HEPATITIS B VACCINE

Introduction

Hepatitis B is caused by hepatitis B virus (HBV), which produces an illness that is clinically indistinguishable from other forms of hepatitis. It is a major cause of acute and chronic hepatitis in the world. It ranges in severity from a mild illness, lasting a few weeks (acute), to a serious long-term (chronic) illness that can lead to liver disease and/or liver cancer.

In 1883, a form of hepatitis transmitted through blood or blood products was first documented in Germany during a smallpox immunization campaign. McCallum proposed the term hepatitis B for ‘serum’ hepatitis in 1947. The Australia antigen, now called the hepatitis B surface antigen (HBsAg), was first identified in 1967 and is the basis of the vaccine.

Hepatitis B virus infection is a major global health problem. Worldwide, an estimated two billion people have been infected with the hepatitis B virus (HBV), and more than 350 million are thought to be chronic carriers of hepatitis B.

A vaccine against hepatitis B has been available since 1982. Hepatitis B vaccine is 95% effective in preventing HBV infection and its chronic consequences, and is the first vaccine against a major human cancer. The vaccine has an outstanding record of safety and effectiveness. Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide. In many countries where 8 - 15% of children were used to become chronically infected with HBV, vaccination has reduced the rate of chronic infection to less than 1% among immunized children.

Virology

HBV is a double-stranded enveloped virus of the Hepadnaviridae family. HBV replicates in the hepatocytes of humans and other higher primates, but does not grow in artificial cell cultures. HBsAg is a lipoprotein of the viral envelope that circulates in the blood as spherical and tubular particles of 22 nanometres in size.

HBV is a virus with three major antigens, known as hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and hepatitis B core antigen (HBCaAg). HBsAg can be detected in serum 30-60 days after exposure and persists until the infection resolves. Any person positive for HBsAg is considered infectious.

Mode of transmission

Hepatitis B virus is transmitted among people by contact with the blood or other body fluids (i.e. semen and vaginal fluid) of an infected person. Modes of transmission are the same for the human immunodeficiency virus (HIV), but HBV is 50 to 100 times more infectious.
Unlike HIV, HBV can survive outside the body for at least 7 days. During that time, the virus can still cause infection if it enters the body of a person who is not infected. Common modes of transmission are; sexual contact, injecting drug use, perinatal (from mother to baby at birth), unsafe injection practices and blood transfusions. HBV is a major infectious occupational hazard for health workers. The virus incubation period is 90 days on average, but can vary from about 30 to 180 days.

**Clinical Features**

The outcomes of HBV infection are age-dependent and include asymptomatic infection, acute HBV infection, chronic HBV infection, cirrhosis and hepatocellular carcinoma (HCC). Acute hepatitis B occurs in approximately 1% of perinatal infections, 10% of early childhood infections (children aged 1–5 years) and 30% of late infections (people aged >5 years). Fulminant hepatitis develops in 0.1–0.6% of acute hepatitis cases; mortality from fulminant hepatitis B is approximately 70%. The development of chronic HBV infection is inversely related to the age of acquisition, occurring in approximately 80–90% of people infected perinatally, about 30% of children infected before the age of 6 years, and in <5% of infections occurring in otherwise healthy adults. People with chronic HBV infection have a 15–25% risk of dying prematurely from HBV-related cirrhosis and HCC.

It is not possible, on clinical grounds, to differentiate hepatitis B from hepatitis caused by other viral agents, hence, laboratory confirmation of the diagnosis is essential. In serological terms, acute HBV infection is characterized by the presence of HBsAg and IgM antibody to the core antigen, HBeAg. During the initial highly replicative phase of the infection, patients are also seropositive for HBeAg. Antibody to HBsAg (anti-HBs) is discernible after a few weeks and is followed by clearance of the HBsAg.

Chronic infection is characterized by the persistence (>6 months) of HBsAg. Persistence of HBsAg is the principal marker of risk for developing chronic liver disease and HCC later in life. The presence of HBeAg indicates that the blood and body fluids of the infected individual are highly contagious.

**Epidemiology**

**Global Situation**

Diseases caused by the HBV has a worldwide distribution. It is estimated that >2 billion people worldwide have been infected with HBV. Of these, approximately 350 million individuals are chronically infected and at risk of serious illness and death, mainly from liver cirrhosis and hepatocellular carcinoma (HCC).
Situation in Sri Lanka
Serological surveys among general population and special groups have found that the presence of HBV is not common in Sri Lanka although located in a region where HBV infection is highly prevalent. Sero-prevalence of HBsAg in the community varies from 0.24 - 2.5% in the community according to findings of Sero-epidemiological studies done before the introduction of Hepatitis B vaccine. Data from several studies carried out by Central Blood Bank shows that HBsAg positivity among blood donors range from 0.1 – 0.7%. Therefore, Sri Lanka is considered a low endemic country for HBV infection.

Hepatitis B vaccine

The main objective of hepatitis B immunization strategies is to prevent chronic HBV infection and its serious consequences, including liver cirrhosis and HCC.

Universal immunization with hepatitis B vaccine has resulted in a dramatic reduction of HBV transmission in many countries with historically high endemicity. This will gradually result in a reduction of HBV-related chronic hepatitis, liver cirrhosis and HCC, which have caused major concerns for public health and the economy in these areas. As of 2008, 177 countries had incorporated hepatitis B vaccine as an integral part of their national infant immunization programmes, and an estimated 69% of the 2008 birth cohort received 3 doses of hepatitis B vaccine. In recent years, the significantly reduced price of hepatitis B vaccine in developing countries has facilitated its introduction into many HBV-endemic areas. Following the primary vaccination schedule, almost all children are protected, probably for life, without the need for booster injections.

Sri Lanka introduced Hepatitis B vaccine into National Immunization schedule in year 2003 (on a phased basis) in the form of liquid monovalent vaccine. With the introduction of Hib vaccine in year 2008, Hep B vaccine is given in the form of liquid pentavalent vaccine (DTP-HepB+Hib).

Characteristics of the Hepatitis B vaccine

Recombinant hepatitis B vaccine was introduced in 1986 and has gradually replaced the earlier used plasma-derived hepatitis B vaccine. The recombinant hepatitis B vaccines use HBsAg synthesized in yeast or mammalian cells into which the HBsAg gene (or HBsAg/pre-HBsAg genes) has been inserted by plasmids. Following thorough purification from host-cell components, alum (and, in certain formulations, thiomersal) is added as adjuvant.

The Hepatitis B vaccines available in Sri Lanka are those developed using recombinant DNA technology.
Types of Hepatitis B containing vaccine preparations

Available hepatitis B vaccine formulations are, either monovalent or in combination with one or more other vaccines (multivalent), such as DTP, Hib vaccine and inactivated polio vaccine. Many countries, including Sri Lanka, give Hepatitis B vaccine combined with DTP and Hib vaccines (DTP-HepB+Hib).

Currently the EPI programme uses pentavalent vaccine (DTwP-Hep-B-Hib) to immunize infants against five diseases including hepatitis B.

♦ DTwP-Hep B-Hib vaccine (Pentavalent vaccine) - Refer to chapter on Pertussis

♦ Monovalent Hepatitis B vaccine

Each 0.5 ml dose contains hepatitis B surface antigen 10μg, Aluminium hydroxide gel as Al+++ 0.25mg and thiomersal as preservative 0.01 v/w%.

When immunizing against HBV at birth, only monovalent hepatitis B vaccine should be used: the other antigens found in combination vaccines are currently not approved for use at birth.

♦ Hepatitis A & B vaccine

Each 0.5 ml dose of paediatric preparation contains 360 ELISA units of HAV antigens, 10 μg recombinant DNA hepatitis B surface antigen protein, 0.225 mg aluminum phosphate/hydroxide, 0.5%w/v phenoxyethanol, traces of formaldehyde and neomycin. May contain yeast proteins.

Each 1 ml dose of adult preparation contains 720 ELISA units of HAV antigens, 20 μg recombinant DNA hepatitis B surface antigen protein, 0.45mg aluminum phosphate/hydroxide, 0.5%w/v phenoxyethanol, traces of formaldehyde and neomycin. May contain yeast proteins.

♦ DTaP-HepB vaccine - Refer to chapter on Pertussis

♦ DTaP-HepB-IPV-Hib - Refer to chapter on Pertussis

Indications

1. Hepatitis B Vaccine:

♦ Primary course of immunization against Hep B infection is
recommended for all infants on completion of 2, 4 and 6 months of age.

- Those at high risk of contracting HBV infection, including persons with high-risk sexual behaviour, partners and household contacts of HBsAg-positive persons, injecting drug users, persons who frequently require blood or blood products, recipients of solid organ transplantations.

- Those at occupational risk of HBV infection, including health care workers.

- International travellers visiting HBV-endemic countries.

- Together with passive immunization if required, for babies born to mothers who have had hepatitis B infection during pregnancy or are hepatitis B surface antigen positive

- Post-exposure vaccination following needle stick injuries.

**Efficacy**

The protective efficacy of hepatitis B vaccination is directly related to the induction of anti-HBs antibodies. The complete vaccine series induces protective antibody levels in >95% of infants, children and young adults. After the age of 40 years, protection following the primary vaccination series drops below 90%; by 60 years, protective antibody levels are achieved in only 65–75% of vaccinees.

According to the current scientific evidence the duration of protection is considered to be lifelong.

**Immunization Schedule**

Multiple options are available for incorporating the hepatitis B vaccine into the national immunization programmes and the choice of schedule depends on the country's epidemiological situation and programmatic feasibility.

Hepatitis B immunization schedule recommended for routine immunization of infants and children in Sri Lanka has been decided on the epidemiology of hepatitis B, feasibility of implementation of the EPI in the country and the objectives of the hepatitis B control Programme. A three-dose schedule has been adopted by the EPI for hepatitis B immunization considering the above factors and to achieve very high levels of immunization coverage.

Therefore, three doses of pentavalent vaccine (DTwP-Hep B-Hib) are given routinely to all infants on completion of 2, 4 and 6 months of age according to the EPI schedule in Sri Lanka.
Anyone who has not received the routine hep B vaccination during infancy can get hepatitis B vaccine at any age, followed by a second dose one month after the first and the third dose 6 months after the first dose.

For the travellers to endemic areas, accelerated schedule of 0, 1, 2 months and a booster at 12 months from the initial dose is recommended.

Countries with high perinatal transmission of hep B have schedules with the first vaccination at birth, followed by a second and third dose at the time of the first and third DTP vaccination, respectively.

Booster doses are not recommended for immunocompetent individuals after a primary course, as there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection.

However, booster doses are recommended for individuals with impaired immunity, in particular those with either HIV infection or renal failure. The time for boosting in such individuals should be decided by regular monitoring of anti-HBs levels.

**Dosage & Administration**

In the National EPI hep B vaccine is given to all infants in the form of pentavalent vaccine (DTwP-Hep B-Hib). The dose is 0.5 ml, administered intramuscularly in the anterolateral aspect of mid thigh in infants and in the deltoid muscle in those 12 months of age and older. The vaccine should be shaken well before use.

The recommended dose of hep B containing vaccines varies by product and with the age of the recipient. Therefore, manufacturer’s recommendation for dosage should be followed. In most cases, infants and adolescents (aged ≤15 years) receive 50% of the adult dose. All hep B containing vaccines are administered by intramuscular route.

**Storage**

Hepatitis B containing vaccine should be stored at +2°C to +8°C temperature. Exposure to freezing temperature must be avoided as it dissociates antigen from the alum adjuvant and lead to lose the vaccine potency.

**Cautions and contraindications**

The following conditions are considered as contraindications for the use of hepatitis B containing vaccine preparations:
♦ presence of one of the general contraindications for any vaccine,
♦ history of an allergy to any of the vaccine components,
♦ anaphylactic reaction to a previous dose of hepatitis B vaccine.

Neither pregnancy nor lactation is a contraindication for use of the vaccine.

**Adverse Events**

Adverse events after hepatitis B vaccination are transient and minor, and include soreness at the injection site, fever, nausea, dizziness, malaise, myalgia and arthralgia. Reports of severe anaphylactic reactions are extremely rare.

**Post-exposure prophylaxis for hepatitis B infection**

Among unimmunized, both passive-active postexposure prophylaxis (PEP) using HBIG & hepatitis B vaccine and active PEP using hepatitis B vaccine alone are highly effective in preventing infection after exposure to HBV. The major determinant of the effectiveness of PEP is early administration of the initial dose of vaccine. The effectiveness of PEP diminishes the longer after exposure it is initiated. HBIG may be administered simultaneously with hepatitis B vaccine but in a different injection site.

**Hepatitis B Immune Globulin (HBIG)**

The standard dose of HBIG is 0.06 mL/kg for all applications in adults. HBIG may be administered simultaneously with hepatitis B vaccine but in a different injection site. HBIG is administered by intramuscular injection. An appropriate muscle mass (i.e., deltoid or gluteal) should be chosen in which to deliver the large volumes of HBIG required by using a needle length appropriate for the person’s age and size. HBIG should be stored at +2°C to +8°C and should not be frozen.

HBIG in conjunction with hep B vaccination (i.e. is, active immunization) is used as Prophylactic treatment to prevent infection after exposure to HBV in the following situations:

♦ **Perinatal exposure**

For the newborn infants whose mothers are HBsAg-positive, HBIG at birth and hep B vaccination at 0, 1, 2, 12 months schedule is recommended.

♦ **Sexual partners of persons with acute hepatitis B virus infection**

People who have been sexually exposed to an HBsAg-positive persons, HBIG and hep B vaccination at 0, 1, 2, 12 months schedule is recommended.
Accidental Percutaneous or mucosal exposure to HBsAg

People who have had percutaneous (e.g. needle stick exposures) or mucous-membrane exposure to HBsAg-positive blood or body fluids, management are as in the table below:

<table>
<thead>
<tr>
<th>Exposed persons vaccination status</th>
<th>If the source is</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBsAg +ve</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>HBIG x 1 &amp; HBV immunization</td>
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<tr>
<td>Vaccinated responder - anti-HBs titre in exposed ≥ 10mIU/ml (tested within the past 24 months)</td>
<td>No immunization</td>
</tr>
<tr>
<td>Vaccinated non responder - anti-HBs titre in exposed &lt; 10mIU/ml</td>
<td>HBIG x 2 one month apart</td>
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<tr>
<td></td>
<td>HBsAg -ve</td>
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<tr>
<td></td>
<td>HBV immunization</td>
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<tr>
<td></td>
<td>HBV immunization</td>
</tr>
<tr>
<td></td>
<td>HBsAg status unknown</td>
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<tr>
<td></td>
<td>No immunization</td>
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<tr>
<td></td>
<td>If high risk source treat as if source was HBsAg +ve</td>
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</tbody>
</table>

Sources


