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The Gambia Hepatitis Intervention Study[1]

The Gambia Hepatitis Study Group[2]

ABSTRACT

The Gambia Hepatitis Intervention Study is a large-scale vaccination project in The Gambia, initiated in July 1986, in which the introduction of national hepatitis B (HBV) vaccination of young infants progressively over a 4-year period is proposed. During this time it is anticipated that about 60,000 infants will receive a course of HBV vaccine and a similar number will not receive the vaccine. All children in the study will receive the normal childhood vaccinations. Identification data for each child will be collected and stored with information on their vaccination records. A national surveillance system will be set up to detect new cases of hepatocellular cancer and other chronic liver diseases over a period of 30 to 40 years. An attempt will be made to trace each case, of relevant age, to determine if they are included in the HBV vaccination study. In this way, the efficacy of HBV vaccine in the prevention of HCC and chronic liver diseases will be evaluated. Details of the study design are discussed.

INTRODUCTION

Chronic liver diseases and HCC[3] are major health problems of adults in many countries, particularly on the continents of Asia and Africa. On a world population basis, HCC is one of the most common cancers and it has been estimated that there are over 250,000 incident cases each year (1). In most developing countries, where the disease has the highest incidence, the curability rate is near zero.

In Senegal, West Africa, the incidence of HCC, age-adjusted to the world population, has been reported to be approximately 25 cases per 100,000 population per year among males and about 3-fold less among females (2), but these may be underestimates and the true incidence may be considerably higher. The disease occurs in West Africa at a considerably earlier age than in China and Southeast Asia. The incidence of cirrhosis and other chronic liver diseases is probably much higher than that of HCC but is difficult to determine from available data. The control of chronic liver disease and liver cancer would have an important public health impact in countries where these conditions are endemic.

There is strong evidence for an etiological association between HBV infection and HCC. It is based on seroepidemiological studies, both retrospective (3) and prospective (4), and on the demonstration of HBV DNA integration with the host cell DNA in liver tumors and in liver cells of persistent carriers of HBV (5). In addition, there are several animal models in which viruses closely related to human HBV can reproducibly induce HCC (6). It seems that in areas of high endemicity for HBV infection the HBsAg persistent carrier state is a major risk factor for HCC as well as for a high proportion of cases of chronic liver diseases.

The development of safe and effective subunit vaccines against HBV offers the potential for preventing a high incident cancer and for reducing the significant morbidity and mortality attendant on the other chronic sequelae of HBV infection.

In this paper we outline the design of a long-term study which has started recently in The Gambia to evaluate the impact of HBV vaccination on the incidence of HCC and other liver diseases.

NEED FOR A CONTROLLED VACCINE TRIAL

A number of trials have been conducted to assess the protective effect of the currently available plasma-derived HBV vaccines against HBV infections. These trials, in selected high-risk groups (*e.g.*, homosexuals, hospital personnel), have shown that the vaccines are effective in the prevention of acute hepatitis B and the HBsAg carrier state (7, 8) and, among infants in West Africa, the most effective schedules of vaccination include a booster dose some months after the initial course (9). The vaccines have not been associated with the transmission of hepatitis and no important adverse side effects have been described. As yet there are few data on the durability of immunity beyond 5 years nor is it known if the vaccine will prevent liver cancer and the other chronic sequelae of HBV infection or whether immunization in infancy will permanently reduce the risk of becoming a carrier. Despite this, many consider that the indirect evidence that HBV vaccination will prevent a significant proportion of liver tumors and other liver diseases is sufficiently strong that mass vaccination campaigns should be started as soon as possible in those areas where the infection has high prevalence. A major obstacle to such campaigns in Africa is the high cost of the vaccine. At present the cost of a single course of HBV vaccination is many times the combined cost of all of the other vaccines that a child receives in routine immunization programs, although the cost of HBV vaccine is falling.

Ideally, it would be desirable to have direct evidence of a protective effect of HBV vaccine against chronic liver diseases and HCC from controlled trials before launching mass campaigns. This would mean delaying such campaigns for 30 years or more; however, as in Asia and Africa HBV infection occurs very early in life but chronic liver diseases and HCC do not have an appreciable incidence until two or three decades later. The best that can be done is either to launch controlled studies at the same time as mass vaccination campaigns start or to design the mass campaigns such that later evaluation of their impact can be made in an unbiased way. The rationale for such studies was summarized in the report of a WHO meeting on the prevention of liver cancer (10).

> "... it was recognized that it would be undesirable to consider immunization on a widespread scale without, at the same time, organizing studies that were designed to establish whether or not the vaccine was producing a reduction in the incidence of the carrier state and subsequently cancer ... The best method of ensuring that a protective effect of immunization could be measured would be to use randomized controlled trials ... Such a randomized trial would present ethical

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[3] The abbreviations used are: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; EPI, Expanded Program of Immunization; DPT, diphtheria-pertussis-tetanus toxoids.

problems if sufficient vaccine were available to treat all newborn children. At present, and probably for the next several years, however, this is not the position as the vaccine is expensive and supplies are limited."

It was with those considerations in mind that the study in The Gambia was planned.

HEPATITIS TRIAL IN THE GAMBIA

In West Africa, including The Gambia, nearly everyone is infected with HBV during childhood (11, 12). In contrast to the situation in Japan and Taiwan (13) where a high proportion of infants are infected perinatally, infection of newborns is uncommon in West Africa as in other parts of the Southeast Asian region, such as Singapore and The Philippines. During the first 2 years of life, however, infection rates increase rapidly so that by the age of 2 years, 40% of the children have already been infected with HBV and 15% have developed persistent infection (14–16). By the age of 10 years, 90% of the children have been infected and 20% have become chronic carriers.

Acute disease caused by hepatitis B infection is not recognized as a major problem in The Gambia. However, the high prevalence of the HBsAg carrier state is believed to be the major risk factor for chronic liver disease and liver cancer, both of which represent significant public health problems.

Pilot trials of HBV immunization of newborns and infants in Senegal and The Gambia have shown that HBV vaccine is immunogenic even when administered at birth and irrespective of the HBV status of the mother, and no important side effects have been observed (9, 12, 16).

The Gambia (Fig. 1) is particularly suitable for the conduct of a long-term trial of HBV vaccine. The country is the smallest

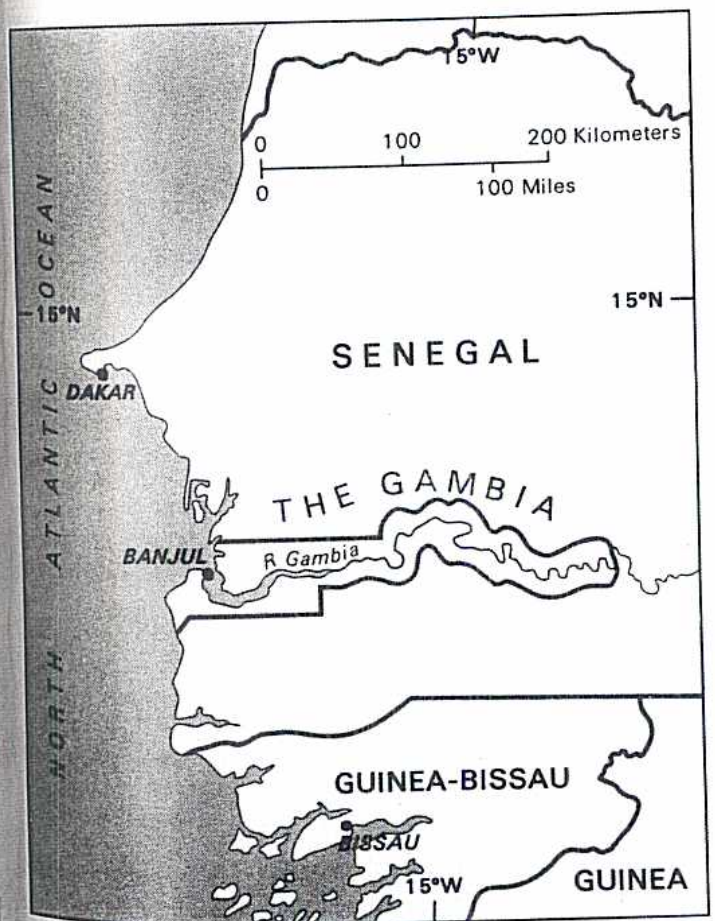

Fig. 1. The Gambia and neighboring countries.

Table 1 *Schedule of immunization in The Gambia*

Age (mo)	Routine EPI vaccines	HBV vaccine
Birth[a]	*Bacillus Calmette-Guérin*	First injection
2	DPT, polio (first dose)	Second injection
3	DPT, polio (second dose)	
4	DPT, polio (third dose)	Third injection
9	Measles, yellow fever	Fourth injection

[a] Within 1 month of birth.

(10,400 km^2) in Africa and its population of about 750,000 is one of the most dense (about 70 persons/km^2) on the continent. The villages are readily accessible and 90% of the population live in about 500 villages which are fairly evenly located throughout the country. In rural areas the crude birth rate is about 40/1000 and the infant mortality rate about 140/1000 live births.[4]

There are two government hospitals in the country, 17 health centers and 15 dispensaries, all of which have full-time staffs. In addition, there are 80 subdispensaries which are regularly visited weekly, every 2 weeks, or monthly by staff from the health centers. The vaccination program is among the best in Africa.

Routine Vaccination Program. In 1979, The Gambian Government initiated an Expanded Program of Immunization in collaboration with WHO. Under this program, it was intended that all children in The Gambia should receive vaccines, other than hepatitis B vaccine, as described in Table 1.

The EPI has a central staff, a refrigeration maintenance group, and 17 immunization teams.[5] Each team is directed by a trained nurse and includes a health inspector who has had 3 years of training in public health at The Gambian School of Public Health and two or three auxiliary nurses. The teams, which are based at the health centers, have their own transport and visit 104 delivery points at least once every 2 weeks.

Each child receives an "Infant Welfare Card" at their first visit in which the dates of all subsequent vaccinations are recorded. The vaccination schedule is shown in Table 1.

The report of an international evaluation of The Gambian EPI in November 1982 (17) documented the successful operation of the Program. The EPI undertakes routine cluster sampling to assess the proportion of the population covered. In 1986, 93% of the eligible infants were found to have received their first DPT vaccination and about 60% had received the full course of immunizations through to measles vaccination by the age of about 18 months (18).

Considerations Underlying the Choice of Study Design. Several factors affected the final design that was adopted: (*a*) the expense of the vaccine and its limited availability prohibiting immediate universal HBV vaccination; (*b*) the desirability of having comparison groups available from the same time period; (*c*) the severe logistic difficulties that would have been encountered with randomization at the individual level in a trial of this magnitude, with a large number of immunization teams working under field conditions and with four vaccine doses per individual being required. Individual randomization might also have appeared ethically questionable; (*d*) the hope that HBV vaccine would be widely available at the end of the study and that by that time a nationwide delivery system should be in place. These considerations led us to the "stepped wedge" design described below.

Phased Introduction of HBV Vaccine. HBV vaccination is to be added to the vaccination schedule of the EPI in a phased

[4] B. M. Greenwood, personal communication.

[5] Since the study was planned the number of immunization teams has been increased but the basic structure of the study design remains unchanged.

manner on a vaccination team by vaccination team basis at approximately 10- to 12-week intervals such that complete national coverage should be achieved within a period of about 4 years. At present, each of the 17 EPI teams are responsible for vaccinating children in a defined area of the country. Initially, in July 1986, one team was selected at random to administer HBV vaccine, in addition to the currently used EPI vaccines, to all newborn children who report to any one of the vaccination points served by the team. The other 16 teams continued with the normal EPI vaccines. After about 3 months, a second team was selected, at random, to administer HBV vaccine in addition to the first team selected. Three months later a third team was selected to administer HBV vaccine. This process will continue over a period of about 4 years until all teams are giving the vaccine. This scheme is illustrated in Fig. 2. The evaluation of the protective effect of HBV vaccination against liver cancer and chronic liver disease will be made through the long-term follow-up of those children born during the 4-year period over which HBV vaccine was introduced. For children born in each 3-month period, the incidence of subsequent HCC and chronic liver diseases will be compared among those who were given HBV vaccine and those who were not. Thus, for entrants in the first 3 months, the subsequent experience of those reporting to one vaccination team will be compared with that of those reporting to any of the other 16 teams. For entrants in months 4 to 6, the subsequent experience of those reporting to either of the two teams giving HBV vaccine will be compared to that of those reporting to any of the remaining 15 teams. Such comparisons will be possible for entrants up to the last 3 months of the "expansion" period when there will be 16 teams giving HBV vaccine and one team not.

After this country-wide coverage has been achieved, newborn children will cease to be registered for follow-up as part of the present study although it is anticipated that HBV vaccination will continue.

The comparison of HBV-vaccinated and unvaccinated children on the above basis will ensure that any changes in the risk of developing HCC affecting children born at different times will not bias the comparison of HBV-vaccinated and unvaccinated groups. Furthermore, bias in the comparison of the vaccinated and unvaccinated groups has been minimized by introducing HBV vaccine into the schedules of the 17 different teams in a random order.

Little is known about the geographical variability in the incidence of HCC in different parts of The Gambia. An important contribution of continuing cancer registration will be to ascertain such variation as does exist. There are fairly distinct ecological zones in The Gambia and it is possible that these may be determinants of, or be correlated with, the incidence of HCC. For this reason it has been considered advisable to stratify the country into four zones and design the randomization scheme to achieve a balanced introduction to HBV vaccination between the different zones.

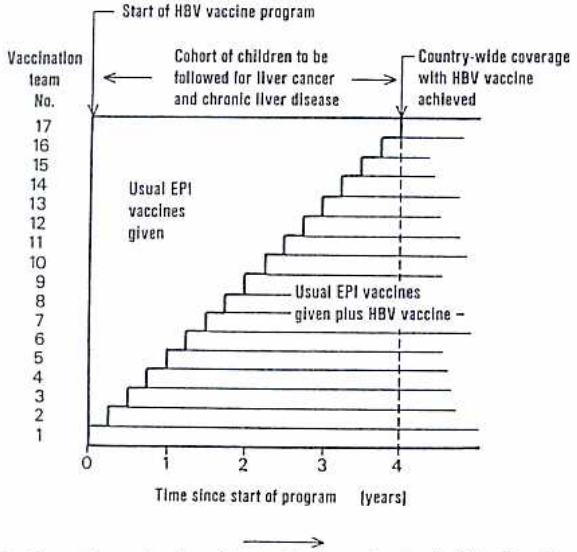

Fig. 2. Phased introduction of hepatitis B vaccination in The Gambia.

The statistical power of this "stepped wedge" design (Fig. 2), in which HBV vaccine is introduced on a vaccination team by vaccination team basis, is over 70% of that of an alternative randomized design in which one-half of the teams are allocated to give HBV vaccine for a 4-year period and the other half are not. Absence of bias for the evaluation of vaccine effect is ensured by randomizing the order in which the vaccine is introduced on a region by region basis. The 17 randomization units (EPI teams) are sufficient for rigorous inferences to be drawn.

A schedule of four doses (10 μg/dose) was chosen on the basis of studies in Senegal (10) and pilot studies in The Gambia.[6] The doses of HBV vaccine are being administered i.m. and according to a schedule which coincides with the existing EPI immunizations (Table 1). The first HBV dose is given shortly after birth at the same time as Bacillus Calmette-Guérin. The second HBV vaccine injection is given 1 month later concurrently with the first DPT and polio shots. The third HBV vaccination takes place at age 4 months, when the infant receives the third DPT and polio vaccines. A "booster" dose of HBV vaccine follows at 9 months with measles and yellow fever vaccines.

The basic comparison is between two individually identified groups, those who present themselves for vaccination by EPI teams administering HBV vaccine and those attending vaccination points at which the EPI team is not administering HBV vaccine. Further refinement will be achieved by limiting the comparison to those who attend the vaccination clinics at all four ages at which HBV vaccine would be given. It is assumed that the selection process which leads an infant to attend the clinic at the four relevant dates is independent of whether or not HBV vaccine is being given.

Identification of the Persons Vaccinated. A prerequisite for the trial is that persons vaccinated shortly after birth are sufficiently well identified that their records can be located if they present with HCC or other liver diseases 30 or 40 years later. In The Gambia individuals sometimes change their names and may not remember their birth date. It has been necessary, therefore, to use several independent identification systems.

The name, sex, birth date, and village of residence, as well as the full names of the natural mother and father, are being recorded for all infants who enter the study by clerks attached to each vaccination team. The site of the BCG vaccination is used as an indicator of whether or not the infant received HBV vaccine. Two sites different from that usually selected have been chosen, one for all children entered into the program who do not receive HBV vaccine and the other for those children who receive HBV vaccine. In addition a handprint and a footprint are being taken from each child at age 4 months as a further means of checking identity. Like fingerprints, the patterns on the hands and feet set down *in utero* do not change, except in size, throughout life. Pilot studies have shown that footprint patterns are easily distinguished in adult Gambians and that

[6] H. C. Whittle, personal communication.

good quality prints can be obtained from young infants.

Long-Term Follow-up. Nationwide cancer registration will be established in the initial phase of the vaccination program. The activities during the period of long-term follow-up include the maintenance and strengthening of the cancer registry and the initiation of active surveillance throughout The Gambia for cases of HCC, cirrhosis, and other types of chronic liver disease. Clinical and laboratory diagnostic screening techniques, designed for field use, will be used (α-fetoprotein, ultrasound, and liver function tests). When cases of liver cancer or liver disease are detected in someone of relevant age, extensive efforts will be made to determine if the subject is included in the study. From the computer-stored immunization records, it should be possible to identify those subjects who received a full course of HBV vaccine and those who did not receive HBV vaccine. These data should permit an analysis of the protective effect of a full course of HBV vaccine against HCC and other chronic liver diseases. Information on the number of people from the original cohort still at risk of appearing in the disease register will also be obtained. Whether complete population enumeration, sample surveys, or a case-control approach is adopted will depend on circumstances at the time. Unpredictable population changes that may arise in the intervening years should not prevent a rigorous comparison.

Size of Study. The minimum number of HCC cases required to give conclusive results depends on the expected protective effect of the vaccine.

Table 2 shows, for various protective efficacies, the approximate number of cases of HCC that must be expected to occur for there to be a good chance (95%) of finding a statistically significant difference between the incidence rates of HCC in two randomized groups. For example, if the vaccine gave a protective efficacy of 80%, it would be necessary for the trial to be of such a size that about 21 cases of HCC would be expected in the control group.

In the first 4 years of the proposed study, approximately 60,000 children will receive HBV vaccine and 60,000 will not. One-half of these children will be males, from whom 80% or more of the HCC cases will arise for the comparative analysis. The reasons for the marked excess of males among cases of HCC in Africa and elsewhere are not known but the excess is much greater than the difference between the sexes in the prevalence of the HBsAg carrier state.

In Table 3, the estimated age-specific rates of HCC up to the age of 50 years are given for The Gambia. These rates are based on only a single year of observation and are lower than those for Senegal (2). Table 3 shows the age-specific rates and the number of cases of liver cancer expected in a cohort of 30,000 newborn males. Various numbers are given assuming different overall attrition rates in the follow-up period. Most of this attrition will be accounted for by infant mortality and outward migration.

The following assumptions regarding vaccine efficacy, program coverage, and the proportion of HCC attributable to HBV are made. Assumption 1: Based on the EPI evaluation survey of 1982 and the improvements that should follow implementation of the program, it is assumed that 85% of eligible children will present themselves for at least one injection in the HBV vaccination series, 80% will present themselves for at least two injections, and 75% for all three injections and the booster injection. Assumption 2: The efficacy of vaccination depends on the number of injections given. Among those not infected perinatally, after one or two injections, without a booster, 20% respond; after one or two injections with a booster, 80% respond; and after a full course of 3 injections and a booster, 95% respond. It is also assumed that response is durable due to continued HBV challenge in the environment. If this assumption proves to be incorrect, a further booster vaccination between 5 and 10 years of age will be considered at a later date. Assumption 3: Among those destined to become HBV carriers, 10% acquire their carrier status perinatally, only 50% of whom would be protected by vaccination. Assumption 4: Between 80 and 90% of HCC occurring under age 50 years is attributable to HBV.

The validity of assumptions 1 to 3 will be assessed during the early phase of the study.

Given these assumptions, it is possible to calculate the prevalence of the carrier state among those fully or partially vaccinated, relative to those not vaccinated. The effect on HCC incidence of reducing the prevalence of the carrier state depends on the proportion of HCCs that are due to HBV infection (the attributable risk). In Table 4, two values are considered: (*a*) an attributable risk of 80% based on data from The Gambia on the prevalence of the carrier state among HCC cases and controls (12); and (*b*) an attributable risk of 90% based on the supposition that more sensitive tests may show a higher proportion of HCC associated with HBV.

As can be seen from Tables 4 and 5, the partially vaccinated groups dilute the protective effect of vaccination and provide

Table 2 *Approximate expected number of cases required in unstratified control and vaccinated groups to be 95% sure of detecting a significant difference at the 5% level of statistical significance*[a]

Protective efficacy[b]	Expected no. of cases required[c]	
	Control group	Vaccinated group
95	13	1
90	15	2
80	21	4
70	29	9
60	42	17
50	65	33
40	109	65
30	205	143
20	487	390
10	2057	1851
5	8443	8021

[a] Based on the approximate formula

$$\text{No. in control group} = (Z_\alpha + Z_\beta)^2(2 - e)/e^2$$

where e is protective efficacy (measured as a proportion) and $Z_\alpha = Z_\beta = 1.645$ for one-sided test at the 5% level with 95% power.

[b] $$\text{Protective efficacy } (e) = 1 - \frac{\text{Incidence of HCC in vaccinated}}{\text{Incidence of HCC in control}}$$

[c] Rounded up to nearest whole number.

Table 3 *Cumulative incidence of liver cancer up to age 50 years in The Gambia*

Age group (yr)	Annual incidence of liver cancer/10^5 males[a]	Cumulative no. of cases in group of 30,000 newborn males (to end of each age group) assuming[b]		
		No attrition	30% attrition	50% attrition
0–4	0	0	0	0
5–9	0	0	0	0
10–14	2	3	2	1
15–19	3	7	5	4
20–24	5	15	10	7
25–29	8	27	19	13
30–34	11	43	30	22
35–39	18	70	49	35
40–44	38	127	89	64
45–49	52	205	144	102

[a] Data from 1981–1982 Gambian case-control study (12).
[b] Estimates based on data for males.

Table 4 *Effect of HBV vaccination on the prevalence of the carrier state and the incidence of HCC*

Vaccination status	Proportion (%) expected among study population targeted to receive HBV	Efficacy (%) assumed in those not infected prior to vaccination	Proportionate reduction (%) in carrier prevalence relative to unvaccinated[a]	Proportionate reduction (%) in incidence of HCC relative to unvaccinated (protective efficacy) assuming	
				80% attributable risk	90% attributable risk
Fully vaccinated (3 shots + booster)	75	95	90	72	81
Partially vaccinated (1 or 2 shots + booster)	5	80	76	61	68
Partially vaccinated (1 or 2 shots without booster)	5	20	19	15	17
Unvaccinated	15	0	0	0	0

[a] Assuming 10% acquire carrier status perinatally and vaccination protects only 50% of these.

Table 5 *Expected relative risks for HCC between various groups, depending on their vaccination status*

Vaccination status of groups compared	Relative risk (protective efficacy) based on	
	80% attributable risk	90% attributable risk
Fully vaccinated/unvaccinated	1:3.6 (72)[a]	1:5.3 (81)
Partially vaccinated[b]/unvaccinated (1 or 2 injections)	1:1.6 (38)	1:1.7 (42)
Full and partially[b]vaccinated/unvaccinated	1:3.1 (68)	1:4.2 (76)

[a] Numbers in parentheses, percentage.
[b] One or two shots with or without booster (see Table 4).

little information. Every effort will be made to minimize the size of these groups.

With the assumption that 80% of HCC under age 50 years is attributable to HBV a difference in risk of 3.6-fold is expected between the fully vaccinated and the unvaccinated (protective efficacy, 72%). With an attributable proportion of 90% the expected differences in risk will be over 5-fold.

The stepped wedge design has an efficiency of about 70% compared to a design in which one-half of the vaccination teams give HBV vaccine for the whole 4-year period and the other half do not. The expected number of cases in the control group required to achieve statistical significance with adequate power are, thus, 40% more than the numbers given in Table 3. Assuming 50% (see Table 3) attrition of the birth cohorts due to death and migration, slightly over 35 years may be needed to obtain unequivocal results.

Assessment of Intermediate End Points. In addition to the follow-up of the entire cohort for chronic sequelae, more detailed surveillance is planned for several subgroups.

From each of the first four vaccination teams introducing HBV vaccine, 250 children will be selected and examined on a regular basis throughout childhood and adolescence. Serological data on these children will given information on antibody induction and the duration of vaccine-induced immunity to the carrier state. The group will be used to monitor whether or not revaccination may be required on a mass basis should there be evidence of waning immunity.

Cross-sectional studies of the unvaccinated and vaccinated cohorts will also be conducted throughout the intake period of the trial to give information on the acquisition of HBV markers at different ages and the antibody response to different batches of vaccine, respectively.

Additional Studies. In addition to HBV infection, aflatoxin has been proposed as the other major risk factor for HCC in high risk populations in Africa and Southeast Asia. The main epidemiological evidence linking aflatoxin exposure with HCC risk is limited to correlation studies showing high levels of aflatoxin contamination of foodstuffs in areas with high incidence of HCC. This evidence could be strengthened by the demonstration of a history of higher individual exposure to aflatoxin among patients with HCC or at high risk of developing HCC than among appropriate control subjects. Immunoassays to detect aflatoxins and/or related metabolites in body fluids are currently being developed and consideration will be given to their application in the surveillance procedures to be developed in the study (19).

Although it is unlikely that the level of aflatoxin exposure will change in such a way to produce a significantly different effect in the vaccinated and unvaccinated groups, monitoring of this exposure in the two groups is desirable.

DISCUSSION

The project described is an ambitious undertaking. It is proposed to recruit into the study most of the newborn population of The Gambia over a 4-year period and these infants must be sufficiently well identified such that their vaccination records can be located in 30 or 40 years time. As much as possible, pilot studies have indicated that this is a feasible goal although there are obvious uncertainties associated with the planning of a study over such a long time period.

It might be questioned whether such a study is worthwhile because when the results become available it is probable that a new generation of hepatitis vaccines will be in use and the plasma-derived vaccines may no longer be used. Unfortunately, this is a problem which is inherent in the evaluation of any intervention the main impact of which is not expected until several years or decades after its introduction. A similar situation has arisen in developed countries with respect to trials of screening for breast cancer. By the time the results of the first controlled trials on the prevention of breast cancer mortality were available, screening technology had advanced considerably. Nonetheless, the value of the early studies was to indicate a beneficial effect of at least some kind of screening.

If the impact of HBV vaccination on liver cancer and chronic liver diseases is great it will probably be apparent in those regions where uncontrolled mass vaccination campaigns have been undertaken. If, for whatever reason, however, the impact is less than some predict it may be very difficult to interpret the information from uncontrolled studies as changes may occur in the incidence of liver cancer independent of any effect of HBV vaccination. Under these circumstances the study in The Gambia may be of critical importance to quantify the precise benefit, if any, derived from mass vaccination with HBV vaccine in early infancy. By setting up controlled studies at an early stage we may avoid confusion of the kind associated with screening for cervical cancer, for which proper assessment of the value of

the procedure was delayed for two decades because of failure to set up controlled trials when the procedure was introduced.

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