vaccination in childhood in the prevention of HB infection, chronic liver disease and primary liver cancer in a population at high risk. The implementation of this trial involves three overlapping phases:

Phase I (1986-1990): Vaccination of approximately 60,000 children. HB vaccine, which was approved by the World Health Organisation, was integrated into the Gambian Expanded Programme of Immunisation (EPI) in a phased manner over a four-year period from July 1986 to February 1990. During this period, two groups of children were recruited, one comprising about 60,000 children who received all vaccines in the EPI schedule plus the HB vaccine, the other comprising a similar number of children who received all vaccines except HB. Since February 1990, HB vaccination is offered to all newborns as part of the EPI schedule in The Gambia.

Phase II (1991-1997): Estimate of efficacy of HB vaccine against infection and chronic carriage. Longitudinal and cross-sectional surveys were carried out in selected groups of vaccinated (Group 1) and unvaccinated (Group 2). These two subsets have provided evidence of the short-term efficacy of HB vaccine in preventing infection and chronic carriage. By the end of the first decade of life, the vaccine prevents 84% and 94% of HBV infections and chronic carriage, respectively, despite waning antibody levels during the period.

Phase III (since 1998): Long-term follow-up through Cancer Registration. The aim of this phase is to carry out a surveillance of the population of The Gambia, to identify cases of chronic liver disease (cirrhosis) and liver cancer. A linkage is made between the records of cases occurring in subjects within the age-range of the GHIS cohort, and the GHIS database of vaccinated children, to determine whether the individual belongs to the vaccinated or unvaccinated cohort. The components of Phase III are:

1. Detection and ascertainment of cancer cases and cases of chronic liver disease in the population of The Gambia, through support to liver cancer diagnosis in the public and private health sector, and support to Laboratory and Histopathology Services.

2. Registration of cancer cases and of cases of chronic liver disease through the National Cancer Registry (NCR), a population-based cancer registry established in 1986.

3. Record linkage of identified cases with the GHIS database of vaccinated/non-vaccinated children, so that the net effect of HB vaccination in preventing liver cancer can ultimately be assessed.

In parallel with the development of the three phases above, the GHIS framework has fostered studies on viral, environmental and genetic factors in hepatocellular carcinoma, biomarkers of HB Infection and aflatoxin exposure, long term efficacy of HB vaccination and monitoring of breakthrough injections.

HCC Biomarkers in China and Taiwan

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A number of different types of biomarkers have been used to understand the etiology and progression of hepatocellular cancer (HCC). Perhaps the most well known are the serum/plasma markers of HBV or HCV infection. These markers include analysis of viral DNA or proteins or antibodies produced against the viral proteins. HBV surface antigen (HBsAg) is most frequently used to determine chronic infection with high or low viral replication, while HBeAg is a measure of chronic infection with high viral replication. Analysis of antibodies includes measurement of anti-HBV core antigen, anti-HBV e antigen and anti-HBsAg. The response to immunization can be monitored by analysis of anti-HBsAg.

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The other major classes of biomarkers used in studies of HCC are biomarkers of exposure to environmental, lifestyle or dietary carcinogens, biomarkers of oxidative stress and early biologic response. In addition, studies of genetic susceptibility have studied polymorphisms in a number of pathways and their role in HCC risk. The biomarkers of exposure include the measurement of carcinogens in urine and carcinogen-DNA and protein adducts. Examples are measurement of aflatoxin and polycyclic aromatic hydrocarbon metabolites, and DNA and protein adducts. Biomarkers of oxidative stress include urinary isoprostanes and 8-oxodeoxyguanosine and oxidized plasma proteins. Most of these assays are immunologic although the use of high performance liquid chromatograph (HPLC) as well as gas chromatography/mass spectroscopy (GC/MS) have been utilized. In nested case-control studies, many of these markers are associated with elevated risk. For example, elevated aflatoxin and polycyclic aromatic hydrocarbon-albumin adducts, aflatoxin metabolites in urine and urinary isoprostanes were observed in baseline samples from those who went on to develop HCC. Biologic response markers include measurement of specific mutations in the p53 gene. These studies have demonstrated dramatic differences in mutational spectra of HCC depending on the geographic location. Other early response markers measure tumor DNA released into the blood stream. This DNA has been shown to carry the same genetic and epigenetic changes as does the tumor. In particular, detection of mutations in p53 and methylation of a number of tumor suppressor genes including p16, RASSF1A, MGMT, etc have been analyzed. While not yet applied to HCC cases, the area of proteomic and metabolomics may also lead to useful biomarkers of HCC.

In terms of genetic susceptibility, a number of investigators are determining whether single nucleotide polymorphisms are related to HCC risk. The genes investigated to date have included those in the carcinogen metabolism, oxidative stress and DNA repair pathways. While definitive studies are still lacking, the data suggest that, in combination with environmental exposures, genetic factors may also be important in HCC risk.

The ultimate goal of these biomarker studies is the early identification of high risk individuals so that they can be targeted for enhanced screening or chemopreventive strategies.

Interplay between viral infections and genetic alterations in liver cancer

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With over 500 000 annual deaths, Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and a leading cause of death in developing countries where about 80% of the cases arise. Risk factors include chronic hepatitis infections (hepatitis B, (HBV) and hepatitis C (HCV) viruses), alcohol, dietary contaminants such as falatoxins The incidence shows important geographic variations, accor In southern Asia, HCC development is mainly related to the endemic Hepatitis B Virus (HBV) infection, cases with hot spot mutation in codon 249 (249ser) of TP53 tumor suppressor gene were also described and associated to a low-intermediate exposure rate to Aflatoxin B1 (AFB1). Presence of Hepatitis C Virus (HCV) infection was also detected in 12 - 17% of HCC cases. Despite the increasing number of studies identifying viral/host interactions in viro-induced HCC or describing potential pathways for hepatocarcinogenesis, precise mechanism has not been identified so far. HBV was demonstrated to enhance hepatocarcinogenesis by different manners; HBV chronic infection is associated to active hepatitis (CAH) and cirrhosis which are hepatic complications considered as early stage for HCC development. These complications mobilise the host immune response, the resulting inflammation initiates and selects the first genetic alteration at the origin of loss of cell control. Moreover, HBV can also promote carcinogenesis through genetic instability generated by its common integration in host DNA. HBV proteins, as HBx, was proven to interact with a variety of targets in the host cell including protein or host transcription factor such as, in particular, the p53 protein or the transcription factor E4F, which is implicated in growth,

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