Nationwide Hepatitis B Vaccination Program in Taiwan: Effectiveness in the 20 Years After It Was Launched

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The national hepatitis B vaccination program in Taiwan is considered one of the most successful and effective public health programs to control chronic hepatitis B infection in the past 20 years. This review illustrates how to implement a successful hepatitis B vaccination program based on Taiwan’s experience. Several important controlled randomized clinical trials on hepatitis B immunoglobulin and vaccine in Taiwan demonstrated an 80–90% protective effect among infants of mothers who were positive for either hepatitis B envelope antigen or hepatitis B surface antigen. A series of prevalence surveys on children born before and after the national vaccination program began disclosed a steady decrease in seroprevalence of hepatitis B surface antigen in Taiwan, with 78–87% effectiveness after the national vaccination program was launched. Studies on the secular trend of liver disease risk also documented a 68% decline in mortality from fulminant hepatitis in infants and a 75% decrease in the incidence of hepatocellular carcinoma in children 6–9 years of age after the national vaccination program began. In conclusion, since 1984, the national hepatitis B vaccination program has been successful in preventing acute and chronic liver diseases in Taiwan.

hepatitis B vaccines; liver diseases; program evaluation; public health; regional health planning; Taiwan; treatment outcome; vaccination

Abbreviations: HBeAg, hepatitis B envelope antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

INTRODUCTION

Hepatitis B virus (HBV) is an important risk factor for chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Chronic HBV infection is a worldwide public health challenge. Over the past decades, it was endemic in Taiwan, where the carrier rate of hepatitis B surface antigen (HBsAg) in the general population was as high as 15–20 percent. To assess the prevalence and significance of chronic HBV infection in Taiwan, a series of community surveys and epidemiologic studies have been carried out. Several important controlled randomized clinical trials on the effectiveness of hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine have been conducted in Taiwan. Based on careful evaluation of all aspects of universal vaccination by the National Hepatitis Control Steering Committee, a nationwide hepatitis B vaccination program was launched in July 1984. During the first 2 years (July 1984–June 1986) of the program, only newborns of high-risk (HBsAg-positive) mothers were vaccinated. The national hepatitis B vaccination program was extended to all newborns after July 1986, to preschool children who did not receive vaccination at the neonatal stage and to susceptible health-care workers after July 1987, and to all primary school children from 1988 to 1990.
HBV

HBV was first discovered by Blumberg in 1965 and is a member of the Hepadnaviridae family. The virus has infected more than 2 billion persons in the world, and the World Health Organization estimated that the number of chronically infected carriers of HBV would reach 400 million worldwide by the year 2000 (1, 2). The distribution of HBV infection varies greatly. Where the prevalence is high, such as in Southeast Asia, China, the Middle East, and sub-Saharan Africa, more than 60 percent of the population is infected at some point in their lives, and the prevalence of chronic infection is more than 8 percent. In these highly endemic areas, the infection occurs through either perinatal (vertical) transmission or horizontal transmission from one child to another. In areas with low levels of endemicity, including North America, western Europe, Australia, and South America, the prevalence of lifelong infection is less than 20 percent, with a prevalence of chronic infection of less than 2 percent. In these low-endemicity areas, only a minority of people come into contact with the virus as a result of horizontal transmission among young adults from sexual activity, injection drug use, or occupational exposure (3, 4).

The risk of becoming chronically infected varies inversely with age at infection. The risk is as high as 90 percent for infants infected in the perinatal period. Between 25 percent and 50 percent of children infected at ages 1–5 years develop chronic infection compared with 6–10 percent of acutely infected older children and adults (5, 6). Compared with areas of low and intermediate endemicity, high-endemic areas have a more serious problem of chronic HBV infection, which was acquired at the time of birth or in early childhood.

HBV-related liver diseases are major public health challenges in Taiwan. Liver cancer was the leading cancer among men and the fourth leading cause among women in 2001, with age-adjusted incidence rates of 48 and 19 per 100,000, respectively. According to the Republic of China’s 2001 mortality report, liver cancer was the first leading cause of cancer death for men and the second for women in Taiwan (7).

EPIDEMIOLOGY OF HBV INFECTION IN TAIWAN

Before the national immunization program was implemented in Taiwan, over 90 percent of the general population under the age of 40 years was infected with HBV, and 15–20 percent of them had chronic HBV infection (8–10). Among patients with chronic liver diseases, the HBV carrier rate was even higher than 80 percent (11). In a large-scale prospective study of 22,707 male government employees in Taiwan, Beasley et al. (12) demonstrated a significantly increased risk of liver cancer for HBsAg carriers compared with noncarriers. Several subsequent case-control and cohort studies have also confirmed these important findings (13). In addition to the strong association between HBsAg positivity and hepatocellular carcinoma, positivity for hepatitis B envelope antigen (HBeAg) is associated with an increased risk of hepatocellular carcinoma (14). A dose-response relation between serum HBV DNA level and risk of hepatocellular carcinoma was found for HBeAg-seronegative chronic carriers in the same study. Most importantly, the vast majority of hepatocellular carcinoma lesions containing integrated HBV DNA sequences implied a causal association with HBV (15). On the basis of the serious impact of hepatitis B infection on public health in Taiwan, health authorities began to search for a control strategy for HBV infection beginning in 1970.

To prevent hepatitis B infection, it was most important to verify the major route of HBV transmission. It has been shown that 40 percent of infants born to HBsAg-carrier mothers will also become chronic carriers early in the postnatal period. The significantly higher HBsAg-positive rate among infants whose mothers were HBsAg positive compared with HBsAg negative illustrated conclusively that HBV is transmitted from mother to infant (16). Overall, HBsAg-positive mothers transmitted the infection to 50 percent of their infants, rendering them carriers (17). From 86 percent to 96 percent of the infants born to HBsAg- and HBeAg-positive mothers were infected by their own mothers (16). In contrast, the infection rate was only 6–21 percent among infants whose mothers were HBsAg positive but HBeAg negative (18, 19). A retrospective study in Taiwan reported that eight of 11 mothers of HBsAg-positive patients affected by hepatocellular carcinoma were also positive for HBsAg, which strongly implied that the prevalent chronic HBV infection in patients with hepatocellular carcinoma is most likely of maternal origin (20). Furthermore, a randomized controlled trial of HBIG with or without HBV vaccine for neonates of HBsAg-positive mothers revealed that HBV infections from carrier mothers to their infants generally occurred during birth rather than pregnancy (21). The annual incidence of HBV infection among children and adults in Taiwan was found to be 5 percent and 1.5–2.7 percent, respectively (10, 22, 23). In children who became HBsAg carriers, most (90 percent) were infected before 3 years of age, whereas children infected with HBV after 3 years of age infrequently became carriers (24).
Several clinical trials on hepatitis B vaccine or HBIG in infants have shown that they are safe and highly effective in preventing HBsAg-positive chronic carrier status resulting from perinatal HBV infection (19, 21, 25–28). Findings are summarized in table 1. According to Beasley et al.’s randomized controlled trial (26), HBIG given to those neonates born to HBeAg-positive mothers at birth, 3 months, and 6 months could reduce the carrier rate of vaccinees to only 26 percent, yielding an effectiveness rate of 71.7 percent (26).

To find out whether a combination of HBIG and hepatitis B vaccine for newborns would provide better protection against a perinatally transmitted HBsAg carrier state from HBeAg-positive carrier mothers, a randomized blind controlled trial of hepatitis B vaccine with three different schedules was also conducted by Beasley et al. (21). The overall effectiveness of combining HBIG and hepatitis B vaccine was 93.6 percent compared with that for the control groups (no prophylaxis). No statistically significant difference was observed among three prophylaxis schedules (21).

To identify the most economical and efficient program for immunoprophylaxis of HBV infection in high-risk neonates, investigators randomly assigned infants born to HBeAg-positive carrier mothers to receive the hepatitis B vaccine alone or in combination with HBIG. Infants whose parents refused vaccination for them constituted the control group. Group 1 neonates received the vaccine alone, group 2

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**TABLE 1. Clinical trials of hepatitis B immunoglobulin and hepatitis B vaccine among neonates in Taiwan**

<table>
<thead>
<tr>
<th>Authors (reference no.)</th>
<th>Study subjects and comparison groups</th>
<th>No. of infants</th>
<th>Outcome (%) at assessment age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Persistent HBsAg rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effectiveness</td>
</tr>
<tr>
<td>Beasley et al. (26)</td>
<td>Infants of HBeAg*-positive mothers</td>
<td></td>
<td>At the 15th month</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>61</td>
<td>92.0</td>
</tr>
<tr>
<td></td>
<td>Three 0.5-ml doses of HBIG* at birth and at the 3rd and 6th months</td>
<td>57</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>One 1.0-ml dose of HBIG at birth</td>
<td>67</td>
<td>54.0</td>
</tr>
<tr>
<td>Beasley et al. (21)</td>
<td>Infants of HBeAg-positive mothers</td>
<td></td>
<td>At the 12th month</td>
</tr>
<tr>
<td></td>
<td>No prophylaxis</td>
<td>84</td>
<td>88.0</td>
</tr>
<tr>
<td></td>
<td>0.5 ml of HBIG at birth and a 2nd dose at the 3rd month, with 20 μg of HBV* vaccine at the 3rd, 4th, and 9th months</td>
<td>51</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>0.5 ml of HBIG at birth, with 20 μg of HBV vaccine at the 4th–7th day and at the 1st and 6th months</td>
<td>50</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>0.5 ml of HBIG at birth, with 20 μg of HBV vaccine at the 1st, 2nd, and 7th months</td>
<td>58</td>
<td>8.6</td>
</tr>
<tr>
<td>Lo et al. (27)</td>
<td>Infants of HBeAg-positive mothers</td>
<td></td>
<td>At the 6th month</td>
</tr>
<tr>
<td></td>
<td>No prophylaxis</td>
<td>29</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td>1 ml of HBIG at birth and a 2nd dose at the 1st month, with 5 μg of HBV vaccine at the 2nd, 6th, and 10th weeks</td>
<td>38</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>1 ml of HBIG at birth, with 5 μg of HBV vaccine at the 2nd, 6th, and 10th weeks</td>
<td>36</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>5 μg of HBV vaccine at the 2nd, 6th, and 10th weeks</td>
<td>38</td>
<td>23.7</td>
</tr>
<tr>
<td>Lo et al. (28)</td>
<td>Infants of HBeAg-positive mothers</td>
<td></td>
<td>At the 12th–14th months</td>
</tr>
<tr>
<td></td>
<td>No prophylaxis</td>
<td>51</td>
<td>78.4</td>
</tr>
<tr>
<td></td>
<td>1 ml of HBIG at birth and a 2nd dose at the 1st month, with 5 μg of HBV vaccine at the 2nd week, 6th week, 10th week, and 12th month</td>
<td>37</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>0.5 ml of HBIG at birth, with 2.5 μg of HBV vaccine at the 1st week, 5th week, and 6th month</td>
<td>40</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>1 ml of HBIG at birth, with 5 μg of HBV vaccine at the 2nd week, 6th week, 10th week, and 12th month</td>
<td>35</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>5 μg of HBV vaccine at the 2nd week, 6th week, 10th week, and 12th month</td>
<td>36</td>
<td>19.4</td>
</tr>
<tr>
<td>Tsai et al. (30)</td>
<td>Infants of HBeAg-negative and HBsAg-positive mothers</td>
<td></td>
<td>At the 14th month</td>
</tr>
<tr>
<td></td>
<td>No prophylaxis</td>
<td>19</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>5 μg of HBV vaccine at the 1st, 5th, and 9th weeks and a booster dose at the 12th month</td>
<td>21</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.5 ml of HBIG at birth, with 5 μg of HBV vaccine at the 1st, 5th, and 9th weeks and a booster dose at the 12th month</td>
<td>24</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus.
TABLE 2. Summary of the nationwide hepatitis B vaccination program in Taiwan

<table>
<thead>
<tr>
<th>Time period</th>
<th>Events and target populations</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td></td>
<td>The National Hepatitis Control Steering Committee and the Hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control Committee were organized. All newborns received four doses of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>plasma-derived hepatitis B vaccine at 0, 1, 2, and 12 months of age.</td>
</tr>
<tr>
<td>July 1984–June 1986</td>
<td>Newborns of HBsAg*-positive mothers</td>
<td>The first plasma-derived hepatitis B vaccine produced by a Taiwanese</td>
</tr>
<tr>
<td></td>
<td></td>
<td>manufacturer was licensed for production and marketing.</td>
</tr>
<tr>
<td>July 1986–now</td>
<td>All newborns</td>
<td></td>
</tr>
<tr>
<td>June 1987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1989</td>
<td>Preschool children who did not receive vaccination at the neonatal</td>
<td></td>
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<tr>
<td></td>
<td>stage, and susceptible medical personnel</td>
<td></td>
</tr>
<tr>
<td>1988–1990</td>
<td>All elementary school children</td>
<td></td>
</tr>
<tr>
<td>July 1991</td>
<td>Vaccine records checked for all elementary school entrants</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Vaccination of teenagers and adults on a fee-for-service basis</td>
<td>After November 1, 1992, the vaccine was changed to a recombinant yeast</td>
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<tr>
<td></td>
<td></td>
<td>vaccine, with three doses at 0, 1, and 6 months of age.</td>
</tr>
</tbody>
</table>

* HBsAg, hepatitis B surface antigen.

received the vaccine plus HBIG at birth, and group 3 received the vaccine plus HBIG at birth and 1 month. Compared with that for the control group, the effectiveness was 74 percent in group 1, 88 percent in group 2, and 94 percent in group 3. The hepatitis B vaccine plus one dose of HBIG at birth was determined to be the method of choice for preventing perinatal transmission of HBV in high-risk neonates (27, 28).

To prevent perinatal and postnatal HBV infection in infants at a relatively lower risk, neonates born to HBsAg-positive and HBeAg-negative mothers were randomly assigned to two groups to receive the vaccine alone or the vaccine plus one dose of HBIG at birth. Neonates whose parents refused HBV vaccination for them served as controls. Of the neonates given the vaccine alone, 100 percent became positive for antibodies to HBsAg at 6 months of age. Therefore, hepatitis B vaccine alone could prevent HBV infection in neonates born to HBeAg-negative mothers, and vaccine should be given as soon as possible after birth (19).

For the infants born to HBsAg-seronegative mothers, the immunogenicity of the three doses of hepatitis B vaccine in 38 healthy neonates showed that 96 percent of vaccinees had detectable antibodies to HBsAg in their serum after the third dose of vaccine, without adverse reactions (29). With regard to the immunogenicity of the hepatitis B vaccine doses, Tsai et al. (30) demonstrated that smaller doses (1 and 2 µg) produced significantly lower antibody titers than the standard dose (5 µg). Therefore, the standard dose was chosen for the hepatitis B vaccination program in Taiwan.

To evaluate possible side effects of the vaccine in neonates, Lo et al. (27) compared the hepatitis B vaccine with the diphtheria-pertussis-tetanus and measles vaccines. The incidence of fever was significantly lower and occurred in only 2.8 percent of neonates vaccinated against HBV compared with 38.4 percent and 28 percent, respectively, in neonates given the diphtheria-pertussis-tetanus and measles vaccines. In the hepatitis B vaccinated group, there were significantly fewer other side effects such as diarrhea and local skin redness, and hepatitis B vaccine was documented as being relatively safe.

NATIONWIDE HEPATITIS B VACCINATION PROGRAM

According to evidence from previous studies, early administration of the HBIG and/or hepatitis B vaccine, at the newborn stage, has been critical for a successful vaccination program in Taiwan. All aspects of universal vaccination were carefully evaluated by the National Hepatitis Control Steering Committee and the Hepatitis Control Committee of the Department of Health, which were organized to provide policy guidance to assure administrative coordination and resources allocation, to implement the national vaccination program, and to monitor progress and effectiveness of the program. A nationwide vaccination program aimed at eradicating HBV was launched on July 1, 1984. It was the first universal hepatitis B vaccination programs for newborns in the world.

The national program of hepatitis B vaccination is summarized in table 2. During the first two fiscal years (July 1984–June 1986) of the program, only newborns born to high-risk (HBsAg-positive) mothers were vaccinated because of the high cost of hepatitis B vaccine and HBIG during the early years. Healthy newborns of highly infectious (HBeAg-positive or high titer of HBsAg) carrier mothers received an additional 0.5 ml of HBIG within 24 hours of birth if they weighed 2,200 g or more. Since July 1986, all newborns who weigh 2,500 g or more have been vaccinated with four doses of plasma-derived hepatitis B vaccine at 0, 1, 2, and 12 months of age. Beginning in 1987, the hepatitis B vaccination program was further extended to preschool children who did not receive vaccination at the neonatal stage and to susceptible medical personnel. Those who missed the scheduled vaccination were encouraged to receive the vaccine on a fee-for-service basis. From 1988 to 1990, the vaccination program was extended to all...
elementary school children. To ensure the completeness of vaccination, vaccine records were checked for all elementary school entrants. Those who failed to be vaccinated in infancy were asked to receive the vaccine. Since 1992, teenagers and adults have been encouraged to be vaccinated on a fee-for-service basis. After November 1, 1992, the vaccine used in the program was changed to recombinant yeast vaccine with three doses at 0, 1, and 6 months of age. In the first 15 months after the vaccination program was implemented, the HBIG coverage rate was 77 percent in 27,375 infants born to highly infectious mothers, and hepatitis B vaccine coverage for the first, second, third, and fourth doses was 88 percent, 86 percent, 84 percent, and 71 percent, respectively, among infants born to 55,620 carrier mothers (31). A survey among preschool children in central Taiwan carried out by Lin et al. (32) demonstrated that the hepatitis B vaccination rate of preschool children was 98 percent, and the complete vaccination rate (three or four doses of hepatitis B vaccine) was 94 percent. The HBsAg-seropositive rate was 4.5 percent among incomplete vaccinees and 1.3 percent among complete vaccinees. According to Center for Disease Control statistics in Taiwan, the overall vaccine coverage rates from July 1984 to December 2002 were 96.6 percent, 95.2 percent, and 92.8 percent for the first, second, and third doses, respectively, among 5,188,929 newborns. The coverage rates for hepatitis B vaccine for targeted birth cohorts from 1984 to 2002 were all more than 90 percent (for the first, second, and third doses). The results are shown in figure 1. Coverage in the nationwide hepatitis B vaccination program has been considered comprehensive in the past 20 years.

EFFECTIVENESS OF THE HEPATITIS B VACCINATION PROGRAM

Decrease in seroprevalence of HBsAg among children born after the nationwide hepatitis B vaccination program began

Serologic surveys of HBV infection are important tools for monitoring and evaluating the effectiveness of a vaccination program. Table 3 summarizes the seroprevalence of HBsAg among children born before and after the national vaccination program was started. A study was conducted among 3,464 randomly selected vaccinees from the national vaccination program when they were 18 months of age. Among 786 infants born to highly infectious carrier mothers, the HBsAg-positivity rates were 14 percent for those who had received both HBIG and vaccine on schedule and 20 percent for those who were given vaccines without HBIG on schedule ($p < 0.05$) (33). Seroprevalence of HBsAg in both groups was far lower than among infants who were not
immunized (86–96 percent) (16, 18). The overall protective effectiveness found in this study was about 85 percent. For infants born to less-infectious carrier mothers, the HBsAg-positivity rate was higher among those who did not receive vaccines on schedule compared with those who did receive vaccines on schedule (7 percent vs. 3 percent; p < 0.003). These results demonstrated that the mass vaccination program is efficacious in preventing perinatal HBV transmission and the occurrence of a chronic carrier state. Most infant vaccinees had adequate levels of protective antibody at 18 months of age (33).

A follow-up seroepidemiologic study carried out in Taipei in 1989 revealed that the prevalence of HBsAg in children under 5 years of age decreased from 9.3 percent in 1984 to approximately 2 percent in 1989; 78% effectiveness of the vaccination program. Ten years after the vaccination program was launched, Chen et al. (36) reported that 87 percent of the children had received at least three doses of hepatitis B vaccine. The overall prevalence rate of HBsAg decreased from 9.8 percent in 1984 to 1.3 percent in 1994, showing a program effectiveness of 87 percent. The overall prevalence rates of antibodies to hepatitis B core antigen were 26 percent in 1984, 15 percent in 1989, and 4 percent in 1994. These authors also concluded that the vaccination program has protected most children younger than age 10 years from becoming carriers and from being infected perinatally and horizontally.

Table 3. Prevalence of seromarkers of hepatitis B virus infection among children born before and after the nationwide hepatitis B vaccination program was launched in Taiwan

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study subjects</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al. (33)</td>
<td>3,464 infants of HBsAg-carrier mothers who were 18 months of age between December 1985 and April 1986</td>
<td>Infants who received HBIG* plus vaccine on schedule had a lower prevalence of HBsAg positivity (14%) than those who did not receive HBIG (20%; p &lt; 0.05); 85% protective effectiveness of the vaccination program.</td>
</tr>
<tr>
<td>Tsen et al. (34)</td>
<td>1,134 apparently healthy children (619 boys and 515 girls) under 13 years of age in the Cheng-Chung District of Taipei</td>
<td>Prevalence of HBsAg in children under 5 years of age decreased from 9.3% in 1984 to approximately 2% in 1989; 78% effectiveness of the vaccination program.</td>
</tr>
<tr>
<td>Chen et al. (36)</td>
<td>1,515 apparently healthy children (193 children 1 month–3 years of age, 709 preschool children, and 613 children 6–12 years of age) under 12 years of age in the Cheng-Chung District of Taipei</td>
<td>Overall prevalence of HBsAg decreased from 9.8% in 1984 to approximately 1.3% in 1994; 87% effectiveness of the vaccination program; overall prevalence of anti-HBc* decreased from 26% in 1984, to 15% in 1994, and to 4% in 1994.</td>
</tr>
<tr>
<td>Hsu et al. (37)</td>
<td>Three groups of 1,500 children (elementary school entrants) born between September 1982 and August 1983, between September 1984 and August 1985, and between September 1986 and August 1987 selected by proportional random sampling</td>
<td>In the three groups, HBsAg positivity rates were 10.5%, 6.3%, and 1.7% (83% effectiveness), respectively; anti-HBs* positivity rates were 36.9%, 62%, and 65.4%, respectively; and hepatitis B infection rates were 25%, 15.9%, and 4.3% (83% effectiveness), respectively.</td>
</tr>
<tr>
<td>Wu et al. (38)</td>
<td>A 10-year follow-up cohort of 972 neonates born to HBsAg-positive mothers during 1981–1984; among them, 805 infants who developed anti-HBs after vaccination at 12 months of age included in the analysis</td>
<td>Cumulative persistence of anti-HBs was 85%, and cumulative incidence of HBV* infection was 15%.</td>
</tr>
<tr>
<td>Ni et al. (39)</td>
<td>1,357 persons under 15 years of age, and 559 persons 15–20 years of age (born after and before the vaccination program began) in the Cheng-Chung District of Taipei</td>
<td>Prevalence of HBsAg in persons younger than 15 years of age decreased to 0.7% in 1999; anti-HBc seropositivity was 2.9% in persons younger than 15 years of age and was 20.6% in persons 15–20 years of age.</td>
</tr>
<tr>
<td>Lin et al. (40)</td>
<td>10,194 freshmen in two Hualien high schools from 1991 to 2001</td>
<td>A significant trend (p &lt; 0.0001) of a decreasing HBsAg carrier rate during the 11 years was found: from 20.3% to 4.4% in males and from 14.3% to 2.4% in females.</td>
</tr>
<tr>
<td>Lu et al. (41)</td>
<td>714 junior high school students born in 1984–1987 (study 1999), 236 students born in 1987–1988 (study 2000), and 504 students born in 1988–1991 (study 2003)</td>
<td>Prevalence of HBsAg decreased 57% (from 12.5% in 1984 to 5.4% in 1991, p &lt; 0.005); anti-HBc positive rate dropped 68% (from 31.9% to 10.2%, p &lt; 0.001).</td>
</tr>
</tbody>
</table>

* HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immunoglobulin; anti-HBc, antibodies to hepatitis B core antigen; anti-HBs, antibodies to hepatitis B surface antigen; HBV, hepatitis B virus.
The results provided evidence that the mass immunization program could effectively control chronic hepatitis B infection in Taiwan (37). The long-term effectiveness of the hepatitis B vaccination program was estimated from data on 805 vaccine responders in a 10-year follow-up study. The cumulative persistence of antibodies to HBsAg was 85 percent, and only three children among the study subjects became carriers (38).

During the 15 years after the vaccination program was implemented, the prevalence of HBsAg among subjects younger than 15 years of age decreased to 0.7 percent in 1999. Among subjects 15–20 years of age, the prevalence of HBsAg was 7 percent (39). To evaluate the effectiveness of the vaccination program, an annual HBsAg survey was conducted among freshmen in two senior high schools in Hualien, eastern Taiwan, from 1991 to 2001. There was a significant trend (*p < 0.0001*) of a decreasing HBsAg carrier rate during the 11 years; the rates decreased from 20.3 percent to 4.4 percent in males and from 14.3 percent to 2.4 percent in females. The HBsAg carrier rate declined from 7.7 percent to 11.9 percent during 1994–1999 (subjects born 1–6 years before the program was launched) to 4.7 and 3.4 percent, respectively, in 2000 and 2001 (for those born after the vaccination program started) (40). Most recently, Lu et al. (41) reported on HBV infection status in a rural township in Taiwan. The prevalence rate of HBsAg decreased from 7 percent in 1981, to 6.4 percent in 1986, to 5.4 percent in 1992, to 3.6 percent in 1997 (42). These results supported the hypothesis that hepatitis B vaccination may decrease the incidence of hepatocellular carcinoma also decreased. The incidence (per 100,000 children) of hepatocellular carcinoma in children 6–9 years of age declined from 0.52 for those born in 1974–1984 to 0.13 for those born in 1984–1986 (*p < 0.001*) (42). This important finding demonstrated that hepatitis B vaccination protected children from not only becoming chronic HBV carriers but also developing hepatocellular carcinoma.

The team from National Taiwan University Hospital further reported that the boy-to-girl incidence ratio of hepatocellular carcinoma decreased steadily from 4.5 in 1981–1984 (before implementation of the universal vaccination program) to 1.9 in 1990–1996 (6–12 years after the vaccination program was launched). The incidence of hepatocellular carcinoma in boys born after 1984 was significantly reduced in comparison with those born before 1978. The relative risk was 0.72 (95 percent confidence interval: 0.59, 0.89; *p = 0.002*). No significant decrease in hepatocellular carcinoma incidence was observed among girls born in the same periods. The results suggested that boys may benefit more than girls from hepatitis B vaccination to prevent hepatocellular carcinoma (43).

A decrease in fulminant hepatitis mortality was reported by Kao et al. (45). The average mortality rate from fulminant hepatitis in infants decreased significantly from 5.4 (95 percent confidence interval: 2.9, 6.7) per 100,000 in years 1975–1984 to 1.7 (95 percent confidence interval: 0.3, 4.6) per 100,000 in years 1985–1998, showing a 68 percent decline (95 percent confidence interval: 58, 76; *p < 0.001*). In other words, mortality from fulminant hepatitis in infants dropped threefold after the mass immunization program was launched in 1984. Chen et al. (46) further demonstrated that within 15 years after the nationwide hepatitis B vaccination program began, the average mortality from fulminant hepatitis in children born in 1984–1986 dropped 68 percent (from 0.48 to 0.16) (*p < 0.001*).

### TABLE 4. Incidence of hepatocellular carcinoma among children aged 6–14 years after a nationwide hepatitis B vaccination program was implemented in Taiwan, summarized from two studies by Chang et al.

<table>
<thead>
<tr>
<th>Year (reference no.)</th>
<th>Study period</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 (42)</td>
<td>1981–1994</td>
<td>Average annual incidence of HCC* in children per 100,000—1981–1986: 0.70 (range, 0.65–0.78), 1986–1990: 0.57 (range, 0.48–0.62), and 1990–1994: 0.36 (range, 0.23–0.48) (<em>p &lt; 0.01</em>); HCC in children has declined significantly.</td>
</tr>
</tbody>
</table>

* HCC, hepatocellular carcinoma; HBV, hepatitis B virus.
of the mass immunization, HBV was found to rarely cause fulminant hepatitis failure in children older than 1 year but remained a significant cause in infants. The reasons for the age difference in the failure to prevent fulminant hepatitis need further investigation.

Although the findings described above provide evidence that the nationwide hepatitis B vaccination program significantly decreased fulminant hepatitis in infants and hepatocellular carcinoma in children, the major limitation of the studies was the lack of individualized information on vaccination records and maternal HBsAg and HBeAg serostatus. Further investigations based on individual data are needed to elucidate the association between hepatitis B vaccination and occurrence of fulminant hepatitis in infants and child hepatocellular carcinoma. Computerized vaccination records of more than 4 million vaccinees are being linked with the national profiles of death certification and the cancer registry. They will be used to assess the effectiveness of HBV vaccination in preventing fulminant hepatitis and hepatocellular carcinoma at the individual level.

REASONS FOR A SUCCESSFUL NATIONWIDE HEPATITIS B VACCINATION PROGRAM

The nationwide hepatitis B vaccination program has been very successful in Taiwan since 1984. The universal immunization program among Taiwanese newborns has not only greatly reduced the HBV infection rate but also prevented the incidence of childhood hepatocellular carcinoma. Reasons for the success of the nationwide hepatitis B vaccination program include the following:

1. The government is very determined to reduce the HBsAg carrier rate, and several institutions have been integrated into the program, including the Department of Health, the Ministry of Education, the Ministry of National Defense, academic institutions, and local government. From 1982 to 1998, the Central Government of Taiwan spent 100 million US dollars on the hepatitis B control program (47).
2. The well-designed infrastructure of the public health and newborn delivery system has provided convenient locations for vaccination, and public health nurses intensively monitor the vaccination schedule for each newborn.
3. The program was designed carefully and implemented step by step.
4. There has been very active research on the effectiveness of and cost-benefit evaluation of the hepatitis B vaccination program. In 2003, major governmental support for liver disease research projects totaled 10.2 million US dollars in Taiwan (48).
5. The efforts of the health administration, the medical care system, and nongovernmental organizations were integrated to educate the general public about liver disease prevention and control.
6. The general public was enthusiastic about participating in the program (with informed consent).
7. The national death certification system (since 1900) and the national cancer registry (since 1979), which have coverage rates of more than 90 percent for all cancer sites, have continued to monitor fulminant hepatitis mortality in infants and the incidence of hepatocellular carcinoma in children.
8. The completeness and accuracy of the national hepatitis B vaccination registry system are important to provide individualized data to evaluate the vaccination program.

FUTURE PERSPECTIVES

Necessity for a booster dose after primary vaccination

Although the effectiveness of hepatitis B vaccination against HBsAg is excellent, a gradual decline in antibodies to HBsAg titer among vaccinees by years after vaccination has been noted (49). Because no vaccinee has been found to become a carrier 5–10 years after primary immunization, many investigators considered booster doses to be unnecessary at 10 years of age in Taiwan (50, 51). In 2000, the European Consensus Group on Hepatitis B Immunity recommended not using boosters of hepatitis B vaccine for immunocompetent individuals 15 years after primary immunization (52). Boosters are not suggested for children or adults of normal immune status (including health-care workers). However, it was recommended that booster doses be used to maintain levels of antibodies to HBsAg of more than 10 mIU/ml in immunocompromised persons. Post-vaccination testing every 6–12 months is advisable for this special group of patients.

The Steering Committee for the Prevention and Control of Infectious Diseases in Asia presented their guidelines for administering hepatitis B vaccine boosters in high-endemicity areas in 2003 (53). Widespread primary vaccination should be the top priority in Asia. Where there are concerns about a highly increased risk of infection, and immunity from primary vaccination is thought to be substandard, physicians should use their own clinical judgment on a case-by-case basis. Guidelines for those who decide to administer hepatitis B vaccine boosters include 1) providing them approximately 10–15 years after primary vaccination; 2) using them rather than not when monitoring of antibody levels is not feasible; 3) providing them to immunocompromised patients when antibodies to HBsAg titer fall below 10 mIU/ml; and 4) administering them to health-care workers based on the endemicity of the particular country.

The necessity of booster vaccination to prevent hepatitis B has been a debatable issue in the last decade. Because the strategy of booster vaccination may have an enormous impact on national medical resources, its cost versus benefit must be evaluated cautiously. More studies are needed to elucidate this issue.

Program effectiveness based on individualized data analysis

All of the previous studies on the effectiveness of the nationwide hepatitis B vaccination program were based on an ecologic comparison. That is, effectiveness was assessed based on comparison of the prevalence of HBsAg, antibodies to hepatitis B core antigen, and/or antibodies to HBsAg; the mortality from fulminant hepatitis in infants; and the
incidence of hepatocellular carcinoma in children between vaccinated and unvaccinated birth cohorts. No individualized data were analyzed to assess program effectiveness and the need for a booster. It is extremely important to carry out post-program surveillance of effectiveness and cost-effectiveness by linking individual data available in computerized national profiles of hepatitis B vaccination records, a cancer registry, death certification, national seroprevalence surveys on HBV infection, and national health insurance files.

It is anticipated that the following five issues might be addressed through such individualized data analysis:

1. The difference in mortality from fulminant hepatitis and the incidence of hepatocellular carcinoma between newborns who did or did not receive hepatitis B vaccination, between newborns who did or did not receive vaccination on schedule, and between newborns born to highly infectious mothers who did or did not receive HBIG. The need for a booster. It is extremely important to carry out post-program surveillance of effectiveness and cost-effectiveness by linking individual data available in computerized national profiles of hepatitis B vaccination records, a cancer registry, death certification, national seroprevalence surveys on HBV infection, and national health insurance files.

2. The difference in the serostatus of HBsAg and antibodies to HBsAg between newborns who did or did not receive hepatitis B vaccination, between newborns who did or did not receive vaccination on schedule, and between newborns born to highly infectious mothers who did or did not receive HBIG.

3. The impact of maternal HBsAg and HBeAg serostatus on the risk of fulminant hepatitis and hepatocellular carcinoma in their children after taking hepatitis B vaccine status into consideration.

4. The difference in the effectiveness between plasma-derived and recombinant hepatitis B vaccines.

5. The likelihood of vaccine failure as a result of missed HBIG, misscheduled hepatitis B vaccines, and maternal HBsAg and HBeAg serostatus.

Possibility for eradicating HBV

Vaccination has been documented to be effective in eradicating smallpox and poliomyelitis in the world. It remains to be evaluated whether HBV infection may also be eradicated through vaccination. Because HBV infects mainly humans, with very rare animal reservoirs, comprehensive vaccination is expected to eradicate the virus. However, the current vaccination program must be better reviewed for possible limitations. The following issues should be studied further:

1. Should all newborns born to HBsAg-seropositive rather than HBeAg-seropositive mothers receive at least one dose of HBIG?
2. Should a booster dose be given to vaccinees 20 or more years after primary vaccination?
3. Is it cost-effective to use antiviral treatment for HBsAg-positive patients to reduce the risk of horizontal transmission?
4. How will the hepatitis B vaccination program be promoted in developing countries?

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