hib disease,
two different vaccines are needed.**

Why is hepatitis B a public health problem?

HBV infection is a major cause of acute and chronic liver disease. About one-third of the world's population, i.e. about two billion persons, have been infected with HBV. Most of the serious consequences occur among persons who develop chronic infection. About a million persons with chronic HBV infection die each year from liver damage (cirrhosis) and liver cancer. HBV is second only to tobacco as a cause of cancer in humans.

Who can get hepatitis B? Who is most at risk?

Anyone can get hepatitis B but infants and young children are most at risk. Infants and young children do not usually become sick when they first become infected but they often develop long-term (chronic) infection with HBV. Chronically infected persons are at high risk of dying from cirrhosis and liver cancer.

How is HBV spread?

HBV is a bloodborne virus that is up to 100 times more infectious than HIV. It is spread efficiently by both skin puncture and mucous membrane contact with blood and other infectious body fluids (e.g. skin sore secretions, semen, vaginal fluid). It can also be spread as a result of contact with saliva through bites or the pre-mastication of food.

The main ways in which HBV is spread are as follows:

- from mother to baby at birth;
- from child to child;
- through unsafe injections and transfusions;
- through unprotected sex with an infected person.

HBV is not spread through the air or by food or water.

Is there a cure for hepatitis B?

There is no cure for hepatitis B; this is why prevention is so important. Hepatitis B vaccine is the best protection against HBV infection.

Hepatitis B immunization

How can hepatitis B be prevented?

Hepatitis B vaccine is effective in preventing HBV infections if given either before or shortly after exposure (within 7 days). Hepatitis B vaccine is the first anti-cancer vaccine because it can prevent a form of liver cancer.

What are the limitations of hepatitis B vaccine?

HBV is one of five viruses known to cause hepatitis in humans. Hepatitis B vaccine only protects against hepatitis B and not other diseases that cause jaundice.

Who should get hepatitis B vaccine?

All infants should receive hepatitis B vaccine. In developing countries, most adults and older children are already immune to HBV and do not need to be vaccinated.

Do older children need hepatitis B vaccine?

In countries where chronic HBV infection is highly endemic, almost all chronic HBV infections are acquired among infants and young children. In these countries, vaccination of older children is not generally needed. In countries of lower endemicity the majority of chronic HBV infections are acquired by adolescents and adults, and catch-up vaccination for older age groups may be desirable.

How many doses are needed? When should they be given?

Hepatitis B immunization schedules differ from country to country. Hepatitis B vaccine can be given as either three or four separate doses. All the doses must be given to ensure long-term protection.

- To prevent the spread of HBV from an infected mother to her baby, the first dose must be given as close as possible to birth, preferably within 24 hours.
- After birth, doses are usually given at the same time as DTP, polio and Hib vaccines.
- If a dose is missed it should be given as soon as possible. There is no need to start the schedule again.
- Booster doses are not needed.

**Ask your supervisor for the hepatitis B
immunization schedule in your area.**

What is the size of a dose?

The size of each dose is 0.5 ml.

How is hepatitis B vaccine given?

Hepatitis B vaccine is given by injection in the thigh (infants) or arm (older children).

It should NOT be given in the buttock.

It can safely be given at the same time as other vaccines, such as DTP, OPV, Hib, measles, BCG and yellow fever vaccines.

If hepatitis B vaccine is given on the same day as another injectable vaccine, it should be administered at another injection site. If more than one injection must be given in the same limb, the thigh is the preferred site of injection because of the greater muscle mass, and the injections should be separated by 2.5-5 cm so that any local reactions are unlikely to overlap.

Ask your supervisor what the recommended injection site is for each vaccine.

What are the side-effects of hepatitis B vaccine?

Hepatitis B vaccine is very safe. The most common side-effects are redness, swelling and pain where the injection has been given. About one in every 11 children vaccinated is affected by such side-effects. These usually start within a day after the vaccine has been given and last for one to three days. Less commonly, fever may occur for a short time after the vaccine has been administered (about one in every 14 vaccinated children is affected).

Serious allergic reactions to the vaccine (hives, difficulty in breathing, shock) are rare (about one in every 600 000 vaccinated children). Allegations have been made that hepatitis B vaccine causes chronic diseases like multiple sclerosis, chronic fatigue syndrome, rheumatoid arthritis, and autoimmune disorders. However, the investigations conducted so far have not found any association between hepatitis B vaccination and these diseases.

Is there any reason why a child should not be given hepatitis B vaccine?

A child who has had a severe reaction to a previous dose of hepatitis B vaccine should not be given another dose. The immunization may be postponed if a child has a high fever.

Children with HIV/AIDS should be immunized with hepatitis B vaccine.

Handling hepatitis B vaccine

How should hepatitis B vaccine be stored?

Hepatitis B vaccine should be stored between 2°C and 8°C.

DO NOT FREEZE the vaccine.

If hepatitis B vaccine is frozen, discard it.

How does the multidose vial policy apply?

In fixed health facilities, opened multidose vials of hepatitis B vaccine may be reused in the next immunization sessions for up to four weeks if all the following conditions are met:

- the expiry date has not passed;
- the vial has been kept refrigerated;

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- the part of the vaccine vial where the needle is put in to withdraw doses has not been put under water (note: to prevent this from happening, well-sealed ice packs should be used in vaccine carriers, and water should not be allowed to accumulate where the vials are stored);
 - an aseptic technique has been used to withdraw all doses;
 - the vaccine vial monitor (VVM), if attached, has not reached the discard point.

In outreach sessions, opened multidose vials of hepatitis B vaccine may be reused in subsequent immunization sessions for up to four weeks if:

- all the conditions for reuse of multidose vials in fixed health facilities are met;
- a VVM is attached to the vial.

Other information

What injection equipment is needed?

The injection equipment used for hepatitis B vaccine is of the same type as is used for all other EPI vaccines (except BCG vaccine).

- Sterile injection equipment is essential for all injections (see Section 6.8).
- 0.5-ml auto-disable (AD) injection devices are recommended as the first choice (see [WHO/V&B/99.25](#)).
- In immunization services where sterilizable syringes are still used, 0.5-ml sterilized syringes should be employed.
- If neither AD nor sterilizable syringes are available, standard disposable syringes (1.0 ml or 2.0 ml) can be employed but must be used **ONCE ONLY** and safely disposed of after use.

Whichever type of syringe is used, a 25-mm, 22- or 23-gauge needle is recommended.

Used needles and syringes must be sterilized or disposed of in accordance with national policy.

What records are needed in order to monitor hepatitis B vaccine use, wastage and immunization coverage?

The monitoring of use, wastage, and coverage gives you information about how effective you are in meeting vaccination targets and how efficient you are in using vaccine.

Ask your supervisor how to monitor and report vaccine use, wastage and coverage.

Annex 2:

Information for parents

What is hepatitis B?

Hepatitis B is a serious liver disease caused by the hepatitis B virus (HBV), which occurs in the blood and body fluids of infected individuals.

When persons are first infected with HBV they may have:

- loss of appetite;
- tiredness;
- pain in muscles, joints or stomach;
- diarrhoea and vomiting;
- jaundice (yellow skin or eyes).

HBV can also cause a chronic (long-term) infection that can stay undetected in the body for decades before it leads to:

- permanent liver damage (cirrhosis);
- liver cancer;
- death.

Who can get hepatitis B? Who is most at risk?

Anyone can get hepatitis B, but infants and young children are most at risk. Although infants and young children rarely become sick on acquiring the infection, they are at high risk of developing chronic infection with HBV. Chronically infected persons are at high risk of dying from cirrhosis and liver cancer.

How is hepatitis B virus spread?

Hepatitis B virus is up to 100 times more infectious than HIV. The main ways in which it spreads are:

- from mother to baby at birth;
- from child to child;
- through unsafe injections and transfusions;
- through unprotected sex with an infected person.

How can hepatitis B be prevented?

Hepatitis B can be prevented by hepatitis B vaccine, which is the first anti-cancer vaccine because it can prevent a form of liver cancer.

- **Hepatitis B is only one of the diseases that cause jaundice. Hepatitis B vaccine only protects against hepatitis B and not other diseases that cause jaundice.**
- **Hepatitis B is NOT the same as Hib disease. To prevent both hepatitis B and Hib disease, two different vaccines are needed.**

Who should get hepatitis B vaccine?

All infants should be given hepatitis B vaccine. In some countries, older children may also need to be immunized.

How many doses are needed? When should they be given?

Hepatitis B immunization schedules differ from country to country. Usually, hepatitis B vaccine is given as three or four separate doses. All the doses must be given to ensure that your child is protected.

- To prevent the spread of HBV from an infected mother to her baby, the first dose must be given as close as possible to birth (preferably within 24 hours).
- After birth, doses are usually given at the same time as DTP vaccine.

If a dose is missed it should be given as soon as possible. There is no need to start the schedule again.

How is hepatitis B vaccine given?

Hepatitis B vaccine is given by injection in the thigh (infants) or arm (older children). It can safely be given at the same time as other vaccines, such as DTP, OPV, Hib, measles, BCG and yellow fever vaccines

What are the side-effects of hepatitis B vaccine?

Hepatitis B vaccine is very safe. The most common side-effects are redness, swelling and pain where the injection has been given. These side-effects usually start within a day after the vaccine has been given and last for one to three days. Less commonly, fever may occur for a short time after the vaccine has been given. Very rarely there may be serious allergic reactions to the vaccine.

Is there any reason why a child should not be given hepatitis B vaccine?

A child who has had a severe reaction to a previous dose of hepatitis B vaccine should not be given another dose.

If a child has a high fever the vaccine may be given at a later visit.