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EXPANDED
PROGRAMME
ON IMMUNIZATION



Hepatitis B
Immunization Strategies

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WORLD
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1. INTRODUCTION

Hepatitis B is unlike any other infection for which a successful immunization programme has been developed. Until now immunization programmes have been directed against microorganisms because of acute manifestations of the infections they cause. No prior immunization programme has been directed against a virus which leads to a chronic infection of which the major illness is cancer occurring many years after original infection. And no other immunization programme uses a vaccine derived from human plasma.

The presently available Hepatitis B virus (HBV) vaccines are safe, immunogenic and effective. By virtually every parameter they are among the best immunogenic agents ever developed against any disease. The HBV vaccine will almost certainly be the first effective major cancer vaccine. But until recently the high price has been a major deterrent to its widespread use. In the past few months, however, vaccine has become available at less than one US \$ per dose bringing it into the range for use in a global control programme.

There have been well publicized efforts to improve the first generation vaccines which are derived from the plasma of human HBV carriers. But the second generation rDNA vaccines do not offer improvements in safety, immunogenicity, or efficacy, and are, at least so far, more expensive. The currently available vaccines have been found to produce no important side effects.

Although at its present price it is still considerably higher than any vaccine in WHO's Expanded Programme on Immunization (EPI), it can almost certainly be assumed that with widespread use the eventual cost will fall considerably. It is therefore reasonable to consider planning the strategies for HBV immunization now.

2. THE DISEASE

HBV infections which become chronic usually occur very early in life, and perinatal infections from the carrier mother are the driving force maintaining high carrier rates in many parts of the world. Because these infections occur so early in life, prophylaxis must be initiated shortly after birth to be effective, earlier than the first dose of DPT, the logical EPI vaccine with which to link it. A large proportion of HBV infections that lead to the carrier state are transmitted from sources other than the mother and occur somewhat later. Protection against these sources can be achieved effectively by immunization timed to coincide with the current EPI schedule for DPT.

Infection with HBV results in massive replication of the virus in the hepatocytes of the liver which is then released into the blood. The replication of the virus in the liver and the host immune responses to it are responsible for the acute and chronic manifestations of the infection. The factors which eventually cause malignant transformation are unknown but are accompanied by viral integration into the host genome and cessation of replication in the transformed cells. Some

individuals have an acute self-limited illness accompanied by jaundice, the hallmark of hepatitis, and elevations in several liver enzymes, reflecting inflammation accompanying the infection. Most infections are not accompanied by an acute illness or go unrecognized because they are mild and non-specific.

The major goal of an immunization programme against HBV should be the prevention of chronic disease associated with the carrier state (there are probably more than 2 hundred million carriers in the world presently), rather than the prevention of acute hepatitis or HBV infections per se.

Of greatest importance is chronic damage to the liver that slowly develops in persons who become carriers. Chronic hepatitis often occurs in carriers with insidious progression to macronodular cirrhosis, from which a large proportion eventually go on to develop hepatocellular carcinoma (HCC). Age of infection is the most important factor determining which infected persons become carriers: the lower the age, the higher the risk.

Hepatocellular carcinoma is one of the ten most common cancers in the world especially in the developing world where the HBsAg carrier state is common. It has been estimated that at least 250 000 deaths from HCC occur each year, and at least 80% of these are attributable to HBV. In some parts of Asia and Africa the age-adjusted incidence of HCC is more than 30/100 000 annually. HCC in all parts of the world is associated with a higher HBsAg seropositivity than in age-sex matched controls, and the

association between HCC and HBV is especially strong in those places in the world where HBsAg carrier rates are high. Macro-nodular cirrhosis also follows chronic HBV infection and approximately 85% of HCC cases have concurrent cirrhosis when they are recognized. In a prospective study of Chinese men in Taiwan the relative risk of HCC among HBsAg carriers was approximately 100 times higher than among non-carriers. It has been estimated that the life time risk of death from cirrhosis and/or HCC among these men is about 40%.

Additional evidence that HBV is the principle causal agent of HCC comes from natural animal models. At least three species of animals (woodchucks ground squirrels and Peking ducks) experience natural infections with viruses which are structurally very similar to HBV. These viruses are all transmitted from mothers to their offspring and are associated with hepatocellular carcinomas. Extensive experimental studies with woodchucks have shown that virtually all animals with chronic infections develop HCC. High rates of liver cancer are also seen in ground squirrels with chronic infections. Although the mechanism of oncogenesis of HBV and the animal hepadna viruses has not been established, integrated sequences of the viral genome can be regularly detected in the liver tumors.

* * *

3. HBV and HBV MARKERS

3.1 THE VIRUS

HBV is a 42 nm particle, originally known as the "Dane particle", containing double-stranded DNA and belongs to a unique virus group unofficially designated "HEPADNA". Man is its only natural host, although chimpanzees and other higher primates can be infected. It has never been cultured in vitro so detection is usually accomplished by immunologic markers.

Infection with HBV is demonstrable by five immunologic markers:

- hepatitis B surface antigen (HBsAg)
- antibody against the surface antigen (anti-HBs)
- antibody against the core antigen (anti-HBc)
- e antigen (HBeAg)
- the antibody against the e antigen (anti-HBe).

3.2 HEPATITIS B SURFACE ANTIGEN (HBsAg)

The surface antigen is found in blood as 18-22 nm spherical particles and as tubular forms. It was the first HBV marker identified, and was named Australia antigen by Blumberg who discovered it in 1967 using agar gel diffusion. Today it is usually diagnosed by passive haemagglutination (PHA),

radioimmunoassay (RIA) or ELISA tests.

HBsAg is clearly the most important marker. It is the protein that makes up the virus coat and is detectable whenever there is viraemia, such as in the early phase following infection (irrespective of whether there is acute clinical hepatitis) and in the chronic carrier state. The definition of a carrier is a person whose serum is repeatedly HBsAg positive, often arbitrarily defined as over a six month period or longer.

Following infection most adults have a period of viraemia which lasts for a few days to weeks, which may or may not be accompanied by illness. A prolonged carrier state develops in less than 10% of infected adults. Once established the carrier state may last many years, even a lifetime.

3.3 ANTIBODY AGAINST SURFACE ANTIGEN (ANTI-HBs)

If the carrier state disappears it is usually followed after some weeks to months by the appearance of anti-HBs which is often detectable for the remainder of the person's life. In adulthood, however, a few persons lose their anti-HBs and are left with anti-HBc as their only residual marker of past infection. Chronic liver disease due to HBV appears only to occur in persons who become chronic HBsAg carriers.

HBV vaccine is purified HBsAg and the immune response it evokes is the production of anti-HBs. A successful immunization is marked by the presence of anti-HBs. As with

all the conventional vaccines, it is unlikely that any susceptibility test will be recommended before immunization.

3.4 ANTIBODY AGAINST CORE ANTIGEN (ANTI-HBc)

HBcAg is present in the serum of people in whom there is active viral replication, but there are no commercial tests available for this marker. Early in the acute phase of infection anti-HBc is produced, and continues to be present for many years (perhaps a lifetime) whether or not there is persistence of HBsAg. Anti-HBc is not a protective antibody and appears to play no role in the immune regulation nor in the immune pathogenesis. It is useful as a stand-in marker for HBcAg. Anti-HBc testing may be of value in programmes for older children and adults because it is the best single test to find HBV-susceptible persons, in the absence of immunization. Such screening is not needed if all individuals in a group are to be immunized, and has no place in immunization programmes for newborns because most infants possess passive maternal antibodies. Immunization with HBV vaccine does not produce an anti-HBc response, thus the presence of anti-HBc in an immunized individual suggests that at some time that person had experienced an active HBV infection, a distinction that is not important in population based immunization programmes.

* * *

3.5 e ANTIGEN (HBeAg)

HBeAg only occurs in the presence of HBsAg and is a marker of infectivity. In immunization programmes the test for HBeAg is only useful if there is a differential immunization policy in relation to the mother's HBeAg status, e.g. administration of HBIG and/or vaccine to infants whose mothers are HBeAg positive. If vaccine is to be given to all newborns or all newborns of HBsAg positive mothers then the HBeAg test need not be performed.

3.6 ANTIBODY AGAINST e ANTIGEN (ANTI-HBe)

When e antigen disappears it is usually replaced by anti-HBe. HBsAg carriers who are anti-HBe positive are much less infectious than those who have HBeAg. However, it is very unlikely that anti-HBe testing would have a place in any immunization programme.

4. EPIDEMIOLOGY

4.1 GENERAL

Hepatitis B is a global problem existing in even the most remote and isolated populations in the world. Humans are the only reservoir. The origins of the virus are unknown and there are no naturally infected wild animals, although chimpanzees and several other higher non-human primates can be infected experimentally. Although HBV is found in all populations, the frequency of infections and of the carrier state has striking geographic and ethnic variability (see table 1).

Table 1. Geographic distribution of levels of HBsAg prevalence

HBsAg prevalence	<2%	2-10%	>10%
	Low	Intermediate	High
Geographic examples	W. Europe N. America Australia New Zealand S. America (partly)	E. Europe S. Europe Middle East Japan S. America (partly)	China SE Asia Pacific Islands Africa S. America (partly)

4.2 TRANSMISSION

4.2.1 General

There are three important mechanisms of transmission of HBV:

- * mother to infant in the perinatal period
- * parenteral
- * person to person.

The relative importance of each varies substantially from population to population around the world.

Because of the viraemia of chronic HBV infections, there has been considerable interest in the possibility that vectors might play

a role in HBV transmission. Biological propagation of HBV has not been demonstrated in an arthropod, so vector transmission, if it occurs, would have to be mechanical. Epidemiological studies in various parts of the world do not suggest that vectors play an important role, if any, in HBV transmission.

4.2.2 Perinatal

Mother to infant transmission, also sometimes referred to as vertical transmission, most often occurs during the time of labour and delivery. This may occur through small leaks across the placenta, and can be precipitated by trauma associated with the birth process. It may also occur through exposure of the infant to maternal secretions in the birth canal.

Transmission in utero before the birth process is initiated appears to be unusual: only about 5% of high

risk infants have established infections when they are born. The mother continues to be infectious after delivery but post-natal infections are not common because most high risk infants have already been infected at birth.

The term vertical transmission, although widely used, should be discouraged in order to avoid confusion with its prior established usage meaning transmission through germ cell lines, which is not the case with HBV.

Perinatal infections most commonly occur from asymptomatic carrier women who have no knowledge of their carrier status, unless they have had a blood test for HBsAg. It also occurs in the rare circumstance when the mother has acute hepatitis B during the later part of pregnancy or shortly after the birth of the child.

Regardless of the method by which the infant is infected, the result is usually an asymptomatic chronic HBV infection manifest by the carrier state which lasts for many years and often for a lifetime. The probability that an infected mother will infect her child during the perinatal period is directly related to the number of infectious virus particles in her circulation.

For reasons that are not well understood, the surface material of HBV (designated as HBsAg and manufactured in the cytoplasm of the hepatocyte), is often produced in amounts far exceeding the core material of HBV (designated as HBcAg), which is produced in the nucleus of the hepatocyte. For this reason uninfected free HBsAg often circulates in great excess of whole virus particles.

In general the amount of infectious material is greater in acute infections and in the earlier chronic phase of the carrier state, and is almost always found in greater amounts in infants and children than in adults. Since no simple test is available to detect whole HBV particles or HBcAg, the infectivity of a carrier can be approximated by either the presence of HBeAg which is located in or near to the virus core, or by the titer of HBsAg.

Carrier mothers are highly infectious when they are HBeAg positive or when they have high titers of circulating HBsAg. Both HBeAg and HBsAg titer are good tests for predicting which HBsAg carrier mothers are likely to infect their infants and can be utilized in immunization programs, if resources are scarce and not all newborns can be immunized, to select the highest risk infants who would benefit the most from immunization.

After an incubation of 2 to 3 months, the infant who is infected becomes a source of large quantities of highly infectious material. HBsAg may be produced in huge amounts by the infant.

4.2.3 Parenteral

It has been known for many decades that HBV can be transmitted by transfusion of blood or blood products from HBV carriers or by inadequately sterilized needles and other inoculation equipment. Very large amounts of infectious material exist in the blood of some carriers so it is not surprising that parenteral transmission by inadequate sterilization of inoculation equipment may occur. It

should be noted that HBV is much more infectious than Human Immunodeficiency Virus (HIV), and remains a considerable risk in the parts of the world where many injections are given without properly sterilizing the injection equipment. At least two studies have shown a clear correlation between the number of injections received by children and the frequency of HBV infection. Ritual scarification, tattooing, and illicit drug use are other circumstances in which parenteral HBV transmission may occur.

4.2.4 Person to person

Person to person transmission, often called "horizontal transmission" (although that term is to be discouraged), of HBV infections are common in many parts of the world, although the exact mechanisms are not well understood. Close body contact with exchange of body fluids such as saliva may play an important role although this has never been proven.

4.2.4.1 Children

HBV infections among children whose mothers are not HBsAg positive are common in many parts of the world. For example, in Asia approximately 50% of HBV infections occur in persons who do not have HBsAg positive mothers. Some of these may be due to parenteral transmission but a significant proportion are probably due to person to person contact, most commonly between children, since they are often more infectious than adults. Because saliva is often HBsAg positive (albeit with a much lower titer than blood), and no

other means of transmission can be identified, it is widely assumed that saliva is a common source of person to person spread of HBV. In some parts of the world adults pre-masticate the food of infants and this may be a common mechanism of transmission.

4.2.4.2 Adults

Adults can be infected by the same routes as children. In addition there is sexual transmission. HBV transmission between sexual partners occurs but the frequency and mechanisms are not well understood. Transmission can occur between heterosexual or homosexual partners. In many Western countries high rates of HBV infection have been demonstrated in homosexual males. It is not clear whether the transmission is via saliva, blood or genital secretions all of which often have detectable HBsAg.

In areas of the world where carrier rates are very high most people are infected before they reach sexual maturity and thus sexual transmission is probably of little importance. Few, if any, studies have been conducted of sexual partners of carriers in geographical areas where HBV infections are of intermediate frequency, however.

* * *

5. IMMUNIZING AGENTS

5.1 VACCINE

By virtually every parameter except cost, the available HBV vaccines are among the best immunogenic agents ever developed against any disease. The current price is the only major deterrent to a global programme to control one of mankind's greatest scourges. The HBV vaccine will almost certainly be the first effective major cancer vaccine. There have been well publicized efforts to improve the first generation vaccines which are derived from the plasma of human HBV carriers but the only really important improvement needed in the present HBV vaccines is a lower purchase price. The available vaccines have no important side effects. It can almost certainly be assumed that the eventual price of HBV vaccine will be less than the most expensive vaccine now being used in the EPI. It is therefore reasonable to begin planning the strategies for HBV immunization now.

5.1.1 Types of vaccine

5.1.1.1 Human plasma derived - The first generation of HBV vaccines consists of highly purified HBsAg derived from plasma of human carriers inactivated by one or more procedures to assure that no living material exists in the vaccine. Most manufacturers have achieved at least 95% HBsAg purity by two steps of ultracentrifugation, one of the major reasons for the high cost of the plasma vaccine. Various inactivation procedures have been used including formalin, heat, pepsin and urea. The extent to which inactivation

alters the immunogenic properties of the vaccine have been the subject of some debate and is unresolved. This debate notwithstanding, even the most severe inactivation leaves a potent vaccine. It should be stressed that only with the plasma derived vaccines has there yet been long and widespread experience. Over 30 million doses of hepatitis B vaccine derived from human plasma have been distributed worldwide and there are now more than ten manufacturers globally. No serious problems with the use of these vaccines are recognized, and concepts of the duration of protection are primarily based on experience with the plasma vaccines.

5.1.1.2 Recombinant - DNA recombinant vaccines are purified HBsAg which are intended to be identical in composition to the first generation plasma vaccines. Both of the presently available recombinant vaccines (Merck and SKF-RIT) are derived from ordinary bread yeast. Several manufacturers are developing recombinant vaccines from mammalian cell lines which have the advantage of a high yield of HBsAg in the supernatant, which is more easily harvested. HBsAg from yeast can only be recovered after lysing the cells. In as much as the recombinant vaccines are more expensive there seems to be no advantage to their use since they appear to be equivalent to the plasma vaccines in other respects.

5.1.1.3 Polypeptide - Polypeptide vaccines are currently only experimental and their feasibility is yet to be established. Their main appeal is that they can potentially be manufactured in very large amounts at very low cost.

5.1.2 Safety

No serious side effects nor problems have occurred with any of the licensed vaccines. Fears that other viruses existing in the donors, eg. HIV, might survive the manufacturing inactivation procedures have not been substantiated, and careful follow-up of thousands of plasma vaccine recipients have not shown any increase in AIDS risk following HBV immunization. The experience to date with the plasma vaccines is now substantial and it seems likely that this is one of the safest vaccines yet developed. Although concern has been expressed that residual components from the source materials (eg. normal human plasma protein components in plasma derived vaccines or yeast proteins in the yeast derived rDNA vaccines) could be cause problems; there are no data to substantiate this theoretical concern.

5.1.3 Immunogenicity

5.1.3.1 General - Purified aqueous preparations of HBsAg alone are poorly immunogenic, but excellent immunogenicity can be achieved by adsorption with an adjuvant, e.g. alum which is used by all current manufacturers of both plasma and recombinant vaccines. The alum is the cause of the slight fever and/or soreness at the site of injection which occurs in about 5% of immunized persons.

Freezing will inactivate the vaccine because it causes vaccine-adjuvant dissociation.

5.1.3.2 Host factors influencing immunogenicity - The immune status of the host is the most important determinant of the ability to respond to HBV vaccine. Persons with immunological diseases or undergoing treatment which adversely influences the immune system (eg cancer chemotherapy, steroids etc) may not respond as well as otherwise healthy people.

Healthy infants and children of all races and ethnic groups respond extremely well to HBV vaccine. Females of all ages have a slightly better response than males but the difference is not great enough to necessitate differential policies for the sexes. The immune response gradually declines with increasing age for reasons that are not well understood. The effects of malnutrition on the response to HBV vaccine have not been studied.

5.1.3.3 Non-responders - Almost all healthy infants, including newborns, mount a good immune response to HBV vaccine. With increasing age the vigor of the immune response diminishes. Repeated immunizations, especially with larger doses results in sero-conversions in some of the initial non-responders.

5.1.4 Efficacy

5.1.4.1 General - The goal of every HBV immunization programme should primarily be the prevention of the HBsAg carrier state from which arises chronic liver disease including hepatocellular carcinoma. Persons who are infected with HBV but do not become HBsAg carriers are probably not at increased risk of

chronic liver disease. In numerous well designed randomized controlled trials HBV vaccine has been shown to provide excellent protection against HBV.

5.1.4.2 Adults - In various studies in healthy adults it has been shown that the vaccine protects against HBV infection and acute clinical manifestations of HBV hepatitis. Vaccine failures were limited to those already infected and in the incubation phase, and a small proportion of vaccinees who were non-responders. Adult vaccine recipients did not become HBsAg carriers (but in any cases that is an unusual outcome of HBV infection after childhood except in immune compromised individuals). Renal dialysis patients were not protected in one study, although they have been in others.

5.1.4.3 Infants and Children - Most importantly, HBV vaccine induces excellent protection of infants and children. Children have a better immune response than adults and infants. Newborns respond as well as older children.

The goal of HBV immunization is protection against the HBsAg carrier state because chronic liver disease, including HCC, only occurs in chronic carriers. Furthermore, acute clinical hepatitis B rarely occurs in infants

5.1.4.4 Immunogenicity as an indicator of efficacy - In infants, children and adults, full protection is achieved when any detectable anti-HBs is present. Thus efficacy

can be assessed by the anti-HBs response to vaccine.

5.1.4.5 Duration of protection - As with all good vaccines this will be one of the last questions to be answered. As expected, anti-HBs titers decline following the peak achieved with each dose of vaccine. Following the last in the regular immunization series (third for Merck; fourth for Pasteur) anti-HBs titers decline with a projected mean extinction at about 5 or 6 years, causing some people to believe that a booster would be desirable at about the time of school entry. There is considerable individual variation in the rapidity of loss of detectable anti-HBs, and there has not been long enough follow up of enough individuals, especially infants and children, to adequately assess this issue.

5.1.4.6 Efficacy against chronic hepatitis, cirrhosis and HCC - The vaccine has not been in use long enough to have shown its expected long term efficacy in preventing chronic hepatitis, cirrhosis, or hepatocellular carcinoma. A study for this purpose is currently being conducted in The Gambia and results are expected in 30 to 40 years. In the mean time scientists are convinced that the clear ability of HBV vaccine to prevent the HBV carrier state, the antecedent of HBV-induced chronic liver disease, fully justifies undertaking immunization programmes.

* * *

5.1.5 Manufacturers

Plasma vaccines are manufactured and are commercially available from several countries, eg. France (Pasteur), United States (Merck), Netherlands (Red Cross), Japan (Green Cross and Kitasato), and S.Korea (Green Cross). (NB: Japan Green Cross and Korea Green Cross are different). Several other plasma vaccines have also been developed including one by the United States NIH, and by several institutions in China. The oldest and most widely used and still available are the Pasteur and Merck vaccines. There has been much less experience with the newer recombinant vaccines which are being made by several manufacturers. Yeast derived DNA recombinant vaccines are now being marketed by Merck and by SKF. Field trials are underway with recombinant vaccines from several other manufacturers as well.

5.1.6 Shipping and storage

HBV vaccines are adjuvanted purified proteins derived from the surface of the virus. They are moderately stable at room temperature, but probably require cold chain protection. At 2 to 8 degrees C, the vaccines appear to be stable for many years; the upper limits of storage life have not yet been defined. Inactivation can occur at high ambient temperatures and by freezing. The stability of the vaccines at higher ambient temperature ranges is being investigated. As with DPT, HBV vaccine must not be frozen because vaccine-adjuvant dissociation. Little or no visible change occurs following freezing and it should be standard practice to include freeze indicators with all shipments. For all practical purposes the HBV vaccine should be handled in the same fashion as DPT.

Table 2. Overview of HBV vaccine manufacturers

Institution	Country	Plasma-derived		Recombinant	
		Licensed	Human trial	Licensed	Human trial
Merck	USA	yes	yes	yes	yes
Pasteur	France	yes	yes	no	?
Kitasato ¹	Japan	yes	yes	no	?
Green Cross ¹	Japan	yes	yes	no	?
Life Guard ¹	Taiwan	yes	yes	no	no
Green Cross ²	Rep. Korea	yes	yes	no	NA
Cheil Sugar	Rep. Korea	yes	yes	NA	NA
4 Factories ²	China	yes	yes	NA	NA
SKF-RIT	Belgium	NA	NA	yes	yes

1 Identical or very similar to Pasteur method

2 Identical or very similar to Merck method

5.1.7 Dose and schedules

Higher doses of vaccine given more often achieve faster and higher antibody responses. Early studies used schedules with quantities as high as 40 µg/dose of vaccine. Because of its high cost, considerable effort has been made to determine the lowest acceptable dose.

There is no final consensus on the best schedule and number of doses. Pasteur has developed a four dose schedule while Merck and many other manufacturers use a three dose schedule. The first generation Merck vaccine (plasma) has been licensed in the United States for use in adults at 20 µg/dose, and in infants at 10 µg/dose, each given in a three dose series at times 0, 1 and 6 months.

All studies with all HBV vaccines in animals and humans indicate the need for at least three doses to establish sufficiently high levels of antibody to provide adequate duration of protection.

The third dose is needed to:

- bring about the desired high conversion rates, especially in older individuals.
- obtain high enough titers to provide long term protection.
- stimulate adequate long term immunological memory.

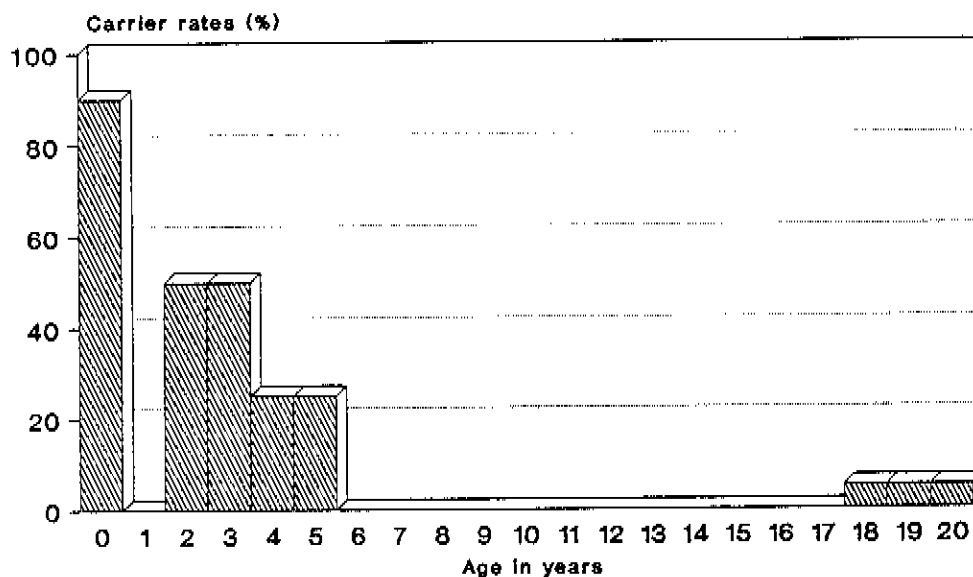
No studies of the efficacy against perinatal transmission of one or two dose schedules have been undertaken. But it is probable that one or two doses will prevent a perinatal transmission as well as three doses, but will be insufficient to provide long term protection. It is possible that many infants receiving only two doses would have initial protection but would be subsequently infected by their still infectious mothers, older siblings, or playmates.

Two aspects of the immunology of hepatitis B infection should be considered:

* The risk of developing the carrier state drops rapidly with increasing age (Figure 1, page 16). Therefore, the value of immunization declines steadily as the child grows older and runs an ever decreasing risk of becoming a carrier, even if infected. The age at which the risk of becoming a carrier has reached its lowest level has not been established.

* Even loss of detectable antibody may not mean total loss of protection because the long incubation of HBV allows the host more time to mount a secondary immune response to infection than is the case with other viral infections. Although further studies will be needed to clarify this point, there is no clear indication that a fourth dose is needed.

Figure 1. Carrier rates following HBV infection at various ages.



5.1.8 Site of administration

All HBV vaccines were designated for intramuscular inoculation since it has been established that subcutaneous administration produces an inferior immune response. Recent data have revealed that adults have a better immune response following deltoid compared with gluteal administration. It has been assumed that this effect may have been because of the thickness of the layer of fatty tissue and that as a result some of the injections may not have been fully intramuscular. In most infants, especially newborns the deltoid muscle mass is too small, so almost all intramuscular injections, including HBV vaccine, are given in the anterior thigh.

Several studies have been undertaken to evaluate the immunogenicity of intradermal inoculation of the adjuvanted HBV vaccines intended for intramuscular use. Studies done with both the Pasteur and Merck vaccines using doses of 0.1 ml administered intradermally with a tuberculin syringe have yielded excellent immune responses without the severe local reactions that had been anticipated by some investigators. Cutaneous erythema is frequent but seldom severe enough to cause concern. The appeal of the intradermal approach is that there can be substantial cost reduction because it requires only about 10% the amount of vaccine to achieve the same level of antibody response

induced by the intramuscular route. The great disadvantage is that it might be inadvertently given intramuscularly or subcutaneously where it would be ineffective and thus leave the child unprotected. Until further studies are done on this subject, intramuscular injection using full dosage is recommended.

5.1.9 Simultaneous administration of HBV vaccine with other vaccines

Two studies on the simultaneous administration, at different injection sites, of HBV vaccine with other EPI vaccines have been undertaken and both show that HBV vaccine neither enhances nor interferes with the immunogenic effect of BCG, DPT, OPV, or measles. Likewise, these vaccines do not effect the HBV response.

5.1.10 Combined administration of HBV vaccine with DPT

Studies of a combination DPT-HBV vaccine are being planned. Since all four immunizing agents are proteins which are adjuvanted and handled in similar fashion it is anticipated that such a combination would be feasible and would not interfere with the immunizing efficiency of any of the individual components.

Of greater concern is whether the age of DPT-1 could be lowered to coincide with HBV-1 which should be given as soon as possible after birth. Administration of DPT as early as six weeks is already advocated by EPI, and studies are now being conducted to determine the safety and immune response of DPT in newborns.

5.2 HEPATITIS B IMMUNE GLOBULIN (HBIG)

5.2.1 Source

HBIG is human immune globulin prepared from pooled human plasma by Cohn fractionation, using exactly the same procedures as for the preparation of conventional immune globulin. HBIG is, therefore, distinguished from immunoglobulin only in that the donor source is plasma from persons with high titers of anti-HBs. Originally, all HBIG was from persons who had experienced natural HBV infections from which they had recovered without becoming HBsAg carriers. A simple HBV infection rarely if ever results in the very high anti-HBs titers needed for HBIG. Therefore, most HBIG donors have to have their anti-HBs titers boosted with the new vaccine.

In addition to anti-HBs, HBIG contains other antibodies from the donor pool such as anti-HBc and anti-hepatitis A virus (anti-HAV) antibody. Some lots of HBIG have also contained antibodies against HIV although there is no evidence that HBIG has transmitted infectious HIV. Cohn fractionation probably inactivates retroviruses. It is also possible that anti-HIV in HBIG recipients is the result of antibodies stimulated in them from inactivated HIV in the HBIG.

5.2.2 Use in perinatal transmission

Although passive prophylaxis has been recommended in several exposure situations, the primary value of HBIG is for prevention of perinatal transmission of HBV. Some mothers are much more infectious than others

and they can be identified using the HBeAg test. Approximately 90% of HBeAg positive HBsAg carrier mothers infect their infants, usually during labor and delivery. In contrast, less than 5% of HBeAg negative mothers infect their babies.

5.2.3 Timing and dose

Although newborns generally mount a vigorous antibody response to HBV vaccine, it is not always early enough to protect against perinatal transmission. An intramuscular injection of HBIG administered to the infant immediately after birth will provide temporary protection until the active immune response has occurred in response to vaccine. It is particularly noteworthy that passive immunization not only provides the necessary early protection but has no inhibitory effect on active immunization. It must be stressed that, to be of value, the HBIG must be given shortly after birth. If delayed more than 48 hours it has no value at all. This fact alone will be a major deterrent to the use of HBIG in many parts of the world.

Empirically it has been determined that optimal protection can be obtained with 0.5 ml of HBIG containing at least 300 mIU and administered within the first few hours of life. Delay is only needed long enough to attend to any urgent procedures related to the delivery itself and washing the baby adequately so that the HBIG injection itself does not transmit infectious material from maternal secretions on the skin of the baby. This is followed by HBV immunization any

time over the next few weeks. There is no immunological value in delaying vaccine administration, however, and since there is individual variation on both the speed of the active immune response as well as the rapidity of loss of passive antibodies, active immunization should be started within the first week of life. Occasionally it may be prudent to delay the first dose until the end of the first week where cultural groups may incorrectly attribute the administration of the vaccine to the early death of an infant.

6. IMMUNIZATION PROGRAMMES

6.1 OBJECTIVES

Prevention of chronic hepatitis, cirrhosis and hepatocellular carcinoma by prevention of the chronic HBV carrier state is the primary objective of an immunization programme using HBV vaccine. The chronic disease manifestations of HBV infection have only been identified in association with the long term carrier state and not with other serological parameters representing prior HBV infection (eg. anti-HBs, and/or anti-HBc in the absence of HBsAg).

Prevention of acute clinical hepatitis due to HBV is of secondary importance because acute clinical manifestations are relatively rare.

Prevention of infections per se is of little importance because infections which do not lead to the carrier state are rarely of clinical or public health significance.

HBV prevention programmes should therefore be targeted at infants and young children who are the group most at risk of becoming carriers. If resources are available and high risk adult populations have been identified then immunization of selected high risk adult populations may be considered.

The possible value of immunizing the mother is often raised. This, is of limited value because if the mother is already a carrier, neither HBIG nor vaccine can alter her carrier status or infectivity. If the mother is not a carrier, immunization with HBV vaccine may stimulate antibody formation or a booster response which is, of course, good and should not be discouraged if adequate resources exist, but is not likely to be an important means of preventing many HBV infections.

6.2 ESTIMATION OF LEVEL OF RISK

6.2.1 Criteria for a programme

Any country considering whether to embark on an immunization programme using HBV vaccine must determine what the level of risk in that country is before committing extensive resources.

The primary determinants of whether to mount an immunization programme in a given area or country should be:

- the HBV carrier frequency in the population,

- the proportion of carriers attributable to perinatal transmission
- the death rate from liver disease attributable to chronic HBV infection where this can be estimated.

The carrier rate indicates the magnitude of HBV as a problem and is the primary guide to the resources which should be allocated to its control. The fraction of carriers attributable to perinatal transmission will determine the extent to which an immunization programme should be targeted at newborns. Immunization safety is not an issue, so the limitation to an ideal programme will be cost and ability to reach the target populations. In considering cost it must be understood that the price of the vaccine will almost certainly be declining over the next several years and that countries will need to be readjusting their immunization strategies accordingly.

6.2.2 Seroprevalence studies

The most useful scientific guide for estimating the risk to infants is a serological survey of women of child-bearing age. If resources permit, it may be extended to include infants and children up to adulthood. The latter will give an indication of what percentage of carriers result from infection in the newborn period, and what percentage results from other routes of transmission.

To some extent, any division into high and low risk populations must be arbitrary. However, from

the knowledge of the epidemiology of HBV (see table 1) it is possible to make an attempt at categorizing areas of HBsAg prevalence, based on serum surveys.

- **A HIGH prevalence of greater than 10%** indicates that a serious problem exists, and an immediate implementation of a programme for neonates is justified.

- **An INTERMEDIATE prevalence of 2% to 10%** indicates an intermediate level of risk. It may be possible to identify some subgroups who are at much higher risk within the population. Some geographic areas in the country may be at high risk. But in general, the intermediate risk group also needs an immunization programme for neonates.

- **A LOW prevalence of less than 2%** generally indicates there is not a significant level of risk to undertake a mass immunization programme. However small subgroups within the population (for instance immigrants from high risk countries) may well need to be offered immunization.

6.2.3 Routine measurement of maternal markers

Where there is high and intermediate seroprevalence, it is unlikely to be necessary to measure the markers of every pregnant women. It may be assumed that every infant is at risk even if not all would necessarily become infected.

In areas of low risk, it may be worthwhile screening all pregnant women to indicate those at risk of perinatal transmission. However if the cost of screening is high, it may be better to commit resources only to the immunization of infants, ignoring any screening procedure.

6.3 STRATEGIES

6.3.1 General

The most effective strategy will vary from country to country with the epidemiology of HBV. The choice will also be affected by available resources. Universally, however, the first and highest priority should be given to the immunization of infants.

6.3.2 Perinatal Transmission - Carrier Rate Reduction Strategies

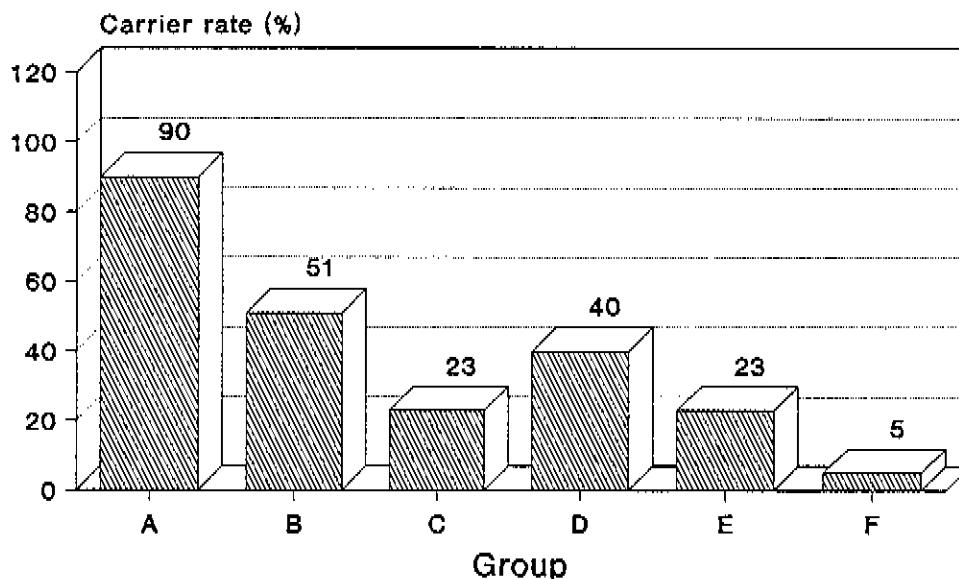
6.3.2.1 Unpreventable Intrauterine Infections

The combination of HBIG and vaccine will protect all but about 5% of high risk infants from becoming carriers. This small proportion of unprotectable infants are those who are infected in utero and already have established infections in their livers when they are born. Although there is no practical reason to do so, these infants can be identified by their high levels of HBsAg in the infant circulation at birth; cord blood testing yields unreliable results and should be discouraged. Neither passive nor active immunization of infected infants has harmful effects, such as antigen-antibody complex disease. HBsAg is produced in such large amounts in infected individuals that it is detectable even after the administration of HBIG.

6.3.2.2 Carrier Rate Reduction Strategies

The effect of five different carrier rate reduction strategies on infants of HBeAg positive mothers is illustrated in Figure 2.

Figure 2. Effect of 5 carrier rate reduction strategies.



Description of groups

A = No prophylaxis	
B = HBIG (1 dose at birth)	- No vaccine
C = HBIG (3 doses: at birth, 3 months, 6 months,	- No vaccine
D = HEV vaccine (3 doses, first at 1 month)	- No HBIG
E = HEV vaccine (3 doses with first at 1 week)	- No HBIG
F = HBIG (1 dose at birth) AND 3 doses of HEV vaccine	

6.3.3 Selective immunization

Within the first few days of life, vaccine may be given selectively to all infants born to HBsAg POSITIVE MOTHERS. Additionally HBIG may be administered to infants whose mothers are found to be highly infectious (HBeAg positive and/or high titer HBsAg)

Selective immunization of HIGH RISK infants and children is advisable if significant amounts of non-perinatal transmission are shown to be occurring

Selective immunization of groups of high risk ADULTS may be indicated.

6.3.4 Mass immunization

The choice between immunization of selected groups or immunization of all infants will be helped by knowing the contribution perinatal maternal transmission makes to the overall carrier rate in the particular area (see table 1).

6.4 Country experiences

In Taiwan the carrier rate in the general population is about 20%, and 40-50% of this is attributable to perinatal transmission. In 1984, a step-wise island-wide programme was started. During the first two years all pregnant women attending the island's widely used prenatal clinics were screened for HBsAg. Those found positive were also tested for HBsAg titer and/or HBeAg. All newborns of HBsAg positive mothers were given HBV vaccine shortly after birth and if the mother was highly infectious the newborn was also given HBIG within the first 24 hours of life. In the first year 77% of the target population was reached. In July 1986 the programme was expanded to include HBV vaccine for all newborns. Over the next several years HBV immunization will be offered to infants and children who were born before July 1984, moving gradually upward in age until complete coverage has been reached.

In the United States, where each State Health Department develops its own policies, California has developed a programme which follows the above outline but aims at the known high risk of perinatal transmission among the large number of Asians residing there. HBsAg screening is

undertaken for Asian women attending prenatal clinics and those found to be positive are tested for HBsAg and for HBeAg. Infants of all carrier mothers are given HBV vaccine. Additionally HBIG is given to those who are HBeAg positive.

In the Federal Republic of Germany, there is a nationally funded programme to screen all pregnant women and administer HBIG and HB vaccine to the infants of those found to be HBsAg positive. This country is also providing free HBV vaccine to all susceptible new persons entering the health care professions.

* * *

7. RECOMMENDATIONS

- Chronic infection with hepatitis B virus is common in developing countries. Such infection is a cause of hepatocellular carcinoma, one of the 10 most common cancers in the world. Hepatitis B vaccine is safe and effective in preventing infection. Its use early in infancy can reduce chronic carrier rates by over 75%.

- Hepatitis B immunization programmes should be considered in all population groups who have chronic carrier rates of hepatitis B virus of over 2%; they become a major public health priority for populations with carrier rates above 10%.

- In countries with chronic carrier rates of hepatitis B of over 2%, hepatitis B immunization should be introduced as an integral part of existing childhood immunization programmes as quickly as resources permit. Efforts to use this vaccine in ways which do not strengthen existing programmes should not be encouraged.

- The specific immunization schedule adopted in national programmes needs to be adapted to national circumstances, bearing in mind the usual age of hepatitis B infection

and the delivery capacities of the health system. The objective is to prevent chronic carriage of hepatitis B virus. National immunization schedules should be formulated so that the use of hepatitis B vaccine minimizes extra contacts with the health system beyond those already needed for vaccines included within national childhood immunization programmes.

- A minimum of three doses of hepatitis B vaccine is recommended, given by the intramuscular route. The first dose is recommended at birth or as soon as possible thereafter. Early immunization is a special priority for those countries in which perinatal transmission is frequent. The second dose should be given 4-12 weeks after the first, timed to coincide with other routine childhood immunizations. The third dose may be given 2 to 12 months after the second, again timed to coincide with other routine childhood immunizations. At present, additional doses of vaccine are considered a low priority.

- While the use of hepatitis B immune globulin is effective in complementing the use of hepatitis B vaccine in preventing perinatal infection, its high cost and the need to administer it within hours of birth will preclude its use in most developing countries.



APPENDIX - A.

Definitions and abbreviations

HBV	Hepatitis B virus
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
Anti-HBs	Antibody to hepatitis B surface antigen
Anti-HBc	Antibody to hepatitis B core antigen without differentiation into immunoglobulin class
Anti-HBc IgG	Antibody to hepatitis B core antigen of the IgG class
Anti-HBc IgM	Antibody to hepatitis B core antigen of the IgM class
Anti-HBe	Antibody to hepatitis B e antigen
HCC	Hepatocellular carcinoma
HEPADNA	The unofficial designation for the group of viruses to which HBV belongs

APPENDIX - B.

RECOMMENDATIONS OF THE NOVEMBER 1987
HEPATITIS TECHNICAL ADVISORY GROUP

"HEPATITIS B VACCINES AND IMMUNIZATION STRATEGIES"

1. The TAG notes that over 30 million doses of plasma-derived HB vaccine have been distributed worldwide and that there are now more than 10 manufacturers of these vaccines globally. The vaccines have an impressive record of safety. In addition, several vaccines manufactured by rDNA technology are now on the market and additional manufacturers are expected to enter the market in the next two or three years. These rDNA vaccines are equivalent to plasma derived vaccines in respect to safety, immunogenicity and efficacy and neither offers any advantage over the other in these respects. Plasma-derived vaccines will continue to play an essential role in Hepatitis B control programmes worldwide for the foreseeable future.

2. There has been a dramatic decrease in the price of HBV vaccines to the level where many countries in Hepatitis B hyperendemic areas may now begin the development and implementation of large scale vaccination programmes. WHO should encourage their implementation and monitor their progress.

3. The TAG encourages the establishment of programmes and liaising with relevant groups within and without the Organization and encourages continued and increasing close collaboration between WHO and such bodies in the development and implementation of the global programme on HBV control.

4. The TAG emphatically reiterates that the most important means to control HB on a global scale and to reduce mortality due to chronic sequelae of this infection, including cirrhosis and HCC, is the large scale immunization of infants. It therefore recommends that HB vaccination be integrated into EPI as soon as possible. For incorporation into EPI, it is recommended that three doses of HBV vaccine will be given and that administration should be intramuscular into the thigh of infants. The first dose (HBV-1) should be given as soon as possible after birth. Although programmes should aim at administration of HBV-1 within the first week of life, it should be initiated at any time if it cannot be given so early. It is also desirable that HBV-1

be given simultaneously with the first EPI immunization.

The second dose (HBV-2) should be given 4 to 12 weeks after HBV-1, as it best fits into the EPI schedule of the particular Region.

A third dose (HBV-3) is currently needed to achieve high levels of antibody and prolonged protection. There is considerable latitude regarding timing of this dose. Countries can adopt schedules with 2 to 12 months following HBV-2, at a time when it best fits into the EPI schedule of the particular Region.

HBIG may be of additional value in HB immunization programmes for infants, but cost of its inclusion into large scale immunization programmes precludes its use in most countries.

5. The TAG encourages operational research to define methods for an optimal integration of HB vaccination into EPI through the establishment of immunization projects in selected countries in hyperendemic areas of the world, and that WHO monitor the results of these projects. In particular the effectiveness of Hepatitis B vaccination in a variety of EPI settings and according to differing schedules of delivery of other EPI immunogens should be evaluated. Also thermal stability of HB vaccines should be further evaluated in order to adapt them to EPI cold chain characteristics.

Model immunization projects in Indonesia, Thailand and China are being established in collaboration with the International Task Force of Hepatitis B Immunization. These projects should be closely monitored and evaluated on an ongoing basis.