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**Cost-effectiveness analysis of antiviral treatment for pregnant women with high viral load to prevent hepatitis B virus vertical transmission**

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**ABSTRACT**

**Introduction:** Vertical transmission of hepatitis B virus (HBV) is higher in infants born to pregnant women with higher HBV DNA viral load despite infants completing both active and passive vaccination. Although antiviral treatment is recommended to pregnant women during the antenatal period to reduce the vertical transmission rate, most of them decline.

**Methods:** A decision tree was made to evaluate the costs and benefits involved when pregnant women agree to take antiviral treatment during the antenatal period as well as when they decline. The cost-effectiveness price was arrived at by multiplying the reduced vertical transmission rate with expenses of future medical care associated with vertical transmission.

**Results:** Given the observed medication price and transmission rate in Singapore, from an individual's perspective, it was not cost-effective to receive antenatal antiviral treatment. However, from the health system's perspective, the current price of antiviral treatment was already far below the cost-effectiveness level, even without Ministry of Health subsidies. Additionally, pregnant women's awareness and perception also made an impact on treatment decisions.

**Conclusion:** By analysing the decision-making process, our result explained the current low uptake rates of antenatal antiviral treatment for HBV among pregnant women. We also concluded that from the health system's perspective, it was worth providing subsidy for perinatal antiviral treatment to prevent huge expenses generated in the future by chronic HBV complications.

*Keywords: antiviral treatment, cost benefit, immunoprophylaxis, vaccination failure, vertical transmission*

## INTRODUCTION

Hepatitis B virus (HBV) infection, as a global health problem, is more likely to occur during infancy and early childhood in developing countries with high prevalence. Mother-to-child transmission (MTCT) usually accounts for almost half of all transmission routes for chronic HBV infections.<sup>(1)</sup>

The World Health Organization (WHO) recommends screening for hepatitis B surface antigen (HBsAg) for all pregnant women and the administration of a birth dose of hepatitis B vaccine. The Centers for Disease Control and Prevention (US) recommends an additional dose of passive vaccination with hepatitis B immune globulin (HBIG) for infants born to HBsAg-positive pregnant women. Subsequently, the infants also receive two or three doses of hepatitis B vaccination in the following six months. However, despite the relatively excellent efficacy of HBIG and HBV vaccination, immunoprophylaxis failure does occur in some cases.<sup>(1)</sup> In Thailand, the risk of MTCT of HBV has been estimated to be 12% for pregnant women with high hepatitis B viral load.<sup>(2)</sup> In Australia, transmission rates are 7% from hepatitis B envelope antigen (HBeAg)-positive pregnant women and 9% from pregnant women with very high HBV DNA levels (> 8 log copies/mL).<sup>(3)</sup> In Taiwan and Korea, the immunoprophylaxis failure rate varies from 1% to 11.8%.<sup>(4)</sup>

From 2011 to 2012, the Health Sciences Authority (HSA) of Singapore has reported at least 21 cases of immunoprophylaxis failure. These infants were born to HBV-carrier pregnant women despite receiving one dose of HBIG at birth and completing the full course of HBV vaccine.<sup>(5)</sup> More recently, local data from our group observed the failure rate of 6.0% and 3.0% in the high and low viral load categories, respectively.<sup>(6)</sup>

A few randomised controlled trials have established that it is safe and effective to offer antiviral therapy, such as lamivudine, tenofovir and telbivudine, to pregnant women with a high viral load in the third trimester.<sup>(7-9)</sup> The short-course treatment consistently reduces

maternal viraemia and vertical transmission to infants. Before 2012, HBV antiviral treatment during the antenatal period was not widely recommended. However, recent guidelines from the European Association for the Study of the Liver<sup>(10)</sup> and American Association for the Study of Liver Diseases<sup>(11)</sup> have advocated treating pregnant women with HBV DNA > 200,000 IU/mL in order to reduce the rates of MTCT. However, the cost-effectiveness of such treatments to prevent MTCT has not been addressed in Singapore. In the last five years, it was estimated that less than 15% of pregnant women with high viral load (> 200,000 IU/mL) agreed to the treatment in Singapore.<sup>(12)</sup> By analysing the decision-making process among carrier pregnant women, we aimed to determine, from personal and health system perspectives, if it was worth taking up antenatal antiviral treatment. These findings may also provide guidance for healthcare subsidies that may be provided to determine the consumer price of antiviral drugs.

## METHODS

A decision tree<sup>(13)</sup> was constructed to help better understand and analyse pregnant women's considerations on taking the antiviral treatment for HBV. We assumed that there was no adverse pharmacological effect on the mother and fetus, and all infants received the recommended HBIG as well as three doses of HBV vaccine after birth. Once the child was found to be an HBV carrier, the mother would be responsible for any cost incurred due to the infection.

As illustrated in Fig. 1, Option A described the scenario where HBsAg-positive pregnant women accepted the antiviral treatment during the third trimester. Those pregnant women with high viral load spent  $C_m$  SGD to take the antiviral therapy during the third trimester period, with a probability of  $P_{a1}$  that infants may not be infected by HBV.<sup>(7)</sup> The probability of vertical transmission was  $P_{a2}$ . In Option B, pregnant women did not mind taking the risk of uncertainty and refused to take antiviral therapy during the third trimester. Without

any antiviral treatment, a percentage of  $P_{b1}$  in children born to pregnant women with high HBV viral load may not be vertically infected, whereas a percentage of  $P_{b2}$  of them may be. The medical care expenses for chronic HBV infection and its complications was X SGD.  $C_m$  was taken as the cost-effectiveness price, and hence any cost below or equal to  $C_m$  was considered as the cost-effectiveness price for the individual.

We evaluated the costs and benefits of these two options. We assumed that pregnant women accepted antiviral treatment only when the cost of Option A was lower than that of Option B. The generalised formula to arrive at the cost of antiviral treatment was:

$$C_m = (P_{a2} - P_{b2}) X \quad (1)$$

where in formula 1, the decision to take treatment or not was made based on two factors. Factor 1 was how the probability of MTCT could be reduced by taking treatment (i.e.  $P_{a2} - P_{b2}$ ). If the drug could effectively reduce the risk of vertical transmission, it was obviously worth taking the treatment; conversely, if taking the drug only brought about minor improvement, the treatment might not be necessary. Factor 2 was the cost of regular care, or X SGD, for the child as an HBV carrier. If MTCT were to generate huge financial burden for the woman, she would likely be more willing to invest additional money to prevent it from occurring.

When the cost of Option A was equal to that of Option B, the two options were likely indifferent. On the other hand, should the cost of Option A be lower than that of Option B, Option A would be the better choice.

## RESULTS

The antiviral medications approved for HBV treatment included lamivudine, entecavir, telbivudine and tenofovir. Table I presents the current costs of antiviral treatment in SGD (1

SGD = 0.74 USD). The recommended treatment period was from Week 32 of pregnancy in the last trimester to Week 4 postpartum.

**Table I. FDA-approved treatments for chronic hepatitis B virus and cost of proposed treatment.**

Antiviral medicine	Total drug cost for treatment	Daily cost	MOH subsidy policy	Daily cost after subsidies
Lamivudine	447.72	5.33	SDL2	2.67
Entecavir	866.88	10.31	MAF	*
Telbivudine	350.28	4.17	NA	—
Tenofovir	961.80	11.45	MAF	*

*Note: all costs are in SGD exclusive of 7% goods and services tax.*

*Source: Department of Pharmacy, National University Hospital, Singapore. \*Subsidies were only applied to subsidised patients and the amount was subject to medical social worker assessment. FDA: US Food and Drug Administration; MAF: Medication Assistance Fund; MOH: Ministry of Health, Singapore; NA: not available; SDL: standard drug list*

According to a previous study from Singapore,<sup>(6)</sup> for HBV-carrier pregnant women with high viral load, the immunoprophylaxis success rate ( $P_{b1}$ ) was approximately 96.8% without treatment, which was further enhanced to 99.9% ( $P_{a1}$ ) following treatment. In other words, pregnant women decided whether it was worth spending a minimum of SGD 350.28 on telbivudine to reduce their child's HBV infection rate by 3.1%.

From the pregnant woman's perspective, should the infant be found to be a carrier, she would be responsible for providing it regular care up to the age of 21 years. Since the likelihood of hepatitis B treatment in the paediatric age group was negligible, the expense of regular care included annual liver function test and other laboratory tests, such as HBeAg, HBsAg and HBV DNA. The expense, X, was estimated as SGD 7,097 in total (Table II), excluding possible subsequent price increases for tests and evaluations.

**Table II. Price of regular medical care for hepatitis B virus-carrier infants up to age 21 years.**

Annual test	Duration	Cost per item (SGD)
Full blood count	Year 1	24
Liver function test	Year 1–5	52
Hepatitis Be antigen	Year 1–5	42
Hepatitis B surface antigen	Year 1	21
Hepatitis B core antibody	Year 1	42
HBV DNA	At least every five years	110
Alpha-fetoprotein	Year 6–21	28
Liver ultrasonography	Year 6–21	180
Consultation	Year 1–21	100

Source: Department of Laboratory Medicine, National University Hospital, Singapore.

According to formula 1,  $C_m$  was SGD 220.00. Thus, from an individual pregnant woman's perspective, the treatment would be cost-effective only when the price was not higher than SGD 220.00 (or SGD 2.62 per day during a 12-week treatment period). In Singapore, the lowest treatment cost was for telbivudine (SGD 350.28), which was actually more than the expenses incurred otherwise. In conclusion, treatment was likely not attractive from the pregnant woman's perspective.

However, from a national perspective, the potential future healthcare costs were huge. HBV, as a chronic disease, remains mostly asymptomatic during the early childhood stage. But the risk of HBV-associated liver disease increases as the child reaches adulthood, as does the potential financial burden. The costs of consequent hepatocellular carcinoma treatment and liver transplantation represent the largest burdens to family and society. Thus, in a child's lifetime, the actual regular care expense ( $X'$ ) would be much higher than an individual's  $X$  (year 1–21).

A previous study involving 157 patients with HBV attempted to estimate the average annual treatment cost for different categories of patients in Singapore over five years from the year 2002.<sup>(14)</sup> We used data from previous study with calculations including the probability of each of the potential complications, as well as 5 years of the screening tests required to estimate the average annual treatment cost of different patient categories (Table III). The average

expected five-year expense in adulthood was SGD 52,803.53 while the expected lifelong expense was at least SGD 76,408.33. This was based on a Singapore life expectancy of 83.1 years (Yearbook of Statistics Singapore 2018.)<sup>(15)</sup>, and lifelong expenses were inclusive of screening costs during childhood (SGD 6,095) before age 21 years, a five-year treatment expense of SGD 52,803.53 and annual screening cost of SGD 308 for the rest of life, including alpha-fetoprotein, liver ultrasonography and consultation.

**Table III. Estimated average annual treatment cost of different patient categories.**<sup>(14)</sup>

Category	No. of patients (n = 157)	Probability (%)	Average annual treatment cost (SGD)
Chronic hepatitis B virus	116	73.9	718.15
Stable cirrhosis	13	8.3	1,194.79
Decompensated cirrhosis	5	3.2	13,162.55
Hepatocellular carcinoma	3	1.9	6,628.97
Liver transplant	20	12.7	73,673.10

Plugging into formula 1, the cost-effectiveness price of antiviral treatment during the perinatal period was SGD 28.20 per day. Extrapolating these expenses to the future, all current drugs listed earlier cost much lower, and thus it was worth taking the antiviral treatment in the long run. However, from the individual pregnant woman's perspective, which may only evaluate the pros and cons of treatment during the first 21 years of her child's life, might not capture possible lifetime adverse consequences or their impact as a public health problem. It thus potentially leaves the economic burden to be borne by the national healthcare system.

## DISCUSSION

In September 2017, the Ministry of Health, Singapore published the latest standard drug list to improve the affordability of medications. With lamivudine being added to the standard drug list,<sup>(16)</sup> subsidised patients would enjoy a 50% subsidy for taking it. Accordingly, medication

cost would reduce to SGD 2.67 per day, which was close to the pregnant women's cost-effectiveness price of SGD 2.62.

With this medication subsidy, drug price was likely to become acceptable to pregnant women and they may agree to take antiviral treatment. From the perspective of the healthcare system, an investment of SGD 2.67 per day on antiviral treatment during a 12-week period (or a total of SGD 224.28 per person) would likely reduce the rate of perinatal transmission of HBV by 3.1%. While the consequent reduction in vertical transmission rates appears small, the measure would prevent huge expenses that would have to be otherwise incurred by the healthcare system due to chronic HBV infection and associated complications in the future by way of attracting more pregnant women to accept antenatal antiviral treatment.

More recently, entecavir and tenofovir have been added to Medication Assistance Fund drugs in Singapore. Patients may also receive subsidies for these two drugs, although the amount varies individually and is subject to means testing by medical social workers.<sup>(16)</sup>

In a situation where the pregnant women's subjective cognition ( $\rho$ ) influences personal decision, formula 1 could be reformulated to:

$$C_m = (P_{a1} - P_{b1}) \rho X \quad (2)$$

Pregnant women with better understanding or those more concerned about the risk of MTCT may be more sensitive to treatment prices during the antenatal period. For instance, in China, many schools, universities and companies require health check-ups for HBV chronic carriage.<sup>(17)</sup> In such a scenario,  $\rho > 1$  and  $C_m$  would be higher. Contrastingly, other pregnant women may be reluctant to receive treatment, as they are unaware of the long-term health consequences of HBV and its impact on their children's education and future employment opportunities. In such a scenario,  $\rho < 1$  and only if  $C_m$  was very low would the treatment be attractive to them. In conclusion, our analysis suggests that, from the pregnant woman's

perspective, antenatal antiviral therapy to reduce MTCT was not cost-effective unless healthcare subsidies apply.

In general, the reasons for pregnant women not choosing antenatal antiviral treatment may include: (a) treatment cost ( $C_m$ ) being too expensive; (b) the difference between the probabilities of MTCT with and without treatment ( $P_{a2} - P_{b2}$ ) being low; and/or (c) regular care expenses ( $X$ ) being affordable.

With the high vaccine efficacy and low immunoprophylaxis failure rate involved, antiviral treatment was unattractive as the reduction in the probability of MTCT due to added antenatal treatment was not significant. Pregnant women may be more inclined to take it up should the antiviral treatment cost become less than SGD 2.62 per day. This is probably a partial explanation for the current low uptake rate seen in antenatal antiviral treatment for HBV.

Reducing the price of drugs and providing more healthcare subsidies could potentially increase the maternal uptake of such treatment, thus helping to reduce the vertical transmission of HBV. While the new subsidy policy has been implemented from September 2017 and will apply to lamivudine, entecavir and tenofovir, its effects on maternal uptake of antenatal antiviral treatment remain to be seen.

Our study had weaknesses. First, we only reported vertical transmission rates of MTCT for children born at the National University Hospital, Singapore, and therefore nationwide MTCT rates may have been higher. Second, expenses that would be incurred due to chronic HBV infection by MTCT transmission may have been underestimated in our study as other ancillary costs involved, such as patient transportation costs to and from medical facilities, time taken off work, drug price inflation in the long term and emotional costs due to anxiety and stress, were not taken into account.

To conclude, in the present scenario, antenatal treatment to prevent HBV vertical transmission is as yet unattractive for pregnant women with high viral load, as the consequent

reduction in MTCT rates appears small. However, the associated long-term expenses for the healthcare system and the impact of chronic HBV on the family and society at large are considerable. Given that pregnant women may be more inclined to take up antenatal antiviral treatment for HBV if treatment becomes more affordable, studies that provide further guidance on healthcare subsidies that may be provided to determine the consumer price of antiviral treatment drugs would be helpful. A comprehensive survey of the concerns and perceptions of HBV-carrier pregnant women is also warranted to better understand and manage the various factors at play during the decision-making process.

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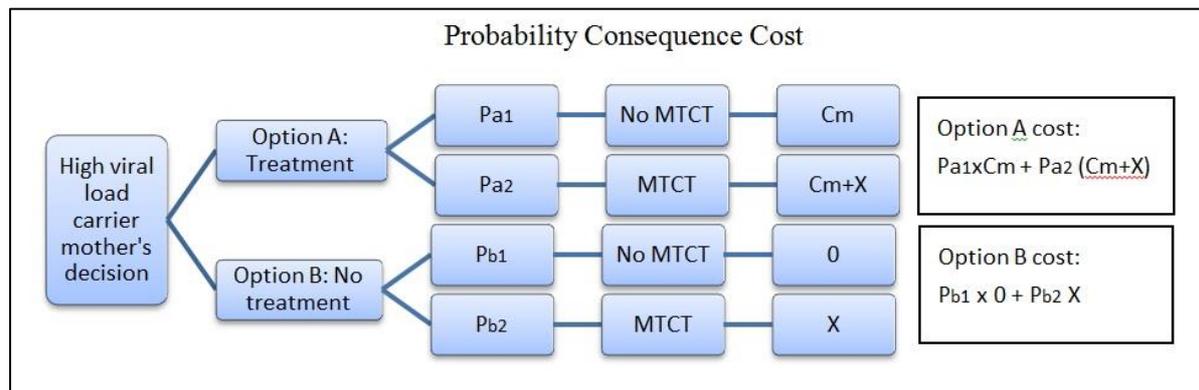
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## FIGURE



**Fig. 1** Flowchart shows the decision tree for pregnant women who are high viral load carriers in Singapore.  $C_m$ : treatment cost (in SGD) for pregnant women to take antiviral therapy during their third trimester; HBV: hepatitis B virus; MTCT: mother-to-child transmission;  $P_{a1}$ : immunoprophylaxis success rate for pregnant women who take antenatal antiviral treatment, or probability that infant may not be infected by HBV;  $P_{a2}$ : probability of vertical transmission for pregnant women who take antenatal antiviral treatment;  $P_{b1}$ : immunoprophylaxis success rate for pregnant women who do not take antenatal antiviral treatment, or probability that infant may not be infected by HBV;  $P_{b2}$ : probability of vertical transmission for pregnant women who do not take antenatal antiviral treatment;  $X$ : medical care expenses (in SGD) for chronic HBV infection and related complications