The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa

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Abstract

There are approximately 50 million chronic carriers of hepatitis B virus (HBV) in Africa, with a 25% mortality risk. In sub-Saharan Africa, carrier rates range from 9–20%. Many studies have suggested that HBV transmission in Africa occurs predominantly in childhood, by the horizontal rather than the perinatal route. The exact mode of transmission is uncertain but probably involves percutaneous infection through saliva or traces of blood, as well through unsterile needles, tribal scarification, and other possible vehicles. Compared with adult HBsAg carriers in the Far East, those in Africa have a low rate of HBeAg positivity, which may account for the relatively low rates of perinatal infection. It is also possible that African infants are less susceptible to perinatal HBV infection compared with their Asian counterparts. Alternatively, it may be that African infants are indeed infected with HBV at birth but, for genetically determined reasons, have persistently negative tests for a number of years until the virus is reactivated. In view of the high HBV carrier rates in the general population, universal immunisation of all infants is recommended. Ways of incorporating the hepatitis B vaccine into the Expanded Programme on Immunisation in each country are being evaluated.

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By any yardstick, hepatitis B stands out as an important public health problem warranting high priority efforts, prevention, and control. Approximately 300 million people – over 5% of the world's population – are chronic carriers of the hepatitis B virus (HBV), of whom it is estimated that 25–30% will die of the sequelae of their infection, principally cirrhosis and hepatocellular carcinoma.[1–3]

In regions of the world where hepatitis B is highly endemic, HBV accounts for around 3% of the total mortality, ranking with other vaccine preventable childhood diseases such as measles, tetanus, pertussis, and polio.[4] Of the world's approximately five billion people, 3·8% live in areas of moderate to high hepatitis B endemicity (carrier rate >2%). The burden of chronic carriage falls predominantly in Asia where 75% of chronic HBV carriers live.[2] Africa has the second largest number of chronic carriers. Of approximately 470 million people living in Africa, about 50 million are lifetime carriers of the virus and as many as 12·5 million will eventually die due to hepatitis B induced liver disease. This represents a risk of 25% among chronic carriers.

Epidemiology of HBV in sub-Saharan Africa

The size and diversity of the African continent, the dispersion of much of its population among vast rural areas, and the frequent lack of resources mean that accurate determination of HBV carrier rates can be extremely difficult. Moreover, assessment of ongoing infectivity and potential precore mutant infection is limited by the lack of polymerase chain reaction testing for HBV-DNA in the great majority of centres. Nevertheless, the epidemiology of HBV infection has been extensively investigated in certain parts of sub-Saharan Africa.[5–24] Table I shows the prevalence of hepatitis B surface antigen (HBsAg) and other HBV markers in some of the countries in sub-Saharan Africa. It is quite clear that the whole of sub-Saharan Africa falls into the high endemicity category (HBsAg carrier rates 9–20%). Between 56% and 98% of the adult population shows evidence of past exposure to and infection with HBV.

The epidemiology of HBV has been studied by various workers in West Africa. In this region, nearly everyone is infected during childhood.[6 7] In contrast with the situation in parts of the Far East where a high proportion of the population acquires infection perinatally, HBV infection of newborns is uncommon in west Africa. However, infection rates increase rapidly

TABLE I *Prevalence of HBsAg and HBV markers in the adult population of sub-Saharan Africa*[5]

Country	*HBsAg+ve (%)*	*HBV marker+ve* (%)*
Ethiopia	11·0	79·0
Kenya	11·4	56·2
Mozambique	14·6	75·2
Nigeria	10·0	72·5
South Africa	9·6	76·0
Namibia	14·0	87·5
Zimbabwe	10·0	76·0
Senegal	11·8	91·0
Gambia	10·0	90·0
Zaire	20·6	78·9
Burundi	11·0	76·0
Mali	11·3	97·7

*HBV marker includes HBsAg, anti-HBc, anti-HBs.

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from the age of 6 months so that, by the age of 2 years, 40% of west African children have already been infected with HBV and 15% have developed persistent infection. By the age of 10 years, 90% of children have become infected and 20% have become chronic carriers.

The precise mode of transmission of the virus in west Africa is unknown but a number of studies have attempted to look at some of the factors that may be responsible for the apparently high rate of transmission, particularly among young children. A study from Liberia[8] looked at the prevalence of hepatitis B among children aged up to 4 years. Children born to mothers who were carriers of HBsAg had significantly higher age specific incidence and prevalence of HBV infection. However, it was estimated that only a minor proportion (less than 5%) of hepatitis B infection in Liberia was due to perinatal transmission from mothers.

Another study from Liberia[9] attempted to link the high prevalence of HBV infection to parasitic infection (onchocerciasis). In a rubber plantation where onchocerciasis was also common, the HBsAg carrier rate was 30% compared with a carrier rate of 13% elsewhere in Liberia where onchocerciasis was rare. The hypothesis was that the high HBsAg carrier rate in Liberia was linked to the immunosuppression associated with parasitic infections such as onchocerciasis and that this could also explain the high carrier rates found elsewhere in Africa.

An interesting study from The Gambia showed considerably different prevalences of HBV infection in two neighbouring villages.[6] Sixty two per cent of children in Manduar village aged 2–4 years were found to be infected, whereas in Keneba, only 27% of this age group were infected. In both villages, few children below the age of 1 year were infected – none under 6 months of age and only two of 58 between the ages of 6 and 12 months. Eighty six per cent of all children under the age of 5 carried HBsAg, thus forming a highly infectious pool. Infection clustered in families with transmission from sibling to sibling being of major importance. The chances of a child being an HBsAg carrier were approximately 42% if an elder sibling carried the antigen, 27% if either the mother or father was a carrier, and 15% if neither parent was a carrier.

A study from Mali[10] showed an HBsAg prevalence of 8·7% in 1860 rural Malians and 11·3% in 764 blood donors. Among 1350 hospitalised patients, no correlation could be established between the HBsAg chronic carrier state and other infectious diseases, malnutrition or genetic deficiencies.

Much of the pioneering work on the epidemiology of hepatitis B was carried out in Senegal.[11–13] Coursaget *et al* looked at HBV infection in 155 infants with a view to determining the factors involved in the development of chronic infection.[13] A chronic carrier state was seen in 50·3% of the infants. The study confirmed that the risk of chronic carriage declined rapidly with increasing age, falling from 82% in infants under 6 months old to 15% in children between the ages of 2 and 3 years. A difference was also seen between males and females in that HBV infection before 2 years of age led to a chronic carrier state in 77% of males compared with 50% of females.

Studies in central Africa have shown similar findings to those in west Africa. In Zambia, the contribution of horizontal transmission to the high prevalence of HBV infection was examined.[14] Six hundred and twenty residents of five Zambian villages were tested for HBV markers. By comparing paired serum samples from 79 children and 80 adults, it was found that new infections occurred during the five years of this study in at least 14 children (18%) and 10 adults (12%). These 24 new infections were distributed among 20 households and were consistent with a pattern of horizontal infection.

Baseline epidemiological studies on HBV infection have also been carried out in Southern Africa. In one such study carried out in KaNgwane, a district in South Eastern Transvaal bordering Mozambique and Swaziland, the HBsAg carrier rate was 14·6% in adult males and 4·6% in adult females while 82·6% of adult males and 69·4% of adult females were positive for at least one marker.[15] When stratified by age, the prevalence varied from 1% during the first 6 months of life to 11·8% at the ages of 3–5 years. The group with the highest infectivity, as determined by the prevalence of HBeAg among HBsAg positive subjects, were children below the age of 5 years, who had an HBeAg positivity rate of 56·5%.

Another noteworthy study was carried out in Namibia (previously South West Africa).[16] The HBsAg carrier rate was found to be 17% in adult males and 11% in females. Fifteen per cent of HBsAg carriers – both males and females – were positive for HBeAg. Anti-HBe antibody was present in 66% of male HBsAg carriers and 73% of female HBsAg carriers. Among children surveyed in this study, only 1% of those up to 6 months of age were HBsAg positive compared with 13% of those over 1 year of age. Only 4% of HBsAg positive children were under 6 months old and only 27% of HBsAg positive mothers had HBsAg positive children. The study supported the view that horizontal transmission of HBV was relatively more important than perinatal transmission in Namibia.

A study of chronic HBV infection among urban black children in Soweto, Johannesburg, South Africa, showed a surprisingly low prevalence of HBV markers with 89% (2097 of 2364 children) negative for all markers.[17] HBsAg was detected in 0·97% of the children, anti-HBc and anti-HBs together in 6·6%, anti-HBc alone in 0·7%, and anti-HBs alone in 3%. By contrast, about 15% of black children from the rural areas of South Africa were found to chronically infected. This remarkable difference in the HBV carrier rate between urban and rural black children in South Africa offers a unique opportunity to investigate the unfavourable influences operating in a rural environment. In rural areas, which are invariably of lower socioeconomic status, there are a

number of factors that could play a part in the significantly higher HBV infection rates. These include poorer hygiene, with greater chances of HBV transmission through skin abrasions, the use of unsterile needles, tribal scarification, insect bites, and many others. They may also play a part in horizontal transmission of HBV in other areas of sub-Saharan Africa.

In east Africa, most of the studies on hepatitis B have been carried out in Kenya and Ethiopia. In Kenya, a number of seroepidemiological studies show a high prevalence of HBV infection, with HBsAg carrier rates ranging from 5 to 30%.[18–20] One early study in a rural community in Kenya, using the counterelectrophoresis method of testing, showed an HBsAg carrier rate of 5·1%.[18] Antigenaemia occurred first in early childhood, reaching a peak of 10·1% at 14 years and then declining to less than 1% in those older than 60 years.[18] One point of particular interest was the finding of a strong intrafamilial spread of HBV. A more recent study has shown no significant perinatal transmission.[20] Instead, HBV transmission was found to be largely horizontal with the first peak occurring in early school age and a second peak during puberty and childbearing age.

In Ethiopia, the prevalence of HBV markers has also been extensively studied.[21–23] For instance, among blood donors, the HBsAg carrier rate was found to be 11% with a total HBV infection rate – including antibodies – of 79%. Once more, the predominant form of HBV transmission in Ethiopia was found to be horizontal intrafamilial spread, with factors such as tattooing, tonsillectomy, circumcision, and ear piercing using unsterile instruments possibly playing a part.

In Zimbabwe, our studies have confirmed what has been found elsewhere in sub-Saharan Africa.[24] Thus, although perinatal transmission of HBV does occur, it is less important than horizontal transmission. Possibly a major reason for the relatively low rate of perinatal transmission is the fact that only 5–15% of HBsAg positive persons in Zimbabwe are also HBeAg positive. In Taiwan, in contrast, where perinatal transmission is common, 40% of HBsAg positive mothers are HBeAg positive.

There is evidence that the expression of HBeAg in different populations may be genetically determined.[25] It is also possible that it is not only the frequency of HBeAg positivity in mothers that is genetically determined but also the susceptibility of infants to perinatal infection. In a study in Saudi Arabia, for example, newborns to HBsAg/HBeAg positive mothers did not acquire HBV infection perinatally and remained free of infection when followed up for two years.[26] In contrast, Chinese babies born to HBsAg/HBeAg positive mothers generally acquire HBV infection in the first 6 weeks to 3 months of life.[27]

The phenomenon of horizontal transmission of HBV has never been adequately explained. It is possible that the so called horizontal infection of HBV in children may not really represent transmission from one child to another. Children may, in fact, be infected with HBV during delivery and remain persistently infected but, for several genetically determined reasons, have no discernible manifestation of infection for many years, using ordinary test procedures. The virus could then be reactivated subsequently. On the other hand, many people believe that true horizontal infection does occur. It is known that the virus replicates in two cell types, the hepatocyte and certain lymphocytes.[28] Nevertheless, viral antigens, and probably also infectious virus, are present in many body fluids and secretions, notably saliva,[29] and possibly very small amounts of blood on skin wounds, and these could be vehicles for horizontal transmission, in addition to the other risk factors described earlier. For instance, transmission of HBV is known to have followed human bites,[30] suggesting that saliva may be infectious when inoculated percutaneously.

In summary, the vehicle in which HBV is transmitted horizontally is not clear but it may be saliva or minuscule quantities of blood. The route of infection is probably percutaneous, through skin abrasions, skin lesions (such as impetigo or eczema), and skin bites, which are not uncommon, particularly among children, in the rural areas of sub-Saharan Africa. However, covert perinatal transmission, with HBV infection manifesting later, cannot be discounted.

Hepatitis B vaccination studies in sub-Saharan Africa

A number of vaccination studies have been carried out in sub-Saharan Africa. The initial studies confirmed the immunogenicity of hepatitis B vaccines in African neonates.[30 31] In Senegal, an inactivated plasma derived vaccine (HevacB, Pasteur Institute) was given to 26 infants aged less than 1 month; 95% of the neonates showed a specific antibody response to HBsAg, similar to those in older children.[30] The vaccine was used in a schedule of three injections at monthly intervals and was without side effects. Immune responses were impaired by maternal anti-HBs. In another study, carried out in KaNgwane, South Africa, three groups of babies were included: newborns, and those aged 3 months and 6 months.[31] A recombinant vaccine (H-B-Vax, Merck, Sharpe and Dohme) was used in three doses of 10 μg, given at intervals of zero, one, and five months. Ninety three per cent of the babies in each age group seroconverted to anti-HBs, clearly establishing the immunogenicity of the vaccine in young babies. In this study, the presence of maternal anti-HBs in the baby's serum did not interfere with immunisation.

Subsequent studies, mainly in Senegal, looked at various aspects of hepatitis B immunisation in an endemic area. One such study looked at hepatitis B vaccination in children with previously acquired hepatitis B surface antigenaemia.[32] Three doses of HevacB were given at one month intervals to 31 Senegalese children aged 3 to 24 months who were positive for HBsAg. A control group of 18 HBsAg positive Senegalese children received diphtheria-tetanus-polio (DTP) vaccine. Immunisation of HBsAg positive infants

with hepatitis B vaccine was safe but ineffective. After a 12 month follow up, the prevalence of chronic carriers of HBsAg was not significantly reduced in the hepatitis B vaccine group compared with the control group (48·4 and 66·7%, respectively).

Another study looked at hepatitis B immunisation in pregnancy.[33] HevacB was given to pregnant Senegalese women to improve passive protection of their children. The vaccine was without side effects in mothers and their newborns. After three injections of hepatitis B vaccine, 77·4% of the mothers were found to have anti-HBs compared with 44·5% of non-immunised mothers. The vaccination did not significantly reduce the number of HBsAg carrier mothers but it ensured the transmission of passive anti-HBs antibodies to 60% of the newborn babies as against 32% in children born to non-immunised mothers. However, such protection was of short duration and difficult to apply in rural areas of tropical Africa. Moreover, no protection was provided to those children born to HBeAg positive mothers, who represent a potential risk factor for infection of their babies.

Several studies have evaluated the simultaneous administration of hepatitis B vaccine and other vaccines. In one such study, the interaction of hepatitis B and DTP vaccine was investigated in Senegal.[34] The immune response was evaluated when the vaccines were given either together or separately to children. The immune response to HBsAg vaccine and DTP vaccine injected simultaneously was equal to the immune response seen after each of these vaccines was given alone. Moreover, no adverse reactions were noted.

Simultaneous administration of hepatitis B and yellow fever vaccines was also studied in Senegalese children.[35] Yellow fever antibodies were detected in a similar proportion of infants immunised with yellow fever vaccine alone or associated with hepatitis B vaccine. However, yellow fever antibody values were slightly lower when both vaccines were given at the same time. Nevertheless, it was felt that the difference in antibody titres between infants receiving yellow fever vaccine alone or associated with hepatitis B vaccine had no implication for the yellow fever programme of immunisation in west Africa, as it is the practice to give booster doses to the general population when new cases of yellow fever appear.

A number of studies also looked at simpler and cheaper ways of hepatitis B vaccine administration, as most developing countries have problems with regard to infrastructure, manpower, and the cost of the vaccine, which, until recently, has been quite expensive. In one such study, using HevacB 350, Senegalese infants aged 3–5 months were randomly allocated to three groups: group A (two doses of 5 μg two months apart), group B (two doses of 2 μg two months apart), and group C (three doses of 2 μg one month apart). All had a booster (5 or 2 μg) six months after the first dose.[36] In group A, the seroconversion rate was 96% after the booster dose and the geometric mean titre (GMT) was 848 mIU/ml. The two doses of 2 μg (group B) provided an unsatisfactory seroconversion rate and GMT. However, the results in group C (three doses of 2 μg) were very good with a GMT after the booster dose of 1660 mIU/ml and 95% protection at six months. Thus, either three doses of 2 μg hepatitis B vaccine with a booster at six months or two doses of 5 μg plus a booster at six months were recommended as being effective and economical.

Another study from Senegal compared the immunogenic effect of hepatitis B vaccine (HevacB) in children using a two and three dose protocol.[37] Seventy two seronegative infants received two doses of 5 μg at a two month interval and 111 infants received three doses of 5 μg at one month intervals. All children had a booster at one year. No difference was seen between the two groups in the seroconversion rate (93·1 and 94·6%, respectively) or GMT (82 and 92 mIU/ml respectively). The study showed that two doses of 5 μg hepatitis B vaccine, with a booster at one year, was sufficient in infants to obtain a high immunogenic effect.

In Nigeria, Ayoola *et al* looked at the efficacy and immunogenicity of hepatitis B vaccine (HevacB) given intradermally to 125 people (aged 1–45 years) who were negative for HBV markers.[38] The subjects were randomised into two groups: group 1 comprised 64 volunteers who were given three doses of 2 μg vaccine mixed with adjuvant, given subcutaneously at monthly intervals; group 2 consisted of 61 volunteers who received three doses of 2 μg vaccine without adjuvant, given intradermally at monthly intervals. One month after the third dose, 83% of group 1 and 71% of group 2 showed a positive anti-HBs response. The levels of antibody were significantly higher in group 1 at each stage of the follow up period, including one month after a booster vaccination was given. The positive response was maintained in almost all the initial responders for the 24 month duration of the study. No significant side effects were reported in any of the participants. The study raised the possibility of protecting the population at risk in developing countries with small doses of vaccine given intradermally. Given the significantly lower anti-HBs antibody titres in group 2 and the difficulties associated with intradermal vaccination on a large scale, however, intradermal hepatitis B vaccination is probably not a viable option for Africa as a whole.

Several studies have provided some insight into the longterm efficacy of hepatitis B vaccine in infants in an endemic area. Coursaget *et al*, in Senegal, looked at the efficacy of HevacB during a three year follow up after the booster dose in 83 infants.[39] These infants, who had previously received three injections of 5 μg at one month intervals plus a booster dose 12 months after the first injection, were compared with 117 infants from a control group vaccinated only with DTP vaccine. In the vaccine group, the HBV infection rate per year was 0·9%, compared with 14·5% in the control group. The protective efficacy rate was

93·8% if all HBV events were considered (HBsAg and anti-HBc positive) and 100% if only HBsAg events were considered. The protective effect was reflected in the levels of anti-HBs antibodies in the vaccinated infants from blood samples taken three years after the booster; 97·5% had anti-HBs antibodies and the median anti-HBs titre was 200 mIU/ml.

Yvonnet *et al* reported the longterm persistence of anti-HBs antibody in 156 Senegalese children vaccinated using the schedule of zero, one, and two months with a booster at 12 months.[40] Six years after the booster dose, 90·4% of the children had detectable anti-HBs antibodies, with 78·1% having titres higher than 10 mIU/ml. The GMT was 60 mIU/ml. Females showed higher anti-HBs values than males. In a group of children who received no booster dose, anti-HBs antibodies were detectable seven years after the first dose. However, the GMT was lower (26 mIU/ml). Revaccination with a booster dose (56 children) led to an increase in the GMT to 469 mIU/ml two months later. The results show that a booster dose at five to six year intervals may be necessary to provide adequate anti-HBs levels.

Another study by the same group followed up the incidence of hepatitis B in 135 children vaccinated against hepatitis B and 143 children constituting the control group (vaccinated with DTP vaccine).[41] Over the following six years, the incidence of hepatitis B was 1·5% per year in the group vaccinated against hepatitis B, compared with 11·5% per year in the control group. In the first four years, the protective efficacy of the vaccine was 100% but during the fifth and sixth years it fell to 67%. For maximum protection, another booster dose was recommended five years after the first booster.

Perhaps the best known study is the Gambia Hepatitis Intervention Study (GHIS).[42] This longterm intervention study was designed to evaluate the effectiveness of hepatitis B vaccination for the prevention of chronic liver disease and hepatocellular carcinoma. The study is a joint venture between the Gambian government, The International Agency for Research on Cancer (IARC), and the Medical Research Council (MRC) laboratories in The Gambia and is financially supported by the Department of Co-operation and Development of the Ministry of Foreign Affairs in Italy. The study comprises three overlapping phases:

Phase I: vaccination programme – five years.

Phase II: longitudinal and cross sectional studies of HBV events in selected groups – 10 years.

Phase III: longterm follow up to monitor incidence and prevalence of HBV related chronic liver disease – 40 years.

The study, which started in 1986, has successfully integrated hepatitis B into the Gambian Expanded Programme on Immunisation (EPI). In 96% of infants, hepatitis B immunisation elicited adequate protective antibody levels, with the number of non-responders being 4% after a three year period of the programme. Serological results from a sample of vaccinated children showed that vaccination was effective in reducing the numbers of persistently infected children. There were no major logistical difficulties and total national childhood immunisation coverage was achieved over a period of four years.

The International Task Force on Hepatitis B Immunisation has recommended the establishment of model immunisation programmes within specific regions before expansion nationwide.[43] In these model programmes, innovative approaches for incorporating hepatitis B vaccination into the EPI can be evaluated, vaccinators can be retrained, and new educational and motivational material developed. Such model immunisation programmes were initially introduced in Kenya and Cameroon. Since then, other countries in sub-Saharan Africa, such as Botswana, Zimbabwe, Mauritius, and South Africa, have introduced universal infant hepatitis B immunisation programmes as part of their national EPI programmes.

Controlling hepatitis B in sub-Saharan Africa

The high incidence of HBV related liver disease, including hepatocellular carcinoma, has made the eradication of HBV one of the most important tasks facing public health authorities in Africa. Although the importance of measures such as blood bank screening for HBV should not be overlooked, immunisation is the single most important factor in any national hepatitis B control programme and has the potential to eradicate hepatitis B and reduce the incidence of chronic liver disease and cancer in Africa. In view of the epidemiology of hepatitis B in sub-Saharan Africa, the concept of high risk groups such as health care personnel, dialysis patients, homosexuals, etc, is irrelevant to immunoprophylaxis. All children should be regarded as being at high risk as most infections are acquired in early childhood.

There are two basic approaches to vaccination programmes in sub-Saharan Africa: mass vaccination of all infants (without screening for HBsAg) and immunisation only of infants born to HBsAg positive mothers. As horizontal, not perinatal, transmission seems to predominate, the second approach can only reduce the HBV chronic carrier rate by a small percentage, while the limited resources available in the region means that large scale testing of pregnant women is not feasible. Therefore, mass vaccination of all infants would be the most effective approach to hepatitis B prevention and control in sub-Saharan Africa.

The target population for hepatitis B vaccination in Africa is enormous. However, in the absence of a childhood vaccination programme, one would expect millions to die from hepatitis B related diseases in adulthood. In Mozambique, for example, the age standardised incidence rate for hepatocellular carcinoma in males is 103·8 per 100 000 per year.[44] It accounts for no less than two thirds of tumours in men and one third of those in women.

The incorporation of hepatitis B vaccine into the EPI is the most cost effective strategy

TABLE II *Options for adding hepatitis B vaccination to the Expanded Programme on Immunisation schedule recommended by the World Health Organisation*

Age	Contact number	Option I	II	III	IV
Birth	1	BCG, HBV 1	HBV 1		
6 weeks	2	OPV 1, DTP, HBV 2	HBV 2	HBV 1	HBV 1
10 weeks	3	OPV 2, DTP 2		HBV 2	HBV 2
14 weeks	4	OPV 3, DTP 3			HBV 3
24–48 weeks	5	Measles, HBV 3	HBV 3	HBV 3	

OPV: oral polio vaccine; DTP: diphtheria, tetanus, and pertussis.

for the prevention of hepatitis B infection in sub-Saharan Africa. The use of the hepatitis B immune globulin (HBIg) as an adjunct to vaccination has been advocated in some areas such as the Far East where perinatal transmission is common. The efficacy of hepatitis B vaccine alone is between 75 and 90%, while the efficacy when HBIg is added to hepatitis B vaccination is as high as 95%. The use of HBIg adds considerable cost to the treatment, however, and is practicable only in countries that can establish and pay for routine resting of pregnant women. It is more cost effective to devote available resources to routine infant immunisation with vaccine alone, and most developing countries will elect to forego use of HBIg.

The schedule of administration of hepatitis B vaccine should be coordinated with the delivery of the other EPI vaccines. Ideally, the first dose of hepatitis B vaccine should be given as soon as possible after birth and, in all cases, at the first immunisation contact. The second dose should be given at the next immunisation contact, and the third dose with the third, fourth or fifth contact. The reason for this variation in scheduling of the third dose of hepatitis B vaccine is that, the longer the interval between the second and third doses, the higher the maximal protective antibody titre achieved. While the achievement of such maximal titres may be theoretically desirable, it is not clear whether such levels have any impact on the duration of protective immunity. The decision to delay the third dose until the time of measles immunisation must be weighed against the possibility that a third dose will not be delivered at all because of lower overall measles immunisation coverage rates.

Table II shows four options for adding hepatitis B vaccine to the recommended EPI schedule. Options I and II emphasise the initial delivery of hepatitis B vaccine at birth and are the recommended options where vaccination at birth is possible. These are particularly relevant to Asia, where perinatal transmission of hepatitis B is common. Options III and IV are for areas where immunisation at birth is not easily accomplished. They might also be more appropriate in regions such as sub-Saharan Africa where perinatal transmission is uncommon. Option IV permits simultaneous delivery with DPT and anticipates the future availability of a combined DPT-hepatitis B vaccine.

As previously mentioned, a number of hepatitis B vaccination programmes have been initiated in sub-Saharan Africa. Perhaps the best known programme is the GHIS, which is the first programme to achieve national coverage in this region. Other important programmes in Kenya and Cameroon, supported by the International Task Force on Hepatitis B Immunisation, have produced a catalytic effect on the launching of hepatitis B immunisation programmes throughout Africa.

A great deal has been learned from the existing hepatitis B vaccination programmes. For the vaccine to be successfully incorporated into the EPI, comprehensive training programmes for health staff are absolutely essential. Health staff need updated information that a safe, effective vaccine now exists at an affordable price for public sector programmes. They also need to know that hepatitis B vaccine can safely be delivered with the other EPI vaccines and that it has very minor side effects. The administrators and the general public also need to know about the disease, its consequences, and its prevention, including hepatitis B vaccination. They need to know that the vaccine is safe, and that three doses are required for full protection. They also need to be kept informed as to the schedule of hepatitis B vaccination.

Vaccines are currently available on the international market from Merck, Sharpe and Dohme, SmithKline Beecham Biologicals, the Korea Green Cross Corporation, and Cheil Food and Chemicals. Hepatitis B vaccines are also produced in China, Cuba, and Japan but are not yet available on the international market. Plasma derived hepatitis B vaccine has been procured for large scale public sector infant immunisation programmes for as little as $0.55 per dose and rDNA-hepatitis B vaccine for as little as $0.95 per dose. These are the kind of prices that can be achieved with a large order on an international rather than a local tender and bid. The International Task Force on Hepatitis B Immunisation has expressed its willingness to undertake this task on behalf of several African nations and it is hoped that more countries in sub-Saharan Africa will be willing to participate.

In conclusion, mass hepatitis B vaccination programmes, such as the one in Gambia and the model programmes in Cameroon and Kenya, should be initiated in the rest of sub-Saharan Africa. Thanks to the efforts of the WHO and the International Task Force on Hepatitis B Immunisation, the dramatic reduction in the price of hepatitis B vaccines now makes this feasible, and the number of countries in sub-Saharan Africa introducing national hepatitis B immunisation programmes continues to grow.

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Discussion

Zuckerman: What is the rate of loss of HBeAg in Zimbabwe?

Kiire: We have not looked at this in a prospective manner, but we know that the HBeAg positivity rate up to the age of 5 years is about 50%, and that only about 10–15% of mothers are HBeAg positive. Extrapolating from those figures, we could work out a rate of loss. I think it is much higher than that seen in the Far East.

Zuckerman: Are there any data from South Africa on the rate of loss of HBeAg or seroconversion to anti-HBe over a period of time?

Kew: The HBeAg positivity rate starts off very high and then falls rapidly. In fact, in South Africa, only 5% of adult black male carriers are HBeAg positive.

Goudeau: It is the same in Senegal. The HBeAg positivity rate starts at 50–60% before the age of 5 but then declines very rapidly – much more rapidly than it does in the Far East. We don't know why.

Hollinger: In clinical trials in the US among immunocompetent adults, in which untreated control groups are used, the frequency for spontaneous loss of HBeAg is in the range of 5–15% per year.

Zuckerman: Why do people seroconvert so quickly without any treatment? Is it age related?

Kew: In South Africa, we wondered whether we might be seeing conversion to precore mutant infection on a massive scale, but we have recently confirmed that is not the answer. Precore mutants are very rare in black South Africans.

Kiire: The same is true for sub-Saharan Africa.

Kew: An interesting piece of information in this regard is that the Chinese who have immigrated to South Africa from China and Taiwan have retained their Eastern pattern. That is, 40% of Chinese women living in Johannesburg are HBeAg positive during their reproductive period despite two or three generations in the new environment. This suggests that it is genetically rather than environmentally determined.

Yao: It is interesting that 10 years ago the adult HBeAg positivity rate in southern China was 50% but this has fallen very rapidly in recent years, to just 30%.

Gordeau: What we need to do is follow up African children that have become infected very early in life – like Chinese children – to see whether very early transmission has a part to play in the persistence of HBeAg.
Zuckerman: Another factor that comes into play is the reliability of the serological tests for HBeAg and anti-HBc.
Goudeau: At least in Europe, we have a problem with testing for anti-HBc. Most of the anti-HBc tests have been prepared for blood transfusion programmes and have therefore been designed to have increased sensitivity to avoid any transmission of hepatitis B. Unfortunately, this means that there are now a lot of false-positive reactions because the assays have poor specificity.
Hollinger: Dr Kiire, you said that after four doses of hepatitis B vaccine given at zero, six, 10, and 14 weeks, only 64% had made antibodies at one year. After three doses, only 32% responded. These figures are really low.
Kiire: This is a field situation. We estimated that we would get about a 75% response rate after four doses, but in fact it was only 64%.
Zuckerman: In the UK, we have found many non-responders even among HIV negative subjects. That is, between 10% and 15% of adults do not respond to the current vaccines. Another very important point is the antibody level that we consider to represent a response to the vaccine. In the UK, we now have legislation that all medical students and hospital personnel have to be immunised against hepatitis B, but what antibody level should we consider to be protective? Should we take 10 IU/l or 100 IU/l as the cut off point?
Hollinger: There seem to be fairly good data that if anti-HBs levels reach at least 10 IU/l, the probability of infection after exposure is very low. Furthermore, if antibody titres reach 100 or 200 IU/l and then fall to less than 10 IU/l, that is not the same as never reaching 10 IU/l in the first place. The first group will certainly retain their immunity, while the second group remains at risk.
Goudeau: The key point is not really the antibody titre. With an anti-HBs level of 100 IU/l, infection will not occur. But as long as a person has some antibody response – even a very low one – they may become infected but they will not become a chronic carrier, which is most important.
Kiire: Another point is that, in an endemic situation, the recommendation may be slightly different from that where contact with a hepatitis B carrier is unlikely. In the Gambian study, even children with very low antibody titres mounted a fairly good anamnestic response when they were exposed to infection, and anyway were unlikely to become chronic carriers.
Hollinger: In reviewing data on durability of immunity, it is important to recognise that results have been obtained from immunisation with the plasma derived vaccine. This seems to be a stronger immunogen than the recombinant vaccine, perhaps because it has some pre-S material in it and also because of its conformation.
Goudeau: To achieve the same immunisation pattern, you need 20 μg of the recombinant vaccine and only 5 μg of the plasma derived one.
Hollinger: We probably need to wait a little longer to see whether the recombinant vaccines are less immunogenic or whether it has to do with the way in which they given. We just don't know what the longterm durability is likely to be with either the plasma derived or the recombinant vaccines, especially the latter.
Zuckerman: Would you recommend a booster dose if someone's antibody titre declines to below 100 IU/l and that person is at risk of exposure to HBV – a surgeon, for example?
Gust: Under those circumstances, boosting is usually recommended, because you know it will do no harm and it may possibly be of benefit. There is, however, no strong scientific basis for that position.
Toukan: Rather than talking about durability of antibody response, perhaps we should be investigating the durability of the immune response in an individual?
Lansang: In the Philippines a few years ago, we tested a single dose of 1·5 μg vaccine against three doses. After three years, we retested these children and many of them no longer had detectable antibody. When we gave them a second dose, 69·7% showed anti-HBs, suggesting that memory cells are still there.
Ahn: What is the seroconversion rate from HBsAg positive to HBsAg negative in Africa?
Goudeau: In Senegal, the carrier rate among young adults is about 15%. About half of these will lose HBsAg over three or four years, but they may still eventually die from hepatitis B related cirrhosis or hepatocellular carcinoma even though the virus itself has disappeared.