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Immunization manual for medical and nursing students "Hepatitis B Disease"

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7.3 HEPATITIS B DISEASE (R Kamenwa)

INTRODUCTION

Approximately 350 – 400 million people worldwide are chronically infected with the hepatitis B virus (HBV), and approximately 1 million die annually of HBV-related disease. The worldwide prevalence of hepatitis B virus ranges from 0.1% to 20%*).* This wide range is largely due to differences in age at the time of infection. Following acute HBV infection, the risk of developing chronic infection varies inversely with age: 90% for perinatal infection, 25–35% for infection at age 1–5 years and less than 10% for adults. About 45% of the world population live in areas where chronic HBV is highly endemic (≥8% of the population are hepatitis B surface antigen (HBsAg) positive), 43% live in intermediate-endemicity areas (2–7% HBsAg-positive) and 12% live in low-endemicity areas (0.6% to <2% HBsAg-positive). In the WHO European Region the HBsAg sero-prevalence ranges from 0.3% to 12% with up to 3.5 million carriers. Central Asian republics and parts of Eastern Europe are high endemic areas. Intermediately endemic areas include eastern and southern Europe and the Russian Federation, while northern and Western Europe are low endemic areas.

More than 2 000 million people alive today have been infected with HBV at some time in their lives. Three quarters of the world's population live in areas where there are high levels of infection. Every year there are over 4 million acute clinical cases of HBV, and about 25% of carriers, 1 million people a year, die from chronic active hepatitis, cirrhosis or primary liver cancer.

In developing countries the majority of Hepatitis B Virus (HBV) infection is acquired in early infancy or childhood. The acute infection often goes unrecognized and most of the morbidity and mortality from this disease occurs many years later. This has resulted in failure of appreciation of the full impact of this disease.

Currently, effective, affordable treatment for Hepatitis B disease is not available. Immunization is the mainstay for **prevention** and **control of** the disease.

Structure of HBV

HBV is a **double stranded DNA** virus belonging to a unique virus group referred to as HEPADNA. Electron microscopically, the whole virus (DANE PARTICLE) is 42nm in diameter.

The virus consists of a central core and an outer coat, both of which are antigenically represented as Hepatitis B core antigen (HBcAg) and Hepatitis B Surface antigen (HBsAg) respectively.

Hepatitis B Markers

The following hepatitis B markers have been identified:

- HBsAg was the first HBV marker identified and was named Australian antigen by Brumberg in 1967. The presence of HBsAg in blood is an indication of acute or chronic infection. Persistence of HBsAg beyond six months in the blood indicates chronic hepatitis B carriage. When it disappaers, the antibodies against hepatitis B (anti-HBs) are formed. This indicates immunity to hepatitis B.
- HBcAg is deeply seated In the nucleus and is not found in the blood. It can be detected in liver tissues after liver biopsy. However its antibody, the anti- HB
- core anti body (anti-HBc) is found in blood. The antigen (HBcAg) andthe antibody(anti-HBc) appear concurrently at the time of infection. The presence of the antibody (anti-HBc) indicates acute or chronic infection which can be differentiated by doing IgM or IgG anti-HBc. IgM anti-HBc indicates acute infection within one year and IgG indicates chronic or past infection.
- HBeAg is found in the blood and its presence indicates viral replication and therefore high infectivity of the patient. Anti-Hepatitis Be antibody (anti-HBe) appears in the blood once the antigen disappears and indicates reduced infectivity.
- DNA polymerase is an enzyme found in the blood during infection and indicates active replication of the virus.
- HBV-DNA is the most sensitive index of viral replication or infectivity.

The table below provides a summary of the markers.

Serological Markers of Hepatitis B Virus*

Term	Abbreviation	Comments
Hepatitis B virus	HBV	Aetiologic agent of 'serum' hepatitis: also known as 'Dane particle'
Hepatitis B surface antigen	HBsAg	Surface antigens of HBV, detectable in large quantity in serum; several subtypes identifiable
Hepatitis B e antigen	HBeAg	Associated with HBV replication, high titre HBV in serum and infectivity of serum
Hepatitis B core antigen	HbcAg	Function uncertain, no commercial test available and so cannot be detected in circulating blood
Antibody to HBsAg	Anti-HBs	Indicates infection with and immunity to HBV, passive antibody from HBIG, or immune response from HB vaccine
Antibody to HBeAg	Anti-Hbe	Presence in serum of HbsAg carrier indicates lower titre of HBV
Antibody to HbcAg	Anti-HBc	Indicates prior infection especially IgG with HBV at some undefined time
IgM class antibody	IgM anti-HBc	Indicates recent infection with HBV, and acute viral hepatiis, detectable for 4 to 6 months after infection. Such patients are highly infectious

* Adapted from 'Protection Against Viral Hepatitis – Recommendations of the Immunization Practices Advisory Committee (ACIP), from Morbidity and Mortality Weekly Report 39 (RR2): 1-26, 2/9/90

Epidemiology

Transmission and Risk Factors

HBV is detected in blood and body fluids (semen, saliva, nasopharyngeal fluids), and there are four major modes of transmission:

- Sexual contact
- Mother-to-child transmission in pregnancy and at birth (perinatal)
- Parenteral (blood-to-blood)
- Horizontal transmission through close personal contact or sharing of infected items. This mode of transmission is seen mainly in early childhood.

The most predominant mode of HBV transmission is perinatal. If a pregnant woman is an HBV carrier and is also hepatitis B e antigen (HBeAg)-positive, her newborn baby has a 90% likelihood of being infected and becoming an HBV carrier. Of these, 25% will die in adult life from chronic liver disease or liver cancer. Although HBsAg, HBeAg and HBV DNA have been detected in breast milk no differences in HBV transmission rate according to feeding practices in early childhood have been demonstrated.

Other conditions that favor HBV transmission include:

Kenyan Situation

In some parts of Kenya up to 12.5% of children under 4 years have been found to be HBsAg positive and by adolescence over 50% have some marker of HBV infection, with 7 -10% being carriers of HBsAg.(13, 14, 15). Results of different studies have varied depending on the geographic area and the diagnostic rnethod used.

Greenfield et al (13,16) established that perinatal transmission is relatively unimportant in Kenya, as a result of low levels of circulating HBV-DNA in the maternal plasma. They found 8% of 3000 mothers to be HBsAg positive and only 4 Ol,lt of 52 samples of HBsAg positive mothers were HBeAg positive and 32 were anti-HBe positive. Based on the above findings in conjunction with the: very low prevalence of anti-HBc at 12 months it would seem that in Kenyan children, perinatal transmission does not play an important role and that HBV transmission is mainly horizontal.

PATHOGENESIS AND PATHOLOGY

HBV is not cytopathic, but it is the immune elimination of infected hepatocytes which results in the clinical symptoms and the histopathological changes of HBV infection. Both the cell mediated immunity (CMI) and humoral immune response play a role.

The CMI response which is modulated by interferons, results in lysis of infected hepatocytes, with the cytotoxic T cells directed against the nucleocapsid protein displayed on the surface of the hepatocyte, playing a major role in this process. Humoral immune response is directed against the envelope proteins of HBV (which include the PreS1, PreS2 and S gene-encoded region).

CLINICAL PRESENTATION

Incubation period averages 75 days. The incubation period for infection acquired via transfusion of blood or blood products may be shorter.

Infection with HBV results in massive replication of virus in the hepatocytes. The viruses are then released into the blood. Replication of the virus in the liver, and the host immune responses to it, are responsible for the acute and chronic manifestation of the infection. Most infections go unrecognized as symptoms may be mild or non specific. Same patients develop an acute self limiting illness accompanied by jaundice and elevations of the liver enzymes.

The likelihood of developing clinical hepatitis as a result of HBV infection varies directly with age. In infancy and childhood, though fatal cases do occur, only 1 - 10% of acute infection are diagnosed clinically. While 33% of patients older than 30 years develop symptomatic disease (17). Fulminant hepatitis is also commoner in older individuals. A fulminant course may be related to enhanced immune response with rapid clearing of virus and high titers of anti-HBs and anti-HBe. This may be associated with features suggesting immune complex disease manifested as fever, urticarial rash and arthralgia.

HBV Carriers

A carrier is a person whose serum is repeatedly HBsAg positive over a six month period or longer. 10% of sufferers of HBV infection will become chronic carriers of the virus, with the possible later development of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC).

The chances of developing~HBsAg carrier state decreases with age. During infancy, it is as high as 90% in infants born to HBeAg positive mothers compared to 7.7% carrier state in persons infected after the age of 30 (17).

Males are 6 times more likely to become carriers than females. Development of the carrier state seems to depend on the humoral and CMI response of the patient. When these are defective, viral replication continues with an increased likelihood of chronic carrier state. This is especially important in neonates, patients with malignancies and other immuno-compromised states.

The carrier state therefore occurs more commonly in:

- males

- those acquiring infection in childhood
- those with immuno-deficiency states

It is this chronic carrier state with its associated Ijver damage that is of importance. It is the stage that immunization programmes are geared to eradicate.

Chronic hepatitis often occurs in carriers, with insidious progression to macronodular cirrhosis and eventual development of hepatocellular carcinoma.

The factors that eventually cause malignant transformation are unknown but viral

integration into the host genome and cessation of replication in the transformed cells has been shown in liver tumours. Other incriminating evidence are:

- HBV-DNA has been isolated in the genome of HCC cells
- HCC in all parts of the world is associated with a higher HBsAg seropositivity than in age-sex matched controls
- In Taiwan a prospective study among Chinese men revealed that the risk of HCC among HBsAg carriers was approximately 100 times higher than among non-carriers(18)
- Experimental studies with woodchucks (small forest animals found in N. America) who experience natural infections with viruses which are structurally very similar to HBV, showed them to be at increased risk for developing HCC.

Complications of HBV infection

Complications of HBV infection include:

- acute hepatitis
- chronic hepatitis
- cirrhosis
- vascular disease
- glomerulonephritis
- primary hepatocellular carcinoma.

Though case fatality for acute HBV infection is estimated at 1.5per 1000, studies have

shown that the relative risk of dying among individuals with serologic markers are higher. When considering males younger than 40 years, Feret et al in Senegal found that those who were HBsAg positive were 3.5 times more likely to die than the controls.

The morbidity of HBV though as yet unmeasured, probably has even a greater negative economic impact in developing countries due to decreased productivity J since chronic hepatitis, cirrhosis, and hepatic cellular carcinoma affect principally individuals from 15 to 59 years of age (8). Beasley et al (18) found that HBsAg carriers had a 280 times greater risk of developing primary Ijver cancer than HBsAg negative individuals. In Asia, the cumulative risk of developing HCC for HBsAg carriers over a 50 year period has been estimated to be 15% (19).

Chronic Hepatitis

Chronic active hepatitis develops in about 25% of HBsAg carriers with eventual progression to cirrhosis or chronic liver failure, or hepatoma.

A person with stabie chronic hepatitis may suffer relapse, marked by elevations in the serum transaminase. Relapse may be spontaneous, (in 10 - 15% of patients annuaHy), or due to super-added infection from delta virus, hepatitis A, Non-A Non-B(NANB) or may follow antiviral therapy.

During HBV infection, the viral genome becomes an integral part of the patients genome, such that viral genes are transcribed along with those of the host. Clones of these integrated cells farm the basis of malignant transformation.

MANAGEMENT

The management of HBV infection will depend on whether it is acute or chronic.

Acute Infection

There is no known effective treatment and case management is geared towards supportive care.

Chronic Hepatitis

Two types of chronic hepatitis are distinguished as treatment varies in these 2 categories:

- Chronic Hepatitis in individuals who are HBeAg positive
- Chronic Hepatitis in those who are anti-HBeAg positive or HBeAg negative.

Chronic Hepatitis with HBeAg Positivity

Antiviral agents are administered to accelerate clearance of HBeAntiginaemia. These agents include adenine-arabinoside-monophosphate (Ara-AMP) and interferon.

Chronic Hepatitis with anti - HBe Positive

In asymptomatic persons or those with only mild symptoms, conservative measures are offered. If symptomatic, with grossly abnormalliver tests, and an active chronic

hepatitis on liver biopsy, then a short course of prednisolone (for about 8weeks) , the withdrawal of which is followed by a course of Ara-AMP or interferon has been shown to have good results.

Co-Infection

Coinfection or superinfection with HDV

Co-infection or superinfection with delta virus has been associated with an increased morbidity and mortality from both acute and chronic HBV infection. Hepatitis Delta virus (HDV) is a defective virus that is only infectious in the presence of active HBV infection. HDV infection occurs as either coinfection with HBV or superinfection of an HBV carrier. Coinfection usually resolves. Superinfection, however, causes frequently chronic HDV infection and chronic active hepatitis. Both types of infections may cause fulminant hepatitis

Coinfection with HIV

- HBV infection is associated with increased severity of liver disease in HIVinfected patients
- In HBV/HIV-coinfected patients, necroinflammatory activity in the liver tends to be milder, but higher HBV replication results in more severe liver fibrosis with increased risk for cirrhosis and a more rapid progression to end-stage liver disease
- Patients coinfected with HIV and HBV, especially those with low CD4+ nadir counts, are at increased risk for liver-related mortality
- HIV appears to be a risk factor for reactivation of hepatitis B in patients who have developed hepatitis B surface antibodies, especially in patients with severe immunodeficiency

Super-infection with Hepatitis C

Acute HCV infection in patients with Chronic HB infection may be associated with more severe symptoms during the acute phase.Patients with HCV superinfection have higher cumulative rates of liver cirrhosis and hepatocellular carcinoma than acute HBV superinfection or CHB. Underlying HBV infection is also an important factor determining the clinical course of acute HCV infection. Fulminant hepatic failure is significantly higher among those with underlying HBV infection.

Super-infection with Hepatitis A

Acute Hepatitis A virus infection is severe and potentially fatal in patients with underlying chronic HBV.

CONTROL AND PREVENTION

Methods of control include:

- **Health education**

Health education aimed at change of behaviour patterns that favour spread of HBV. Blood is considered as an important vehicle for infection and thus its screening for HBV markers is essential. Sharing of razors and toothbrushes and the use of unsterilized needies and syringes should be avoided. It should be remembered that the primary source of infection is the acutely infected individual and the chronic carrier.

- **Immune Serum Globulin (Hepatitis B immunoglobulin HBIG)**

HBIG is human immune globulin prepared from pooled human plasma from persons with high titers of anti-HBs.

It is used primarily for prevention of perinatal transmission of HBV in mothers who are HBeAg positive. 90% of HBeAg positive carrier mothers infect their babies while only 5% of HBeAg negative mothers infect their babies. To be effective it should be given within 48 hours of delivery.

The dose of HBIG is 0.5mls, containing at least 300 IU and can be given concurrently with HBV vaccine using different injection sites. It has been shown that concurrent use of vaccine and HBIG for infants born to mothers with high levels of circulating HBeAg can prevent the chronic carrier state in 85-95% of such infants, whereas use of vaccine alone can prevent the chronic carrier state in 70-90% of such infants

Limitations of HBIG include high cast and short duration of prophylaxis. In newborns, antibodies to HBsAg decline 2-3 months after HBIG therapy, leaving the infant at risk of infection. Because of these reasons, many countries, for economic and logistic reasons would opt for HBV vaccination alone.

- **Immunization**

No effective therapy has been found for treating the chronic HBV carrier state. Change of some of the behaviour patterns associated with transmission are difficult to modify, therefore the main stay of control of this disease depends on prevention of transmission by immunization of populations at risk.

What Levels are Protective?

Several studies have shown that anti-HB titres greater than 1O IU/L are protective against the disease, though Szmuness in his study found that after immunization, the vaccine efficacy was protective regardless of the antibody levels

Goal of HBV Immunization

The goal of immunization is protection against HBV carrier state with its consequent development of liver disease and hepatocellular carcinoma. HBV has been claimed to be the first anti-cancer vaccination.

Rationale for Immunization

- The goal of vaccination is particularly to prevent the carrier state and hence avoid its sequelae. The risk of developing the carrier state is highest in infancy and early childhood and dropsrapidly with increasing age. The age at lowest risk of becoming a carrier is not known.
- In same areas of Kenya up to 25% of the population have HBsAg, with 90% showing markers of previous or past infection. Most of these infections start early, though perinatal transmission is not important.
- This set-up is ideal for justification of hepatitis vaccination during infancy.
- If used in early infancy, it can reduce chronic carrier rates by over 75%. HBV infection differs from other EPI-targeted diseases in that the majority of the related morbidity and mor1alityoccurs during the adult period following relatively asymptomatic perinatal or childhood infection.
- The importance of HBV is stressed by the fact that more than 40% of persistently infected persons who survive to aduit life will die as a consequence of their infection.
- Mortality from HBV must thus be viewed with regard to effect ot deaths ot an economically productive adult. A moriality rate ot 0.5% per year from HBV related Ijver disease in adult carrier males has been observed in hyper-endermic area. Since HBV carriage rate in hyperendemic areas is about 10-15%, death due to liver disease would therefore account for 3% of the deaths.
- Incorporating HBV vaccine into the existing EPI programme would be economically teasible since logistical support, cold-chain provisions, and the vaccination schedule would allow administration ot other antigens at little additional cost for delivery. With reductions ot oost ot HBV vaccine, the cost ot preventing death from the HBV related HCC and cirrhosis approaches that reported for the EPI diseases.
- Since **EPI** vaccination schedules differ from country to country, there should be some flexibility in dosage schedules for HBV vaccine in order to allow for integration of this vaccine with the other EPI antigens.
- In the high risk adult population HBV vaccine protects from development of acute infection which though more severe than in childhood, has lower risks of progressing to a chronic carrier state.

VACCINE DEVELOPMENT AND USE

Epidemiologic studies of natural hepatitis B infection showed that the development of anti-HBs conferred protection against subsequent infection. Consequently an effort was made to produce a vaccine using purified HBsAg as the immunogen. Two generations of HB vaccine have been developed namely:

- First generation plasma derived vaccine
- Second generation HB vaccine

First Generation Vaccines

Development of a HB vaccine was initially hampered by the inability to grow HBV in cell culture, but the pioneering work of Krugman et al established the feasibility of producing a vaccine from serum containing HBV Ag.

First generation plasma derived vaccines were developed by separating these particles from the complete virus in the blood ot chronic carriers, and were licensed for use early in the 1980's.

Usually, during HBV infection or even in the carrier state, apart from the whole virus particle (Dane particle) there are several tubular and spherical particles about 22nm diameter representing surplus viral coat protein (HBsAg). These particles are antigenic and stimulate the production of anti-HBs. Anti-HBs is believed to be the protective anti body and the aim of vaccination is to stimulate production of anti-HBs.

To render this vaccine safe, it undergoes several purification processes. major purification processes.

- heat inactivation
- formalin
- hyperosmolar urea

Each of these methods can destroy whole HBV as well as any other infective agent currently identified (including HIV).

Plasma from the donor is also screened for HIV antibodies and reverse transcriptase activity (to detect retroviruses).

Second Generation HB Vaccines

Three approaches have been used to produce second generation HB vaccines:

- **Recombinant DNA Technology**

  Molecular cloning and sequencing of the HBV genome and the identification and

  cloning of the S-gene which codes for the major viral surface polypeptide led to the production of HBsAg by genetic engineering.

  Currently yeast derived HB vaccines are in use and several studies have shown them to be safe, highly immunogenic and effective.

- **Synthetic Peptides**

  Peptides of 8 to 12 amino acids following the amino acid sequences of hydrophilic regions of the surface antigens that are thought to be the specific antigenic sites have been produced. The main disadvantage of this type of vaccine has been it's low immunogenicity. Research is currently focused on enhancing the response by attachment of the peptide to large carrier molecules.

- **HBsAg - Producing Hepatoma Cell Lines**

  HBsAg particles produced by hepatoma ceillines are identical to those detected in

  plasma of HBsAg carriers. The main concern about the use of vaccine derived in this way has been the safety of using a vaccine that might contain oncogenes, especially since other "safer" HBV vaccines are available.

Vaccine Dosage

The vaccine dosage depends on the type of vaccine being used. Manufacturers process and formulate their vaccines differently, preventing meaningful comparison of dosages of vaccine from different sources.

According to data submitted to WHO/EPI/Geneva by manufacturers in 1990, an efficacious paediatric dose may include anywhere from 1.5 to 10.0 ug ot active material, depending on the manufacturing process.

Vaccine Storage and Handling

Most HBV vaccines are moderately stable at room temperature but appear to be stabie for many years at 2 to 8 degrees C. The upper limit of storage life has not yet been defined and can be expected to vary among different manufacturers. Inactivation of the vaccine occurs at highc ambient temperature and by freezing. The Kenya Expanded Programme on Immunization's recommendation is 0 to $+8^0$

As with other adjuvanated vaccines such as DPT, freezing results in vaccine - adjuvant dissociation. Freezing does not result in any visible changes in the vaccine, thus emphasizing the precaution to avoid freezing and to include freeze indicators during shipment and storage. HB vaccine should be handled the same way as DPT vaccine.

The prospect of using a quadruple vaccine (DPT -HB) holds great promise for facilitating the introduction ot HB vaccination. It would obviate the need for a great deal. more cold chain and storage space as well as for more needles and syringes.

Compatibility with other Vaccines

Studies moniforing post-vaccination anti body titers have shown that HB vaccine can be given with BCG, diphtheria, tetanus, pertussis, polio,. measles and yellow fever vaccination, with no reduction in immune response to any of the vaccines (28,29).

A quadruple vaccine of DPT - HB is being planned. All 4 immunizing agents are proteins which are adjuvanated and handled in a similar fashion.

Indications for Vaccination

The hepatitis B vaccine is recommended specifically for all infants and children**.** It is also recommended that adults in high-risk groups be vaccinated.

The following list is a general guide for vaccination, but since every person is at some risk for infection, these guidelines should be individualized for each situation.

- All infants at birth and all children up to 18 years.
- Health care professionals and emergency personnel.
- Sexually active teens and adults
- Men who have sex with men.
- Sex partners or close family/household members living with an infected person.
- Patients with kidney disease or undergoing dialysis.
- Residents and staff of correctional facilities and group homes.
- Any person who may fall into a high risk group due to occupation or lifestyle choices.

Age at Vaccination

The epidemiology of the carrier state is the primary determinant of the age at first doge. In Kenya, as in other parts of sub-Saharan Africa, transmission is primarily horizontal rather than vertical or perinatal. While early vaccination is strongly recommended to minimize the time period during which there is risk of acquiring infection, it is not essential that the first do se be given immediately after birth. Therefore, vaccination can be given at birth, or soon after birth.

For practical purposes it could be given as three doses, 4 weeks apart concurrently with DPT starting at the age 6 weeks. Reasons for giving it at this time are:

- hospital deliveries account for less than a half of all deliveries in developing countries, therefore not all babies will be seen at birth. In Kenya, only about 30% of all deliveries are conducted in hospitals, therefore this would not be an opportune time.
- giving HB vaccine at birth may meet with same obstacles, as mothers may not like their babies receiving 2 injections (BCG is normally given at birth in Kenya)
- it would be logistically simplier and more cost effective to incorporate HB vaccine into the existing KEPI immunization schedule if it was given together with the DPT. This would also improve compliance as it avoids increasing the number of hospital visits
- with the development of the quadruple vaccine (DPT,HB) this would mean administering one injection instead of two.

Recommended Route and site

The recommended route of administration for **HB** vaccine is intramuscular.

Though the intradermal route would be cheaper in terms of using a lower dosage, it is technically more difficult to administer an intradermal injection in infants. ff such an injection is inadvertently given subcutaneously or intramuscularly, then it would be ineffective and leave the child unprotected.

For **neonates** the recommended site is the anterior aspect of the thigh. In **adults** it is the deltoid region (gluteal region produces an inferior immune response - probably because of thickness of fatty layer, the injection may not be truly intramuscular).

Duration of Protection

Following the third and last dose in the HBV immunization series, anti-HBs titres decline after about 5-6 years(7). There is individual variation in the rate of decline. In infants and children there have not been long enough follow-up studies to determine when to give booster doses.

Studies have shown that even when anti body levels become undetectable, individuals seem to remain protected against clinically significant disease (HBsAg carriage or liver inflammation) , provided that the initial anti body response was effective. Boostering to maintain anti-HBs levels above 1 OU/mi were found to be unnecessary in endemic areas. Beasley, found that in Taiwanese children the initial fair in anti body titers does not continue probably because of "natural boosters"(30). Booster doses may therefore be unnecessary to maintain effective immunity and to prevent new carriers.

The vaccine has not been used long enough to establish documented evidence in prevention of chronic hepatitis, cirrhosis or HCC. However the ability of the vaccine to reduce or prevent HBV carrier state - the forerunner of HBV induced chronic hepatitis, more than justifies promotion of immunization programme's.

Immunogenicity

HBsAg antigenicity is enhanced by absorption to an alum adjuvant.

Factors influencing immunogenicity

Immunization in early childhood is more effective than in adults and immunogenicity in neonates is excellent irrespective of HBV marker status of the mother. Maternal antibodies or even HBIG administration does not inhibit anti body production after vaccination. freezing inactivates the vaccine because it causes vaccine-adjuvant dissociation.

Non Responders

Although the majority of persons vaccinated against hepatitis B successfully respond to vaccination, an estimated 5-15% of persons may not respond. It is possible that a person who does not respond to the vaccine may already be infected with hepatitis B. Therefore, testing for the presence of the virus (HBsAg) is recommended before diagnosing a person as a "vaccine non-responder".

- Non-responders who are HBsAg-negative should be considered susceptible to HBV infection and should be counselled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known exposure to HBsAg-positive blood.
- Non-responders who prove to be HBsA*g-positive* should be counselled regarding how to prevent HBV transmission to others and regarding the need for medical evaluation.

Repeated immunizations result in seroconversion in some of the initial non-responders. This effect is enhanced if larger doses are used.

Efficacy of Vaccine

The complete vaccine series induces protective antibody levels in more than 95% of infants, children and young adults. After 40 years, protection level drops below 90%; by 60 years protective antibody levels are achieved in only 65-75% of vaccines. The duration of protection based on current evidence is life long

Side Effects

Side effects are few and are local and transient. They include pain and swelling at the injection site. Fever and flu-like symptoms have been reported in a few cases. These side effects are mainly due to the adjuvant (alum) used in the vaccine.

Acceptance and tolerance have been shown by widespread use of plasma derived vaccine in European health workers and Asian EPI Programmes. Among 8 million doses of Pasteurs vaccine no cases of AIDS, HBV, NANB or autoimmune disease has been associated with the vaccine. Anxieties have been expressed about safety of plasma derived vaccine and AIDS. However follow up of male homosexuals and medical staff vaccinated in US found no evidence to implicate the vaccine in the transmission of AIDS. This is not surprising because the processing of the plasma-derived vaccine does not permit survival of infectious agents.

Contraindications

There are no contraindicators to giving **HB** vaccine. It can be administered to patients incubating HBV, subjects positive for HBsAg, anti-HBc or anti-HBs and immunocompromised individuals.

Cost Effectiveness of Vaccine

When reviewing cost effectiveness of HB vaccine it should not be looked at only as preventing the acute infection but rather at the sequelae of the acute infection i.e cirrhosis and hepatocellular carcinoma which seem to affect males more, and afflicts at the prime of an individuals life. The economic impact of curtailing such productive resource persons is enormous especially in developing countries, leave alone the economic resources required for provision of health care to such patients.

Where prevalence of HBV carrier is low, targeted immunization of high risk individuals is appropriate. This, however depends upon the cost of the vaccine and of screening tools.

In areas of high endemicity or areas where acquisition of infection is in early childhood, the universal vaccination of all children in the first 6 months of life is reccomended.

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