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Cost-effectiveness of tenofovir prophylaxis during pregnancy for the elimination of mother-to-child transmission of the hepatitis B virus: real-world analysis from Thailand

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ABSTRACT

Objective Despite implementing hepatitis B immunoglobulin (HBIG) and vaccination, data suggest it would not be sufficient to reach the elimination targets. Tenofovir disoproxil fumarate (TDF) has been added to the Thai national standards of care for prevention of transmission of the hepatitis B virus during birth. To optimise national strategies in Thailand, we assessed TDF's effectiveness for prevention of mother-to-child transmission and conducted cost-effectiveness analyses of different TDF-based strategies.

Research design and methods We retrospectively reviewed medical records of mother and infant pairs whose mothers were positive for hepatitis B e-antigen (HBeAg) and received TDF to prevent maternal transmission of viral hepatitis B during 2018–2020. Based on the available data on transmission rate, we also applied a decision tree to estimate the cost-effectiveness of different TDF-based strategies to eligible mothers. These included: (1) HBIG for all hepatitis B virus (HBV) exposed infants; (2) HBIG for only infants of HBeAg-positive mothers ('HBIG for e-positive') and (3) without HBIG to infants ('HBIG-free'). The incremental cost-effectiveness ratio between the different strategies and baseline intervention without TDF was calculated. The one-way sensitivity analysis was used to adjust prevalence of HBeAg-positive mothers, cost of HBIG, cost of TDF and transmission rate.

Results Of 223 infants enrolled, 212 (95.0%) received HBIG, while 11 (5.0%) did not. None of the infants had chronic HBV infection. The most cost-saving intervention was 'HBIG-free' followed by 'HBIG for e-positive'. The one-way sensitivity demonstrated that the results were reasonably robust to changes. The cost-saving was greater with a higher hepatitis B virus surface antigen (HBsAg) prevalence. The HBIG-free strategy remained best at 0%–1.4% transmission rates, meeting the additional target for eliminations.

Conclusion The study is the first cost-effectiveness analyses to provide evidence supporting an HBIG-free strategy in an antiviral era. This approach should be considered to prevent mother-to-child transmission in resource-constrained settings, particularly in countries with a high HBsAg prevalence.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Limiting the generalisability of the study to healthy term infants born to mothers who took tenofovir disoproxil fumarate adequately.
⇒ Potential selection bias because we tended to select the participants who had completed lab results.
⇒ Differential misclassification bias could occur in the drug adherence variable; however, this was randomly verified with the mothers.
⇒ Uncertainty of HBsAg prevalence among pregnant women could occur due to missing data in the national health data centre database.
⇒ The economic evaluations were focused only on payer perspective, not societal perspective.

BACKGROUND

Vertical or mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is a major cause of chronic HBV infection and remains a critical concern in eliminating HBV infection.[1] The WHO Global Health Sector Strategy on viral hepatitis calls for eliminating viral hepatitis as a public health threat by 2030, including elimination of MTCT of HBV, defined as ≤0.1% prevalence of hepatitis B virus surface antigen (HBsAg) with an additional target of ≤2% MTCT rate (required for countries with selective hepatitis B birth dose policy).[2]

Thailand introduced universal infant immunisation with hepatitis B vaccine in parts of the country in 1988, then expanded to the whole country in 1992 with at least 95% of 1 year-olds are receiving three to four hepatitis B doses by 1999. The birth dose was included

from the beginning.[3 4] The current hepatitis B vaccination schedule includes a birth dose within 12 hours of delivery followed by three additional doses at 2, 4 and 6 months of age; HBV-exposed infants also receive a hepatitis B vaccine dose at 1 month of age.[3] In addition, Thailand has a well-developed system for antenatal care. All pregnant women are routinely screened for hepatitis B at a first antenatal clinic (ANC) visit, and each HBsAg positive specimen is tested for hepatitis B virus e antigen (HBeAg) together with alanine aminotransferase (ALT). However, the universal screening of HBeAg is not fully performed in Thailand. Administration of hepatitis B immune globulin (HBIG) to all HBV-exposed infants regardless of mother's HBeAg status was introduced for decades while still not fully implemented throughout Thailand. HBIG availability in some parts of Thailand is limited due to storage and stock management problems, and its cost is not covered by most provincial programmes.[4] Follow-up of HBV-exposed infants, including postvaccination serological testing, conducted at 12 months of age after completion of the hepatitis B vaccine series, is also recommended but is not implemented consistently.[5]

Implementation of these interventions has substantially reduced the prevalence of HBV in Thailand – from 6%–8%[6] in a prevaccine era to 0.7 among the population by 2014.[3] However, perfect use of this strategy still resulted in the 5.7% MTCT among children of HBeAg-positive mothers rate, suggesting it alone would not be sufficient for reaching the elimination targets.[7] Even earlier administration (within 1 hour after birth, median 0.17 hours) of HBIG resulted in 2.4% MTCT that is unlikely to contribute to the elimination. However, this strategy might be possible for children of mothers with HBeAg-negative or low viral load.[8] These data highlight that even with timely infant immunoprophylaxis, MTCT can still occur among HBeAg-positive mothers or those who have a high viral load.

To further reduce MTCT and help attain the elimination goal, in 2020, WHO recommended providing antiviral prophylaxis to HBV-infected mothers with high viral load (HBV DNA ≥200 000 IU/mL) or, if DNA testing is not available, to HBeAg-positive mothers.[1] Thailand launched guidelines on 'tenofovir disoproxil fumarate (TDF) prophylaxis during pregnancy' and began its implementation in pilot provinces in 2018.[5] According to these guidelines, prophylaxis with TDF (300 mg daily) in the last trimester of pregnancy beginning with 28–32 weeks until 4 weeks postpartum is recommended to HBeAg-positive pregnant women and mainly using HBeAg to assess eligibility for antiviral prophylaxis. The cost of TDF is currently not supported by the government fund due to limited data on infant outcomes.[9]

To optimise national strategies in Thailand, there is a clear need for additional information, including a comprehensive analysis of real-world outcomes after antiviral prophylaxis and an assessment of the feasibility and cost-effectiveness analyses of preventive strategies. Vertical transmission of HBV occurs predominantly during or shortly after birth but is possible at any stage of pregnancy.[10] Antiviral treatment can reduce intrauterine transmission, which occurs before the newborn can be given hepatitis B vaccine or HBIG. We hypothesised that since treating HBV with TDF during pregnancy would decrease HBV DNA to undetectable or very low levels by the time of delivery, HBIG might not be necessary for interrupting MTCT, a concept that has already been proven with HIV.[11] In addition, previous evidence on cost-effectiveness of universal HBIG treatment concluded that targeting HBIG to neonates of higher risk HBeAg-positive mothers may be preferred where willingness to pay is moderate. However, in very resource-limited settings, universal vaccination alone is optimal.[4]

Considering the limited access to HBIG[4] and antiviral prophylaxis concept, the use of HBIG-free strategies, such as vaccination in conjunction with antivirals administered peripartum, could be a less expensive and more accessible option compared with HBIG. For example, the national policy for prevention of MTCT in Cambodia only includes TDF and hepatitis B vaccination.[12] However, the assessment of HBIG-free regimens was highlighted by WHO as a research gap.[1] To support optimisation of national strategies for prevention of MTCT of HBV in Thailand, we conducted a retrospective assessment of effectiveness of TDF-based interventions by reviewing medical records of eligible mothers and their infants. We also assessed cost-effectiveness of different TDF-based options for inclusion in the universal health coverage (UHC) benefits package.[13]

METHODS

The study population included HBeAg-positive mothers aged 16–49 years who received TDF treatment according to national guidelines during 2018–2020 and their infants. Twelve provinces of Thailand with the highest number of TDF prescriptions in the national databases were included in the study.[1] HIV-positive women and preterm infants born before 34 weeks of gestational age were excluded.

Analysis of MTCT

Sample size was determined based on the primary outcome measure – MTCT rate (proportion of infants born to HBeAg-positive mothers who became chronically infected with HBV). Chronic infection was defined as HBsAg-positivity for ≥6 months. Minimum required sample size was estimated as 113 using one population proportion method with reference values of (p0)=MTCT rate of baseline intervention=0.057,[7] proportion (p)=MTCT rate of new intervention=0.02,[14] alpha (α)=0.05, Z(0.975)=1.959964, beta (β)=0.20, Z(0.80)=0.841621.

Medical records were reviewed after obtaining written informed consent from mothers. Variables of interest included ANC history, hepatitis B status and laboratory results, TDF history and delivery details for mothers,

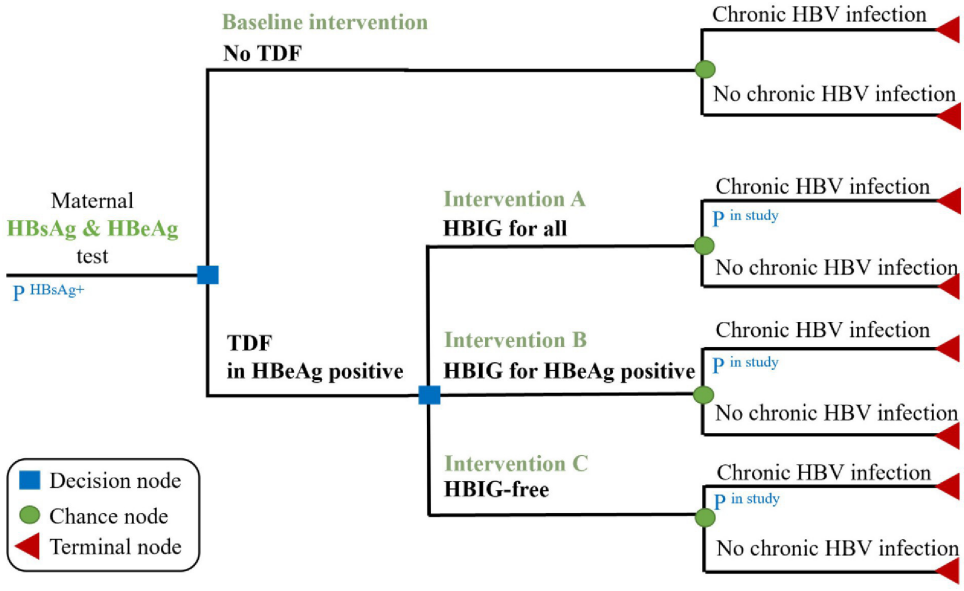

Figure 1 Decision tree models used in cost-effectiveness analyses. HBeAg, hepatitis B envelope antigen; HBIG, hepatitis B immunoglobulins; HBsAg, hepatitis B surface antigen; HBV hepatitis B virus; TDF, tenofovir disoproxil fumarate.

birth history, hepatitis B vaccination history, and infant screening results (HBsAg, anti-HBs) for children. Children with no infant screening results were asked to provide blood samples for HBsAg, anti-HBs and anti-HBc testing at a nearby hospital. An additional outcome for children was primary vaccine failure rate, defined as the proportion of children with negative results of anti-HBs testing after a full course of HBV vaccination.

Cost-effectiveness analyses

The cost-effectiveness analyses of three alternative strategies was tested by a decision tree model (figure 1). All strategies included the standard hepatitis B screening process and vaccination programme. Input values were described in table 1.

Baseline intervention (intervention 0), which included HBIG for all HBV-exposed infants with no TDF for

Table 1 Input parameters included in the model for cost-effectiveness assessment

Base case values	Probability/amount	Range (95% CI)
Population attending antenatal clinics in 1 year (5-year mean of birth in 2017–2021)	623 799	
Prevalence of HBsAg positive in pregnancy	1.72% (in study)	1.47% to 2.32% (in study)
Prevalence of HBeAg positive in pregnancy	34.4% (15)	25.6% to 44.3% (15)
HBV vaccine series+HBIG	5.7% (7)	2.0% to 9.3% (1), (7), (16)
HBV vaccine series+HBIG + TDF	0 (in study)	0% to 1.78% (in study)
HBV vaccine series+TDF	0 (in study),(12)	0% to 25.88% (in study) 0% to 1.41% (12)
Base cost values	**Price ($US*)**	**Price range ($US*)**
Test cost for all maternal screening (HBsAg)	4.07 (17)	
Test cost for maternal screening after HBsAg positive (HBeAg)	9.39 (17)	
Test cost for infant screening: HBsAg and anti-HBs	9.70 (17)	
Cost per month of TDF	11.27 (18)	+ 50% (11.27 to 16.90)
Duration 4 months (until 4-week postpartum)	45.07	
Cost per dose of HBIG	46.95 (18)	+ 100% (46.95 to 93.90)
Cost per course of HBV vaccination series	19.82 (17)	

*1 $US=31.9 THB average exchange rate in 2021.[21]
HBeAg, hepatitis B e-antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

mothers, was compared with the following TDF-based interventions: intervention A – TDF to eligible mothers plus HBIG for all HBV-exposed infants ('HBIG for all'); intervention B – TDF to eligible mothers plus HBIG for only infants of HBeAg-positive mothers only ('HBIG for e-positive') and intervention C – TDF to eligible mothers without HBIG to infants ('HBIG-free'). All activities in comparison with different interventions were described in online supplemental table S1. The main outcome measure was cost-effectiveness – the number of cases of chronic HBV infection averted per cost unit by the given intervention.

We used MTCT rates from in-study outcomes and previously published data for comparable settings to support the input values for MTCT rates (table 1). Prevalence of HBsAg among pregnant women was determined based on the analysis of the national health data centre (HDC) database. Information on HBsAg test results, maternal year of birth, year of ANC, health region and province were obtained for pregnant women who underwent antenatal screening for hepatitis B from 1 January 2017 to 31 December 2021, and the percent of HBsAg-positive women was calculated.

The method to analyse the cost-effectiveness analyses was adapted from a previously published study in Thailand.[15] For each of the strategies, the total direct costs of the strategies, including cost of testing,[16] drugs[17] and vaccine[16] using payer perspective as well as the expected perinatal HBV infections, were calculated and plotted on a cost-effectiveness plane. After ordering the three strategies from the least to the most expensive, any strategy that averted fewer perinatal infections than the previous less expensive strategy was considered dominant and thus removed. For the non-dominated strategies, the incremental cost-effectiveness ratio (ICER) was calculated using the following formula:

$$\text{ICER} = \frac{(\text{Cost}_{\text{intervention X}} - \text{Cost}_{\text{intervention 0}})}{(\text{Effect}_{\text{intervention X}} - \text{Effect}_{\text{intervention 0}})}$$

where Cost is the cost of intervention and Effect is the infections averted for two strategies. Options with extended dominance were removed from the analysis. We compared the cost per infection averted. The cost per infection averted results were compared against Thailand's cost-effectiveness threshold that explicitly defined since 2013 that they are willing to pay 160 000 THB per quality-adjusted life year (QALY).[18] QALY gained for chronic HBV infection in Thailand was 13.6 life-years from previous publication, calculated by modelling of direct (medical and non-medical) and indirect costs in Thailand of patients aged 30 years old who would be giving standard chronic hepatitis B treatment that could have 13.6 QALYs gained.[19] We selected the best two cost-effective interventions to test for impact of each of the stated parameters on ICER. First, we conducted one-way sensitivity analyses on three parameters that had effect on the base case ICER including prevalence of HBeAg, price of HBIG and price of TDF. Second, to ensure that the best intervention was certain with a range of transmission rates that still considered that it was exactly the best, we adjusted the perinatal infection rate of the best intervention until the point of change was reached, which means cost-effectiveness of another intervention became equal to the best intervention ($/infections averted B = $/infections averted C). In addition, we also vary the transmission rate of baseline intervention (5.7%[7]) to lower limit (2.0%[20]) and upper limit (9.3%[7]) to define the interval.

Budget impact analysis

Budget impact analysis comparing different treatment strategies was calculated based on the following scenarios: payer perspective, time horizon of 5 years, close cohort and no changing of costs. Data used for estimating the budget impact were annual direct medical costs from reference values in table 1. Total budget of each intervention for 5 years was calculated and presented in a percentage of change compared with standard intervention (budget change). The ranges of budget change were calculated by varying four related values, including prevalence of HBsAg-positive mothers, prevalence of HBeAg-positive mothers, cost of HBIG and cost of TDF.

Unit costs were taken from the 2020 financial records of the Comptroller General's Department and Thai Red Cross Society and included costs for diagnostic tests, vaccination and HBIG. Costs used to fill in the decision tree model were converted from Thai baht into US$ using the midyear exchange rate for 2021 (1 US$=31.9 Thai baht).[21]

STATA V.14.0 was used to analyse the data. Decision tree model, sensitivity analysis and budget impact analysis were analysed by Microsoft Excel. Descriptive statistics included percentage, ratio and median with range (min, max or Q1, Q3) or mean with SD were used to describe characteristics and prevalence of HBsAg.

Patient and public involvement

Our study conducted a secondary data analysis using existing public data; therefore, we used a traditional research approach without explicit patient and public involvement. All mother and infant pairs were not involved in setting the research question, the research process, the outcome measures or the implementation of the intervention.

RESULTS

Analysis of MTCT rates

The study enrolled 223 mother and infant pairs (online supplemental table S2). None of them were excluded (online supplemental figure S1). For mothers, mean age was 29.34±5.73 years old; 84.12% had ALT less than 40 U/L, 214 (96.0%) used HBeAg to assess eligibility for antiviral prophylaxis and 202 (93.95%) received TDF 300 mg daily for more than 4 weeks. Infants had median weight 3060 (Q1, Q3=2820, 3300) g, 210 (94.17%) were term, 212 (95.07%) received HBIG at birth, 222 (99.55%)

completed HBV vaccine series and 125 (56.05%) had infant screening performed by 18 months of age (69.5% had previous infant screening results).

Out of the 223 infants enrolled in the study, 212 (95.0%) had received HBIG and 11 (5.0%) had not. Infant outcomes are presented in online supplemental figure S1. None (0%, 95% CI 0 to 1.69) of the infants in the study (with or without receipt of HBIG) had chronic HBV infection. However, 6 (12.29%, 95% CI 6.72 to 27.84) infants were anti-HBc positive and, thus, had evidence of HBV infection. Postvaccination, anti-HBs antibodies were present in 167 (84.8%) and were undetectable in 30 (15.23%, 95% CI 10.88 to 20.91) infants (defined as primary vaccine failure). Children with primary vaccine failure did not differ from those with anti-HBs antibodies in terms of demographic parameters, delivery methods or interventions.

HBV carriage among pregnant women

Cost-effectiveness analyses

The input parameters for values used in the model are given in table 1. The data set used for estimating HbsAg prevalence contained records on average, for 255 897 women annually, which is approximately 41% of the birth cohort of Thailand from the National Statistical Office.[22] Overall, 97.07% of women were screened for hepatitis B screening during ANC. To avoid reporting bias, we limited this analysis to provinces where <15% of HBsAg test results were missing, resulting in the average HBsAg prevalence of 1.72% during the assessed 5-year period among pregnant women. Of note, stratification of pregnant women by year of birth before and after hepatitis B vaccine introduction into the expanded programme on immunisation (EPI) in Thailand in 1992 revealed the decline in HBsAg prevalence from 2.95%–3.31% among women born in 1978–1992 to 1.72% among those born in 2003–2008. The decline in HBsAg prevalence by years of ANC screening was from 2.32% to 1.47%, which we used as a range in the calculation (online supplemental figure S2).

Since the MTCT rate in the study was 0%, applying this strategy to the cohort size and values in table 1, the estimated 623 799 pregnant women who enter antenatal care each year in Thailand, all TDF-based interventions resulted in equal 210 cases averted by them, but there were differences in incremental costs resulting in differences in ICER between interventions (table 2). Although equally ICER within intervention, we also found that cost-saving was greater with higher HBsAg prevalence.

There were two cost-saving scenarios, that is, the most cost-saving intervention was intervention C – 'HBIG free' with the least expensive saving US$337 387 and saving 210 more chronic HBV infections, followed by intervention B – 'HBIG for e-positive' with saving the same amount of chronic HBV cases and saving US$164 100. Although equally effective in case averted, intervention A – 'HBIG for all' had the highest cost among all interventions, needed to pay more than the baseline intervention and not being cost-effective when comparing the ICER to standard Thailand's threshold (figure 2).

Overall, interventions B and C were determined to be cost-effective interventions and were included in a sensitivity analysis. The one-way sensitivity analysis demonstrated that the results were reasonably robust to changes in single parameter values with no values pushing the ICER in intervention C and changing the cost-effectiveness ordering. One extreme condition where the highest prevalence of HBeAg-positive mothers, the highest cost of TDF and the lowest cost of HBIG was only a condition that made intervention B not cost-saving (online supplemental table S3).

When adjusting the perinatal transmission rate of intervention C until equally cost-effective as intervention B, the point of change was at 1.4%. We varied the range of transmission rate of baseline intervention between 2.0 to 9.3;

Table 2 Comparison of cost-effectiveness of TDF-based interventions, HBsAg prevalence 1.72 (1.47–2.32)%

Intervention	Cost (US$)	Incremental cost (US$)	Infections (person)	Infections averted (person)	ICER
0 No TDF	794 704	base	210 (180 to 284)*	base	base
A TDF (HBIG for all)	961 060	166 356 (142 176 to 224 387)*	0	210 (180 to 284)*	790.7
B TDF (HBIG for e-positive)	630 605	–164 100 (–221 343 to –140 247)*	0	210 (180 to 284)*	Cost-saving
C TDF (HBIG-free)	457 317	–337 387 (–455 079 to –288 347)*	0	210 (180 to 284)*	Cost-saving

*HBsAg prevalence range: 1.47%–2.32%.
HBIG, hepatitis B immune globulin; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B virus surface antigen; ICER, incremental cost-effectiveness ratio; TDF, tenofovir disoproxil fumarate.

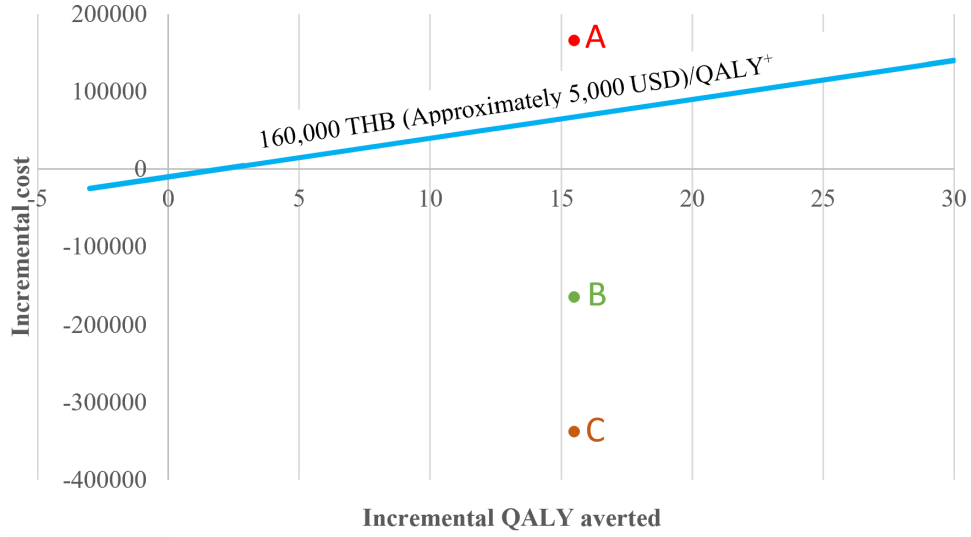

Figure 2 ICER of three TDF-based interventions comparing to Thailand's willingness to pay threshold (160 000 THB per QALY). +Cost-effectiveness threshold in Thailand is 160 000 THB per QALY,[18] and QALY of chronic HBV infection was 13.6 years.[19] ICER, incremental cost-effectiveness ratio; TDF, tenofovir disoproxil fumarate.

the range of intersects was 0.3–2.5 (figure 3). The MTCT transmission rate of 'HBIG free' was equal to 'HBIG for e-positive' at 1.4% MTCT rate, resulting in the negotiable range between 0% and 1.4%, which meets the additional target of <2% MTCT rate for eliminations.

Budget impact analyses

We calculated budget impact analyses from a payer perspective to adopt the different alternative TDF-based interventions to the package for pregnant women. The total cost for screening tests, drugs and treatment for PMTCT of HBV by different interventions for the next 5 years was projected, assuming that 623 799 pregnant women are receiving antenatal care. It was found that budget effect of adopting 'HBIG-free' and 'HBIG for e-positive' TDF-based interventions affected budget change less than spending on standard intervention for 2.83 (1.51, 8.98)% and 1.72 (0.33, 6.64)%, respectively (online supplemental table S4).

DISCUSSION

Three decades of successful HBV vaccination through EPI programme with high coverage in combination with antenatal HBV screening in Thailand resulted in verification of the achievement of the South East Asia regional hepatitis B control goal by the country in 2019.[23] There has been a significant decline in HBsAg prevalence in general population[4] and among pregnant women born after vaccine introduction. However, additional efforts are needed to achieve the elimination of mother-to-child transmission (EMTCT).

This study demonstrated that pilot intervention of using TDF to prevent MTCT of HBV in Thailand has been successful. We found zero chronic HBV infections (upper limit of CI, 1.69%) in infants born to HBeAg-positive mothers after maternal TDF prophylaxis and full course of HBV vaccination. The HBIG-free intervention with TDF prophylaxis was the most cost-effective option

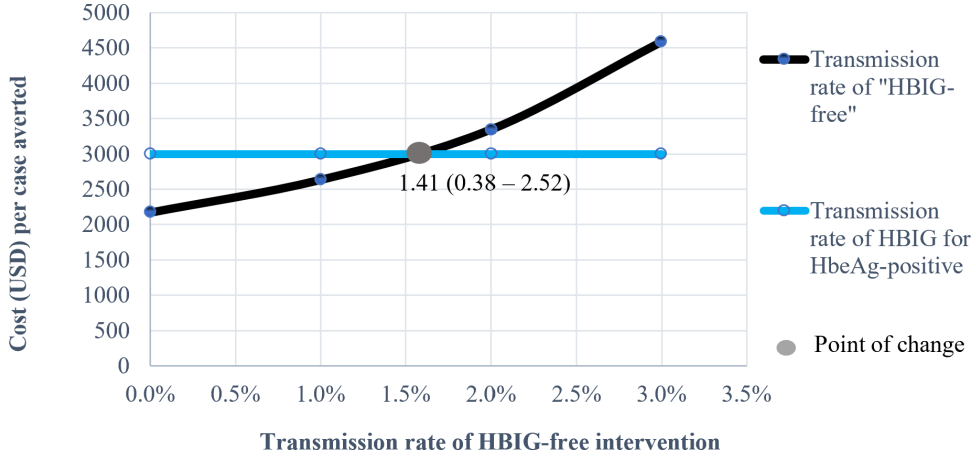

Figure 3 Comparing transmission rates of best two interventions (HBIG-free intervention, HBIG for e-positive) by adjusting transmission rate of the best intervention (HBIG-free intervention). HBeAg, hepatitis B virus e antigen; HBIG, hepatitis B immunoglobulin.

among three TDF-based interventions assessed. We could not reliably assess MTCT rate of the HBIG-free option due to the small sample size of infants who did not receive HBIG resulting in wide 95% CIs of estimate. However, in Cambodia,[12] a comparable country where the HBIG-free approach with TDF treatment has been adopted as the national policy, MTCT rate has been zero in mothers who taking TDF for at least 4 weeks with upper limit of the estimate still <2% of WHO target (1.61%). Additionally, economic evaluation demonstrated that if perinatal transmission rate with HBIG-free intervention would remain within the negotiable range, it would still be the best option from the cost-effectiveness standpoint.

In addition to cost consideration, implementing the HBIG-free approach addresses current challenges with HBIG administration in Thailand related to difficulties of stock management and limited awareness among clinicians and pregnant women, leading to low demand.[4] After the vast shift of Thailand's HBsAg incidence that became increasingly rare, HBIG was rarely used in local healthcare facilities. New investment in HBIG storage infrastructure and cold chain systems in resource-limited areas could be challenging in affordability, budget impact and the feasibility of implementation.[4] Previous cost-effective studies also supported that with the presence of low coverage of HBIG, their full benefits may not be attained. The idea of an intervention excluding HBIG, thus, becomes attractive.[24] Another study from Taiwan suggests that the choice of the optimal strategy depends on the prevalence of HBV and the willingness-to-pay threshold of countries. In high-income countries with adequate financial resources and medical capacity, a strategy combining universal vaccination plus maternal HBsAg screening and HBIG administration to infants born to positive HBsAg mothers is likely cost-effective. On the contrary, in low-income and middle-income countries (LMICs), a more accessible and affordable strategy without HBIG would be preferred.[4] Therefore, further studies should explore HBIG-free intervention as a potentially optimal intervention even though Thailand has recently invested in the facilities, transport and cold chain systems to make HBIG accessible to all.

In rare cases, perinatal transmission could still occur even with preventive interventions due to occult HBV infection in mothers, non-adherence to TDF treatment regimen or delays in administration of the birth dose vaccine or HBIG.[25] Transmission from occult infection was seen in 5% of infants in Taiwan.[26] Nevertheless, none of these infants had sustained viremia or positive HBsAg after completing the HBV vaccine series. In this study, 12.29% (95% CI 3.25 to 25.52) of infants had isolated anti-HBc positivity and, therefore, might have serological evidence of HBV infection. However, none of them were HBsAg positive, suggesting that the interventions they had received protected these infants from developing chronic HBV infection.

Because of the higher risk of infection in certain situations, HBIG administration to exposed newborns will still be needed in specific groups and depending on the obstetrician's and paediatrician's decisions. We recommend HBIG to infants as soon as possible after birth for the following groups with significantly increased risk of transmission: newborns with preterm birth, premature rupture of membrane or low birth weight (<2000 g) regardless of HBeAg status of mothers; newborns with any conditions associated with mixing of maternal and fetal blood during delivery; newborns with meconium aspiration syndrome; and poor adherence to TDF regime by mother.[10 27]

The study demonstrated that TDF-based interventions could be a promising approach to achieving the HBV MTCT elimination goal and proposed the HBIG-free option for adoption. The national implementation of TDF treatment for eligible pregnant women is planned for 2023. However, challenges observed during our visits to pilot provinces will need to be addressed before the programme can be fully rolled out. These include no HBeAg testing before prescriptions, delayed TDF initiation and no follow-up infants for HBV screening. Nationwide adoption of the proposed intervention would require political decisions, adequate resources, communication campaign to increase awareness and generate demand among healthcare providers and pregnant women, ensuring all components of the intervention are included in the UHC benefits package. HBIG should be included in the package as a benefit for infants with an increased risk of HBV transmission due to specific indications.

Higher prevalence in the older age groups seen among pregnant women in this analysis and in the nationwide serosurvey conducted in 2014[3] underscores substantial burden of chronic HBV infections in Thailand in population born before vaccine introduction. To ensure appropriate follow-up and timely care and treatment of persons living with chronic HBV infection, early identification of chronic HBV carrier status is needed. Implementation of the population screening hepatitis B would be a useful and cost-effective strategy to prevent wide-ranging complications of hepatitis B affecting the quality of life.[28]

This study had several limitations. First, there was a potential selection bias because we tended to collect data from participants who had completed lab results, but there were some children lost to follow-up who could not retake blood exams. Second, we could not verify drug adherence and relied on data from regular ANC visits and prescriptions filled in, which could have resulted in misclassification bias. To address this issue, we randomly verified adherence with some pregnant women and found that all of them had good adherence for taking the drug. Third, missing data in the HDC database could have resulted in uncertainty about the prevalence of HBsAg-positive mothers. This limitation was addressed by limiting the analysis of HBsAg prevalence among pregnant women to provinces with lower proportion of missing data. Fourth, the national database had no record of HBeAg-testing results; we used prevalence from a recent previous study in Thailand instead. Fifth, due to the limited study period, we could not re-evaluate the anti-HBs

antibodies after repeat vaccination of anti-HBs-negative infants and defined 'primary vaccine failure' based on the initial PVST results. Sixth, economic evaluations were focused only on payer perspective and did not consider societal costs. Lastly, the study included only healthy term infants born to mothers who adequately had taken TDF during their pregnancy, limiting its generalisability. For more generalisable results, further studies including preterm and other any high-risk infants would be helpful.

Despite these limitations, this report is the first cost-effectiveness analyses and budget impact analyses that provides evidence supporting HBIG-free strategy in the era of highly effective antivirals such as TDF. It is time to recognise that the current immunoprophylaxis regimen for HBV-exposed infants might not be the only approach for interrupting MTCT. These study results also provided insight into the range of interventions aimed at achieving the EMTCT of HBV, demonstrated the effectiveness of TDF-based programme for the prevention of MTCT and identified the most cost-effective approach to achieving the elimination goal in Thailand. The HBIG-free approach could also be applicable to other LMICs, particularly to countries with high HBsAg prevalence, such as African countries[25 29] based on the greater cost-effectiveness of HBIG-free intervention with higher HBsAg prevalence among mothers. Furthermore, several Southeast Asian countries that have not yet fully implemented HBIG, such as Myanmar and Thailand's deep south provinces, may be prioritised for TDF implementation.[23] Thus, to accelerate EMTCT globally, promoting the use of peripartum prophylaxis with antivirals in primary health centres is necessary, especially among LMICs with low coverage of HBIG.

CONCLUSION

We found zero chronic HBV infections in infants born to HBeAg-positive mothers after maternal TDF prophylaxis and a full course of HBV vaccination. The study is the first cost-effectiveness analyses to provide evidence supporting HBIG-free strategy with TDF prophylaxis in the era of antivirals. This approach should be considered for prevention of MTCT in resource-constrained settings, particularly in countries with high HBsAg prevalence.

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