Mini-review

Control of hepatocellular carcinoma through Hepatitis B vaccination in areas of high endemicity: Perspectives for global liver cancer prevention

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ABSTRACT

There are approximately 360 millions chronic carriers of Hepatitis B virus worldwide. Patterns of HB carriage are variable from one region to the other. Regions with rates of carriage over 8% are commonly considered as “high endemicity” regions. HB carriers have a very significant lifetime risk of developing chronic liver diseases such as cirrhosis and/or liver cancer (hepatocellular carcinoma, HCC). An efficient HB vaccine is available since the early eighties and has been used since for universal infant vaccination in regions of high endemicity. Observations from Taiwan, where universal infant vaccination was introduced from 1984, show a remarkable, long-lasting protection against carriage and reduction of HCC rates in adolescent and young adults born after the initiation of the programme. Two population-based trials have been set up in the mid-eighties to evaluate lifelong protective effects of infant HB vaccine against liver cancer, in The Gambia (West Africa) and in the area of Qidong, China. In other high-endemicity regions of Asia and Africa, universal infants vaccination has consistently showed a long-lasting high protection against chronic carriage and this is expected to lead to a dramatic decrease of chronic liver disease and liver cancer within the next decades. Here we briefly review the lessons of vaccination programmes and trials in high-endemicity regions, based on data gathered during 15–20 years of implementation.

1. Introduction

Hepatitis B (HB) is one of the major diseases of mankind. It is estimated that more than two billion people have serological evidence of current or prior Hepatitis B virus (HBV) infection, resulting in a pool of approximately more than 360 million chronic HB carriers worldwide. In 2004, WHO estimated that between 500,000 and 700,000 deaths worldwide each year are due to chronic diseases caused by HBV, mainly liver cirrhosis and hepatocellular carcinoma (HCC) [1]. However, rates of infection and chronic carriage show dramatic geographic variations across regions. In many low- and middle-resource countries, historical rates of chronic carriage over 8%, and sometimes as high as 10–15% have been consistently reported. These areas include large regions of Sub-Saharan Africa and of South-East Asia including China. These regions can be defined as areas of high endemicity.

Hepatitis B infection and chronic carriage acquisition is preventable with safe and effective vaccines that have been available since 1982. It is a non-infectious viral particle that contains purified surface antigen (HBsAg) of the virus. Early vaccines were plasma-derived. Second generation vaccines are produced by recombinant DNA technology using modified yeast cultures. The vaccine is given as a series of three intramuscular doses. Studies have shown that three doses of HepB vaccine are 95% effective in preventing children and adults from developing chronic infection if they have not yet been infected. Efficacy is long lasting [2].
Population-based studies show that HB vaccination programmes significantly reduces the Hepatitis B virus chronic carrier prevalence in immunized cohorts of children in highly endemic regions [3–6]. In some programmes the evaluation of the effectiveness of Hepatitis B vaccine in preventing primary liver cancer has been considered as one of the measurable endpoints. They include both observational studies following introduction of universal HB vaccination and specifically designed field efficacy trials (Table 1). Here we discuss current lessons of such programmes in areas of high endemicity for HB infection.

2. Patterns of infections and genetic diversity of HBV

Chronic carriage is defined as presence of detectable Hepatitis B surface antigen (HBsAg) in at least two blood tests performed six months apart. Chronic carriers have a very significantly elevated risk of developing chronic liver disease and liver cancer later in life [7–9]. The probability that infection will become chronic is inversely related to age at infection. It is estimated that 15–40% of chronic carriers may develop serious, life-threatening liver diseases such as cirrhosis and HCC [10]. HBV infections are considered to be responsible for about 50–60% of the worldwide attributable risk of HCC, and this proportion may be higher than 70–80% in high endemicity area [11,12].

Patterns of infection and acquisition of chronic carriage vary according to geographic areas. In high endemicity areas, infection is more common among infants and children than among adults. Routes of infections include both perinatal (mother to child) and horizontal transmission. Horizontal transmission is predominant in West Africa where virtually everyone is exposed to the virus at 2–3 years of age and HBsAg prevalence in infants and young children can be between 15% and 20% [13–15]. A considerable proportion of infection in West Africa also occurs after 2–3 years of age. Perinatal transmission is highest in South-East Asia where the proportion of chronic carriers who have acquired their status perinatally is estimated to be as high as 50% [16]. It is estimated that about 90% of infants infected during the first year of life and 30–50% of children infected between 1 and 4 years of age become chronic carriers. Males are more likely to become chronic carriers than females but the mechanism behind this is poorly understood [13,15,17].

The epidemiological patterns of liver cancer vary considerably among different countries as well as among regions within countries. In South-East Asia, incidences of HCC start to rise as early as in infancy [18,19], whereas in West Africa it starts in young adults [20,21].

Worldwide HCC is more frequent in males compared to women with a ratio of 2–4:1 in most places [9,11,20–22].

Hepatitis B viruses are genetically diverse and eight distinct genotypes have been identified (denoted A–H; one genotype regroups viruses with >8% divergence among their genomes). Each genotype has distinct geographical and ethnic distributions. Genotypes A and D occur frequently in Africa, Europe, and India, while genotypes B and C are prevalent in Asia. Genotype E is restricted to West Africa, and genotype F is found in central and South America. The distribution of genotypes G and H is less clear. There are remarkable pathological and clinical differences among genotypes (reviewed by Pujol et al. in this special issue). Prospective studies in Asia have shown that the risk of HCC was increased approximately fivefold among men infected with HBV genotype C compared with other genotypes. HBsAg positivity, severe hepatic inflammation and fibrosis and HCC are more frequently associated with genotype C [23].

3. Universal vaccination programmes

3.1. Lessons from Taiwan

The most successful and best documented vaccination programme so far is the one implemented in Taiwan, where, as in many other regions of Asia, the incidence of primary liver cancer is high among children as early as six years of age. In Taiwan, Beasley and colleagues [7] reported that HCC mortality was 223-fold higher for HBsAg seropositive men than for those who were HBsAg-seronegative. Perinatal transmission of HBV could be prevented by administering Hepatitis B immune globulin to neonates [24]. As HepB vaccines became available in quantity, these results motivated the initiation of a population-wide HBV screening and vaccina-

<table>
<thead>
<tr>
<th>Country/region</th>
<th>Type of programme</th>
<th>Initiated in</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>Universal vaccination of neonates (since 1987)</td>
<td>1984</td>
<td>Chen et al. [25], Chang et al. [26], Lin et al. [17]</td>
</tr>
<tr>
<td>Thailand</td>
<td>Universal neonate vaccination</td>
<td>1992</td>
<td>Poovorawan et al. [52,38], Chongsrisawat et al. [29]</td>
</tr>
<tr>
<td>Senegal</td>
<td>Cohort of infants n = 522 (less than 2 years)</td>
<td>1978</td>
<td>Coursaget et al. [31], Maupas et al. [32]</td>
</tr>
<tr>
<td>People’s Republic of China</td>
<td>Universal neonate vaccination</td>
<td>2002</td>
<td>CDC [33]</td>
</tr>
<tr>
<td>The Gambia</td>
<td>Infant and adolescent vaccination in two sentinel villages</td>
<td>1984</td>
<td>Whittle et al. [5,15,43], van der Sande et al. [51]</td>
</tr>
<tr>
<td>Alaska</td>
<td>Universal</td>
<td>1983</td>
<td>Harpaz et al. [34], Livingston et al. [36]</td>
</tr>
<tr>
<td>South Africa</td>
<td>Universal neonate vaccination</td>
<td>1995</td>
<td>Tsebe et al. [40], Hino et al. [35]</td>
</tr>
<tr>
<td>The Gambia</td>
<td>Population trial, n = 125,000</td>
<td>1986</td>
<td>Hall et al. [42,44], Fortuin et al. [46], Viviani et al. [49]</td>
</tr>
<tr>
<td>PR China, Qidong area</td>
<td>Population trial, n = 90,000</td>
<td>1987</td>
<td>Sun et al. 1991 [41]</td>
</tr>
</tbody>
</table>
tion programme, which was launched in July 1984. For the first two years, the programme covered only neonates born to mothers who were HBsAg carriers, where the infants received a 4-dose regimen of Hepatitis B vaccine [25]. The programme was extended to all neonates in July 1986, to preschool children in July 1987, to primary-school children in 1988, to middle-school children in 1989, and to adults in 1990, where a 3-dose regimen of Hepatitis B vaccine was given [26].

In 1997, Chang et al. published the first report demonstrating a sharp decline of primary liver cancer in children vaccinated with Hepatitis B in Taiwan [26]. In this report, they analysed the incidence of HCC in children from 1981 to 1994, using data on liver cancer in children from Taiwan’s National Cancer Registry. They found that the average annual incidence of HCC in children 6–14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994. The corresponding rates of mortality from hepatocellular carcinoma also decreased, since fatality rates for HCC are close to 100% [12,21]. These observations provided strong evidence that, 10 years after the institution of Taiwan’s programme of universal Hepatitis B vaccination, the incidence of HCC in children had significantly declined. This report is of particular public health significance since it is the first report showing that a cancer with high fatality rate such as primary liver cancer can be prevented by vaccination. Since HCC is rare in children and adolescent, this demonstration was only possible in a region where such cancers are more frequent than elsewhere, and with excellent medical care and epidemiological surveillance. Further studies on Taiwanese vaccinated subjects evaluated the long-term antibody persistence after vaccination and the vaccine efficacy in preventing chronic carriage status. In 15 year old subjects vaccinated at birth, despite a sharp decline in antibody titres observed with time, vaccine efficacy against chronic carriage was sustained and no booster vaccination was deemed necessary at this age. In a series of 1357 persons who were born after the implementation of the vaccination programme, only 9 (0.7%) became chronic carriers vs. 7% (39 of 559) observed in participants older than 15 years of age, who were born before the universal vaccination programme (P < 0.001) [27]. Among them, most were from families with a positive history of HBV infection and, in particular, had HBsAg carrier mothers. This observation suggests that a small proportion of newborns exposed to vertical transmission may acquire their infectious status before vaccination, despite the first dose being delivered before one week of age [17,27,28].

3.2. Other programmes

Reports from other areas of high endemicity for HBV infection such as Thailand [29,30], Senegal [31,32], several areas of China [33], Alaska [34] and South Africa [35] consistently demonstrate that the Hepatitis B vaccination given in infancy within the expanded programme on immunization (EPI) reduces dramatically infection and chronic carriage of the virus with long-lasting duration in children and adolescents. In Alaska, chronic carrier rates are above 20% in adults. Genotype F, which is associated with HCC in adolescents and young adults, is present in 20% of these chronic carriers [36]. A programme to eliminate HBV transmission was started in April 1983. This programme included routine screening of pregnant women to identify those infected by HBV, routine vaccination of infants as part of the childhood immunization schedule, and catch-up vaccination of persons susceptible to HBV infection (aged 11–30). Ten years after the inception of the programme, a seroprevalence study was conducted in seven villages with a total population of 1847. HB vaccine coverage was 93% among children aged less than 10 years old, and 62% among the “catch-up” population of susceptible persons aged 11–30 years old. None of the tested children less than 10 years old were chronically infected with HBV, and just four had evidence of resolved infections. In contrast, 16% of the persons born before implementation of routine vaccination were chronic carriers [34]. A further study was conducted on 74 adolescents aged 11.7–14.9 years to assess the long-term immune protection [37]. No participant had evidence of chronic Hepatitis B virus infection. Of the group of children who received recombinant Hepatitis B vaccine, 99% had an anamnestic response to a booster dose, demonstrating persistent immune memory despite waning antibody titres over time.

In Senegal, a 9–12 year period of follow-up of infants immunized against Hepatitis B showed that HBsAg was detectable in 19% of infants from the control group compared to only 2% of immunized infants, corresponding to a protective efficacy of 88%. The results show that long-term protection against HBsAg carriage of Hepatitis B vaccination is very high and that a booster dose at school age does not significantly increase this protection [31].

In Thailand, universal HB vaccination of newborns with a 3-dose regimen of Hepatitis B vaccine has been integrated into the national EPI since 1992 [38]. A study carried out in 2004 on children below the age of 18 years, to evaluate the impact of the universal HB vaccination programme on the prevalence of HBsAg carriers and immunity to HBV, showed that the HBsAg seropositive rate was 0.7% among participants born after HB vaccine integration into EPI and 4.3% among participants born prior to HB vaccine integration into EPI. This finding supports the efficacy of universal HB immunization in reducing the prevalence of HB infection in Thailand which is a highly endemic country [29].

In China, HepB was first recommended for routine vaccination of infants in 1992, using a 3-dose regimen. However, because of high vaccine prices and user fees charged to parents by local health departments for vaccine purchase and administration, until 2002, infant vaccination occurred primarily in large cities of the wealthier eastern provinces. Beginning in 2002, infant Hepatitis B vaccination was added to China’s National Immunization Programme [33]. Completion of the 3-dose HepB series has increased from 70.7% to 89.8% among children born in 2003 compared to those born in 1997. Among the economically disadvantaged populations in western and middle provinces targeted by the China-Global Alliance for Vaccines and Immunization (China-GAVI) project, completion of the 3-dose HepB series increased from 52% in 2001
to 92% in 2006. China has established a goal to reduce chronic HBV infection among children aged <5 years to <1% by 2010. Achieving this goal will require continued commitment to increasing vaccination coverage in impoverished regions and ensuring that infants born at home are vaccinated within 24 h of birth.

South Africa implemented a vaccine against Hepatitis B virus into the EPI in April 1995. The HBV vaccine is given at 6, 10, and 14 weeks [39,40]. Two cohorts were followed-up, consisting of 459 children born before the introduction of vaccination in 1995, and 1213 children born between 1 and 2 years after the introduction of the vaccination programme. At 12–24 month of age, the frequency of detection of HBV DNA was reduced from 6.5% in unvaccinated children to 0.3% in vaccinated children [35].

There is evidence that HB infection can persist in the absence of any serological markers. This is the case for so-called “occult” infections as well as for infections by immune response escape mutant viruses. The prospective study in South Africa, to determine whether universal vaccination of infants affect the prevalence of serologically negative infections as well as the emergence of escape mutants in a highly endemic context, showed that no unique amino-acid substitution were found within the major antigenic determinant of the S gene. Thus, universal vaccination reduced the frequency of serologically negative infection without leading to selection of immune escape variants [35].

4. Designed field efficacy trials

Only two specifically designed field efficacy trials to evaluate lifelong protective effects of infant HB vaccine against liver cancer have been implemented so far, in the Qidong Province of China and in The Gambia.

The Qidong trial [41] started with a pilot phase in 1984. The target population consisted of 45 cities of the Qidong County in the Jiangsu Province of China, one of the regions of the world with the highest rates of HCC ever reported both in men and women. The trial was designed as a randomized at the community levels. Communities were assigned by lottery to either vaccine or control group and all children born in local hospitals during the period 1985–1990 were recruited. A total of 38,000 children were enrolled in each arm. Three doses of recombinant vaccine were given, with the first one given within 30 min after birth. Five year result of the pilot phase was published in 1991 [41]. The HBsAg positive rate was 2.52% in children vaccinated with 5 μg of recombinant vaccine and 3.08% in those who received a 2.5 μg dose, as compared with 12.5% in the unvaccinated controls. The evaluation of vaccine efficacy against HCC is through population-based cancer registration.

The Gambia Hepatitis Intervention Study (GHIS) is a collaborative undertaking by the International Agency for Research on Cancer (IARC), The Government of the Republic of The Gambia and the Medical Research Council of the United Kingdom (MRC). This programme was launched in 1986 with the objective of evaluating the efficacy of Hepatitis B vaccination in childhood for the prevention of HB infection, chronic liver disease and HCC in a population at high risk [42]. In The Gambia, liver cancer is the most common form of cancer in men and the second most common form in women [20]. A pilot study, initiated in 1980, consisted in the introduction of infant vaccination in two communities which are excluded of the main GHIS [43]. HB vaccine was introduced in the EPI using a “stepped wedge” design. Recruitment started in July 1986. A 4-dose vaccine schedule was used with the first dose given as soon as possible after birth (during the child’s first attendance at a welfare clinic) and subsequent doses given at the ages of 2, 4 and 9 months. Randomisation in introducing HB vaccination was achieved on a geographical basis. The unit of randomization was the EPI team, stratified according to four ecological zones [42,44]. This design was deemed to have a statistical power of over 70% of that of a conventional randomised design. Since 1990, all EPI teams in the country use HB vaccine, with a population coverage consistently over 90%. By February 1990, a cohort of 124,577 children was recruited, 61,065 of whom received HB vaccine. Since the start of the GHIS, a population-based National Cancer Registry was set up to evaluate the protective ness of the Hepatitis vaccination against HCC [20].

With the aim of evaluating the immunogenicity of the vaccine and its efficacy in preventing infection and chronic carriage, two subgroups of the GHIS cohort have been studied in detail. Group 1 was a cohort of 1041 children, including approximately the first 250 HB-vaccinated children in each of the four ecological zones. These children have been followed-up annually (except for the 6th and 8th year) [45]. Group 2 consisted of two cross-sectional surveys, each including 800 unvaccinated subjects aged 4 and 9 years old. Vaccine efficacy did not significantly change over time, and was 84% against infection and 94% against chronic carriage at 9 years of age. No difference was observed between the four ecological zones [46,47]. A further follow-up was carried out in adolescents aged 15. Vaccine efficacy after 15 years was 67.0% against infection as manifest by anti-HBc positivity and 96.6% against chronic carriage (as manifest by HBsAg positivity). A subgroup of the participants to this study was offered a booster dose. Two weeks after the booster, 3.2% of the subjects had undetectable anti-HB antibodies, compared to 65.8% prior to the booster. In the boosted subjects, high antibody titres persisted at 12 month after receiving the booster dose [48].

The implementation of GHIS was based on several assumptions (on vaccine coverage, vaccine efficacy, risk of HCC attributable to HBV and attrition in the trial cohort). On the basis of these assumptions, it was estimated that a follow-up between 35 and 40 years would be required for final evaluation of the protective efficacy of HB vaccine against HCC. Recently, the duration of the trial was reassessed using data acquired in field studies conducted since the inception of the trial [49]. Actual data on vaccine coverage and efficacy exceed the initial assumptions. The rate of perinatal acquisition of chronic carriage was found to be negligible (0.2%). A case-control study performed between 1997 and 2001 confirmed that in The Gambia the risk of HCC attributable to HBV was about 70% before 50 years of age, and between 80% and 90% in cases younger than
35 years [8]. Based on the hypothesis of attributable risk of 70%, the conservative estimate of the protective effectiveness of Hepatitis B vaccination against hepatocellular carcinoma is 68% [49]. Based on these new data, the overall duration of the trial was estimated to be shorter than initially assumed, with the final evaluation possible in years 2015–2017.

5. Perspectives for global Hepatitis B control and HCC prevention

Lessons from programmes of infant vaccination against HBV show remarkable protection against infection in early years and long-lasting protection against chronic carriage, the sequela of infection which is the most important factor associated with further development and progression of life-threatening liver diseases including HCC.

In all studies, the Hepatitis B vaccine was reported to remarkably show high safety profile [50]. Despite being raised against HB genotype A, the vaccine is effective against all genotypes and there is no evidence that vaccination increases the rate of emergence of immune escape variants. Infant vaccination shows a remarkable long-term protective efficacy against the acquisition of chronic carriage [13,17,27,31,34,37,43,46–48,51,52] even in contexts where vertical (mother to child) transmission is predominant [17,52]. However, in this context, the time elapsed between birth and vaccination may be critical. WHO currently recommends that the first dose of vaccine should be given within 24 h of birth in high endemic areas. In children born to HB-infected mother, administration of HB immunoglobulins has been proposed as an additional recommendation. In a systematic review and meta-analysis of the effects of HB vaccine and immunoglobulins, Lee et al. (2006) concluded that HB immunoglobulins alone or in combination with vaccine reduced Hepatitis B occurrence. These findings were mostly based on immune prophylaxis in infants of mothers positive for HBsAg and HBe antigens. However, the cost effectiveness and logistic feasibility of this intervention has not been assessed in low-income countries [53]. In the Qidong trial, results in children aged 12–24 months did not demonstrate a benefit over vaccination alone [41]. The need for updating recommendations on strategies for prevention of perinatal HB virus transmission is currently being considered by the WHO Strategic Advisory Group of Experts (SAGE) Working Group on Hepatitis B [54].

Since 1995, WHO has called for all countries to add Hepatitis B vaccine into their national immunization programmes [1]. By the end of 2007, a total of 162 (84%) of the 193 WHO member states reported having integrated HepB into their routine infant vaccination schedules; coverage with 3-dose HepB had increased from 32% in 2000 to 65% in 2007, with 2007 coverage varying by WHO region (South-East Asia: 30%; Africa: 69%; Eastern Mediterranean: 85%; Europe: 78%; Americas: 88%; Western Pacific: 85%). The Global Alliance for Vaccines and Immunization (GAVI Alliance), created in 1999, is a unique coalition of public and private institutions where WHO has taken a leading role. The main mission of GAVI is to vaccinate as many children as possible against vaccine-preventable diseases. GAVI has introduced a new approach to international health funding: the Global Fund for Children’s vaccines (GFCV). This fund helps 74 low-income countries to reinforce their national vaccine programmes and introduce Hepatitis B, yellow fever and haemophilus influenzae type b (Hib) vaccines into their national immunization programmes. GAVI’s tremendous boost in getting the vaccines to the children in the poorest countries in the world has been facilitated by the availability of affordable infants vaccines (DTP, HepB, Yellow Fever, Measles) and more recently by the availability of pediatric combination vaccines containing Hep B for use in low-income countries, where HBV is often of high endemicity.

So far, the only data available on the effectiveness of HB vaccination against HCC are those from Taiwan. However, within the next few years, large vaccination trials in Qidong and in The Gambia will be in a position to provide comparative estimates of incidence of HCC in young adults born before or after the introduction of the vaccine. The public health impact of universal Hep B infants vaccination on the decrease of chronic liver disease and HCC is expected to be impressive. Assuming that protection against chronic liver disease and cancer will be as high as the long-term protection observed against chronic carriage, and taking into account an attributable risk of HBV for HCC of about 70% in intermediate and high endemic area, the protective effectiveness of Hep B vaccination against HCC in adulthood can be estimated to be 68% [49]. This will have a remarkable impact in that major cancers such as HCC can be prevented by the means of a simple and affordable vaccination.

However, some scientific issues remain to be addressed to better elucidate the long-term effects of Hep B vaccination on Hepatitis infections, on chronic liver disease and on HCC. Different patterns between males and females in the decline of HCC in Taiwan have been reported with a significant decrease in boys born after the launch of the HepB vaccination in comparison with those born before (RR, 0.72; P = 0.02). No significant decrease in HCC incidence was observed in girls born in the same periods (RR, 0.77; P = 0.2) [55]. This gender pattern is difficult to understand. Despite earlier studies in Africa and Taiwan reporting the highest risk for males to become chronic carriers [5,13,28], no gender significant difference in vaccine efficacy against chronic carriage has ever been reported. The study of the contribution of other risk factors as well as of emerging etiological factors in women population should be further explored.

The presence of other risk factors for HCC such as aflatoxins and HCV either acting alone or as co-factors to HBV infection should be monitored as the residual AR to HCC once this will start to decrease, particularly in high endemicity areas.

The interference in the long-term efficacy of HepB vaccine with HIV infection in Sub-Saharan Africa is of some concern in those areas where both HBV and HIV are highly endemic [56].

In summary, an overall dramatic decrease of HBV chronic infection, chronic liver disease and HCC is expected in the next 10–20 years as more countries in high ende-
micity areas have been introducing HepB vaccine in the infant vaccination programs. This will represent a major public health achievement. However, as in high endemicity areas about 20–30% of HCC is not attributable to HBV infection, a fraction of HCC will still be present. To establish the extent of it, sentinel surveillance systems such as cancer registration should be implemented in high HBV endemicity areas, or if any does exist, should be supported.

Conflict of interest
None declared.

References


