GASTROENTEROLOGY 2012;xx:xxx

Effects of Maternal Screening and Universal Immunization to Prevent Mother-To-Infant Transmission of HBV

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BACKGROUND & AIMS: Mother-to-infant transmission is the major cause of hepatitis B virus (HBV) infection among immunized children. There has been much debate about screening pregnant women and administering hepatitis B immunoglobulin (HBIG) to newborns. We analyzed the rate of HBV infection among children born to hepatitis B surface antigen (HBsAg)-positive mothers and whether HBIG administration reduces transmission. **METHODS:** We analyzed data from 2356 children born to HBsAg-positive mothers, identified through prenatal maternal screens. In addition to HBV vaccines, HBIG was given to all 583 children with hepatitis B e antigen (HBeAg)-positive mothers and to 723 of 1773 children with HBeAg-negative mothers. Serology tests for HBV were performed from 2007 to 2009, when children were 0.5–10 years old. **RESULTS:** A significantly greater percentage of children with HBeAg-positive mothers tested positive for antibodies against the hepatitis B core protein (16.76%) and HBsAg (9.26%) than children with HBeAg-negative mothers (1.58% and 0.29%, respectively; $P < .0001$ and $<.001$). Among the HBV-infected children, the rate of chronicity also was higher among children with HBeAg-positive mothers than children with HBeAg-negative mothers (54% vs 17%; $P = .002$). Similar rates of antibodies against the hepatitis B core protein (0.99% and 1.88%; $P = .19$) and HBsAg (0.14% and 0.29%; $P = .65$) were noted in children born to HBeAg-negative mothers who were or were not given HBIG. Infantile fulminant hepatitis developed in 1 of 1050 children who did not receive HBIG (.095%). **CONCLUSIONS: Children born to HBeAg-positive mothers are at greatest risk for chronic HBV infection (9.26%), despite immunization. Administration of HBIG to infants born to HBeAg-negative mothers did not appear to reduce the rate of chronic HBV infection, but might prevent infantile fulminant hepatitis. Screening pregnant women for HBsAg and HBeAg might control mother-to-infant transmission of HBV.**

Keywords: Vaccination; Screening Pregnant Women; HBsAg Carrier; Pediatric Liver Disease.

Hepatitis B virus (HBV) infection is a worldwide health problem, with approximately 360 million people chronically affected and 1 million deaths each year attributed to HBV.[1,2] Because of the high rate of mother-to-infant transmission of HBV, and because of the highest chronic infection rate and the risks of developing hepatocellular carcinoma (HCC) among subjects who are infected early in life, the immunization of newborns has been proven to be the most effective way of reducing chronic HBV carrier rates and HCC in the population.[2–9] The World Health Organization has integrated HBV immunization into the Expanded Program on Immunization. In 2008, 177 countries had introduced hepatitis B vaccination into their national immunization programs.[10]

Despite the significant reduction of HBV carrier rate and HCC after universal infant immunization, we should be aware of the fact that current immunoprophylaxis cannot eradicate mother-to-infant HBV transmission completely. Neonatal immunization may result in a 75% to 90% reduction of the carrier rate, with active immunization (vaccines) alone or active plus passive immunization (ie, hepatitis B immunoglobulin [HBIG]) at birth.[5–8,11] At least 10% of the HBV carriers cannot be prevented by immunization. Moreover, children with breakthrough HBV infection have a higher risk of developing HCC, compared with nonvaccinated HBV carrier children.[12] Fulminant hepati-

Abbreviations used in this paper: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HCC, hepatocellular carcinoma.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.12.035

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tis may develop in infants born to hepatitis B e antigen (HBeAg)-negative, hepatitis B surface antigen (HBsAg)-carrier mothers despite immunization.[13–16] We have shown in a population-based study that 88% of the children with breakthrough infection had HBsAg-positive mothers,[17] indicating that maternal-infant transmission is the major source of HBV infection in the postimmunization era. Although there were previous reports of breakthrough infection rates in immunized infants born to HBeAg-positive mothers, those data were mostly from small-scale studies or performed in the 1980s when universal vaccination had just began.[6,11,18–20] There have been no clear large-scale data from the universal vaccinated population regarding the rate of breakthrough infection among children with HBV-carrier mothers, and there especially are a lack of data on the different infection rates in those born to HBeAg- negative vs HBeAg-positive mothers.

Currently, there are 3 main strategies of universal immunoprophylaxis against HBV infection, including active immunization only (such as in Thailand), active immunization of all newborns plus passive immunization (ie, HBIG) of neonates born to HBsAg-carrier mothers (such as in the United States), and active immunization of all newborns plus passive immunization of neonates born to HBsAg- and HBeAg-positive mothers (such as in Taiwan).[2,3,21,22] In the latter 2 strategies, the screening of pregnant women for HBsAg and/or for HBeAg is required. However, these policies have been based on previous small-scale vaccine trials conducted mostly in children born to HBsAg- and HBeAg-positive mothers.[6,7,23] A controversy exists as to whether to give or not to give HBIG at birth to neonates born to HBeAg-negative, HBsAg-carrier mothers, owing to a lack of convincing evidence comparing the breakthrough HBV infection rate and immunization efficacy in this group with or without HBIG at birth. These data are of great importance in helping to determine the government's strategy for screening pregnant women, administering the neonatal HBV vaccines and the HBIG program, and surveillance of high-risk children in the immunized population.

A universal HBV immunization program was launched in Taiwan in July 1984, making it one of the first programs in the world. A significant decrease in the chronic HBV carrier rate in the population, from 10%–20% to 1%–2%, a reduction in the incidence of HCC by two thirds, and a decreased incidence of infantile fulminant hepatitis, have been observed.[4,12,17,24–28] The program entails that HBV vaccines be given to all newborns and that HBIG be given only to those born to HBeAg-positive, HBsAg-carrier mothers.[18,28] In the past 10 years, a growing number of parents have chosen to administer self-paid HBIG to their newborns born to HBeAg-negative, HBsAg-carrier mothers, despite no solid data pointing to the benefit of HBIG for this group. In recent years, many medical professionals and parents strongly urged administering HBIG to children born to HBeAg-negative mothers, as per US guidelines. This study then was conveyed under the request of the Center of Disease Control, Department of Health of Taiwan, to seek evidence supporting a change of the national program.

Immunized children with breakthrough HBV infection comprise a population of chronic liver disease patients who have a higher risk of developing HCC than the HBsAg-carrier children born in the pre-immunization era.[12] This population has been overlooked, and this problem hinders the success of eradicating HBV infection. Recently, new insights of interrupting such maternal-infant transmission have been reported using nucleoside analogs to reduce maternal viral load during the last trimester of pregnancy.[29,30] Chronic HBV infection in pregnant women, as it pertains to maternal and child health, is an issue attracting growing attention but with many unresolved problems.[31,32] In this study, we conducted a multicenter survey of children born to HBsAg-carrier mothers. Based on our particular universal HBsAg/HBeAg screening program for pregnant women that has been applied only in a small number of countries, we were able to accurately define prenatal maternal HBeAg positivity, and to determine the breakthrough infection rates of children born to HBsAg-carrier mothers, with respect to the maternal HBeAg status in a large population.

Materials and Methods

Universal Immunization Program

The universal HBV immunization program in Taiwan was implemented in July 1984. During the first 2 years (July 1984 to June 1986), only children of HBsAg carrier mothers were covered by the immunization program. Plasma-derived vaccines were used before July 1992 and thereafter were shifted to 3-dose recombinant vaccines (administered at 0, 1, and 6 months). HBIG is administered within 24 hours after birth to newborns born to HBeAg-positive, HBsAg-carrier mothers.[17,18,24,28] The option of receiving self-paid HBIG for infants born to HBeAg-negative, HBsAg-carrier mothers is provided in most hospitals. The national HBV vaccine coverage rate of 3 or more doses in infants was higher than 92%.[4]

Study Design and Population

A total of 9177 children born to HBsAg-positive mothers delivered in 9 tertiary referral hospitals in northern, central, and southern Taiwan from 1996 to 2008 were invited to join this study. Children born with a gestational age of 35 weeks or younger, with a body weight of 2300 g or less, or with apparent birth defects were excluded. Among them, 2379 agreed to participate in the study with parental consent. Blood sampling was performed once for each subject from January 2007 to January 2009, when children were at a chronologic age of 6 months to 10 years (Figure 1).

Maternal serum HBsAg and HBeAg levels were tested in the third trimester of pregnancy and recorded in the charts of mothers and newborns according to the national screening program for pregnant mothers. A computerized national registration system for maternal HBsAg and HBeAg status and for infant immunization records in the Department of Health was started with the launch of the universal HBV immunization program.[28] The children's HBV immunization records, including the dates of each dose of HBIG and vaccines, were confirmed

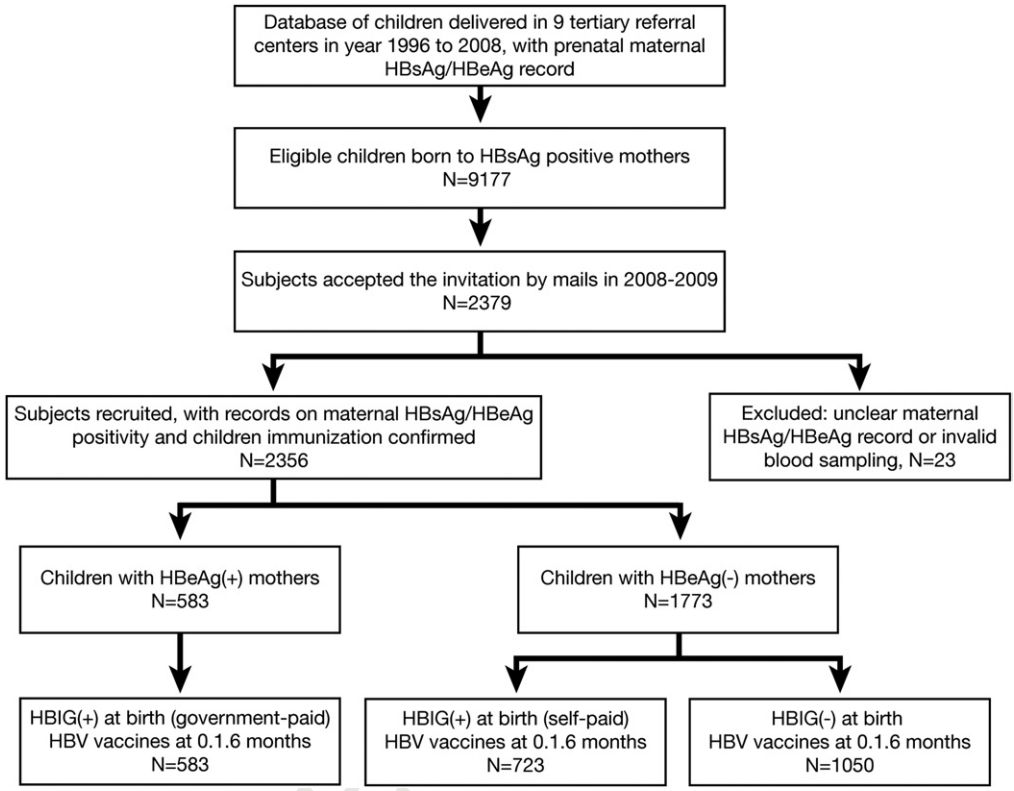

Figure 1. Flow of subject recruitment for this study. According to the universal immunization program, maternal HBsAg and HBeAg were screened during pregnancy. Universal vaccination was given to all newborns irrespective of maternal status. HBIG was given only to HBeAg-positive mothers according to our program. Infants born to HBeAg-negative mothers may choose to receive self-paid HBIG at birth.

from at least 2 of the 3 sources: hospital charts, immunization records in the official child health booklets held by the parents, and the database of the national registry system. The on-schedule rate of immunization was defined as the administration of HBIG, the first, second, and third dose of HBV vaccines no later than 24 hours, 7 days, 1.5 months, and 7 months after birth, respectively. The children's medical history was obtained from their parents at the time of blood sampling by questionnaire. The study was approved by the institutional review boards.

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HBV Serology and Virology Tests

Serum HBV markers, including HBsAg, hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc), were tested using an enzyme immunoassay (Abbott Laboratories, North Chicago, IL). Humoral immunity from vaccination was defined as an anti-HBs titer greater than 10 mIU/mL in those children who were negative for HBsAg. The serologic markers were tested at the time of blood sampling when the children were 6 months to 10 years old.

The sera of the children who tested positive for HBsAg were analyzed further for HBV viral load. Serum samples from their mothers were obtained at the time of the study. The HBV viral load and genotype were tested using a real-time polymerase chain reaction assay, as has been described previously.[33] Twenty-five HBsAg-positive mother-child pairs were tested further for HBV surface mutants and HBV subtype using polymerase chain reaction and direct sequencing of the viral genome within the surface gene. The changes in amino acid sequences at the *a* determinant (amino acids 121–149) were compared among the mother-child pairs.[34]

Definition of Breakthrough Infection

Children positive for anti-HBc or HBsAg were defined as having breakthrough infection. The anti-HBc–positive rate at age 0–24 months largely resulted from the passive transfer of the maternal antibody.[35] Therefore, the rate of anti-HBc was calculated only in those ages 2–10 years. Children positive for HBsAg for more than 6 months were defined as chronic HBV carriers. Chronicity rate was defined as persistent HBsAg seropositivity rates among all children with breakthrough infection.

Sample Size Estimation

The estimated HBV infection rates in the children born to the HBeAg-positive and HBeAg-negative/HBsAg carrier mothers were based on the results of a previous study performed at the beginning of universal immunization. This study found that children born to highly infectious mothers (high HBsAg reverse passive hemagglutination titer or HBeAg-positive) and children born to less-infectious mothers (low HBsAg titer or HBeAg-negative) had HBsAg-positive rates of 13.7% and 3.1%, respectively.[18] The sample size required to detect the estimated differences between the children born to the HBeAg-positive and HBeAg-negative mothers was 142 in each group. In addition, we assumed that HBIG administration would further reduce the rates of HBsAg and anti-HBc positivity from 3.1% and 6.1%, respectively, to 1% and 2%, respectively, in children born to HBsAg(+)/HBeAg(−) mothers. Given a type I error (α) of 0.05, a power of 0.9 requires total sample sizes of 1910 and 968 in the 2 groups of children, and a power of 0.8 requires 1428 and 724.

Statistical Analysis

Statistical analysis was performed using SAS software version 9.1.3 (SAS Institute, Inc, Cary, NC). The chi-square test and the Fisher exact test were used to compare HBsAg and anti-HBc rates between groups. The age-adjusted anti-HBs positivity rate was compared using a Mantel–Haenszel test. A 2-sided *P* value of .05 or less was considered statistically significant.

Table 1. The HBsAg(+) Rate in Children Born to HBeAg (+) and HBeAg (-)/HBsAg(+) Mothers After Universal Immunization

	Children born to HBeAg(+) mother			Children born to HBeAg(−) mother					
	HBIG(+)			HBIG(−)			HBIG(+)		
Age, *y*	N	HBsAg+(%)	95% CI	N	HBsAg+(%)	95% CI	N	HBsAg+(%)	95% CI
<1	28	3 (10.71)	(0.00–22.17)	25	0 (0.00)	(0.00–0.00)	81	0 (0.00)	(0.00–0.00)
1	42	5 (11.90)	(2.11–21.70)	70	0 (0.00)	(0.00–0.00)	137	0 (0.00)	(0.00–0.00)
2	52	9 (17.31)	(7.03–27.59)	66	0 (0.00)	(0.00–0.00)	123	0 (0.00)	(0.00–0.00)
3–4	113	10 (8.85)	(3.61–14.09)	182	1 (0.55)	(0.00–1.62)	130	0 (0.00)	(0.00–0.00)
5–6	113	9 (7.96)	(2.97–12.96)	196	0 (0.00)	(0.00–0.00)	120	0 (0.00)	(0.00–0.00)
7–8	122	9 (7.38)	(2.74–12.02)	295	0 (0.00)	(0.00–0.00)	94	1 (1.06)	(0.00–3.14)
9–10	113	9 (7.96)	(2.97–12.96)	216	2 (0.93)	(0.00–2.20)	38	0 (0.00)	(0.00–0.00)
Total	583	54 (9.26)	(6.91–11.62)	1050	3 (0.29)	(0.00–0.61)	723	1 (0.14)	(0.00–0.41)

NOTE. The age groups were defined as follows: age < 1 y, age 6–11 months; age 1, age 12–23 months; age 2, age 24–35 months, and so forth.
95% confidence interval (CI), lower bound and upper bound of 95% CI (rate ± 1.96 × standard error).

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Results

Among the 2379 subjects who responded to the study invitation, a total of 2,356 children, ages 6 months to 10 years, were included in the analysis with unequivocal prenatal maternal HBsAg/HBeAg data, childhood immunization records, and valid blood sampling. They comprised 583 children born to HBeAg-positive mothers and 1773 children born to HBeAg-negative mothers. All children had received 3 doses of HBV vaccine, and all of the 583 children with HBeAg-positive mothers received the mandatory HBIG within 24 hours after birth. Of the 1773 children born to HBeAg-negative carrier mothers, 1050 did not receive HBIG as per Taiwan guidelines, and 723 had received self-paid HBIG by parental choice and consent (Figure 1). The HBIG self-paid rate in the collaborating hospitals was 51% ± 26%. We found no correlation between HBIG self-paid rates and income levels in the study cities. The vaccine completion rate was 100%. The on-schedule rates for HBIG and the first, second, and third doses of the vaccine were 98%, 91%, 95%, and 93%, respectively.

Rates of Breakthrough Infection

The overall HBsAg-positive rate was 2.46% (58 of 2356; 95% confidence interval [95% CI], 1.84%–3.09%) in all the children born to HBsAg-positive mothers. The HBsAg-positive rate was much higher in the children born to the HBeAg-positive mothers than in those born to the HBeAg-negative mothers: 9.26% (54 of 583; 95% CI: 6.91%–11.62%) vs 0.23% (4 of 1773; 95% CI: 0.00%−0.45%) ($P < .001$). In the children born to HBeAg-negative mothers, the HBsAg-positive rate was 0.14% (1 of 723; 95% CI: 0.00%, 0.41%) for those with HBIG at birth and 0.29% (3 of 1050; 95% CI: 0.00%, 0.61%) for those without HBIG at birth ($P = .65$) (Table 1). All of the HBsAg-positive children were also positive for anti-HBc and had been persistently HBsAg positive for at least 6 months of follow-up evaluation. All of the mothers of the HBsAg-carrier children were born before July 1984, when the universal immunization program started.

The overall breakthrough infection rate, as defined by anti-HBc positivity at more than 24 months of age (including HBsAg positivity), was 5.52% (109 of 1973; 95% CI: 4.52%−6.53%) in all of the children born to the HBsAg carrier mothers; it was much higher in the children born to the HBeAg-positive mothers than in those born to the HBeAg-negative mothers: 16.76% (86 of 513; 95% CI: 13.53%−20.00%) vs 1.58% (23 of 1460; 95% CI: 0.94%−2.21%) ($P < .001$). In the children born to the HBeAg-negative mothers, there was no significant difference in the anti-HBc positive rate for those with or without HBIG at birth: 0.99% (95% CI: 0.13%, 1.85%) vs 1.88% (95% CI: 1.02%, 2.75%) ($P = .19$) (Table 2). The HBsAg- and anti-HBc–positive rates were stable across the 0.5- to 10- and 2- to 10-year age groups, respectively, without statistically significant differences between the age groups. Therefore, the earlier-mentioned HBsAg and anti-HBc rates were calculated using pooled age groups. We also analyzed the HBsAg rates after excluding all children younger than 12 months of age. The results were similar to the rates that we obtained without the exclusion.

We analyzed the HBsAg carrier rate in the fathers of the subjects and found no correlation between the paternal HBsAg-carrier status and HBsAg positivity in the children. Of the 1304 subjects with known paternal HBV status, 3 children of the 236 HBsAg-positive fathers and 33 children of the 1068 HBsAg-negative fathers became HBsAg carriers ($P = .19$).

Estimation of Chronicity Rates

The children with HBeAg-positive mothers had a 10.6-fold greater anti-HBc rate and a 40.3-fold greater HBsAg rate than the children with HBeAg-negative mothers, indicating that the infected children with HBeAg-positive mothers had a greater chance of becoming HBsAg carriers. The estimated chronicity rates among all the infected children (the HBsAg positivity rates among the anti-HBc–positive children >24 mo) were 54% (46 of 86; 95% CI: 43%−64%) of the children born to the HBeAg-positive mothers and 17% (4 of 23; 95% CI: 19%−33%) of

Table 2. The anti-HBc(+) Rate in Children Born to HBeAg(+) and HBeAg(−)/HBsAg(+) Mothers After Universal Immunization

	Children born to HBeAg(+) mother			Children born to HBeAg(−) mother					
	HBIG(+)			HBIG(−)			HBIG(+)		
Age, *y*	N	Anti-HBc+ (%)	95% CI	N	Anti-HBc+ (%)	95% CI	N	Anti-HBc+ (%)	95% CI
2	52	12 (23.08)	(11.63–34.53)	66	1 (1.52)	(0.00–4.46)	123	0 (0.00)	(0.00–0.00)
3–4	113	20 (17.70)	(10.66–24.74)	182	4 (2.20)	(0.07–4.33)	130	1 (0.77)	(0.00–2.27)
5–6	113	15 (13.27)	(7.02–19.53)	196	1 (0.51)	(0.00–1.51)	120	1 (0.83)	(0.00–2.46)
7–8	122	23 (18.85)	(11.91–25.79)	295	5 (1.69)	(0.22–3.17)	94	2 (2.13)	(0.00–5.04)
9–10	113	16 (14.16)	(7.73–20.59)	216	7 (3.24)	(0.88–5.60)	38	1 (2.63)	(0.00–7.72)
Total	513	86 (16.76)	(13.53–20.00)	955	18 (1.88)	(1.02–2.75)	505	5 (0.99)	(0.13–1.85)

NOTE. The age groups were defined as follows: age 2 y, age 24–35 months; age 3–4 y, age 36–59 months; and so forth. The anti-HBc at younger than 24 months of age was possibly owing to maternal placental transfer and not natural infection, and therefore is not shown.
95% confidence interval (CI), lower bound and upper bound of 95% CI (rate ± 1.96 × standard error).

the children born to the HBeAg-negative mothers, with an odds ratio of 5.46 (1.72−17.40; $P < .01$). The chronicity rates of the children born to HBeAg-negative mothers with or without HBIG were not significantly different: 20% (1 of 5; 95% CI: 0%−55%) vs 17% (3 of 18; 95% CI: 0%−34%; $P = .17$).

Estimation of Vaccine Efficacy

Based on previous data on the infection rates of nonimmunized children with HBeAg-positive and HBeAg-negative mothers,[6,18,23] the vaccination efficacy in preventing HBsAg carriers was estimated to be 89.5% (95% CI: 86.3%−91.9%) in children born to HBeAg-positive mothers with vaccines and HBIG, and 97.9% (95% CI: 84.7%−99.7%) and 95.6% (95% CI: 86.1%−98.6%) in children born to HBeAg-negative mothers with and without HBIG, respectively (Table 3). T3

Humoral Immune Responses (Anti-HBs Rate) in Children Negative for HBsAg

The anti-HBs–positive rate was high (>90%) among those younger than 2 years of age and decreased gradually with time, as shown in Figure 2. The age-adjusted anti-HBs–positive rate was higher among children born to prenatal HBeAg-positive mothers than among those born to prenatal HBeAg-negative mothers ($P = .02$, Mantel–Haenszel test), and there were no differences between children of prenatal HBeAg-negative mothers with HBIG at birth and without it ($P = .41$, Mantel–Haenszel test). F2

Case of Fulminant Hepatic Failure

Occurrence of fulminant hepatic failure in infancy was confirmed in 1 of the 1050 (0.095%; 95% CI: 0.00%−0.28%) children born to HBeAg-negative mothers and without HBIG administration, as compared with none of 723 children receiving HBIG. None of the children born to HBeAg-positive mothers had a history of fulminant hepatitis.

Virology Study in Infected Children and Mothers

A total of 58 children, including 31 boys, tested positive for HBsAg. All but 4 of them were born to HBeAg-positive mothers. All sera from these children tested positive for HBV DNA (58 of 58), with a mean value

Table 3. Vaccine Efficacy of Active/Passive Immunization in Children Born to HBeAg(+) and HBeAg(−)/HBsAg(+) Mothers Based on Current Study and Historical Controls

Subject group	HBsAg (+) no. (rate; 95% CI) in vaccinated children (present study)	HBsAg (+) no. (rate; 95% CI) in unvaccinated children	Relative risk	Vaccine efficacy (95% CI)
The efficacy of active/passive immunization in children born to HBeAg(+) mothers	54/583 (9.3%; 6.9%−11.6%)	74/84 (88.1%; 81.2%−95.0%)[a] 56/61 (91.8%; 84.9%−98.7%)[b]	0.11 0.10	89.5% (86.3%−91.9%) 89.9% (86.9%−92.3%)
The efficacy of active/passive immunization in children born to HBeAg(−) mothers[d]	1/723 (0.14%; 0%−0.41%)	53/811 (6.5%; 4.8%−8.2%)[c]	0.02	97.9% (84.7%−99.7%)
The efficacy of active immunization only in children born to HBeAg(−) mothers[d]	3/1050 (0.29%; 0%−0.61%)	53/811 (6.5%; 4.8%−8.2%)[c]	0.04	95.6% (86.1%−98.6%)

95% confidence interval (CI), lower bound and upper bound of 95% CI.
[a,b,c]Comparison of data from the current study with historical control data: Beasley et al,[6,23] (for HBeAg-positive mothers), and Hsu et al[18] (for HBeAg-negative mothers).
[d]The definition of HBeAg(−), or less-infectious mothers in previous studies, was HBeAg negativity or low HBsAg reverse-passive hemagglutination titers.

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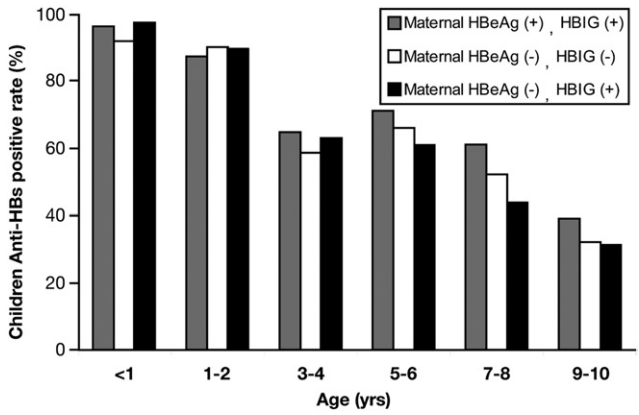

Figure 2. Age-stratified seropositive rate of anti-HBs in children born to HBV-carrier mothers, with respect to maternal HBeAg status and infant HBIG administration after universal immunization. All the children had received 3 doses of HBV vaccines (at 0, 1, and 6 months after birth). The age-adjusted anti-HBs–positive (>10 mIU/mL) rate was higher in children born to HBeAg-positive mothers than those born to HBeAg-negative mothers (P = .02). There was no difference in anti-HBs rates in children born to HBeAg-negative mothers receiving or not receiving HBIG at birth (P = .41).

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of 7.37 ± 1.39 $\log_{10}$ copies/mL. We compared the HBV genotypes of 44 mother-infant pairs and found that 98% (43 of 44; 95% CI: 93%−100%) of the pairs had identical genotypes. We then tested for HBV surface mutants in 25 of the HBsAg-positive mother-child pairs. Mutations in the *a* determinant were found in 32% (8 of 25; 95% CI: 14%−50%) of the children, suggesting the effect of immune pressure by HBIG and HBV vaccines on selection of viral strains (Supplementary Table 1).

Discussion

Our study presents a large-scale data set of children born to HBsAg-carrier mothers after universal HBV immunization. Our study found that prenatal maternal HBeAg positivity accurately distinguished between the groups of their offspring with high and minimal breakthrough infection and HBsAg-carrier rates. There are several important implications from these data. First, the differences in the breakthrough infection rates between the maternal HBeAg-positive and HBeAg-negative groups are so large that applying different preventive strategies to the 2 groups within a population-based program can be justified. Second, we have identified breakthrough infection in a certain high-risk subpopulation under the current active/passive HBV immunization program; further reductions in the maternal-infant transmission rates should rely on novel preventive methods for this specific group, such as antiviral therapy in the third trimester of pregnancy to reduce the maternal viral load at the time of delivery. Third, with the major risk group for breakthrough infection in the immunized children identified, evidence-based, nationwide surveillance should be initiated for earlier detection, monitoring, and treatment of HBV carriers in the era of universal HBV immunization. Despite breakthrough infection still occurring, HBV-related complications (such as cirrhosis and HCC) in the next generation may be minimized as much as possible through a well-conducted surveillance and secondary preventive system and good antiviral therapies.[9,36]

There have been scanty data on the infection rate among children born to HBeAg-negative mothers, particularly after the universal HBV immunization program. In the early vaccine trials and in the beginning years of universal immunization, the definition of "less infectious mothers" in previous reports largely was based on low HBsAg titers or HBeAg negativity using early HBeAg detection methods,[17,37,38] rendering the early data not applicable to the current situation. In the current study, a strikingly low rate (<1%) of HBsAg positivity among children born to HBeAg-negative mothers was found. The data indicate that active immunization alone was effective in blocking most of the mother-to-infant transmission in infants of HBeAg-negative, HBsAg-carrier mothers (Tables 1 and 3). Importantly, currently applied HBeAg laboratory tests are highly accurate in defining highly infectious and less-infectious groups. Because HBeAg-negative mothers comprise about 25%–75% of all HBsAg-carrier mothers in a population, the data on this group are very important for the development of a universal immunization program.

The benefit and necessity of HBIG for children born to HBeAg-negative, HBsAg-carrier mothers has been an issue of controversy for a long time.[13,14,39,40] The limitation of this study was that in children born to HBeAg-negative mothers, the 2 groups with or without HBIG at birth were not randomized, but chosen by parental will. It is hard to conduct randomized trial because both strategies are formal government-supported programs (with no HBIG in Taiwan and with HBIG in the United States). Although we have found a seemingly 52% reduction in the HBsAg rates in those with HBIG compared with those without HBIG, the evidence to support the routine use of HBIG in infants born to HBeAg-negative, HBsAg-carrier mothers is inadequate because the anti-HBc rates and HBsAg-carrier rates in the vaccine-only group without HBIG were already very low: 1.88% and 0.29% (Tables 1 and 2). An extremely large sample size would be needed to test the difference in the HBsAg(+) rates between the 2 groups, approximately 20,461 subjects would be required in each group (total, 40,922 subjects); and 3718 subjects would be required in each group (total, 7436 subjects) to detect the difference in the HBsAg(+) and anti-HBc(+) rates with an α value of .05 and statistical power = 0.9. Although it is still possible that there is a true difference in either the HBsAg(+) rates or the anti-HBc rates between the HBIG(-) and HBIG(+) children born to HBeAg(-) mothers, it does not seem feasible to detect.

An important concern associated with administering HBIG to children with HBeAg-negative mothers is preventing fatal fulminant hepatitis. Few studies have reported on fulminant hepatitis B in immunized infants. Aside from our previous nationwide survey of 25 cases, only 3 previous reports have described 4 cases of immu-

nized infants developing fulminant hepatitis; 2 of them had received HBIG (Supplementary Table 2).[13–16] We performed a brief cost-benefit analysis of preventing fulminant hepatitis by administering HBIG to the children of HBeAg-negative mothers, based on an estimate of 15,000 neonates born to HBeAg-negative mothers annually. Administering HBIG to these neonates would cost approximately $1,573,427 in US dollars. We assumed that fulminant hepatitis would develop in 1 of 1050 of these infants (0.00%−0.28%), and the cost associated with hospitalization, intensive care, transplantation, and potential mortality was estimated to be $2,132,867 in US dollars, yielding a cost-benefit ratio of 1.36 (0–3.97 in the sensitivity analysis). The details are provided in Supplementary Table 3. The data support a policy of administering both HBIG and HBV vaccines to all the infants born to HBsAg-positive mothers in the United States, regardless of the maternal HBeAg status. The cost-benefit ratio of administering HBIG to the maternal HBeAg-negative group should be thoroughly considered in determining the strategy of universal immunization programs in each country.

By contrast, the children born to the HBeAg-positive mothers had much higher rates of anti-HBc (16.8%) and HBsAg (9.26%), despite being given full HBIG treatment at birth and 3 doses of recombinant HBV vaccine. The discrepancy between anti-HBc and HBsAg may reflect a significant population of children who had contracted HBV infection but had undergone HBsAg seroconversion later. A limitation of this study was that we did not follow up these children longitudinally. Because anti-HBc persists long after the primary natural infection, however, the differences in the HBsAg and anti-HBc seropositive rates well represent the proportion of children who contracted HBV infection and recovered. The HBsAg/anti-HBc rate was higher in the children born to HBeAg-positive mothers (54%) than in the children born to HBeAg-negative mothers (17%), indicating that the children with HBeAg-positive mothers were both more likely to be infected and more likely to become chronic carriers once infected with HBV. Immune tolerance induced by HBeAg placental transfer may play an important role in establishing chronic infection. A higher chronic infection rate may be related to an earlier age at infection, including intrauterine, perinatal, and postnatal infection, in the children of the HBeAg-positive mothers.[41] In addition, the anti-HBc rates across the age groups may reflect the accumulation of new horizontal infections that occurred over time. Our results cannot exclude the possibility of postnatal infection from family contacts. However, the role of horizontal infection seems to be small. Data from the current study and from previous surveys after the implementation of universal immunization show minimal or no increases in childhood HBsAg- and anti-HBc–positive rates after 2–3 years, in contrast to observations from before universal immunization that show increasing anti-HBc rates with age.[17,27] Because immunized children with HBV infection have a higher risk of developing HCC than do HBV-carrier children born in the prevaccination era[12] and because the total burden of HBV-infected children in endemic areas is still large, children born to HBeAg-positive mothers who experience breakthrough HBV infection is a significant issue that requires more attention and active intervention.

For children who successfully were prevented from contracting HBV infection in infancy, we have shown that the humoral responses to the HBV vaccines were good. There have been concerns about the interference of the administration of HBIG on active immunization,[39] which has not been found in our study. The anti-HBs rates in children born to HBeAg-negative mothers did not differ between those who did and those who did not receive HBIG at birth. Overall, neonatal immunization provided satisfactory protection against HBV infection for at least 10 years despite these children having close contact with their HBV-carrier mothers.

From the view of global HBV prevention, it is suggested that HBV vaccines be given universally to all newborns, irrespective of maternal HBsAg status, in both high- and low-endemic countries.[10] It is noteworthy that the screening program of pregnant women has had great impact on the tightly linked, multistep strategies in maternal-child health in the control of HBV-related diseases. The choice of pregnant women HBsAg and/or HBeAg screening strategy not only lead to different children's immunization program, but also have impacts on maternal health related to HBV-associated disease/complications,[41,42] and selects different target population for surveillance program of children with risk of breakthrough infection. The link between strategies of screening pregnant women, neonatal immunization, and surveillance of high-risk children is listed in Table 4. Compared with maternal viral load, HBeAg testing costs much less, is widely available, could be linked to screening pregnant women, and thus is a suitable screening marker with a high call rate (1 in 10 cases) to identify children with a risk of breakthrough HBV infection. Without screening pregnant women, the childhood postimmunization surveillance program could not possibly be established, and as a result the control of HBV in the second generation would be delayed. Furthermore, future strategies to lower the rate of breakthrough infection in children born to highly infectious mothers are being investigated actively. These strategies will be applied most readily in countries with adequate HBsAg and HBeAg screening of pregnant women.

In conclusion, the children born to HBeAg-positive mothers are a major risk group for breakthrough HBV infection in the era of universal immunization. A low (<1%) rate of HBsAg positivity was observed in the children born to HBeAg-negative mothers with vaccinations only. HBIG administration in infants born to HBeAg-negative mothers has not been proven to reduce chronic HBV infection rates, but a benefit in preventing infantile fulminant hepatitis is still possible. Maternal HBsAg screening with HBeAg testing is suggested, not only as a useful maternal health marker, but also as being valuable for determining preventive strategies in their children, as well as for surveillance of children at risk for break-

Table 4. Current Screening of Pregnant Women and Universal Infant HBV Immunoprophylaxis Strategies in Different Countries and Proposed Surveillance Program for High-Risk Children With Breakthrough Infection Linked to the Specific Strategies

Strategy type	Screening pregnant women		Neonatal immunization		Surveillance of children with risk of breakthrough infection by HBsAg at 12–18 months (proposed)	
	HBsAg	HBeAg	HBV vaccines and HBIG to children of HBsAg(+) mothers	HBV vaccines and HBIG to children of HBsAg/HBeAg(+/+) mothers	All children born to HBsAg-positive mothers	All children born to HBeAg-positive mothers
I	+	−	+		+	
II[a]	+	+		+		+
III	−	−	(————HBV vaccines only———)		−	−

NOTE. Reference 2,3,10,19,22. Examples of applied countries: type I strategy, United States, Italy, Korea; type II strategy, Taiwan and Singapore; type III strategy, Thailand.

[a]In the type II strategy, simultaneous or sequential HBsAg and HBeAg tests can be applied. For example, all pregnant women are screened for HBsAg and HBeAg at the same time; or, all pregnant women are screened for HBsAg, and with HBeAg tested only in those positive for HBsAg; the latter strategy is budget saving.

through infection. In the real world, the rates of HBV infection may be higher than the rates shown in this study, which reflect the results of optimal compliance with HBV vaccination on schedule and HBIG within 24 hours. The data from this study are important for further efforts to eliminate HBV infection using strategies to interrupt mother-to-infant transmission, for better care of HBV-infected women of childbearing age, and for treating children with chronic HBV infection and related liver diseases early in life.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi:10.1053/j.gastro.2011.12.035.

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Received January 21, 2011. Accepted December 09, 2011.

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Acknowledgments

The authors thank Ms Cheng Chung Liu and Dr Ding-Ping Liu of The Center of Disease Control, Department of Health (Taiwan); Dr. Wen-Yi Shau for statistical consultation; and the Hepatitis Research Center at National Taiwan University Hospital. All individuals acknowledged here performed their roles as part of their regular duties and were not additionally compensated for their contributions.

Huey-Ling Chen and Mei-Hwei Chang were responsible for the concept and design of the study; Huey-Ling Chen, Lung-Huang Lin, Jian-Te Lee, Wen-Terng Lin, Yao-Jung Yang, Fu-Chen Huang, Shu-Fen Wu, Solomon Chih-Cheng Chen, Wan-Hsin Wen, Chia-Hsiang Chu, Pei-Lin Tsai, Yen-Hsuan Ni, and Ming-Kwang Shyu were responsible for the acquisition and analysis of the data; Huey-Ling Chen, Fu-Chang Hu, Pei-Lin Tsai, and Mei-Hwei Chang were responsible for drafting the manuscript; Huey-Ling Chen, Solomon Chih-Cheng Chen, Yen-Hsuan Ni, Hong-Yuan Hsu, Ping-Ing Lee, Feng-Yee Chang, and Mei-Hwei Chang were responsible for critical revision of the manuscript for important intellectual content; Huey-Ling Chen and Fu-Chang Hu were responsible for statistical analysis; and Lung-Huang Lin, Hong-Yuan Hsu, Cheng-Lun Chiang, Ming-Kwang Shyu, Ping-Ing Lee, and Feng-Yee Chang were responsible for administrative, technical, or logistic support.

Conflicts of interest

The authors disclose no conflicts.

Funding

This research was funded by grants from The Center for Disease Control, Department of Health (Taiwan) (DOH98 -DC-10181), a joint research grant from the National Taiwan University and Cathay General Hospital, and partly from En-Chu Kong Hospital.

Supplementary Table 1. HBV Genotype, Subtype, and Surface Mutants in the *a* Determinant in Infected Mother-Child Pairs

Subject number	Genotype		Subtype		Surface mutants in mothers	Surface mutants in children
	Mother	Child	Mother	Child		
1	C	C	adr	adr	—	—
2	B	B	adw	adw	—	—
3	C	C	adr	adr	—	—
4	B	B	adw	adw	—	—
5	C	C	adw	adw	K122R	K122R
6	C	C	adr	adr	—	—
7	C	B	adr	adr	—	—
8	B	B	adw	adw	—	—
9	B	B	adw	adw	—	G145R
10	B	B	adw	adw	—	—
11	B	B	adw	adw	—	—
12	C	C	adr	adr	—	G145R
13	B	B	adw	adw	—	G145R
14	B	B	adw	adw	—	G145R
15	B	B	adw	adw	—	G145R
16	B	B	adw	adw	—	—
17	B	B	adw	adw	—	—
18	C	C	adr	adr	—	I126T
19	C	C	adr	adr	—	—
20	C	C	adr	adr	—	—
21	B	B	adw	adw	—	G145R
22	B	B	adw	adw	—	—
23	C	C	adr	adr	—	—
24	C	C	adr	adr	—	—
25	B	B	adw	adw	—	—

—, no mutations detected.

Supplementary Table 2. Reported Cases of Infantile Fulminant Hepatic Failure After Hepatitis B Vaccination and/or HBIG

Study	Case no	sex, age	HBV vaccines	HBIG	Maternal HBeAg status
Rosh et al,[13] 1994, United States	1	M, 5 m/o	+	+	+
Hawkins et al,[16] 1994, United Kingdom	1	M, 10 w/o	+	−	−
Cacciola et al,[15] 2002, Italy	2	F, 11 w/o	+	+	+
		F, 13 w/o	+	−	−
Chen et al,[14] 2004, Taiwan	25	M (18), F (7) 3.4 ± 1.3 m/o	All +	All −	− (21) + (2) unknown (2)

w/o, age in weeks; m/o, age in months.
+, positive; −, negative.

Supplementary Table 3. A Brief Cost-Benefit Analysis of Using HBIG in Children Born to HBsAg(+)/HBeAg(−) Mothers to Prevent Fulminant Hepatitis

Policy A: providing HBIG to children born to HBeAg-negative mothers
$Cost_A$: additional cost of HBIG (per year)
= HBIG cost ($3000 NTD) × 15,000 live births[a] born to HBeAg(−) carrier mothers
= $45,000,000 NTD (approximately $1,573,427 US dollars)
$Benefit_A$: no cases of infantile fulminant hepatitis caused by HBV occur

Policy B: Not providing HBIG to children born to HBeAg-negative mothers
$Cost_B$: $0 NTD
$Benefit_B$: annually, 15 cases of infantile fulminant hepatitis B occur
Costs of hospitalization = –$400,000 NTD/person × 15 persons[b] = –$6,000,000 NTD
Costs of liver transplantation = –$1,000,000 NTD/person × 10 persons[c] = –$10,000,000 NTD
Costs of lost lives from disease or transplantation = –$15,000,000 NTD/person × 3 persons[d] = –$45,000,000 NTD
Sum of medical care and lost lives from fulminant hepatic failure each year = –$61,000,000 NTD (approximately –$2,132,867 USD)

Incremental cost-benefit ratio (ICBR) $= \frac{\text{Benefit}_A - \text{Benefit}_B}{\text{Cost}_A - \text{Cost}_B} = \$61{,}000{,}000/\$45{,}000{,}000 = 1.36$

The sensitivity analysis[e] provides a range of 0–3.97

NOTE. In policy B, developing fulminant hepatitis is a negative benefit (disadvantage). Therefore, the benefit effect is shown as a negative value. The current cost-benefit analysis only considers the effect of immunization in preventing infantile fulminant hepatitis. A complete cost-benefit analysis also should include the decreased morbidity and mortality from chronic HBV infection and the decreased need for antiviral therapy.
[a]Using an estimation of a total of 200,000 live births in Taiwan, and 15,000 neonates born to HBsAg-positive/HBeAg-negative mothers.
[b]Occurrence of fulminant hepatic failure = 1 in 1050 (0.00%, 0.28%); case number estimation of fulminant hepatic failure = 15,000 × (1 in 1050) = 14.29, approximately 15 patients.
[c]Occurrence of poor prognosis in patients with fulminant hepatic failure that requires liver transplantation: 65% (50.74%, 79.26%); case numbers need liver transplantation among patients with fulminant hepatic failure: 15 × 65% = 9.75, approximately 10 persons.
[d]Mortality rate from disease or transplantation in patients with a poor prognosis: 30% (21.02%, 38.98%); mortality cases were estimated to be 10 × 30% = 3 persons.
[e]Sensitivity analysis: find the possible range of incremental cost-benefit ratio by considering the lower and upper limits of the 95% confidence intervals for all parameters used including occurrence of fulminant hepatitis, occurrence of poor prognosis, and mortality rates.
NTD, New Taiwan dollar