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Optimization of Mother-to-Child Hepatitis B Virus Prevention Program: Integration of Maternal Screening and Infant Post-Vaccination Serologic Testing

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Background. Evaluation of the impact of a hepatitis B virus (HBV) prevention program that incorporates maternal antiviral prophylaxis on mother-to-child transmission (MTCT) is limited using real-world data.

Methods. We analyzed data on maternal HBV screening, neonatal immunization, and post-vaccination serologic testing (PVST) for hepatitis B surface antigen (HBsAg) among at-risk infants born to HBV carrier mothers from the National Immunization Information System during 2008–2022. Through linkage with the National Health Insurance Database, information on maternal antiviral therapy was obtained. Multivariate logistic regression was performed to explore MTCT risk in relation to infant–mother characteristics and prevention strategies.

Results. In total, 2 460 218 deliveries with maternal HBV status were screened. Between 2008 and 2022, the annual HBsAg and hepatitis B e antigen (HBeAg) seropositivity rates among native pregnant women decreased from 12.2% to 2.6% and from 2.7% to 0.4%, respectively (P for both trends < .0001). Among the 22 859 at-risk infants who underwent PVST, the MTCT rates differed between infants born to HBsAg-positive/HBeAg-negative and HBeAg-positive mothers (0.75% and 6.33%, respectively; P < .001). MTCT risk increased with maternal HBeAg positivity (odds ratio [OR], 9.29; 95% confidence interval [CI], 6.79–12.73) and decreased with maternal antiviral prophylaxis (OR, 0.28; 95% CI, .16–.49). For infants with maternal HBeAg positivity, MTCT risk was associated with mothers born in the immunization era (OR, 1.40; 95% CI, 1.17–1.67).

Conclusions. MTCT was related to maternal HBeAg positivity and effectively prevented by maternal prophylaxis in the immunized population. At-risk infants born to maternal vaccinated cohorts might possibly pose further risk.

Keywords. screening pregnant women; HBsAg carrier; mother-to-child transmission; HBV vaccination; post-vaccination serologic testing.

In 2019, the estimated global prevalence of hepatitis B surface antigen (HBsAg) was 4.1% [1], with particularly high burdens in sub-Saharan Africa and East Asia [2]. Hepatitis B virus (HBV) infection leads to liver-related morbidity and mortality, which can be effectively prevented by hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine (HepB), screening and treatment, harm-reduction strategies, and peripartum antiviral prophylaxis [3, 4]. Mother-to-child transmission (MTCT) during childbirth is the primary route of chronic HBV infection in the pre-vaccination era [5, 6]. To eliminate chronic HBV infection, the World Health Organization (WHO) has specifically targeted MTCT. It established global targets of reducing HBsAg prevalence to 0.1% among children aged 0–4 years and the MTCT rate to ≤2% via surveillance of post-vaccination serologic testing (PVST) in at-risk infants by 2030 [3, 4, 7–9].

Despite the effectiveness of timely HBV immunization, breakthrough HBV infections in children born to mothers with high HBV DNA viral loads contribute to perinatal infections [10]. Since 2020, the WHO has recommended that mothers with an HBV DNA level >200 000 IU/mL receive peripartum tenofovir prophylaxis from the 28th week of pregnancy and continuing at least until birth. This additional measure further reduces the risk of MTCT [10–13]. HBV DNA testing is important for efforts to identify highly infective mothers [10, 12, 14]. In situations where antenatal HBV DNA testing

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is unavailable, the WHO recommends performing hepatitis B e antigen (HBeAg) testing as an alternative method to determine eligibility for tenofovir prophylaxis to prevent MTCT [10].

Universal neonatal vaccination, coupled with timely administration of the birth dose and peripartum antiviral prophylaxis in mothers, can effectively prevent HBV MTCT [12]. However, these approaches are not widely used in most countries [2]. In Taiwan, maternal HBV screening includes HBsAg testing and HBeAg testing to identify infants at high MTCT risk, enabling immediate postnatal administration of HBIG. This practice has been in place since the implementation of a universal HBV prevention program in 1984 [6, 15]. Taiwan has implemented a nationwide policy of antiviral prophylaxis for mothers with high HBV viral loads. This policy has been reimbursed by the National Health Insurance Administration since February 2018.

The implementation of the PVST program in September 2010 for at-risk infants has enabled the collection of nationwide data regarding MTCT rates over the past 15 years. The goal of this study is to evaluate the impact of the multistep optimization of an HBV prevention program on MTCT rates. We also aimed to explore the risk factors for children with breakthrough HBV infection despite current prophylaxis procedures. Using data from the nationwide registration of maternal screening and PVST results, our study provides real-world evidence concerning the implementation and impact of MTCT prevention programs using infant–mother pairs to assess HBsAg prevalence, with a particular focus on the inclusion of maternal antiviral prophylaxis as the standard of care.

METHODS

HBV MTCT Prevention Programs

Original Program

Maternal HBsAg and HBeAg screening and the universal infant hepatitis B vaccination program in Taiwan were implemented in July 1984 [6, 16]. Figure 1 shows the progression of the national HBV MTCT prevention program, which includes the replacement of HepB dose 1 (HepB-1) with the birth dose of HepB (HepB-BD) in 2011, a shift in the timing of maternal HBV screening from the third trimester to the first trimester in 2014, and expansion of the public-funded HBIG strategy to include infants born to HBeAg-negative carrier mothers in 2019.

Surveillance of Infant Outcomes

The PVST program for infants born to HBeAg-positive mothers was initiated by the Taiwan Centers for Disease Control (CDC) in September 2010 (for infants who were born after July 2008), then expanded to HBsAg-positive mothers (regardless of HBeAg status) in July 2019. Under this program, both HBsAg and hepatitis B surface antibody (anti-HBs) testing are recommended to be performed at age ≥12 months in accordance with routine childhood immunization and 2 well-child visits at age 12–24 months. When PVST identifies HBV infection in an at-risk infant, a public health worker or healthcare provider refers the child to a pediatric hepatologist. Furthermore, if both HBsAg and anti-HBs are negative in PVST enrollees, the government provides a booster HepB dose.

Maternal Antiviral Therapy

Maternal antiviral prophylaxis with telbivudine and tenofovir disoproxil has been reimbursed by the National Health Insurance Administration from 27 weeks of gestation until 4 weeks postpartum since February 2018 and May 2019, respectively. Pregnant mothers with HBV DNA levels ≥6 $\log_{10}$ IU/mL can consult with a hepatologist to determine the need for maternal antiviral therapy and to ensure timely administration of HBIG and HepB to newborn infants.

Study Design and Data Sources

National Immunization Information System

The National Immunization Information System (NIIS), established by the Taiwan CDC, was used to identify infant–mother pairs with delivery dates between 1 January 2008 and 31 December 2022. Data were obtained from the NIIS regarding maternal HBsAg and HBeAg statuses, infant immunization records, infant birth order, number of live births, number of mothers screened, and demographic characteristics (eg, sex and birthday) of infant–mother pairs. Data were collected and compiled as described in previous studies [6, 16]. Data regarding PVST for HBsAg and test date among infants born to HBeAg-positive or HBsAg-positive mothers were collected between September 2010 and December 2022.

National Health Insurance Database

The National Health Insurance Database (NHID) was searched to identify women who received antiviral therapy with telbivudine and tenofovir disoproxil during pregnancy based on payment years 2018–2022. Data on the maternal HBV DNA level at the time of maternal antiviral prescription was not required for physicians to key into the NHID and was not available as a covariate in this study. We also identified pregnant mothers who received antenatal tenofovir alafenamide, because it can be prescribed as antiviral treatment rather than prophylaxis.

This nationwide retrospective cohort study was approved by the Taiwan CDC Department of Health Institutional Review Board, which waived the requirement for informed consent due to minimal participant risk and the use of de-identified data.

Statistical Analyses

The annual screening and registration rates of pregnant women and maternal HBsAg and HBeAg seropositivity rates, stratified by maternal nationality, were determined for delivery years 2008–2022. The Cochran–Armitage test was used to assess

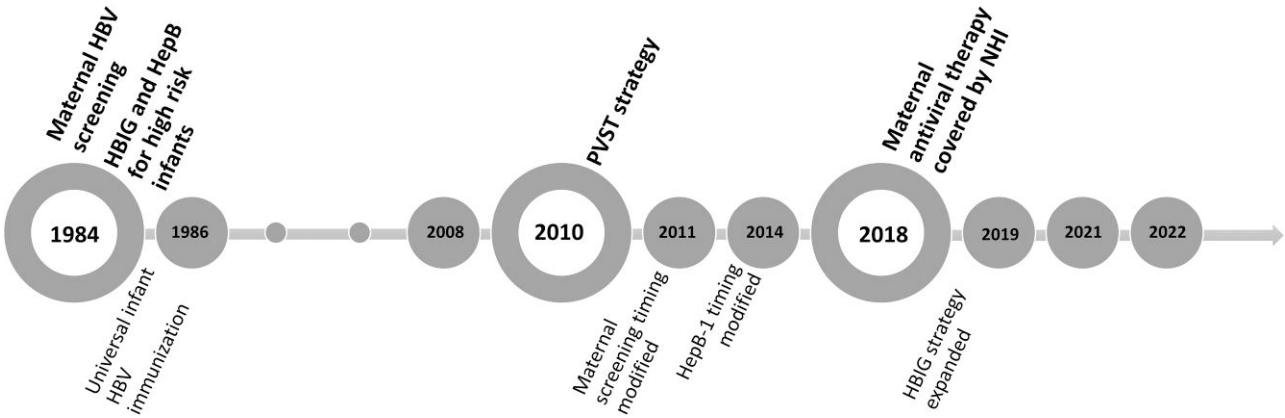

Figure 1. Mother-to-child hepatitis B prevention programs in Taiwan. Taiwan has consistently endorsed maternal HBV screening since July 1984. Publicly funded maternal screening for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) was performed in the third trimester between July 1984 and October 2014; it has been performed in the first trimester since November 2014. In May 2011, the Taiwan Centers for Disease Control changed the recommendation for timely administration of the first dose of HepB from 3–5 days after birth (HepB-1) to within 24 hours after birth (HepB-BD). Since July 2019, HBIG administration has been expanded to infants born to HBsAg-positive but HBeAg-negative mothers. Abbreviations: HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HepB, hepatitis B vaccine; HepB-1, hepatitis B vaccine dose 1; HepB-BD, the birth dose of hepatitis B vaccine; NHI, national health insurance; PVST, post-vaccination serologic testing.

trends in maternal HBsAg and HBeAg seropositivity rates. PVST of babies born to HBV-infected mothers provides the prevalence of HBsAg positivity for at-risk infants, the MTCT rate. The χ^2 test and Fisher exact test were applied to compare the categorical data between groups. The main outcome of the study was the HBsAg status for at-risk infants who underwent PVST with delivery years between 2008 and 2021 and with testing age ≥9 months [17, 18]. Definitions of covariates and concerns about a collinearity problem between variables in multivariate logistic regression models are described in the Supplementary Material. The effects of an HBV prevention program, including maternal antiviral prophylaxis, HBIG, and HepB vaccination, on MTCT were evaluated using multivariate logistic regression, while variables of infant–mother characteristics with P values <.05 in the univariate analysis were entered in the multivariate model [19, 20]. Statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc, Cary, NC).

RESULTS

Decreasing Trends of Maternal HBsAg and HBeAg Positivity

During the 15-year study period, there were 2 818 269 live births among women aged 15–49 years (Supplementary Table 1). Of those live births, 2 460 218 (87.3%) underwent maternal HBsAg and HBeAg screening, and the screening rate was ≥90% starting in 2014. In total, 2 378 469 (96.7%) infants were born to native mothers.

The HBsAg and HBeAg seropositivity rates in native pregnant women decreased from 12.2% and 2.7% in 2008 to 2.6% and 0.4% in 2022, respectively (P for both trends < .0001). However, the annual HBsAg and HBeAg seropositivity rates among foreign pregnant women did not decrease over time (Figure 2). The HBsAg seropositivity rate was lower for native mothers in the vaccinated cohort and for native mothers with a younger delivery age (Supplementary Table 2).

Uptake of HBIG and HepB

The vaccine uptakes of HBIG and HepB for HBV at-risk infants and for all native infants are presented in Supplementary Figures 1 and 2, respectively. Between 2008 and 2021, the HBIG coverage rates for infants born to HBeAg-positive mothers ranged from 97.4% to 99.7%. The average HBIG coverage for infants born to HBsAg-positive/HBeAg-negative mothers increased from 74.5% in 2008–2018 (self-paid HBIG) to 98.0% in 2019–2021 (public-funded HBIG). After HepB-1 was replaced with HepB-BD, the coverage of HepB-BD for at-risk infants and all native infants increased from 53.8% and 49.8% in 2011 to >90% in 2013 and 2014, respectively.

PVST Coverage

In total, 22 859 at-risk infants with birth years between 2008 and 2021 were screened for PVST; 16 913 (74.0%) underwent PVST at the age of 12–23 months. Of those infants, 14 981 were born to HBsAg- and HBeAg-positive mothers and 7878 were born to HBsAg-positive/HBeAg-negative mothers. The coverage of PVST for infants born to HBeAg-positive mothers increased from 19.0% (12 239 of 29 768) in the pre-maternal antiviral prophylaxis period (2008–2017) to 71.4% (2742 of 3822) in the post-maternal antiviral prophylaxis period (2018–2021). The PVST coverage for infants born to HBsAg-positive/HBeAg-negative mothers was 35.0% (7094 of 20 261) in 2018–2021.

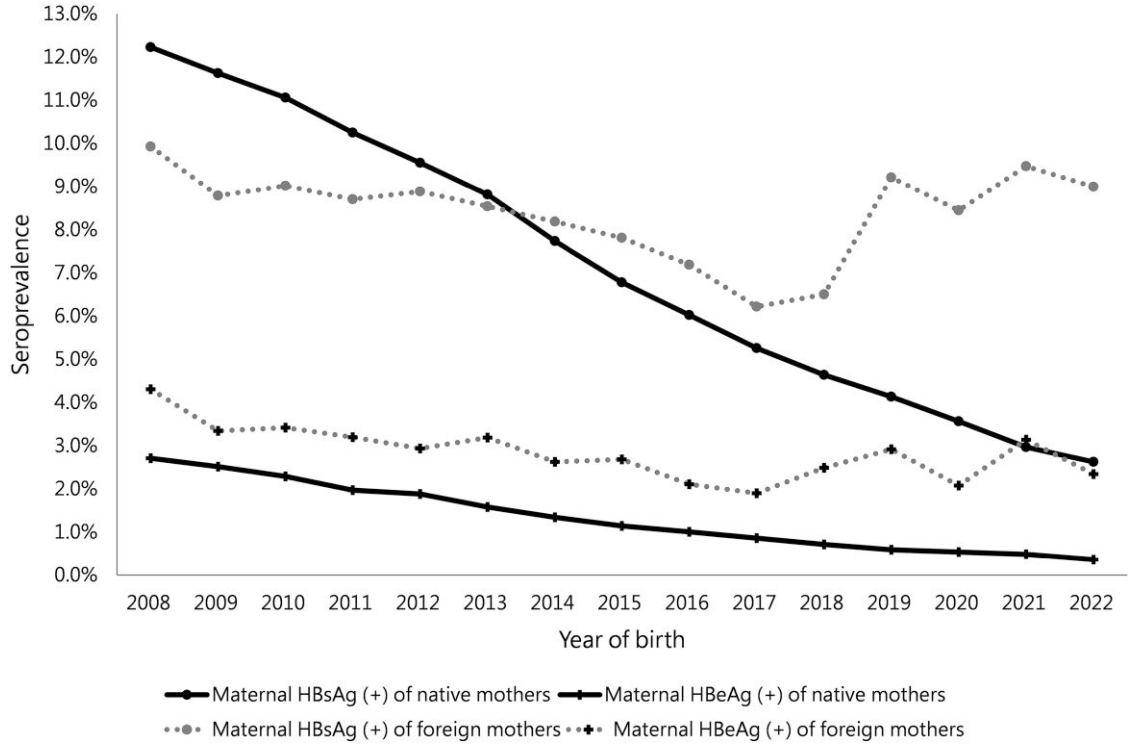

Figure 2. Annual HBsAg and HBeAg seropositivity rates among pregnant women according to maternal nationality with delivery year between 2008 and 2022. Abbreviations: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

HBV MTCT Rates

The average MTCT rate in at-risk infants was 4.4% (1007 of 22 859). Of the perinatal HBV-infected infants, 948 of 1007 (94.1%) were born to HBeAg-positive mothers (Table 1). The MTCT rates differed between infants born to HBsAg-positive/HBeAg-negative and HBeAg-positive mothers (0.75% and 6.33%, respectively; $P < .001$). MTCT rates were higher among infants without timely HBIG administration (7.39%), with screening at the age of 9–11 months (7.30%), and with maternal HBeAg positivity (6.33%).

Among PVST infants born to HBeAg-positive mothers, MTCT rates according to delivery year significantly decreased after the implementation of maternal antiviral prophylaxis in 2018 (Figure 3). The increase in screening numbers since 2019 was related to the expansion of screening targets for infants born to HBsAg-positive/HBeAg-negative mothers. The MTCT rate reached the target of <2% for infants born to HBsAg-positive mothers (irrespective of maternal HBeAg status) in 2020 (1.2%), 2 years after implementation of nationwide maternal antiviral prophylaxis in Taiwan. However, the MTCT rate for infants born to HBeAg-positive mothers was >2% (158 of 2742) in the post-maternal antiviral prophylaxis period (2018–2021). Of them, the coverage of timely HBIG and HepB-BD administration was 98.7% (153 of 155) and 94.3% (149 of 158) for perinatal HBV-infected infants and 99.4% (2533 of 2548) and 95.4% (2466 of 2854) for uninfected infants, respectively ($P = .255$ for HBIG coverage; $P = .512$ for HeB-BD coverage).

Risk Factors for Breakthrough MTCT

In multivariate logistic regression analysis (Table 2), the risk of MTCT demonstrated the greatest increase with maternal HBeAg positivity (odds ratio [OR], 9.29; 95% confidence interval [CI], 6.79–12.73) and the greatest decrease with maternal antiviral prophylaxis (OR, 0.28; 95% CI, .16–.49). Table 2 presents an analysis of infants born to mothers with both HBsAg and HBeAg positivity and a higher risk of MTCT. Among infants with maternal HBeAg positivity, the risk of breakthrough HBV infection was higher if their mothers were born in the immunization era (OR, 1.40; 95% CI, 1.17–1.67) compared with the maternal unvaccinated cohort and was also significantly lower with maternal antiviral prophylaxis (OR, 0.27; 95% CI, .15–.46). Considering potentially correlated covariates of clinically relevant variables associated with MTCT, we investigated the joint effect of various pairs of variables for infants born to native mothers with HBeAg positivity, which also demonstrated similar results (Supplementary Table 4).

At-Risk Infants With Maternal Antiviral Prophylaxis

A total of 9836 at-risk infants who underwent PVST were born between 2018 and 2021. Of them, 9826 (99.9%) could be linked

Table 1. Mother-to-Child Transmission Rates of At-Risk Infants With Birth Years Between 2008 and 2021 Screened for Post-Vaccination Serologic Testing, Stratified by Maternal Hepatitis B e Antigen Status

Characteristic	No. of Infants Born to HBsAg (+) Mothers	PVST HBsAg (+)	MTCT Rate (%)	No. of Infants Born to HBeAg (+) Mothers	PVST HBsAg (+)	MTCT Rate (%)[a]	No. of Infants Born to HBeAg(−) Mothers	PVST HBsAg (+)	MTCT Rate (%)[a]
Infant birth years[b]									
2008–2010	3788	215	5.68	3631	209	5.76	157	6	3.82
2011–2017	9235	589	6.38	8608	581	6.75	627	8	1.28
2018–2021	9836	203	2.06	2742	158	5.76	7094	45	0.63
Gender									
Male	11 753	506	4.31	7726	477	6.17	4027	29	0.72
Female	11 106	501	4.51	7255	471	6.49	3851	30	0.78
Birth order									
First	6144	250	4.07	3382	232	6.86	2762	18	0.65
Second	12 060	567	4.70	8384	537	6.41	3676	30	0.82
Third	3592	149	4.15	2475	142	5.74	1117	7	0.63
Fourth and above	1063	41	3.86	740	37	5.00	323	4	1.24
Days of the week of infant's birthday									
Monday to Thursday	13 862	596	4.30	8955	563	6.29	4907	33	0.67
Friday to Sunday	8997	411	4.57	6026	385	6.39	2971	26	0.88
Maternal age group, y									
40–49	1771	27	1.52	454	20	4.41	1317	7	0.53
30–39	14 968	617	4.12	9268	572	6.17	5700	45	0.79
15–29	6120	363	5.93	5259	356	6.77	861	7	0.81
Maternal nationality									
Native	21 405	919	4.29	13 852	862	6.22	7553	57	0.75
Foreign	1454	88	6.05	1129	86	7.62	325	2	0.62
Mother's birth cohort[c]									
Unvaccinated	15 521	682	4.39	10 647	643	6.04	4874	39	0.80
Partially vaccinated	2934	113	3.85	1738	105	6.04	1196	8	0.67
Vaccinated	4404	212	4.81	2596	200	7.70	1808	12	0.66
Maternal antiviral prescription during third trimester[d]									
Without antivirals	22 034	992	4.50	14 240	933	6.55	7794	59	0.76
Telbivudine, tenofovir disoproxil fumarate, or tenofovir alafenamide	812	14	1.72	730	14	1.92	82	0	0.00
PVST testing age									
9–11 m	178	13	7.30	130	13	10.00	48	0	0.00
12–23 m	16 913	674	3.99	10 112	626	6.19	6801	48	0.71
≥2 y	5768	320	5.55	4739	309	6.52	1029	11	1.07
Hepatitis B immunoglobulin administration[e]									
Within 1 d after birth	22 113	973	4.40	14 624	921	6.30	7489	52	0.69
>1 d after birth	176	13	7.39	146	12	8.22	30	1	3.33
Hepatitis B vaccine dose 1 administration[e]									
Within 1 d after birth	17 550	696	3.97	10 227	645	6.31	7323	51	0.70
>1 d after birth	5306	311	5.86	4752	303	6.38	554	8	1.44
Hepatitis B vaccine dose 2 administration[e]									
At 1–2 m	22 589	995	4.40	14 794	936	6.33	7795	59	0.76
<1 or ≥3 m	259	12	4.63	181	12	6.63	78	0	0.00
Hepatitis B vaccine dose 3 administration[e]									
At 4–7 m	21 345	938	4.39	13 929	881	6.32	7416	57	0.77
<4 or ≥8 m	1397	67	4.80	975	65	6.67	422	2	0.47
Total	22 859	1007	4.41	14 981	948	6.33	7878	59	0.75

Abbreviations: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; MTCT, mother-to-child transmission; PVST, post-vaccination serologic testing.

[a]MTCT rates for those who underwent timely hepatitis B immunoglobulin and hepatitis B vaccine series were around 6.30%–6.32% and 0.69%–0.77% for infants born to HBeAg-positive mothers and HBsAg-positive/HBeAg-negative mothers, respectively.

[b]Infants birth years were divided into 3 groups according to the change in hepatitis B vaccine dose 1 administration timing in 2011 and the implementation of maternal antiviral prophylaxis for pregnant women with a high hepatitis B viral load in 2018.

[c]Maternal birth cohorts were defined as maternal unvaccinated cohort (maternal birthday before 30 June 1984), partially vaccinated cohort (maternal birthday between 1 July 1984 and 30 June 1986), and vaccinated cohort (maternal birthday after 1 July 1986).

[d]Antivirals with lamivudine and entecavir were excluded in the analysis due to small sample size.

[e]Missing data were not included in the statistical analysis.

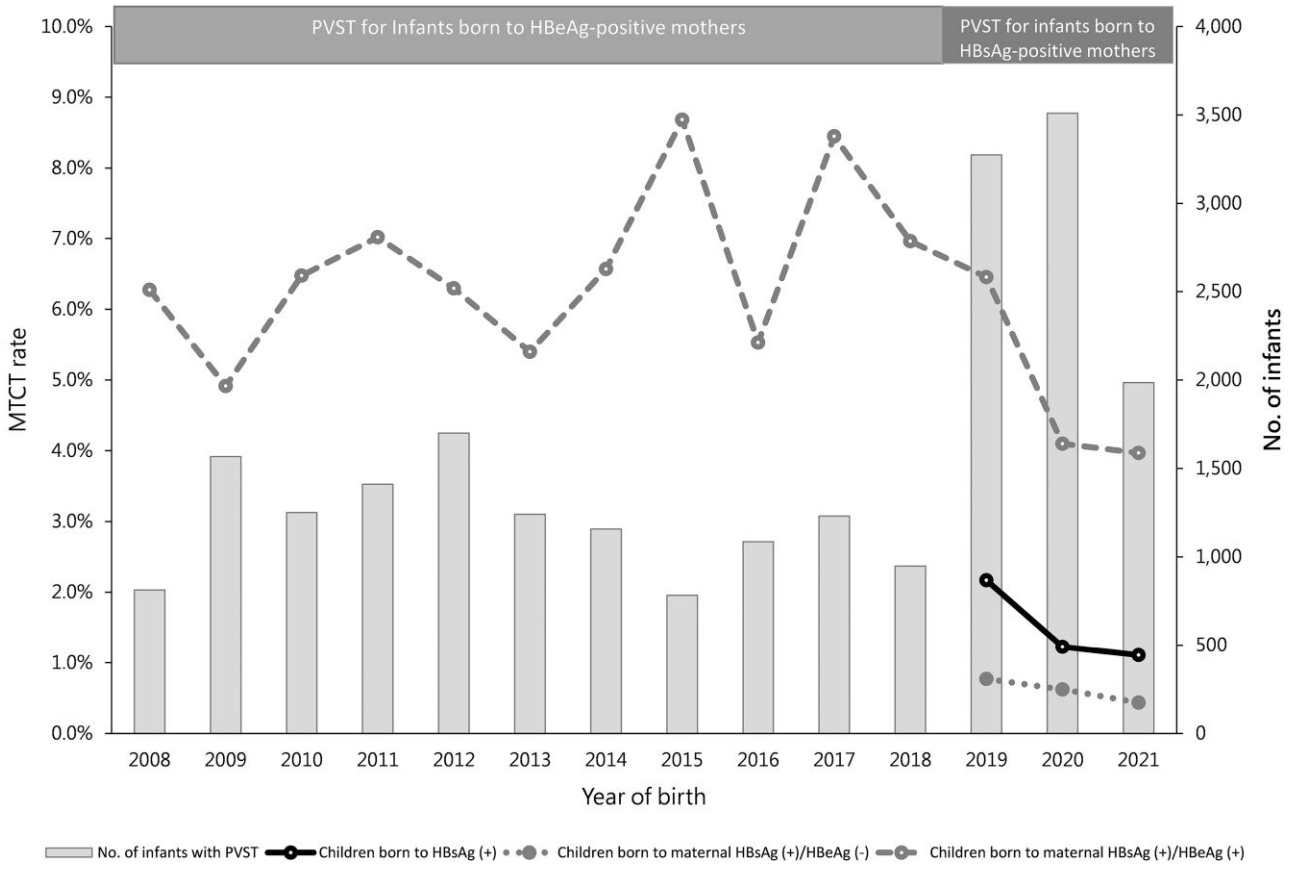

Figure 3. MTCT rates among infants born to HBV carrier mothers with delivery year between 2008 and 2021. Abbreviations: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, mother-to-child transmission; PVST, post-vaccination serologic testing.

to NHID with unique identifiers. Among 9826 infants with PVST, 7092 were born to HBsAg-positive/HBeAg-negative mothers and 2734 were born to HBeAg-positive mothers (Supplementary Table 3). In total, 721 infants were born to mothers who received antenatal antiviral prophylaxis, and 641 (88.9%) of their mothers were HBeAg-positive.

The coverage rate of maternal antiviral prophylaxis for infants born to HBeAg-positive mothers, the assumed high-infectivity mothers, was 23.4% (641 of 2734) and increased from 13.4% in birth year 2018 to 35.2% in 2021. The MTCT rate was 1.72% (11 of 641) for PVST infants born to HBeAg-positive mothers with antiviral prophylaxis (Table 3), which was significantly lower than 6.98% (146 of 2093) for those born to HBeAg-positive mothers without antivirals ($P < .0001$, χ^2 test). There were 11 breakthrough perinatal HBV-infected infants who underwent maternal antivirals and received both HBIG and Hep-BD on time.

DISCUSSION

This study highlights 3 important findings for HBV MTCT prevention programs. First, the enhancement of the nationwide program through the implementation of maternal antiviral therapy on top of universal neonatal immunization can further decrease perinatal HBV infection rates in the subgroup with the highest risk of breakthrough MTCT [15]. Second, a generational transition effect is evident among pregnant women born in the vaccination era, as indicated by significant reductions in maternal HBsAg and HBeAg prevalence rates and the significantly lower burden of perinatal HBV infection in the next generation [6]. Third, HBeAg-positive pregnant women born in the vaccination era, the HBeAg-positive maternal vaccinated cohort, might pose higher risk of MTCT to their infants compared with the HBeAg-positive maternal unvaccinated cohort.

Our study is valuable in terms of assessing the effectiveness of strategies and challenges for HBV MTCT elimination in Taiwan. In the past 10 years, the government has implemented various strategies to optimize the HBV MTCT prevention program. Although breakthrough MTCT occurs despite both maternal antiviral and timely administration of HBIG and HepB, high uptake of maternal antiviral prophylaxis is important for achieving the WHO goal of chronic HBV elimination [19].

Taiwan has achieved the WHO goals of coverage of HepB-BD and maternal antenatal HBsAg screening at ≥90%

Table 2. Risk Factors Associated With Mother-to-Child Transmission of Hepatitis B Virus Among Infants Who Received Post-Vaccination Serologic Testing

	Infants Born to HBsAg (+) Mothers						Infants Born to HBeAg (+) Mothers					
	Univariate			Multivariable			Univariate			Multivariable		
Risk Factor	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Infant birth years[a]												
2008–2010	1	ref.		1	ref.		1	ref.		1	ref.	
2011–2017	1.13	(.96 to 1.33)	.131	1.41	(1.11 to 1.79)	.005	1.19	(1.01 to 1.40)	.041	1.33	(1.05 to 1.69)	.017
2018–2021	0.35	(.29 to .43)	<.001	1.42	(1.05 to 1.91)	.024	1.00	(.81 to 1.24)	.992	1.26	(.93 to 1.70)	.135
Gender												
Male	1	ref.		…	…		1	ref.		…	…	
Female	1.05	(.93 to 1.19)	.449	…	…		1.06	(.93 to 1.20)	.424	…	…	
Birth order												
First	1	ref.		…	…		1	ref.		…	…	
Second	1.16	(1.00 to 1.35)	.052	…	…		0.93	(.79 to 1.09)	.366	…	…	
Third	1.02	(.83 to 1.26)	.849	…	…		0.83	(.67 to 1.03)	.083	…	…	
Fourth and above	0.95	(.68 to 1.32)	.746	…	…		0.71	(.50 to 1.02)	.065	…	…	
Days of the week of infant's birthday												
Monday to Thursday	1	ref.		…	…		1	ref.		…	…	
Friday to Sunday	1.07	(.94 to 1.21)	.334	…	…		1.02	(.89 to 1.16)	.801	…	…	
Maternal age group, y												
40–49	1	ref.		1	ref.		1	ref.		…	…	
30–39	2.78	(1.88 to 4.10)	<.001	1.44	(.95 to 2.17)	.084	1.43	(.90 to 2.25)	.126	…	…	
15–29	4.07	(2.74 to 6.04)	<.001	1.55	(1.02 to 2.37)	.043	1.58	(.99 to 2.50)	.053	…	…	
Maternal nationality												
Native	1	ref.		1	ref.		1	ref.		…	…	
Foreign	1.44	(1.15 to 1.80)	.002	1.16	(.92 to 1.48)	.217	1.24	(.99 to 1.56)	.065	…	…	
Mother's birth cohort[b]												
Unvaccinated	1	ref.		…	…		1	ref.		1	ref.	
Partially vaccinated	0.87	(.71 to 1.07)	.185	…	…		1.00	(.81 to 1.24)	.997	1.01	(.81 to 1.26)	.910
Vaccinated	1.10	(.94 to 1.29)	.235	…	…		1.3	(1.10 to 1.53)	.002	1.40	(1.17 to 1.67)	<.001
Maternal HBeAg status												
Negative	1	ref.		1	ref.		…	…		…	…	
Positive	8.95	(6.87 to 11.66)	<.001	9.29	(6.79 to 12.73)	<0.001	…	…		…	…	
Maternal antiviral prescription during third trimester[c]												
Without antivirals	1	ref.		1	ref.		1	ref.		1	ref.	
Telbivudine, tenofovir disoproxil fumarate, or tenofovir alafenamide	0.37	(.22 to .63)	<.001	0.28	(.16 to .49)	<.001	0.28	(.16 to 0.48)	<.001	0.27	(.15 to .46)	<.001
Post-vaccination serologic testing age												
9–11 m	1.9	(1.07 to 3.36)	.028	1.73	(.97 to 3.10)	.063	1.68	(.94 to 3.00)	.078	…	…	

Table 2. Continued

	Infants Born to HBsAg (+) Mothers						Infants Born to HBeAg (+) Mothers					
	Univariate			Multivariable			Univariate			Multivariable		
Risk Factor	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
12–23 m[d]	1	ref.		1	ref.		1	ref.		…	…	
≥2 y	1.42	(1.23 to 1.62)	<.001	1.10	(.94 to 1.29)	.225	1.06	(.92 to 1.22)	.441	…	…	
Hepatitis B immunoglobulin administration[e]												
Within 1 d after birth	1	ref.		1	ref.		1	ref.		1	ref.	
>1 d after birth	1.73	(.98 to 3.06)	.058	1.38	(.78 to 2.45)	.273	1.33	(.74 to 2.42)	.343	1.26	(.70 to 2.30)	.442
Hepatitis B vaccine dose 1 administration[e]												
Within 1 d after birth	1	ref.		1	ref.		1	ref.		1	ref.	
>1 d after birth	1.51	(1.31 to 1.73)	<.001	1.17	(.94 to 1.44)	.157	1.01	(.88 to 1.17)	.871	1.22	(.98 to 1.51)	.071
Hepatitis B vaccine dose 2 administration[e]												
At 1–2 m	1	ref.		1	ref.		1	ref.		1	ref.	
<1 or ≥3 m	1.06	(.59 to 1.89)	.855	1.02	(.51 to 2.04)	.966	1.05	(.58 to 1.90)	.865	1.07	(.53 to 2.16)	.853
Hepatitis B vaccine dose 3 administration[e]												
At 4–7 m	1	ref.		1	ref.		1	ref.		1	ref.	
<4 or ≥8 m	1.10	(.85 to 1.41)	.479	1.01	(.78 to 1.32)	.932	1.06	(.82 to 1.37)	.672	1.03	(.78 to 1.35)	.855

Abbreviations: CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; OR, odds ratio; ref., reference.

[a]Infants birth years were divided into 3 groups according to the change in hepatitis B vaccine dose 1 administration timing in 2011 and the implementation of maternal antiviral prophylaxis for pregnant women with a high hepatitis B viral load in 2018.

[b]Maternal birth cohorts were defined as maternal unvaccinated cohort (maternal birthday before 30 June 1984), partially vaccinated cohort (maternal birthday between 1 July 1984 and 30 June 1986), and vaccinated cohort (maternal birthday after 1 July 1986).

[c]Antivirals with lamivudine and entecavir were excluded in the analysis due to small sample size.

[d]In multivariate logistic regression analysis, the reference group of post-vaccination serologic testing age was 12–23 months, given that few at-risk infants were tested at between 9 and 11 months in this study.

[e]Missing data were not included in the statistical analysis.

Table 3. Post-Vaccination Serologic Testing Among Infants Born to Hepatitis B e Antigen–Positive Mothers Between 2018 and 2021, According to Maternal Antiviral Prophylaxis

	With Maternal Drug Prophylaxis[a]				Without Maternal Drug Prophylaxis[b]			
Infants Born to HBeAg(+) Mothers	No. of Infants Screened	PVST HBsAg (+)	MTCT Rate (%)	*P* Value	No. of Infants Screened	PVST HBsAg (+)	MTCT Rate (%)	*P* Value
Total	641	11	1.72		2093	146	6.98	
Birth year				.143[c]				.050
2018	126	1	0.79		817	64	7.83	
2019	197	2	1.02		608	50	8.22	
2020	185	7	3.78		423	18	4.26	
2021	133	1	0.75		245	14	5.71	
Gender				.870				.679
Male	334	6	1.80		1081	73	6.75	
Female	307	5	1.63		1012	73	7.21	
Birth order				.330[c]				.364
First	249	5	2.01		688	54	7.85	
Second	305	5	1.64		1027	73	7.11	
Third	68	0	0.00		275	13	4.73	
Fourth and above	19	1	5.26		103	6	5.83	
Days of the week of infant's birthday				1.000[c]				.969
Monday to Thursday	399	7	1.75		1287	90	6.99	
Friday to Sunday	242	4	1.65		806	56	6.95	
Maternal age group, y				.509[c]				.112
40–49	52	0	0.00		151	5	3.31	
30–39	448	10	2.23		1432	99	6.91	
15–29	141	1	0.71		510	42	8.24	
Maternal nationality				1.000[c]				.131
Native	600	11	1.83		1919	129	6.72	
Foreign	41	0	0.00		174	17	9.77	
Mother's birth cohort				1.000[c]				.242
Before July 1984	273	5	1.83		928	60	6.47	
July 1984 to June 1986	92	1	1.09		336	19	5.65	
After July 1986	276	5	1.81		829	67	8.08	
PVST testing age				.483[c]				.897
9 to 11 m	3	0	0.00		15	1	6.67	
12 to 23 m	604	10	1.66		1942	137	7.05	
2+ years	34	1	2.94		136	8	5.88	
Hepatitis B immunoglobulin administration[d]				1.000[c]				.280[c]
Within 1 d after birth	632	11	1.74		2046	141	6.89	
>1 d after birth	2	0	0.00		15	2	13.33	
Hepatitis B vaccine dose 1 administration[d]				1.000[c]				.299[c]
Within 1 d after birth	609	11	1.81		1999	137	6.85	
>1 d after birth	32	0	0.00		94	9	9.57	
Hepatitis B vaccine dose 2 administration[d]				1.000[c]				.142[c]
At 1–2 m	634	11	1.74		2074	143	6.89	
<1 or ≥3 m	7	0	0.00		19	3	15.79	
Hepatitis B vaccine dose 3 administration[d]				.455[c]				.397[c]
At 4–7 m	604	10	1.66		1938	138	7.12	
<4 or ≥8 m	34	1	2.94		146	7	4.79	

Abbreviations: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; MTCT, mother-to-child transmission; PVST, post-vaccination serologic testing.

[a]Antivirals prescribed is restricted to the 3 drugs: telbivudine, tenofovir disoproxil, and tenofovir alafenamide.

[b]"Without antiviral" is defined as pregnant mothers without prescriptions of antivirals for hepatitis B virus treatments including lamivudine, entecavir, telbivudine, tenofovir disoproxil, and tenofovir alafenamide. Among the 2093 infants born to HBeAg-positive mothers without antiviral prophylaxis, MTCT rates seemed higher for those without proper hepatitis B immunoglobulin, hepatitis B vaccine dose 1, or hepatitis B vaccine dose 2 administered after birth, although the statistical significances were not present.

[c]Fisher exact test was applied.

[d]Missing data were not included in the statistical analysis.

in 2013 and 2014, respectively. The MTCT rate has reached <2% (1.2%) for infants born to HBsAg-positive mothers since 2020, and it was 1.7% for infants born to HBeAg-positive mothers with antiviral prophylaxis. However, the maternal antiviral coverage was lower than expected in the first few years after implementation of nationwide antiviral prophylaxis for high-risk pregnant women, despite the fact that HBV DNA testing and antiviral therapy have been widely accessible in medical facilities and reimbursed by the National Health Insurance Administration since 2018. To face this challenge and to encourage eligible carrier mothers to be adequately evaluated or treated, we propose improvement plans to streamline the process for the National Health authorities, including 1) integrating HBV DNA testing into routine prenatal care in the first or second trimester; 2) providing data on HBV DNA levels to mothers, obstetrician, and public health workers and integrating this data into the national registry database, the same process used for antenatal HBsAg/HBeAg screening that was established in 1984; and 3) involving obstetricians in prescribing prophylaxis antivirals for pregnant women [3, 4, 8]. Alternatively, if HBV DNA testing or HBV antiviral prescriptions are unavailable in obstetric clinics, an efficient referral system that allows HBsAg-positive pregnant women to receive appropriate care in hospitals or clinical services should be implemented [3, 4, 8, 20].

We found that infants born to HBeAg-positive mothers had an approximately 9-fold higher risk of MTCT compared with infants born to HBsAg-positive but HBeAg-negative mothers. Conversely, maternal antenatal antiviral therapy decreased the MTCT risk by 73% (95% CI, 54%–85%) for infants born to HBeAg-positive mothers. The effectiveness of maternal antiviral therapy was lower in our real-world dataset than in previous clinical trials [10, 12]. There are several possible reasons for this discrepancy. First, it is challenging to comply with the complex procedures related to maternal HBV screening, viral load testing, and referral of pregnant women from obstetricians to hepatologists for antiviral treatment prescription. Second, in the real-world setting, the optimal timing of maternal antiviral therapy initiation may not be achieved. Third, our study included data from the initial years of program implementation. Therefore, awareness of prophylactic strategies may have been inadequate among medical professionals. Finally, some mothers may have exhibited other medical or obstetric conditions that compromised the effectiveness of antiviral therapy.

Our previous study demonstrated that the birth-cohort effect in relation to the universal infant HBV immunization program has effectively reduced the HBV carrier rate in pregnant women [6]. In the present study, no birth-cohort effect was observed for foreign mothers. In Taiwan, most immigrant mothers were born in other Asian countries, which introduced universal neonatal immunization programs after 2000 [21]. This may explain the lack of decline in maternal HBsAg and HBeAg prevalence rates among foreign mothers.

Notably, the risk of MTCT was 40% (95% CI, 17%–67%) higher among infants of HBeAg-positive mothers born in the immunization era compared with those born before implementation of the universal infant HBV vaccination program. Possible biological explanations including virus-related factors of HBV genotype, viral variants, hypervariability of the HBV genome, and extremely high viral loads in mothers selected from immunization programs merit further investigation [19, 22–24]. The previous study in Taiwan demonstrated that maternal HBV genotype C and the pre-S1 wild-type sequence were potential risk factors for perinatal HBV infection in infants independent of maternal viremia [19]. On the other hand, pregnant carrier mothers who harbored the "a" determinant mutants, the HBsAg escape mutants, did not increase the risk of transmitting HBV to their immunized infants who developed a protective level of anti-HBs [19]. In the prevaccination era in Taiwan, about 80% of the HBV-infected population were genotype B, and even fewer with genotype C [22]. This allows us to observe a shift of genotype distribution toward an increased proportion of genotype C. HBV genotype C infection has been proven to delay HBeAg seroconversion, and genotype C–infected women would be more likely to be HBeAg-positive and infect their offspring at birth [19, 22–24]. Another study also showed that a trend toward genotype C in immunized children with HBV breakthrough infection may be linked to the immunization program, which raises the threshold of the maternal viral load, causing perinatal infection [19, 22]. A larger survey to investigate the viral factors of carrier infant–mother pairs from the immunization era in relation to MTCT is warranted in the future.

Although HBV prevention strategies have been successfully implemented in Taiwan, several challenges remain. Approximately 35% and 72% of at-risk infants born to HBsAg-positive/HBeAg-negative and HBeAg-positive mothers undergo PVST, respectively. Additional resources are needed to develop case-management strategies for at-risk HBV infant–mother pairs before and after delivery, which will help to improve medical care and follow-up. Regular, close monitoring of the coverage of timely HBIG and HepB administration and identifying the reasons for the missing immunizations are also essential.

CONCLUSIONS

Our data provide real-world evidence for HBV MTCT prevention and control, which can improve the uptake of prevention and treatment programs by raising awareness among HBV-carrier mothers, obstetricians, pediatricians, hepatologists, infection specialists, and public health workers. Continuous efforts to enhance implementation of the maternal antiviral prophylaxis strategy are required to eliminate perinatal HBV infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. W. J. S., Y. L. L., and S. F. C. had full access to the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: W. J. S., H. L. C., and M. H. C. Acquisition, analysis, or interpretation of data: W. J. S., S. F. C., Y. L. L., Y. C. H., and T. A. W. Drafting of the manuscript: W. J. S., H. L. C., and M. H. C. Critical revision of the manuscript for important intellectual content: S. F. C., Y. L. L., and T. A. W. Administrative, technical, or material support: W. J. S, Y. L. L., and Y. C. H. Supervision: S. F. C., H. L. C., and M. H. C. All the authors read, contributed to, and approved the final manuscript and agreed to transfer the copyright ownership in the event of acceptance.

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