Hepatitis B vaccines

WHO position paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; limited vaccination, as executed mostly in the private sector, may be a valuable supplement to national programmes but is not emphasized in these policy documents. The position papers summarize essential background information on the respective diseases and vaccines and conclude with the current WHO position concerning vaccine use in the global context. The papers have been reviewed by a number of experts within and outside WHO and are designed for use mainly by national public health officials and immunization programme managers. However, the position papers may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community and the scientific media.

WHO position on the use of hepatitis B vaccines

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

Routine vaccination of all infants against HBV infection should become an integral part of national immunization schedules worldwide. High coverage with the primary vaccine series among infants has the greatest overall impact on the prevalence of chronic HBV infection in children and should be the highest HBV-related priority.

A variety of schedules may be used for hepatitis B immunization in national programmes, depending on the local epidemiological situation and programmatic considerations. However, in countries where a high proportion of HBV infections are acquired perinatally, the first dose of hepatitis B vaccine should be given as soon as possible (<24 hours) after birth.

In countries where a lower proportion of HBV infections are acquired perinatally, the relative contribution of perinatal HBV infection to the overall disease burden, and the feasibility and cost-effectiveness of providing vaccination at birth, should be carefully considered before a decision is made on the optimal vaccination schedule.

Catch-up strategies targeted at older age groups or groups with risk factors for acquiring HBV infection should be considered as a supplement to routine infant vaccination in countries of intermediate or low hepatitis B endemicity. In such settings, a substantial proportion of the disease burden may be attributable to infections acquired by older children, adolescents and adults. In countries of high

endemicity, large-scale routine vaccination of infants rapidly reduces the transmission of HBV. In these circumstances, catch-up vaccination of older children and adults has relatively little impact on chronic disease because most of them have already been infected.

Background

The pathogen and the disease

The hepatitis B virus (HBV) is a double-stranded, enveloped virus of the Hepadnaviridae family. With a genome of only 3200 base pairs, HBV is one of the smallest DNA viruses known. HBV replicates in the hepatocytes of humans and other higher primates but does not grow in artificial cell cultures. The hepatitis B surface antigen (HBsAg) is a lipoprotein of the viral envelope that is produced in conspicuous excess and circulates in the blood as spherical and tubular particles 22 nm in size. HBsAg includes a neutralizing epitope, the so-called *a* determinant. Two other HBsAg determinants, *d/y* and *w/r*, have been described, defining four subtypes of HBV: *adw*, *adr*, *ayw* and *ayr*. Certain amino acid substitutions within this epitope, particularly in the region of amino acids 137–147, may render the *a* determinant unrecognizable by common screening tests as well as by vaccine-induced antibodies. Although, in theory, selection pressure by vaccination or antiviral therapy may favour replication of such mutants, their possible clinical importance remains unclear and they have not proved to be of public health significance.

The outcomes of HBV infection are age-dependent and include acute (clinically apparent) hepatitis B, chronic HBV infection, cirrhosis and HCC. Acute hepatitis B occurs in approximately 1% of perinatal, 10% of early childhood (1–5 years old) and 30% of late (>5 years old) HBV infections. 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 age and occurs in approximately 90% of persons infected perinatally, in 30% infected in early childhood and in 6% infected after 5 years of age. The likelihood of progression to chronic infection does not differ among persons with symptomatic or asymptomatic infection. Persons 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. For this reason, laboratory confirmation of the diagnosis is essential. In serological terms, acute HBV infection is characterized by the presence of HBsAg and of IgM antibody to the core antigen, HBc (IgM anti-HBc). During the initial, highly replicative phase of infection, patients are also seropositive for the hepatitis B e-antigen (HBeAg). Antibody to HBsAg (anti-HBs) occurs after a few weeks and is followed by clearance of the HBsAg. Chronic infection is characterized by persistence (>6 months) of HBsAg (with or without concurrent HBeAg). Persistence of HBsAg is the principal marker of risk for development of chronic liver disease and hepatocellular carcinoma later in life. Presence of HBeAg indicates that the concerned individual is highly contagious.

Each year, about 10% of chronic cases become HBeAg-negative and develop anti-HBe, signalling a change to the low-replication stage. Loss of HBsAg in untreated chronic cases occurs at an estimated rate of 1% per year.

Long-term combined treatment with interferon alfa 2-b and modern nucleoside analogues may result in elimination of viral replication in 40–50% of cases with chronic HBV infection. This treatment is very expensive and often complicated by severe side-effects, induction of HBV mutants and high relapse rates.

IgG antibody to the HBsAg (anti-HBs) is used as a marker of immunity, and immune globulin containing high titres of anti-HBs (HBIG) is used for passive immunization, often in combination with hepatitis B vaccine. However, studies of previously vaccinated persons have shown that, despite low or undetectable antibody levels years after vaccination, vaccinees were still protected against asymptomatic as well as symptomatic HBV manifestations following exposure. These persons also mounted a typical anamnestic response to revaccination, indicating that long-term protection depends upon memory T-cells. Both the severity of clinical disease and the viral clearance correlate with the cellular immune response to various viral proteins. Immune tolerance to viral antigens acquired at birth is believed to play an important role in neonatal HBV persistence, whereas the immune mechanisms underlying the less common chronic HBV infection in older children and adults are poorly defined.

Public health aspects

HBV infection has a worldwide distribution. It is estimated that, currently, more than 2 billion of the global population have been infected. Of these, approximately 360 million are chronically infected and at risk of serious illness and death from cirrhosis and HCC, diseases that are estimated to cause 500 000–700 000 deaths each year worldwide.

Humans are the only reservoir of HBV. The virus is highly contagious and is transmitted by percutaneous and permucosal exposure to infected blood and other body fluids (i.e. semen and vaginal fluid). Common modes of transmission include mother-to-infant, child-to-child, unsafe injection practices, blood transfusions and sexual contact. The incubation period is 75 days on average, but may vary from about 30 to 180 days. HBV may be detected in serum 30–60 days following infection and persist for widely variable periods of time.

In areas with high prevalence of hepatitis B ($\geq$8% of the population HBsAg-positive), up to 20% of the population may be chronically infected. Based on serological criteria, high prevalence of chronic HBV infection is found in areas of sub-Saharan Africa, South-East Asia, the Eastern Mediterranean countries, south and western Pacific islands, the interior of the Amazon basin and in certain parts of the Caribbean. Chronic hepatitis is moderately prevalent ($\geq$2 – <8 % of the population HBsAg-positive) in south-central and south-west Asia, eastern and southern Europe, the Russian Federation and most of central and South America. In Australia, New Zealand, northern and western Europe, and North America, the prevalence of chronic HBV infection is low (<2% of the population HBsAg-

positive). In highly endemic areas, HBV is most commonly spread from mother to child at birth, or from person to person in early childhood. In countries with low HBV endemicity, sexual transmission and the use of contaminated needles, especially among injecting drug users, are the major routes of infection. However, perinatal transmission may account for 15% of HBV-related deaths, even in low-endemic areas.

Vaccines and vaccination against hepatitis B

Two types of hepatitis B vaccines are available: plasma-derived vaccines and recombinant vaccines. The two vaccines show no differences in terms of reactogenicity, efficacy or duration of protection. Their thermostability is also similar: both should be shipped and stored at 2–8 °C; freezing must be avoided as it dissociates antigen from the alum adjuvant. Both vaccines tolerate temperatures of up to 45 °C for one week and of up to 37 °C for one month without change in immunogenicity or reactogenicity. The two types of hepatitis B vaccine can be used interchangeably; in this article they are jointly referred to as the hepatitis B vaccine.

Plasma-derived vaccines are prepared from purified HBsAg obtained from the plasma of persons with chronic HBV infection. These vaccines have been commercially available since 1982. Following extensive purification, potential residual infectious particles are eliminated by a number of inactivation steps. Aluminium phosphate or aluminium hydroxide is added to the vaccine as adjuvant and for multi-dose vials; thiomersal is used as a preservative.

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. The transformed cells are grown in large vessels, and the expressed HBsAg self-assembles into immunogenic, spherical particles that expose the highly immunogenic *a* antigen. The recombinant particle differs from the natural ones only in the glycosylation of the HBsAg. Following thorough purification from host-cell components, alum (and, in certain formulations, thiomersal) is added.

Given differences in the manufacturing process, the quantity of HBsAg protein per dose of vaccine that will induce a protective immune response differs between the various vaccine products (from 2.5 to 40 µg per adult dose). For this reason, there is no international standard of vaccine potency expressed in µg HBsAg protein per ml.

Hepatitis B vaccine is available as monovalent formulations or in fixed combination with other vaccines, including DTwP, DTaP, Hib, hepatitis A and IPV. 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.

Immunogenicity and clinical efficacy.
The protective efficacy of hepatitis B vaccination is directly related to the

induction of anti-HBs antibodies. An antibody titre of $\geq$10 mIU per ml measured 1–3 months after the administration of the last dose of the primary vaccination series is considered a reliable marker of immediate and long-term protection against infection. The clinical efficacy of hepatitis B vaccines in preventing hepatocellular carcinoma in older children who were vaccinated in infancy has been demonstrated.

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. The duration of protection is at least 15 years and, based on current scientific evidence, lifelong. Some infants born prematurely with low birth weight (<2000 g) may not respond well to vaccination at birth. However, by one month of chronological age, all premature infants, regardless of initial birth weight or gestational age, are likely to respond adequately. Immunosuppressive illnesses such as advanced HIV infection, chronic liver disease, chronic renal failure, and diabetes are associated with reduced immunogenicity of the vaccine.

Vaccination schedules.

There are multiple options for incorporating the hepatitis B vaccine into national immunization programmes. The choice of schedule depends on the local epidemiological situation and programmatic considerations. The minimum recommended interval between the doses is four weeks. Longer dose intervals may increase the final anti-HBs titres but not the seroconversion rates. More than 3 doses of the vaccine are not required, regardless of duration ($\geq$ 4 weeks) of the interval between them.

Recommended schedules for vaccination can be divided into those that include a birth-dose and those that do not. Schedules with a birth-dose call for the first vaccination at birth, followed by a second and third dose at the time of the first and third diphtheria–tetanus–pertussis (DTP) vaccination, respectively (column II, *Table 1*). Alternatively, a four-dose schedule may be used where the dose at birth is followed by three additional doses; these doses may be given either as monovalent vaccine or as a combination (e.g. with DTP and/or Hib) following the schedules commonly used for those vaccines (column III, *Table 1*). These schedules will prevent most perinatally acquired infection.

Some countries have chosen not to implement universal immunization and instead use comprehensive HBsAg screening of pregnant women with immunization of newborn infants born to HBsAg-positive women. This strategy is usually not feasible in developing countries with high prevalence of disease and may not be the most reliable and convenient option even in countries where HBsAg screening in pregnancy is well established. When administered without the birth-dose, hepatitis B vaccine is usually given at the same time as DTP, either as a monovalent presentation or in combination with DTP and/or Hib vaccine (column I, *Table 1*).

Table 1 summarizes schedule options for routine infant vaccination against hepatitis B.

Countries that opt for schedules with a birth-dose should vaccinate preterm infants at birth and subsequently enter the respective national hepatitis B vaccination schedule. However, if the birth weight is <2000 g, the vaccine dose at birth should not be counted towards the primary series, and three additional doses should be given.

Immunocompromised children and adults can also benefit from vaccination. However, the immune response may be reduced and additional injections of the vaccine may be required. Where possible, the anti-HBs antibody titres should be followed up after immunization of immunocompromised individuals.

Vaccine dose and administration.

The recommended dose varies by product and with the age of the recipient. In most cases, infants and adolescents receive 50% of the adult dose. The vaccine is administered by intramuscular injection in the anterolateral aspect of the thigh (infants and children aged <2 years) or in the deltoid muscle (older children and adults). Administration in the buttock is not recommended because this route of administration has been associated with decreased protective antibody levels as well as injury to the sciatic nerve. Intradermal administration is not recommended because the immune response is less reliable, particularly in children. The hepatitis B vaccine does not interfere with the immune response to any other vaccine, and vice versa. Specifically, the birth-dose of hepatitis B can be given safely together with bacillus Calmette–Guérin (BCG) vaccine; BCG does not interfere negatively with the response to hepatitis B vaccine. However, unless formulated as fixed combinations, hepatitis B vaccine and other vaccines administered during the same visit should be given at different injection sites.

Post-vaccination testing. Testing to determine antibody responses is not necessary after routine vaccination. However, when feasible, knowledge of response to vaccination is important in the following groups: (i) persons at risk of occupationally acquired infection; (ii) infants born to HBsAg-positive mothers; (iii) immunocompromised persons; and (iv) sexual partners of HBsAg-positive persons. Testing for anti-HBs should be performed by a method that allows determination of whether the anti-HBs concentration is protective ($\geq$10 mIU per ml). Adults should be tested 1–2 months after completion of the vaccination series. In settings where resources are available, infants born to HBsAg-positive mothers should be tested at 8–15 months of age, after completion of the vaccination series. Persons found to be antibody-negative after the primary series should be referred for appropriate follow-up.

Adverse events.

In placebo-controlled studies, with the exception of local pain, reported events such as myalgia and transient fever have not been more frequent than in the placebo group (<10% in children, 30% in adults). Reports of severe

anaphylactic reactions are very rare. Available data do not indicate a causal association between hepatitis B vaccine and Guillain–Barré syndrome, or - demyelinating disorders including multiple sclerosis, nor is there any epidemiological data to support a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritis, autoimmune disorders, asthma, sudden infant death syndrome, or diabetes.

Indications and contraindications.
All children and adolescents aged less than 18 years and not previously vaccinated should receive the vaccine. Hepatitis B vaccination is also indicated for certain groups 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 transplantation, those at occupational risk of HBV infection, including health care workers, as well as for international travellers to HBV-endemic countries.
Hepatitis B vaccine is contraindicated for individuals with a history of allergic reactions to any of the vaccine's components. Neither pregnancy nor lactation is a contraindication for use of this vaccine.

Passive immunization against hepatitis B

Temporary immunity may be obtained using hepatitis B immune globulin (HBIG) for post-exposure prophylaxis. HBIG prophylaxis may be indicated (i) for newborn infants whose mothers are HBsAg-positive, (ii) following percutaneous or mucous membrane exposure to HBsAg-positive blood or body fluids, (iii) following sexual exposure to an HBsAg-positive person, and (iv) to protect patients from recurrent HBV infection following liver transplantation. As a rule, HBIG should be used as an adjunct to hepatitis B vaccine. However, in full-term newborns, the protection against perinatally acquired infection achieved by immediate (<24 hours) hepatitis B vaccination is not significantly improved by the addition of HBIG.

General WHO position on vaccines

Vaccines for large-scale public health interventions should:

- meet the current WHO quality requirements;[1]

- be safe and have a significant impact against the actual disease in all target populations;

- if intended for infants or young children, be easily adapted to the schedules and timing of national childhood immunization programmes;

- not interfere significantly with the immune response to other vaccines given simultaneously;

- be formulated to meet common technical limitations, e.g. in terms of refrigeration and storage capacity;

- be appropriately priced for different markets.

WHO position on hepatitis B vaccine

Universal infant immunization is by far the most effective preventive measure against HBV-induced disease, and successful hepatitis B vaccination programmes will gradually result in a reduction of HBV-related chronic hepatitis, liver cirrhosis and HCC in endemic areas. Following the primary vaccination schedule, almost all children are protected, probably for life, without the need for booster injections. So far, more than 160 countries have followed the WHO recommendation to incorporate hepatitis B vaccine as an integral part of their national infant immunization programmes. In recent years, the significantly reduced price of hepatitis B vaccine in developing countries has facilitated its introduction into many HBV-endemic areas. The cost-effectiveness of large-scale vaccination against hepatitis B has been convincingly proved except in countries of very low endemicity, where economic evaluations have yielded contradictory - results, depending on the type of model used.

Hepatitis B vaccine schedules are very flexible, and there are several options for adding the vaccine to existing national immunization programmes without requiring additional visits for immunization. The choice of schedule depends on the local epidemiological situation and programmatic considerations. National strategies for the prevention of perinatal transmission of HBV should take into account the relative contribution of such transmission to the overall hepatitis B disease burden and the feasibility of delivering the first dose of hepatitis B vaccine at birth.

In countries of high disease endemicity (HBsAg prevalence $\geq$8%), HBV is mainly spread from mother to infant at birth or from child to child during early childhood (<5 years). In this epidemiological setting, schedules providing the first vaccine dose at birth are recommended. This approach prevents HBV transmission from HBsAg-positive mothers to their offspring in >90% of cases. The vaccine should be given as soon as possible (<24 hours) after birth.

Routine infant hepatitis B vaccination should also be given high priority in countries of intermediate or low HBV endemicity (HBsAg prevalence of $\geq$2–<8% or <2%, respectively) because, even in these settings, an important proportion of chronic infections are acquired through HBV transmission during early childhood. Although HBsAg screening of all pregnant women and vaccination at birth only of infants born to HBsAg-positive mothers may be an option in areas with low HBV transmission, this strategy may be only partially effective, since women at highest risk of infection often fail to attend prenatal clinics.

In most cases, one of the following two options is considered appropriate to prevent perinatal HBV infections: a three-dose schedule of hepatitis B vaccine, the first dose (monovalent) being given at birth and the second and third (monovalent or combined vaccine) given at the same time as the first and third doses of DTP vaccine; or a four-dose schedule in which a monovalent birth-dose is followed by three monovalent or combined vaccine doses, usually given with

other EPI[2] vaccines. This approach may be more costly but programmatically simpler than the three-dose schedule and does not result in under-immunization of those who do not have access to the birth-dose.

Generally, it is easier to deliver hepatitis B vaccine at birth to infants who are born in health facilities. However, availability of monovalent hepatitis B vaccine in pre-filled single-dose injection devices facilitates the administration of the vaccine by health care workers and birth attendants to infants born at home.

Despite increasing coverage in infants and children, hepatitis B vaccine has been consistently underused by high-risk adult groups, including health professionals. In most settings, low rates of completion of the vaccine series and lack of funding for adult immunizations have contributed to this situation. There is evidence to suggest that routine vaccination of high-risk adults in settings such as prisons, sexually transmitted disease clinics, drug treatment centres and needle exchange programmes could be cost-saving.

The need for catch-up vaccination of older age groups, including adolescents and adults, is determined by the baseline epidemiology of HBV infection in the country and, in particular, the relative importance of reducing HBV-related acute disease. In countries of high endemicity, large-scale routine vaccination of infants rapidly reduces infection and transmission of HBV. In this situation, catch-up vaccination of older children and adults has relatively little impact because most of them will have already been infected. In countries of intermediate or low hepatitis B endemicity, a relatively large part of the disease burden results from HBV-related acute disease and is attributable to infection acquired by older children, adolescents and adults. In these epidemiological settings, catch-up strategies targeted at adolescents could be considered as a supplement to routine infant vaccination. Possible additional target groups for catch-up vaccination include persons with risk factors for acquiring HBV infection, such as health care workers who may be exposed to blood or blood products, dialysis patients, persons interned in prisons, injecting drug users, household and sexual contacts of persons with chronic HBV infection, and persons with multiple sexual partners. Catch-up vaccination should be considered only if the continuity of the infant vaccination programme can be ensured.