Cost-effectiveness of Augmenting Universal Hepatitis B Vaccination With Immunoglobulin Treatment

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KEY WORDS

hepatitis B, carrier rate, vaccination, cost-effectiveness analysis, immunoglobulin

ABBREVIATIONS

HBeAg—hepatitis B e-antigen

HBIG—hepatitis B immunoglobulin

HBsAg—hepatitis B surface antigen

HBV—hepatitis B virus

ICER—incremental cost-effectiveness ratio

WHO—World Health Organization

WTP—willingness-to-pay

(−)—negative

(+)—positive

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WHAT'S KNOWN ON THIS SUBJECT: Universal hepatitis B virus (HBV) vaccination is a cost-effective strategy to control HBV infection. Giving hepatitis B immunoglobulin to neonates of HBV carrier mothers additionally reduces transmission but is not widely used because of its expense and infrastructure requirements.

WHAT THIS STUDY ADDS: Maternal screening for hepatitis B surface antigen and hepatitis B immunoglobulin treatment of neonates of hepatitis B virus carrier mothers could be a cost-effective addition to universal vaccination in settings in which health infrastructure can support such an intervention.

abstract

OBJECTIVE: To compare the cost-effectiveness of hepatitis B virus (HBV) control strategies combining universal vaccination with hepatitis B immunoglobulin (HBIG) treatment for neonates of carrier mothers.

METHODS: Drawing on Taiwan's experience, we developed a decision-analytic model to estimate the clinical and economic outcomes for 4 strategies: (1) strategy V—universal vaccination; (2) strategy S—V plus screening for hepatitis B surface antigen (HBsAg) and HBIG treatment for HBsAg-positive mothers' neonates; (3) strategy E—V plus screening for hepatitis B e-antigen (HBeAg), HBIG for HBeAg-positive mothers' neonates; (4) strategy S&E—V plus screening for HBsAg then HBeAg, HBIG for all HBeAg-positive, and some HBeAg-negative/HBsAg-positive mothers' neonates.

RESULTS: Strategy S averted the most infections, followed by S&E, E, and V. In most cases, the more effective strategies were also more costly. The willingness-to-pay (WTP) above which strategy S was cost-effective rose as carrier rate declined and was <\$4000 per infection averted for carrier rates >5%. The WTP below which strategy V was optimal also increased as carrier rate declined, from \$1400 at 30% carrier rate to \$3100 at 5% carrier rate. Strategies involving E were optimal for an intermediate range of WTP that narrowed as carrier rate declined.

CONCLUSIONS: HBIG treatment for neonates of HBsAg carrier mothers is likely to be a cost-effective addition to universal vaccination, particularly in settings with adequate health care infrastructure. Targeting HBIG to neonates of higher risk HBeAg-positive mothers may be preferred where WTP is moderate. However, in very resource-limited settings, universal vaccination alone is optimal. *Pediatrics* 2013;131:e1135–e1143

Hepatitis B virus (HBV) infection is a worldwide health problem, with ~350 million people chronically infected and 1 million deaths each year.¹ Vaccination is the most effective way to control HBV infection and its chronic complications on a global scale. Universal HBV vaccination has proved to be a highly cost-effective strategy, both in developing and developed countries.^{2–7} Following the recommendation of the World Health Organization (WHO), universal vaccination has already been implemented in >170 countries.⁸

In addition to vaccination, hepatitis B immunoglobulin (HBIG) given to neonates after birth also plays a significant role in reducing mother-to-infant vertical transmission, the major route of HBV infection.^{9–12} Neonates of mothers carrying hepatitis B surface antigen (HBsAg) are at elevated risk of infection. When mothers are also positive for hepatitis B e-antigen (HBeAg), the risk of infection is several times higher. In either case, HBIG administered shortly after birth reduces transmission risk.^{13,14} Due to its expense, HBIG is usually reserved for high-risk neonates born to mothers with positive HBV markers detected with maternal screening tests.

In 1984 Taiwan started its vaccination-based HBV prevention program and has since augmented universal HBV vaccination with maternal screening

and HBIG treatment.¹⁵ Free HBIG is administered within 24 hours after birth to neonates born to HBeAg-positive (+) HBsAg(+) carrier mothers. Optional HBIG for neonates born to HBeAg-negative (–) HBsAg+ carrier mothers is also available as requested and self-paid by families.¹⁶ The coverage rate of HBV prevention program is >97%.¹⁶ This program has successfully reduced HBV carrier rates as well as the incidence of infantile hepatitis and childhood hepatocellular carcinoma^{16–21}; the HBV carrier rate decreased from 15% to 20% in the 1980s,¹⁴ to 0.78% among first-graders in primary school²¹ and 1.2% among those persons <20 years old.¹⁵

Universal HBV vaccination has led to a declining trend in HBV carrier rate in many countries, which could be accelerated with the use of HBIG. Yet, there is currently no worldwide consensus on the maternal screening test for HBV markers or on the use of HBIG in neonates. The choice of strategy depends mainly on local endemicity of HBV infection, the health system's capacity to conduct maternal screening and administer HBIG, and financial considerations in each country. Table 1 summarizes 4 possible combinations of maternal screening test and the use of HBIG to augment a universal vaccination policy.^{4–6,22} Maternal screening tests for HBV and HBIG treatment are most

common in developed countries.^{4,6,16} In developing countries, mothers are not routinely screened to determine HBV carrier status and HBIG is not given.^{5,22} The objective of this study was to compare the cost-effectiveness of 4 strategies for HBV screening and HBIG treatment to augment a universal vaccination policy under different HBV prevalences. Some developed countries with low HBV endemicity such as Japan and the Netherlands do not have universal HBV vaccination and rely exclusively on screening tests and HBIG,^{23,24} but because our focus is on policies for less developed countries with universal HBV vaccination policies, we did not consider strategies without vaccination. We also did not consider administering HBIG to all newborns without first administering a maternal screening test, because even at the highest plausible levels of carrier rate, the nearly perfect screening test saves the high cost of unnecessary HBIG use.

METHODS

Model and Strategies

We developed a decision analysis model to estimate the clinical and economic outcomes of HBV for a hypothetical cohort of 100 000 neonates. The model focused on the number of infections averted and costs. The 4 strategies are summarized in Table 1 and are as follows:

TABLE 1 Strategies of Hepatitis B Virus Control Programs and Country Examples

Strategy	HBV Control Programs	Universal Vaccines	Maternal Screening for HBsAg	Maternal Screening for HBeAg	HBIG for Neonates Born to HBeAg(+) Mothers	HBIG for Neonates Born to HBeAg(–) Mothers	Country Examples
V	No maternal screening, no HBIG, only universal vaccination	X	NA	NA	NA	NA	China, ⁵ Thailand ²²
S	Maternal screening for HBsAg, HBIG for positive result, plus universal vaccination	X	X	NA	X	X	United States, ⁴ Italy ⁶
E	Maternal screening for HBeAg, HBIG for positive result, plus universal vaccination	X	NA	X	X	NA	No known country
S&E	Maternal screening for HBsAg, then HBeAg; HBIG for HBeAg(+) and optional for HBeAg(–) HBsAg(+), plus universal vaccination	X	X	X	X	Optional	Taiwan ¹⁸

NA, not applicable.

1. Strategy V: universal vaccination for all neonates, no routine screening or HBIG treatment. Countries with this policy include China and Thailand.^{5,22}
2. Strategy S: universal vaccination plus maternal screening for HBsAg, HBIG given for neonates born to HBsAg(+) mothers. Countries with this policy include the United States and Italy.^{4,6}
3. Strategy E: universal vaccination plus maternal screening for HBeAg, HBIG given for neonates born to HBeAg(+) mothers. We know of no country with this policy.
4. Strategy S&E: universal vaccination plus maternal screening for HBsAg followed by screening for HBeAg among HBsAg(+), HBIG given for neonates born to HBeAg(+) carrier mothers, and HBIG optional for neonates of HBeAg(−) HBsAg(+) mothers. This is the policy of Taiwan.¹⁸

Because universal vaccination has been recommended by the WHO and widely accepted in many countries,⁸ we used the strategy V in the decision analysis model as a baseline for comparison. Details of the decision analytic model are provided in Fig 1.

Epidemiology

The estimates of the epidemiologic variables are based on a critical review of the literature and summarized in Table 2.^{10,13,14,25–32} To understand the benefit and costs of screening and HBIG treatment in a wide range of settings, we conducted the analysis over a range of HBV carrier rates from 1% to 30%. According to the WHO classification, the HBV prevalence ranges of <2%, 2% to 8%, and >8% are defined as low, intermediate, and high endemicity, respectively. Building on these definitions, we classified the carrier rates into 4 endemicity categories, adding a “very high endemicity” (>20%) category.

The probability of vertical transmission depends on maternal status. Among those mothers who are HBV carriers detected by HBsAg test, just under one-third are HBeAg positive, indicating a 5 times higher risk of vertical transmission. Mothers with HBsAg but negative for HBeAg have a moderate risk (6.6%; range: 0% to 13.2%^{12,27,29}) of transmitting HBV to their newborns. HBeAg(+) mothers have a much higher transmission risk (33.8%; range: 21% to 43%^{13,27,28}), because they have a much higher viral load of HBV in the body.

Costs

The study used a modified societal perspective. Costs were confined to direct medical costs including vaccines, HBIG, and laboratory costs, whereas other costs such as transportation costs incurred in the course of receiving medical care were not considered. Nor did we model costs associated with downstream health care utilization in HBV-infected children. Cost estimates for HBV vaccine, maternal HBsAg and HBeAg screening tests, and newborn HBIG treatment were obtained from the Taiwan National Health Insurance reimbursement data and reported in 2011 US dollars.³³

Efficacy of Intervention

We considered the sensitivity and specificity of the maternal screening tests for HBsAg and HBeAg in the modeling. But, in fact, these 2 tests are both well developed and have almost 99% to 100% sensitivity and specificity as shown in Table 2.^{34–36} Among newborns of HBsAg(+) HBeAg(−) mothers, HBIG treatment additionally reduces the probability of transmission by >85%, from 6.6% to 1.0%.^{12,27,31,32} Among newborns of HBeAg(+) mothers, HBIG additionally reduces the probability of transmission by two-thirds, from 33.8% to 12.5%.^{10,12,13,27,28,31}

These references support an additional benefit of HBIG to prevent HBV vertical transmission.^{10,12,13,27,28,31,32}

Outcomes

Outcomes included costs, incremental cost, number of infections, incremental infections averted, and incremental cost-effectiveness ratio (ICER). We eliminated those strategies that were dominated, that is, less effective and more costly than another strategy or combination of strategies. For the efficient (nondominated) strategies, the ICER was calculated as the incremental cost divided by the incremental infections averted associated with 1 strategy compared with the next less costly strategy. We present cost-effectiveness results for 4 subjectively selected HBV carrier rates of 25%, 15%, 5%, and 1% to represent each endemicity category in Table 3.

RESULTS

Outcomes of Strategies

Among the 4 strategies, vaccination alone (strategy V) prevented the fewest infections. The most aggressive strategy for augmenting vaccination, HBIG for all neonates with HBsAg(+) mothers (strategy S) averted the most infections, followed by strategy S&E and strategy E, which primarily cover neonates born to the subset of carrier mothers who are also HBeAg(+) (Fig 2A). With all strategies, the number of HBV infections decreased linearly as the HBV carrier rates declines. For example, at an HBV carrier rate of 2%, the numbers of HBV infections per 100 000 births for strategies V, E, S&E, and S were 297, 168, 122, and 91, respectively. At an HBV carrier rate of 8%, the numbers of HBV infections for strategies V, E, S&E, and S were ~4 times higher.

Costs of Strategies

Increases in effectiveness were associated with higher costs. For most

FIGURE 1

This decision analysis tree outlines 4 immunization strategies. The compared strategies are represented as branches from a square decision node. Probabilistic events are represented as circular chance nodes. Chance nodes with only 1 outgoing branch indicate events that occur with certainty. Outcomes are represented as triangular terminal nodes. neg, negative; pos, positive.

TABLE 2 Model Parameter Values for Base Case, and Ranges Considered in Sensitivity Analysis

Parameter	Base Case	Range	Sources
Probability HBsAg(+) (ie, carrier rate), %	1, 5, 15, 25	1–30	Assumed
Probability HBeAg(+) given HBsAg(+), %	30.3	18.1–42.6	Lin et al (25), Liu et al (26)
Probability of HBV perinatal infection, %			
Neonates without HBIG born to HBeAg(+) carrier mothers	33.8	21–43	Wong et al (13), Wheeley et al (27), Sehgal et al (28)
HBeAg(–) carrier mothers	6.6	0–13.2	Chen et al (12), Wheeley et al (27), Edmunds et al (29)
Neonates with HBIG born to HBeAg(+) carrier mothers	12.5	6.4–29	Zanetti et al (10), Chen et al (12), Wong et al (13), Wheeley et al (27), Sehgal et al (28), Wiseman et al (31)
HBeAg(–) carrier mothers	1.0	0–3	Chen et al (12), Wheeley et al (27), Wiseman et al (31), Zanetti et al (32)
Probability of giving HBIG to neonates born to			
HBeAg(+) carrier mothers, %	100	99–100	Liu et al (26)
HBeAg(–) carrier mothers, %	50	0–100	Assumed
Sensitivity and specificity of screening tests, %			
Sensitivity of HBsAg test	99.5	96.3–100	World Health Organization (34), Scheiblaue et al (35)
Specificity of HBsAg test	98.98	95.2–100	World Health Organization (34), Scheiblaue et al (35)
Sensitivity of HBeAg test	100	100	Ratnam and Tobin (36)
Specificity of HBeAg test	100	100	Ratnam and Tobin (36)
Program costs, 2011 US\$			
Hepatitis B vaccination	120	96–144	Bureau of National Health Insurance, Taiwan (33)
Maternal screening for HBsAg	5	4–6	Bureau of National Health Insurance, Taiwan (33)
Maternal screening for HBeAg	10	8–12	Bureau of National Health Insurance, Taiwan (33)
HBIG (0.5 mL, intramuscularly)	200	160–240	Bureau of National Health Insurance, Taiwan (33)
Effectiveness			
Infected	1	1	Assumed

carrier rates, the most expensive strategy was strategy S, followed by S&E, E, and V (Fig 2B). At low carrier rates, strategy E was higher cost than strategies S&E and S, due to higher test cost. The cost of universal vaccination (strategy V) was fixed at \$12 per birth across all HBV carrier rates. The costs of the other strategies declined with carrier rate because fewer neonates required HBIG.

The cost per birth was similar for each screening strategy in low-endemicity settings, but more disparate in higher-endemicity settings. For example, at an HBV carrier rate of 1%, the cost of the HBV program per birth was

\$13.05, \$12.63, and \$12.70 for strategies E, S&E, and S, respectively. In contrast, at an HBV carrier rate of 15%, the cost of the HBV program per birth was \$13.76, \$14.51, and \$15.47 for strategies E, S&E, and S, respectively.

At a carrier rate of <5%, strategy E became more expensive than strategy S&E because the need for sequential HBeAg test decreased in strategy S&E. At a carrier rate of <2%, strategy E became more expensive than strategy S because the cost of HBeAg testing for all mothers outweighed the cost of HBIG treatment of neonates born to all HBV carrier mothers.

ICER Among 4 Endemicity Categories

Cost-effectiveness results for the 4 selected endemicity levels are summarized in Table 3. Figure 3 shows 4 areas of optimal strategy according to the ICER (vertical axis) and HBV carrier rates (horizontal axis) from 1% to 30%. Only efficient (nondominated) strategies are shown. Of note, strategy E was efficient only at carrier rate >12%, and strategy S&E was efficient at carrier rates of between 2% and 23%. The ICER of strategy S increased gradually from \$3200 to \$4000 as carrier rate declined from 30% to 5% and then rose more rapidly as carrier rates dropped below 5% (Fig 3). In the extreme case of the HBV carrier rate of 1%, the ICER of strategy S reached \$8800 per additional infection averted (Table 3).

The selection of an optimal maternal screening test and HBIG strategy depends in part on the ICER and its comparison with the decision makers' willingness-to-pay (WTP) to avert additional HBV vertical transmissions (Fig 3). For example, at a carrier rate of 25%, strategy V was optimal for settings with WTP <\$1600 per infection averted, strategy E was optimal where WTP was in the range of between \$1600 and \$3300 per infection averted, and strategy S was optimal where WTP >\$3300 per infection averted. The E and S&E strategies were optimal over a range of WTP values that became narrower as carrier rate declined.

Sensitivity Analyses

Univariate sensitivity analyses showed that results were most sensitive to HBV carrier rate, probability of HBeAg(+) among HBsAg(+) mothers, and probability of HBV infection for neonates without HBIG administration born to HBeAg(+) or HBeAg(–) carrier mothers. Results were moderately sensitive to costs of HBV vaccines. In

TABLE 3 Comparison of Costs, Incremental Costs, Outcomes, Incremental Infections Averted, and ICER Among 4 Strategies at 4 Representative Hepatitis B Virus (HBV) Carrier Rates in a Hypothetical Cohort of 100 000 Persons

HBV Immunization Programs	Cost, US\$	Incremental Cost, US\$	Outcome, No. of Infections	No. of Incremental Infections Averted	ICER, US\$/per Incremental Infection Averted
Very high endemicity (eg, HBV carrier rate = 25%)					
Strategy V	12 000 000	0	3690	0	
Strategy E	14 500 000	2 500 000	2092	1598	1565
Strategy S	17 628 000	3 128 000	1125	967	3234
High endemicity (eg, HBV carrier rate = 15%)					
Strategy V	12 000 000	0	2214	0	
Strategy E	13 900 000	1 900 000	1255	959	1982
Strategy S&E	14 684 900	784 900	968	288	2728
Strategy S	15 658 400	973 500	675	293	3328
Intermediate endemicity (eg, HBV carrier rate = 5%)					
Strategy V	12 000 000	0	738	0	
Strategy S&E	13 303 100	1 303 100	323	415	3137
Strategy S	13 688 800	385 700	225	98	3956
Low endemicity (eg, HBV carrier rate = 1%)					
Strategy V	12 000 000	0	148	0	
Strategy S	12 901 000	901 000	45	103	8783

Strategy V (universal vaccination only) was used as reference strategy. Strategies that were dominated in some endemicity categories are not shown in the table. All costs reported in 2011 US dollars.

contrast, the results were insensitive to other variables including costs of screening test for HBsAg or HBeAg, cost of HBIG, sensitivity or specificity

of screening test for HBsAg or HBeAg, and the probability of giving HBIG to neonates born to HBeAg(–) carrier mothers.

DISCUSSION

In Taiwan, the HBV carrier rate declined gradually from 20% to 1% over the past 3 decades since the introduction of the universal HBV prevention program.^{16–21} The success in preventing HBV transmission in Taiwan suggests the elimination of HBV worldwide could be possible in the future.²¹ The use of HBIG could accelerate progress toward this goal but may be costly to implement in some settings. Previous cost-effectiveness studies of HBV vaccination have not considered the value of maternal screening and HBIG treatment.^{3–6,22} Our study, which compared 3 possible strategies for augmenting vaccination with maternal screening and the use of HBIG, predicts their impact over a wide range of HBV prevalence levels, and thus could be helpful for other countries facing different levels in HBV prevalence.

Our model suggests that the choice of optimal HBV immunization strategy depends on HBV prevalence and WTP threshold. For developed countries with adequate financial resources and medical capabilities, strategy S will likely be cost-effective and provides the most protection.⁴ For less-developed

FIGURE 2 HBV infections and costs of 4 hepatitis B immunization strategies among a hypothetical cohort of 100 000 newborns across HBV carrier rates from 30% to 1%. A, HBV infections per 100 000 newborns; B, cost (in millions of US dollars) per 100 000 newborns.

FIGURE 3

The optimal strategy of a hepatitis B control program according to the ICER (in US dollars per incremental infection averted) at different HBV carrier rates. Lines show the ICERs of different strategies compared with the next most effective strategy. The labels mark the areas divided by the 3 ICER lines, indicating the range of conditions under which each strategy is optimal.

countries with insufficient logistic support, an easier and more affordable strategy such as strategy V would be preferred (Fig 3). Strategies involving E were optimal for an intermediate range of WTP that narrowed as carrier rate declined. Strategy E was only efficient where carrier rates exceed 12%, which may be a reason why no country uses it (Table 1). Strategy S&E may be a reasonable choice for some high and intermediate endemicity settings; but, where carrier rates were low, it was optimal only for a narrow WTP range (eg, between \$3140 and \$3960 per infection averted at 5% carrier rate).

Within a country, HBV prevalence can vary among subpopulations. Different prevalence may require different strategies to fit the specific needs of individuals or population. Targeting HBIG to high-risk groups, such as immigrants with higher HBV prevalence,³⁷ may be a good use of scarce resources.³⁸ For example, more than one-tenth of neonates in Taiwan are born to foreign-bride mothers,³⁹ who have, on average, higher HBV carrier rates than Taiwanese pregnant women (28.6% vs 3.1%).⁴⁰ Most of these foreign-bride mothers are married to men in families with lower socioeconomic status. Although Taiwan's current

policy (strategy S&E) provides an option for HBeAg(–)/HBsAg(+) carrier mothers to choose the self-paid HBIG for their neonates, the high price of HBIG of up to US\$200 dollars per dose may limit uptake of HBIG in this high-risk group. Thus, those neonates born to foreign-bride mothers may have a higher possibility of contracting an HBV infection.

Figure 3 shows that the ICER of strategy S increases rapidly as endemicity declines, reaching \$8800 per additional infection averted at 1% carrier rate (Table 3). Children who become infected with HBV can go on to have disease that not only diminishes health status and life expectancy but also has significant treatment costs. Treatment costs that could be averted with more intensive neonatal intervention were not considered formally in our analysis. However, in settings in which these HBV-associated diseases are likely to be treated, the economic benefits of prevention could be large. One recent study in Taiwan recognized that the averted medical costs for infantile fulminant hepatitis were 1.36 times the cost of providing HBIG to all neonates born to HBeAg(–)/HBsAg(+) mothers.¹² Thus, even the most expensive strategy, strategy S, may be cost-saving in many settings if future treatment costs for

HBV-related conditions such as chronic hepatitis, liver cirrhosis or failure, or even liver transplantation are averted.

Because the cost of HBIG is more than the cost of screening tests for HBsAg and HBeAg, we used these tests as screening tools to find those neonates born to HBV marker–positive mothers. As HBV prevalence decreases, the screening tests for HBsAg and HBeAg will reveal more negative results and the use of HBIG will be reduced. In general, the strategies with screening tests are more favorable in the high- and intermediate-endemicity settings than in low-endemicity settings because the ICERs of screening strategies increase as HBV prevalence declines (Fig 3). Although the strategies with screening tests may be cost-effective, they require more infrastructure than is needed for vaccination, including laboratory services and adequate numbers of medical professionals to interpret test results and administer HBIG. Our analysis presupposes a health system with the infrastructure and capacity to deliver the interventions. However, both of these essential elements may be difficult for some developing countries that suffer from limited medical facilities and health professionals. In this case, an investment decision might be considered and would depend in part on the level of downstream treatment costs averted.

The variables used in this study were based on Taiwan's experience, which may not be generalizable to other settings. For example, the cost of screening tests, HBIG, and vaccine may be different; however, we expect that the decreasing pattern of HBV prevalence after the launching of universal HBV vaccination will be similar across settings, given similar vaccine coverage levels, and the cost-effectiveness results may still be applicable to other countries after adjusting for cost differences.

A fuller assessment of the value of preventing HBV infections should include the lifetime impact of HBV infection on morbidity, mortality, and costs. However, this study was principally concerned with evaluating strategies to prevent vertical transmission of HBV, and we therefore chose to focus on infections averted as the main effectiveness outcome. This analytic approach has the advantage of minimizing model complexity and uncertainty by focusing the decision analysis on the most proximal and direct results of strategy alternatives. But it also limits our ability to assess the full value of preventing HBV infections. It would be worthwhile to model the pathways from HBV vertical infection to diseases later

in life, such as fulminant hepatitis, chronic active hepatitis, and liver cirrhosis. In our ongoing work, we are developing more complex Markov models of HBV-related morbidity and mortality to address these related questions. Outcomes of analysis using those models will include quality-adjusted life-years.

CONCLUSIONS

In summary, our results suggest that maternal screening for HBsAg and HBIG treatment of neonates of HBV carrier mothers could be a cost-effective addition to universal vaccination in settings in which health facility infrastructure can support such an intervention. Particularly if the expected future treatment

costs of HBV-infected children are moderately high, more intensive prevention efforts using screening and HBIG are likely to provide good value by averting those treatment costs. As HBV carrier rates decline, HBIG treatment of neonates of HBsAg(+) mothers is more likely to be the preferred policy for those adopting HBIG treatment. This study may provide a roadmap for augmenting vaccine-only HBV prevention programs in countries with different HBV prevalences.

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