Seroepidemiologic Survey for Hepatitis B Virus Infection in Taiwan: The Effect of Hepatitis B Mass Immunization

Hsu-Mei Hsu, Chih-Feng Lu, Shin-Chwen Lee, Sheue-Rong Lin, and Ding-Shinn Chen

A hepatitis B mass immunization program was launched in Taiwan in July 1984, beginning with newborns of hepatitis B carrier mothers for the first 2 years of the program, which was then extended to all newborns. Seroepidemiology was studied in 3 cohorts at age 6 years. Each cohort consisted of 1500 children proportionally and randomly sampled from those entering elementary school in 1989, 1991, and 1993, representing those born 1 year before the program began and years 1 and 3 of the program, respectively. By RIA, the hepatitis B surface antigen positivity rates in the groups were 10.5%, 6.3%, and 1.7%, respectively; hepatitis B surface antibody positivity rates were 36.9%, 62.0%, 65.4%; and hepatitis B infection rates were 25.0%, 15.9%, 4.3%. Thus, universal immunization was more effective in reducing hepatitis B carriage than selective immunization of newborns of carrier mothers only. The program has proved effective in controlling chronic hepatitis B infection in Taiwan.

Hepatitis B virus (HBV) infection creates health problems worldwide. In Taiwan, the carrier rate of hepatitis B surface antigen (HBsAg) in the general population has been as high as 15%–20% [1, 2], one of the highest in the world. This has resulted in chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the carriers [3, 4]. The cancer is so common that it has ranked first for cancer mortality in men and second in women since the early 1980s [5]. In addition, chronic liver diseases rank sixth among causes of death [5]. In about half of the Taiwanese chronic HBsAg carriers, the infection is attributed to perinatal transmission of the virus from mothers to infants [6]. To control this serious public health problem in Taiwan, a mass immunization program against hepatitis B was launched on 1 July 1984, one of the earliest national programs in the world [7]. This program provided us with an excellent opportunity to observe the effects of hepatitis B mass immunization.

Several studies have evaluated the immunogenicity and efficacy of hepatitis B vaccination, mostly by following up those who were vaccinated in early infancy [8–14]. However, there have been few studies of children, and in those done, the sample sizes were small and the areas investigated were limited [15, 16]. Therefore, we conducted a nationwide population-based random sampling study of three birth cohorts at age 6 years. Because the time of birth in these cohorts spanned three different stages of the Taiwanese vaccination program, the results will be of use for evaluating the program. In addition, the World Health Organization endorsed the inclusion of hepatitis B vaccine into routine childhood immunization programs in all countries by 1997 [17]. Thus, our results may provide important information for hepatitis B immunization programs.

Materials and Methods

Hepatitis B mass immunization program. Because of the risk of HBV infection in Taiwan, priorities were set for immunization against the virus [7], and a program was launched in July 1984 in a step-wise way. In the initial 2 years, only infants born to HBsAg carrier mothers were immunized. From the third year on, all infants were immunized. To ensure wide coverage, the government covered all expenses for immunizations in newborns and infants, the most important primary target in this program. The program was extended to preschool children in 1987–1990, to primary school children in 1988–1991, and to teenagers in 1989–1991 on a fee-for-service basis. From October 1990, the free-charge service was extended to first graders in elementary schools. Since July 1991, the vaccine records of elementary school entrants have been checked for evidence of the following vaccinations: hepatitis B, bacille Calmette-Guérin, diphtheria-tetanus toxoids–pertussis, oral polio, Japanese B encephalitis, and measles-mumps-rubella. Nonor incompletely vaccinated pupils are given catch-up vaccinations.

All pregnant women were screened for HBsAg, and HBsAg-positive serum specimens were further tested for hepatitis B e antigen (HBeAg) to identify highly infectious carriers. All infants were vaccinated with 4 doses of plasma-derived vaccine (Havac B; Pasteur-Mérieux, Lyon, France, or its equivalent derivative, Lifeguard hepatitis B vaccine; Hsin-Chu, Taiwan) at 0, 1, 2, and 12 months of age. Newborns of highly infectious carrier mothers were also
given 0.5 mL of hepatitis B immune globulin at birth. After 1 November 1992, the plasma-derived vaccine was replaced by recombinant yeast vaccine with a 3-dose regimen at ages 0, 1, and 6 months. In the transition period, newborns who had received earlier doses of plasma-derived hepatitis B vaccine were still given 4 doses of vaccine, regardless of whether they were to receive plasma-derived or recombinant vaccine in the remaining doses. The recombinant vaccines provided in the national program after November 1992 were HB-Vax II (5 μg/0.5 mL; Merck Sharp & Dohme, Rahway, NJ) and Engerix-B (20 μg/1 mL; SmithKline Beecham, Rixensart, Belgium). The preschool children and the first graders were immunized with hepatitis B vaccine without pre-screening for HBV markers, although children in other age groups were screened before vaccination.

Subjects. Children at age 6 years in Taiwan were consecutively assigned into 3 groups by birth cohort: Cohort 1 included children born between September 1982 and August 1983, 1 year before the hepatitis B immunization program was initiated; cohort 2 comprised children born between September 1984 and August 1985, when the immunization program covered only newborn infants of HBsAg carrier mothers; cohort 3 included children born between September 1986 and August 1987, when all infants were covered (figure 1).

Sampling. From each cohort, 1500 children were selected by proportional random sampling. In Taiwan, children at age 6 are admitted to primary school; the admission rate is extremely high [18]. Using school lists from the Ministry of Education as the sampling frame and the total number of entrants in Taiwan primary schools as the sampling denominator, we first stratified the schools by county/city and then by township/district. Based on the proportions of entrants, the sample size of each stratification was calculated. If the sample size of entrants was <13 in a given township/city, only one school was randomly selected. If the sample size was 13–20, two schools were randomly selected. In the school targeted for the study, a class in the first grade was randomly selected, and then a set of numbers (more than the sample size) was picked up from the random table, and the assigned target children in the class were reached sequentially until the sample size was fulfilled.

Questionnaire and blood collection. Each questionnaire sought demographic data for the child and his or her parents and the child’s vaccination history. Well-trained public health nurses visited and interviewed the parents. In the meantime, the vaccination records were checked, and a blood sample was collected from the child by venepuncture. The study was done during August to October of 1989, 1991, and 1993 for the 3 cohorts, respectively.

Laboratory studies. Serum HBsAg, its antibody (anti-HBs), and hepatitis B core antibody (anti-HBc), were tested by RIAs using Ausria II, Ausab, and Corab (Abbott Laboratories, Abbott Park, IL), respectively. Seronegativity was defined as the negative results of these three hepatitis B markers. Those who had anti-HBc, HBsAg, or both were defined as HBV-infected. We used SAS Institute (Cary, NC) programs for statistical analysis. The differences in the prevalence of HBV markers among the 3 cohorts were examined by χ² test. P ≤ .05 was considered statistically significant.

Results

Background data. There were 385,135, 353,790, and 309,106 first grade pupils in Taiwan in 1989, 1991, and 1993, respectively. Of 23 counties/cities, there were 190, 210, and 292 township/districts in 1989, 1991, and 1993, respectively. As for elementary schools, there were 2484, 2495, and 2525 in the respective years. Based on proportional random sampling, 229, 263, and 349 schools were selected in 1989, 1991, and 1993, respectively. Each cohort comprised 1500 6-year-old children. There were no statistically significant differences among the 3 cohorts in the geographic distribution of the recruited children throughout Taiwan.

Vaccination status. The coverage rate of vaccination against hepatitis B was highest (92.4%) in cohort 3 (table 1). The proportion of those who received a complete course of 4 doses of hepatitis B vaccine was also highest (79.3%) in this cohort. The cohort 1 children were born before the mass vaccination program was implemented and had lowest vaccine coverage; 67.3% had never received hepatitis B vaccine. The results in cohort 2 were intermediate: 35.3% were not vaccinated (table 1).

Hepatitis B markers. The seroprevalence of HBsAg was 10.5%, 6.3%, 1.7% in the 3 cohorts, respectively. The corresponding anti-HBs positivity rates were 36.9%, 62.0%, and 65.4%, and the HBV infection rates were 25.0%, 15.9%, and 4.3%. The seronegativity rates were 51.6%, 31.3%, and 32.8%.


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<tr>
<td>None</td>
<td>1009 (67.3)</td>
<td>530 (35.3)</td>
<td>91 (6.1)</td>
</tr>
<tr>
<td>1 dose</td>
<td>41 (2.7)</td>
<td>25 (1.7)</td>
<td>43 (2.9)</td>
</tr>
<tr>
<td>2 doses</td>
<td>33 (2.2)</td>
<td>34 (2.3)</td>
<td>35 (2.3)</td>
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<tr>
<td>3 doses</td>
<td>105 (7.0)</td>
<td>567 (37.8)</td>
<td>118 (7.9)</td>
</tr>
<tr>
<td>4 doses</td>
<td>231 (15.4)</td>
<td>290 (19.3)</td>
<td>1190 (79.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>81 (5.4)</td>
<td>54 (3.6)</td>
<td>23 (1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>1500 (100)</td>
<td>1500 (100)</td>
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a Hepatitis B vaccination comprised 4 doses given at age 0, 1, 2, and 12 months.
in the respective cohorts. The differences in the rates among the 3 cohorts were statistically significant \((P < .0001; \text{table } 2)\).

**Discussion**

In the present study, all recruited subjects were children aged 6 years at elementary school entry. Compulsory education in Taiwan is nearly 1 century old and has been extremely successful. The elementary school admission rates in 1989, 1991, and 1993 were 99.60%, 99.59%, and 99.72%, respectively [18]. Thus, sampling from this system reliably represents the child population in Taiwan. With this sampling, the geographic distribution of the children selected for our study were evenly and widely distributed throughout the country; therefore, the results should be representative for Taiwan. The 3 cohorts were deliberately chosen to represent the three phases of the Taiwanese hepatitis B mass immunization, so that the effects of the immunization program could be explored more explicitly. In total, 4500 randomly recruited children were reached with serum collection and questionnaires. This reduced the selection as well as participation biases.

The seroprevalence of HBsAg at age 6 years in our study showed a striking decline from 10.5% in the first cohort (born 1 year before the program began) to 6.3% in the second cohort (born when only babies of HBsAg carrier mothers were immunized) to 1.7% in the third cohort (born when all infants were covered). Likewise, HBV infection rates also decreased significantly from cohort 1 to cohort 3 (25.0%, 15.9%, 4.3%, respectively). Thus, 10 years after the national vaccination program against hepatitis B was implemented, among first graders, HBsAg-positive rates were reduced by 84% (from 10.5% to 1.7%), and the HBV infection rate dropped 83% in parallel (from 25% to 4.3%). This decline was observed in a previous seroepidemiologic study in a small district of the Taipei City [16]. In that study, among 226–371 children at age 5–6 years, the HBsAg prevalence decreased from 10.6% in surveys done in 1984 to 3.9% in 1989 to 0.8% in 1994. In these two studies, the HBsAg positivity rates were comparable in those born before 1984. However, the positivity rates after the vaccination program were higher in the children in our study, likely because of the higher hepatitis B vaccination coverage in Taipei City (97% for ≥3 doses in 1994 [16] vs the present study 87.2%). We believe our study is more representative of the whole country, since we sampled randomly and proportionally from the entire population of 6-year-olds in Taiwan. These data show the importance of a high vaccination coverage rate.

The coverage rate for hepatitis B vaccines among children in cohort 3 was high, showing that the national immunization program against hepatitis B for newborns was quite successful in the past 10 years. Even among children in cohort 1, who were born 1 year before the program began, 27.3% had received hepatitis B vaccine, which was paid for by their parents when we promoted the immunization for preschool children. In cohort 2, 60.1% of the children received ≥1 dose of hepatitis B vaccine: 12.5% received the first dose at age 1 month, 1.9% at age 6–12 months, and 85.6% before beginning school. In cohort 3, 92.4% of the children had ≥1 dose of the vaccine. Of these, 92.7% received the first dose before age 12 months; only 7.3% were vaccinated during their preschool years. While the preschool vaccination may have affected the results in cohorts 1 and 2, the effect was much lower in cohort 3. Nonetheless, the results still indicate that universal immunization of all infants at birth against hepatitis B exerts the strongest effects on the reduction of chronic HBV infection.

Since October 1990, catch-up hepatitis B vaccination without charge has been extended to elementary school first graders, and since July 1991, vaccination records have been checked for all first graders. None or incompletely vaccinated pupils are placed in an expanded immunization program that includes HB vaccine. Immunization records for all children in the present study were checked; those who needed further immunizations were given catch-up vaccine after a blood sample was drawn for the study. The catch-up immunization strategy should further reduce HBsAg carriage and HBV infection.

In this study, we did not collect information on the type of hepatitis B vaccine received, because in the newborn and preschool vaccination program, the only vaccine available for children in the national program was the plasma-derived hepatitis B vaccine. The recombinant vaccine was not available in Taiwan until July 1990. In the national program, the recombinant vaccine was given to infants born after 1 November 1992. Thus, cohort 1 children, whose serum specimens were collected during August to October 1989, received only plasma-derived vaccines. In cohorts 2 and 3, if children were immunized at hospitals or clinics not under contract after June 1990, they might have received recombinant vaccines. However, only 8 children in cohort 2 and 2 in cohort 3 received their vaccine at noncontract hospitals or clinics. The recombinant vaccines available for the national program (Merck Sharp & Dohme [5 µg/0.5 mL] and SmithKline Beecham [20 µg/1 mL]) were given only after November 1992. No Merck Sharp & Dohme 2.5-µg dose was available in Taiwan. All 542 seronegative children received plasma-derived hepatitis B vaccines. Therefore, the effect of recombinant vaccine is negligible.

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<td>HBsAg</td>
<td>158 (10.5)</td>
<td>94 (6.3)</td>
<td>26 (1.7)</td>
<td>&lt;.001</td>
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<tr>
<td>Anti-HBs</td>
<td>553 (36.9)</td>
<td>930 (62.0)</td>
<td>981 (65.4)</td>
<td>&lt;.001</td>
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<td>Infected*</td>
<td>375 (25.0)</td>
<td>239 (15.9)</td>
<td>64 (4.3)</td>
<td>&lt;.001</td>
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<tr>
<td>Seronegative*</td>
<td>774 (51.6)</td>
<td>470 (31.3)</td>
<td>492 (32.8)</td>
<td>&lt;.001</td>
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* Those who had anti-HBc and/or HBsAg
* Those who had negative results for HBsAg, anti-HBs, and anti-HBc.
Of the 4500 children studied in the 3 cohorts, 2501 had 3 or 4 doses of hepatitis B vaccine. Of these, 1875 (75%) still had anti-HBs markers. Most of these may be vaccine responders who have relatively low anti-HBs after vaccinations 5–6 years earlier, and the antibody may have declined to undetectable levels at the time of our study. Alternatively, a small proportion of these seronegative children may not respond to the vaccine as previously shown [8–11]. Whether these seronegative children are protected from HBV infection remains to be seen. A booster dose of hepatitis B vaccine will be suggested only when there is evidence showing they are not protected against HBV. Nevertheless, for ethical reasons, the seronegative children in our study were given a booster dose of hepatitis B vaccine. No postbooster follow-up was done.

Although seroepidemiologic surveys have revealed an anticipated decrease of HBsAg carriage in the Taiwanese children covered by the mass vaccination program, the ultimate effect of this prevention program on liver diseases remains to be established. Of interest, the incidence of hepatocellular carcinoma in children in Taiwan is significantly decreasing [19, 20]—from 0.52 per 100,000 children born between 1974 and 1984 (i.e., before the vaccination program) to 0.13 per 100,000 in those born between 1984 and 1986 (i.e., after implementation of the vaccination program). Thus, the universal HBV vaccination among Taiwanese newborns has not only decreased chronic HBV infection but also prevented childhood hepatocellular carcinoma. We anticipate that the decrease in hepatocellular carcinoma in Taiwan will continue and steadily extend to teenagers and young adults and finally to older adults.

During its 1992 annual meeting in Geneva, the World Health Assembly endorsed the 1997 global vaccination targets for the Expanded Programme on Immunization. These targets were set by the global advisory group in October 1991 and called for all countries with HBV carrier rates of >8% to integrate hepatitis B vaccination into their routine immunization programs by 1995 and for all countries to establish such programs by 1997 [17]. Such measures are important and effective as shown in Taiwan [21]. We urge that mass immunization against hepatitis B be implemented as soon as possible globally, particularly in countries where HBV infection and chronic liver diseases are prevalent.

Acknowledgments

We thank the county and city health bureau directors for their unstinting support and the public health nurses for their invaluable help and assistance in carrying out this study.

References