Impact and cost-effectiveness of hepatitis B virus prophylaxis in pregnancy: a dynamic simulation modelling study

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Summary

Background In 2020, WHO recommended the addition of peripartum antiviral prophylaxis (PAP) to hepatitis B birth dose vaccination (HepB-BD) and hepatitis B infant vaccination (HepB3) to reduce mother-to-child transmission of hepatitis B virus (HBV) infection in pregnant women who have a marker of high infectivity (ie, HBV DNA ≥200 000 international units per mL or HBeAg-positive). We aimed to evaluate the impact and cost-effectiveness of this recommendation and of a theoretical simplified strategy whereby PAP is given to all pregnant women who are HBsAg-positive without risk stratification.

Methods This modelling study used a dynamic simulation model of the HBV epidemic in 110 countries in all WHO regions, structured by age, sex, and country. We assessed three strategies of scaling up PAP for pregnant women: PAP for those with high viral load (PAP-VL); PAP for those who are HBeAg-positive (PAP-HBeAg); and PAP for all pregnant women who are HBsAg-positive (PAP-universal), in comparison with neonatal vaccination alone (HepB-BD). We investigated how different diagnostic and antiviral drug costs affected the cost-effectiveness of the strategies evaluated. Using a health-care provider perspective, we calculated incremental cost-effectiveness ratios in cost (US$) per disability-adjusted life-year (DALY) averted in each country's population and compared these with country-specific cost-effectiveness thresholds. We also calculated new neonatal infections averted for each of the strategies.

Findings Adding PAP-VL to HepB-BD could avert around 1·1 million (95% uncertainty interval 1·0 million–1·2 million) new neonatal infections by 2030 and around 3·2 million (95% uncertainty interval 3·0 million–3·4 million) new neonatal infections and approximately 8·8 million (7·8 million–9·7 million) DALYs by 2100 across all the countries modelled. This strategy would probably be cost-effective up to 2100 in 28 (26%) of 106 countries analysed (which included some of the countries that have the greatest HBV burden) if costs are as currently expected to be, and in 74 (70%) countries if diagnostic and monitoring costs were lowered (by about 60–75%). The relative cost-effectiveness of PAP-VL and PAP-HBeAg was finely balanced and depended on the respective diagnostic and monitoring costs. The PAP-universal strategy could be more cost-effective than either of these strategies in most countries, but the use of antiviral treatment could be five times as high than with PAP-VL.

Interpretation PAP can provide substantial health benefits, and, although the current approach might already be cost-effective in some high-burden settings, decreased diagnostic costs would probably be needed for PAP to be cost-effective in most countries. Therefore, careful consideration needs to be given about how such a strategy is implemented, and securing reduced costs for diagnostics should be a priority. The theoretical strategy of offering PAP to all women who are HBsAg-positive (eg, if diagnostic tests to identify mothers at risk of transmission are not available) could be a cost-effective alternative, depending on prevailing costs of diagnostics and antiviral therapy.

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Introduction

Hepatitis B virus (HBV) infection is a leading cause of global mortality and mother-to-child transmission of HBV is a major mode of transmission.[1] WHO's Global Health Sector Strategy on Viral Hepatitis[2] set a target for elimination of mother-to-child transmission of HBV, with the aim to reach a prevalence of less than 0·1% in children younger than 5 years by 2030. The primary recommendation to accomplish this target has been the use of a birth dose of HBV vaccine given to the neonate within 24 h of birth (HepB-BD), and a further two or three vaccine doses usually given to the infant as part of the Expanded Programme on Immunizations (HepB3).[2] The addition of immediate passive immunisation with hepatitis B immunoglobulin (HBIg) to exposed neonates can reduce the risk of mother-to-child transmission of HBV further, although HBIg is not used routinely in most settings owing to its high cost and low availability.[3] However, HepB-BD (even with HBIg) does not completely interrupt transmission if the mother has a high HBV viral load.[4]

Prophylaxis of transmission by adding antiviral therapy for the mother during pregnancy (ie, peripartum antiviral

Research in context

Evidence before this study

We searched PubMed for all English language publications from database inception to Dec 31, 2022, using the terms: ("Hepatitis B" OR "HBV") AND ("peripartum treatment" OR "PPT" or "peripartum antiretroviral prophylaxis" OR "peripartum antiviral prophylaxis" OR "PAP" OR "peripartum prophylaxis"). WHO has set a goal to reach less than 0·1% prevalence of chronic hepatitis B virus (HBV) infection in children younger than 5 years by 2030, which will require substantial efforts in reducing HBV mother-to-child transmission—now the major route of ongoing transmission. Building on the longstanding WHO recommendation of universal neonatal and infant vaccination, the first guidelines for the addition of peripartum antiviral prophylaxis (PAP) in pregnancy were released in 2020. These guidelines recommended that pregnant women who are HBV-positive and at high risk of mother-to-child transmission of HBV (defined as HBV DNA >200 000 international units per mL) are offered PAP with tenofovir disoproxil fumarate from 28 weeks of pregnancy to (at least) delivery. However, because HBV viral load testing is costly and often not available, a conditional recommendation was added that HBeAg-positivity can be used instead if viral load is not available, as HBeAg-positivity has been found to be a reasonable marker of high HBV viral loads (with a sensitivity of 88·2% and a specificity of 92·6%). The relative impact of these approaches and their cost-effectiveness were not known. Moreover, it was not known whether a presumptive approach of providing PAP to all pregnant women who are HBsAg-positive (if tests to identify mothers at risk of mother-to-child transmission of HBV are not available) would be a reasonable alternative strategy.

Added value of this study

This study quantifies the health impact and cost-effectiveness of the WHO recommendations for HBV PAP strategies in 110 low-income and middle-income countries that collectively represent 92% of people living with chronic HBV infection worldwide. We found that the PAP strategy guided by HBV viral load might be cost-effective at central cost assumptions to 2100 in only 26% of countries evaluated but, if diagnostic costs were lowered, it could be cost-effective in 70% of countries. The choice of whether a strategy guided by viral load or HBeAg would be more cost-effective would depend on the relative costs of these two diagnostic modalities in the country under consideration. A theoretical universal PAP strategy, whereby all pregnant women who are HBsAg-positive are given PAP without risk stratification, might improve cost-effectiveness but could lead to a five-times increase in the use of antiviral treatment compared with the viral load-guided PAP strategy.

Implications of all the available evidence

The addition of PAP for the prevention of mother-to-child transmission of HBV in pregnancy for those at high risk of transmission could have an important impact in averting new HBV infections and might be cost-effective in most countries if there were access to lowered diagnostic costs. Careful consideration needs to be given as to how such a strategy is implemented and how lowered costs for diagnostics are sought. Treating all pregnant women who are HBsAg-positive, without accompanying risk stratification, could also be cost-effective if the costs we have assumed for diagnostics and treatment are realised. However, the actual impact and cost of such a strategy will be driven by many factors, such as patterns of antenatal-care attendance, adherence to and uptake of tenofovir disoproxil fumarate, and features of the health-care system that will shape the health opportunity costs of providing such care, which will mean that effects and costs vary between settings and implementation research will be required for a full evaluation.

prophylaxis [PAP]) has been shown to be effective against mother-to-child transmission of HBV in women who are classified as being at high risk of transmission.[5] This approach is similar to the use of antiretroviral prophylaxis for HIV in pregnancy, which is already a well established intervention, with 81% of pregnant women who are HIV-positive receiving antiretrovirals for the prevention of mother-to-child transmission globally.[6] A systematic review[5] found that a reduction in mother-to-child transmission of HBV was associated with maternal PAP, in concert with HepB-BD and HBIg given to the neonate; for the five randomised controlled trials included in the systematic review in which tenofovir disoproxil fumarate was used as the antiviral of choice, the odds of mother-to-child transmission of HBV with PAP versus without PAP was 0·10 (95% CI 0·03–0·35).

Considering these emerging data, in 2020, WHO recommended also providing PAP (using tenofovir disoproxil fumarate) to pregnant women at the highest risk of transmission, in addition to providing the infant with HepB-BD.[7] Women at the highest risk were defined as those with HBV DNA concentrations of at least 200 000 international units (IU) per mL. However, given the high cost and inadequate availability of HBV viral load testing in many low-income and middle-income countries, WHO also recommended that HBeAg-positivity can be used instead, as this measure has been found to be a reasonable marker of high HBV viral loads (with a sensitivity of 88·2% and a specificity of 92·6%).[3]

The currently recommended approach to the prevention of mother-to-child HBV transmission requires a two-step risk-stratification strategy, whereby pregnant women are tested for HBsAg and, for those found to be HBsAg-positive, either a HBV DNA or a HBeAg test is required to determine eligibility for PAP. However, the need to provide that second diagnostic test

could be a barrier to implementation, because both of these tests are expensive and rarely available (outside of clinics that have access to high-throughput laboratories),[8] and currently there are no rapid diagnostic tests for HBV DNA or HBeAg that work sufficiently well.[9,10] An alternative, simplified model of care would be for PAP to be offered to all pregnant women who test HBsAg-positive (irrespective of HBV DNA concentration or HBeAg status).[8,11] This approach would overcome the need for a second diagnostic test but could lead to overtreatment of a substantial proportion of pregnant women for whom HepB-BD is likely to be sufficient to prevent mother-to-child transmission. However, the acceptability, safety, effectiveness, and cost-effectiveness of such a strategy are not known.

By use of mathematical simulations, we aimed to evaluate the effect and cost-effectiveness of scaling up PAP (in addition to HepB-BD, without HBIg) according to WHO recommendations and to evaluate the difference in cost-effectiveness between a HBV DNA-guided and a HBeAg-guided strategy. This study also investigated the effect and cost-effectiveness of a hypothetical strategy to treat all pregnant women who are HBsAg-positive and aimed to identify the factors that could make such a strategy increasingly effective and cost-effective.

Methods

Model

In this modelling study, we adapted de Villiers and colleagues'[12] dynamic simulation model of the global HBV epidemic structured by age, sex, and country. 110 countries that collectively represent a large share of the burden of HBV (appendix 1 p 12) were each modelled independently by use of national demographic data on fertility, mortality, and population structure and national intervention coverage levels of infant vaccination (HepB3) and HepB-BD vaccination (appendix 1 p 3). Transmission and natural history progression rates were parameterised following reviews of the literature (appendix 1 pp 2–3). In the model, transmission occurred from mother to child, from child to child, and across the whole population, and the relative strength of each mode of transmission was inferred through a calibration procedure that fitted the model to data on HBsAg prevalence, the proportion of women of childbearing age who were HBsAg-positive, and HBV-related deaths (appendix 1 p 8). For the regional analyses, the country models were grouped into sets that corresponded with the countries assigned to each WHO region (appendix 1 pp 9–11). The demographic data used in the model simulations were obtained from the UN 2019 World Population Prospects[13] (appendix 1 pp 3–4), and we therefore had no influence over sex ratios in the model simulations.

Scenarios modelled

We defined four main intervention strategies that added further interventions to HepB3: neonatal vaccination (HepB-BD); PAP for HBsAg-positive pregnant women with a high viral load (PAP-VL); PAP for HBsAg-positive pregnant women who are also HBeAg-positive (PAP-HBeAg); and PAP for all pregnant women who are HBsAg-positive (PAP-universal; table 1). These strategies were compared with HepB3, or with HepB3 plus HepB-BD. For the three PAP strategies, PAP was accompanied by antenatal screening. We assumed that pregnant women would be tested on only one occasion for HBsAg (notionally, on their first pregnancy) as part of routine antenatal care. This approach was reasonable because the risk of new chronic infection in adulthood is low in high-endemic settings because previous exposure is high and therefore most adults have immunity or existing chronic infection.[14] By contrast, any test for HBV DNA or HBeAg would be done at each pregnancy.

We assumed that the PAP intervention was incremental to HepB3 and HepB-BD, and was without the use of HBIg (given cost and availability issues). We note that this assumption is different to what has been evaluated in most of the existing literature on PAP efficacy, in which HBIg is also used.[5] A study from Cambodia in which PAP was given to pregnant women who were HBeAg-positive, with HepB-BD and no HBIg, showed a residual transmission risk of 1%.[15] A study in the Democratic Republic of the Congo showed no transmission from nine mothers at high risk of HBV transmission (ie, HBV viral load ≥200 000 IU/mL, HBeAg-positive, or both) who were HBsAg-positive and received tenofovir disoproxil fumarate and whose newborns received HepB-BD.[16] We therefore assumed that the risk of mother-to-child transmission when both HepB-BD and PAP are used is 1% for women at high risk of transmission.

See Online for appendix 1

Costing model and economic evaluations

When available, data for costs were taken from work by WHO on costing the elimination of hepatitis through testing and treatment (table 2).[17] The costs were taken to be the same for all world regions and were intended to represent the price available if countries were to purchase via optimal procurement rather than currently available costs. There were two main costing scenarios, one of which was our central estimate and another (based on expert opinion[17]) that represented a more optimistic set of assumptions (representing about a 60–75% reduction in the central diagnostic costs; table 2). We did analyses in which the costs of the diagnostics and treatment were varied from the value in these scenarios, across wide ranges up to high costs. All costs were normalised to the value of the US$ in 2019. As the major incremental cost for peripartum treatment is from the diagnostic and treatment process itself, and the service would be delivered through existing antenatal services, we did not include any additional human resources costs or programme costs. We also excluded any averted downstream costs from the management of HBV-related liver disease. Our

economic analyses adopted a health-care provider perspective (ie, we considered the costs born by the health-care provider and not, for instance, by the patients themselves or wider society), with a time horizon starting from the time when the change was introduced to 2100 or 2030. Incremental cost-effectiveness ratios (ICERs) were computed with respect to the next-best non-dominated strategy (ie, a strategy that has the greatest effect for a given cost), with costs and health outcomes discounted at 3% per year. When comparisons were made against a cost-effectiveness threshold, we used the country-specific values for health opportunity costs as calculated by Ochalek and colleagues.[21] Cost-effectiveness thresholds were calculated for 106 (96%) of the 110 countries, as there were insufficient data to calculate thresholds for North Korea, Somalia, Syria, and Yemen (appendix 1 p 12).

	Strategy components	HepB3 coverage (%)*	HepB-BD coverage (%)*	Diagnostic test		Criteria for eligibility for PAP
				For all pregnant women	For pregnant women who test HBsAg-positive	
HepB3	HepB3	≥90%	Status quo†	..	..	..
HepB-BD	HepB3 and HepB-BD	≥90%	≥90%	..	..	..
PAP-VL	HepB3, HepB-BD, and PAP guided by HBV viral load	≥90%	≥90%	HBsAg	HBV viral load	High viral load (>200 000 IU/mL)
PAP-HBeAg	HepB3, HepB-BD, and PAP guided by HBeAg	≥90%	≥90%	HBsAg	HBeAg	HBeAg-positive
PAP-universal	HepB3, HepB-BD, and PAP guided by HBsAg	≥90%	≥90%	HBsAg	..	HBsAg-positive

All newborns are eligible for both HepB-BD and HepB3, irrespective of maternal HBsAg status. For the PAP strategies, PAP is accompanied by antenatal screening and it is assumed in the main analysis that each pregnant woman is tested only once (on their first pregnancy) as part of routine antenatal care. HBV=hepatitis B virus. HepB-BD=hepatitis B birth-dose vaccination. HepB3=hepatitis B infant vaccination. PAP=peripartum antiviral prophylaxis. PAP-VL=PAP viral load. *Data are for all children born and coverage listed as 90% or higher indicates either 90% coverage or the coverage level already achieved in the country, whichever is higher. †HepB-BD to be maintained at the most recently recorded amount of coverage until 2100.

Table 1: **Modelled PAP strategies**

	Central cost assumptions (US$)	Optimistic cost assumptions (US$)	High cost assumptions (US$)	Cost assumptions, comments, and referenced sources
HBsAg test	$1·60	$0·40	$2·80	Costs were for HBsAg rapid point-of-care tests;[17] assumption of optimistic and high costs[18]
HBeAg test	$7·50	$3·00	$40·00	Laboratory-based HBeAg test with high diagnostic accuracy; expert opinion was based on the cost price that would be available if optimal procurement for purchasing tests was available to countries
HBV viral load test	$15·00	$5·00	$100·00	Assumption of use of GeneXpert for HBV DNA;[19] assumption of optimistic and high costs[18]
Peripartum antiviral prophylaxis: drug	$10·00	Costs kept constant*	Costs kept constant*	Assumption of use of generic tenofovir disoproxil fumarate and 4 months of antiviral drug therapy for prevention of mother-to-child transmission; annual cost of tenofovir disoproxil fumarate assumed to be $30·00[17]
Peripartum antiviral prophylaxis: monitoring	$10·00	$5·00	$40·00	Exact recommendations around monitoring of patients taking tenofovir disoproxil fumarate were not detailed in WHO guidelines; on the basis of expert consensus opinion, a cost was applied to incorporate any additional visits required (eg, for the cost to the hospital of a patient having to visit a doctor to monitor the response to treatment) or laboratory tests before or during peripartum antiviral prophylaxis
HBV birth-dose vaccination	$1·00	Costs kept constant*	Costs kept constant*	UNICEF vaccine price was $0·24–0·60 per vaccine dose; total cost per administered dose was for vaccine supplies, human resources, storage, distribution, waste management, and strategies for boosting coverage; $0·50–0·97 per dose (ten-dose vial), $1·08–1·64 per dose (single-dose vial);[20] taken together, a cost of $1·00 was assumed
HBV infant vaccination	$1·00	Costs kept constant*	Costs kept constant*	UNICEF pentavalent vaccine price per dose was $0·75–1·15; costs were shared across the five diseases targeted by the pentavalent vaccine, but costs were per dose

The main results are shown using central cost assumptions and optimistic cost assumptions (see figures 1–3). High cost assumptions were used for figures 4 and 5. HBV=hepatitis B virus. *Drug unit costs were kept constant across cost assumptions.

Table 2: **Unit costs of modelled strategy interventions**

Statistical analysis

We calculated the impact (ie, disability-adjusted life-years [DALYs] averted, new neonatal infections averted, HBV deaths averted, and reductions in new chronic infections) and costs of the HepB-BD strategy and the two PAP strategies (ie, PAP-VL and PAP-HBeAg). Two sets of assumptions for diagnostic costs (ie, central estimates and optimistic estimates) and two sets of assumptions for the implementation of testing (ie, whether pregnant women would be tested only for their first pregnancy or for each pregnancy) were used. We calculated the threshold in the costs of the two diagnostic tests to determine which of the two PAP strategies would be more cost-effective.

We also calculated the impact and cost-effectiveness of PAP-universal versus the HepB-BD strategy. We found the threshold changes in the cost of antiviral therapy and the HBV viral load test that determined when such a strategy would be more cost-effective than the approach recommended by WHO (PAP-VL). This analysis was done on the WHO African and Western Pacific regions, the two WHO regions with the highest HBsAg prevalence.

For the analyses described, model outcomes were estimated to the years 2030 and 2100. The percentage reduction in new chronic infections from 2015 to 2030 was calculated. The number of new neonatal infections averted, DALYs averted, and HBV deaths averted was calculated by subtracting the model outcome in the strategy of interest (ie, PAP-VL, PAP-HBeAg, or PAP-universal) from the model outcome in the comparator strategy (ie, HepB-BD or hepB3). This process was repeated for each of the set of assumptions for the fitted model for each country from the model calibrations (appendix 1 p 8), and uncertainty was summarised in terms of the mean and the 2·5th and 97·5th percentiles of these 200 differences in model outcomes. HBsAg test costs were calculated by using the model to estimate the number of pregnant women to be screened, and then multiplying this number by the unit cost of the HBsAg test. HBeAg and viral load test costs were each calculated by using the model to estimate the number of pregnant women who were HBsAg-positive, and then multiplying this number by the unit cost of the HBeAg test and viral load test, respectively. Treatment costs were calculated by using the model to estimate the number of pregnant women who were HBsAg-positive that were to be treated (ie, PAP-VL for pregnant women with a high viral load; PAP-HBeAg for pregnant women who were HBeAg-positive; and PAP-universal for all pregnant women who were HBsAg-positive; table 1), and then multiplying this number by the unit cost of treatment. Birth-dose vaccination (HepB-BD) and infant vaccination (HepB3) costs were each calculated by using the model to estimate the number of infants to be vaccinated, and then multiplying this number by the unit cost of the birth dose and infant vaccine, respectively. Discounting (3%) was applied to all cost calculations for computation of ICERs. For the regional results, country-level model outcomes were added within each WHO region before costs and uncertainty were calculated for each region.

For the main analyses, it was assumed that pregnant women were tested only once for HBsAg as part of routine antenatal care. We did a sensitivity analysis to investigate the cost-effectiveness (using central and optimistic cost assumptions) of the PAP-VL and PAP-HBeAg strategies by country if instead pregnant women were tested for HBsAg during each pregnancy.

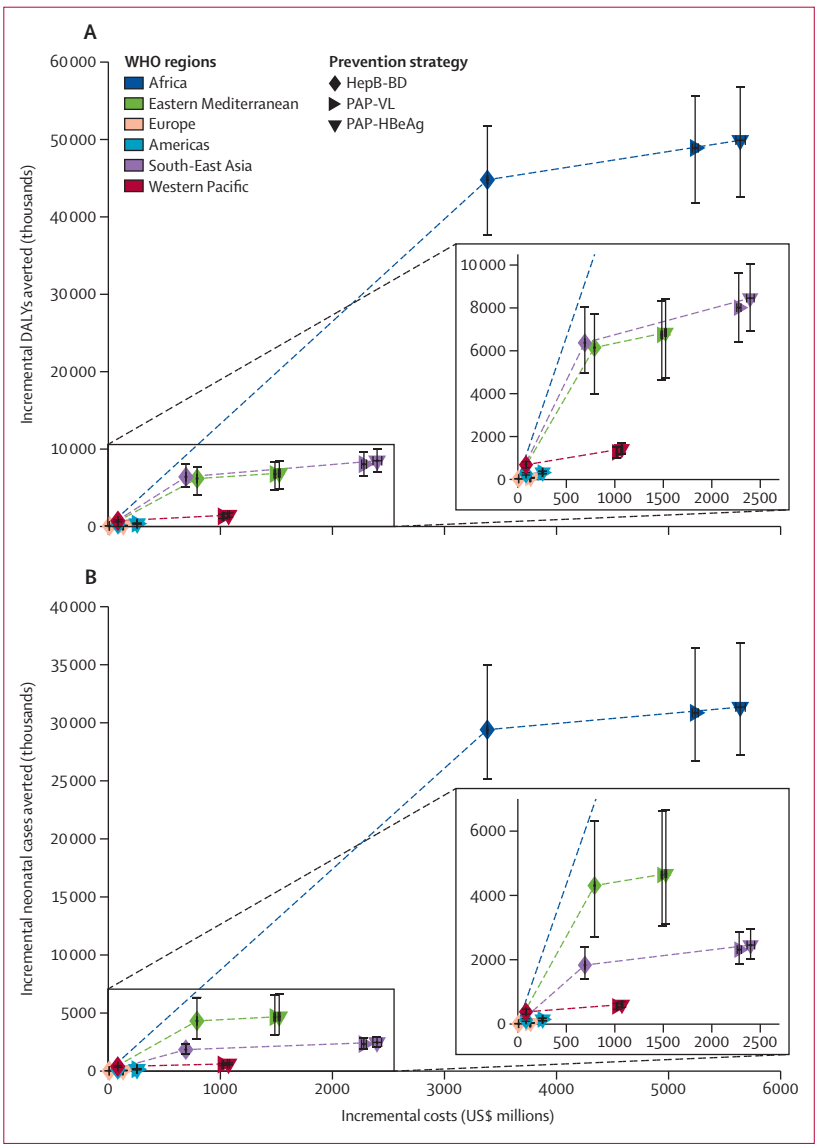


Figure 1: **Impact and costs of interventions for the prevention of mother-to-child transmission of HBV, by strategy and WHO world region**

The effect of prevention strategies on the number of DALYs (A) and neonatal infections (B), incremental to hepatitis B infant vaccination and undiscounted to 2100. Central cost assumptions were used to calculate costs. Dots denote the estimate and the error bars denote the 95% uncertainty interval. Insets show enlargements of the lower left-hand corner of each panel. DALYs=disability-adjusted life-years. HBV=hepatitis B virus. HepB-BD=hepatitis B birth-dose vaccination. PAP=peripartum antiviral prophylaxis. PAP-VL=PAP for pregnant women with high viral load.

See Online for appendix 2

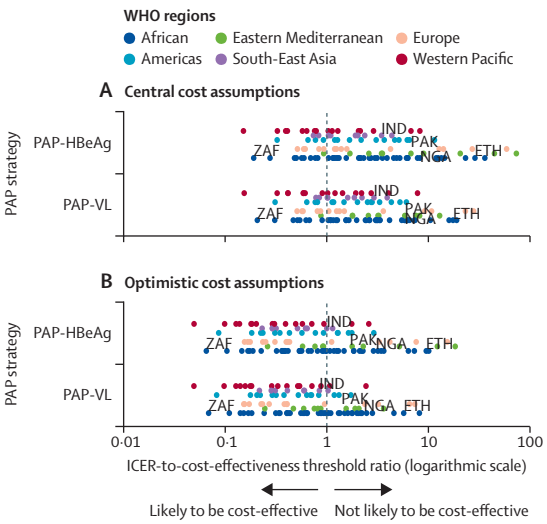


Figure 2: **Comparison of the cost-effectiveness of different PAP strategies, by cost assumption and WHO region**

Comparison of cost-effectiveness up to 2100 of PAP strategies recommended by WHO (ie, PAP-VL and PAP-HBeAg) compared with HepB-BD, based on central costs assumptions (A) and optimistic cost assumptions (B). Screening was assumed to occur once in a lifetime. Cost-effectiveness was defined as an ICER lower than the cost-effectiveness threshold (ie, ICER-to-cost-effectiveness threshold ratio <1), with thresholds for specific countries taken from Ochalek and colleagues.[21] Health impacts and costs were both discounted at 3%. Results for North Korea, Somalia, Syria, and Yemen are not shown, owing to insufficient data for the calculation of cost-effectiveness thresholds. HepB-BD=hepatitis B birth-dose vaccination. ICER=incremental cost-effectiveness ratio. PAP=peripartum antiviral prophylaxis. PAP-VL=PAP for pregnant women with high viral load. ETH=Ethiopia. IND=India. NGA=Nigeria. PAK=Pakistan. ZAF=South Africa.

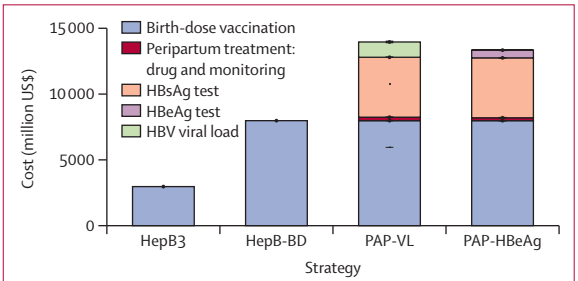


Figure 3: **Breakdown of major cost components of total strategy expenditure**

Cost components of the interventions in 110 countries were modelled for each of the strategies. Costs were calculated with central cost assumptions and were undiscounted up to 2100. HepB3=hepatitis B infant vaccination. HepB-BD=hepatitis B birth-dose vaccination. HBV=hepatitis B virus. PAP=peripartum antiviral prophylaxis. PAP-HBeAg=PAP for pregnant women who are HBeAg-positive. PAP-VL=PAP for pregnant women with high viral load.

Analyses were done in MATLAB R2022a (version 9.12.0.2009381).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In terms of the cost and impact of scaling up HepB-BD and PAP, guided either by HBV DNA or HBeAg in all modelled countries, compared with HepB3, the scale up of HepB-BD had the greatest incremental effect in every region and could avert approximately 6·0 million (95% uncertainty interval [UI] 5·6 million–6·5 million) new neonatal HBV infections and 2969 DALYs (95% UI 2605–3371) from 2024 to 2030 (figure 1). The WHO region in which HepB-BD would probably have the highest impact is the African (figure 1).

The addition of PAP to the strategy guided by HBV viral load (PAP-VL) could avert around an extra 1·1 million (95% UI 1·0 million–1·2 million) new neonatal infections by 2030, and approximately 3·2 million (3·0 million–3·4 million) new neonatal infections and about 8·8 million (7·8 million–9·7 million) DALYs by 2100 (table 3; appendix 2). The incremental effect of such a strategy varied widely by region; the highest impact would probably be in the African and South-East Asia regions, with approximately 1·9 million (95% UI 1·8 million–2·1 million) new neonatal infections averted in the African region and 622 000 (521 000–727 000) averted in South-East Asia, to 2100. From 2015 to 2030, HepB-BD could result in more than a 75% reduction in new chronic HBV infections in all WHO regions, and PAP-VL could result in more than a 90% reduction in all regions (appendix 2), which is consistent with WHO targets for a 90% reduction by 2030 in the incidence of new chronic HBV infections.

We assessed the incremental cost-effectiveness of the PAP-VL and PAP-HBeAg strategies relative to the HepB-BD strategy to 2100 in each country (figure 2). The PAP-VL strategy would probably be cost-effective at central cost estimates in only 28 (26%) of 106 countries analysed, including China (ICER $8131 [95% UI 3958–17 538]), South Africa ($1431 [943–2494]), and Viet Nam ($1374 [960–1832]), and a PAP-HBeAg intervention could be cost-effective at central cost estimates in 29 (27%) of 106 countries. However, if diagnostic and monitoring costs were lower (table 2), a PAP-VL intervention could be cost-effective in 74 (70%) of 106 countries, including 24 in the African region and 14 in the Western Pacific region, and a PAP-HBeAg intervention could be cost-effective in 70 (66%) of 106 countries. If women were to be screened at each pregnancy, this approach could reduce the cost-effectiveness of a PAP-VL strategy (only cost-effective in eight [8%] countries at central cost assumptions and in 46 [43%] countries at optimistic cost assumptions, to 2100) and a PAP-HBeAg strategy (only cost-effective in eight [8%] countries at central cost assumptions and in 42 [40%] countries at optimistic cost assumptions, to 2100; appendix 1 p 13).

In all scenarios, the major cost component was vaccination, as all children are eligible for vaccination irrespective of their mothers' antigen status (HBsAg and HBeAg) and viral load status (figure 3). For the PAP-VL

	Number of neonatal cases averted	Number of DALYs averted	Number of HBV deaths averted	Incremental cost at central cost assumptions (US$)	ICER per DALY averted at central cost assumptions (US$)	Incremental cost at optimistic cost assumptions (US$)	ICER per DALY averted at optimistic cost assumptions (US$)
African	1 944 349 (1 774 190–2 120 100)	5 109 765 (4 436 450–5 814 668)	321 847 (279 282–365 046)	2 257 038 762 (2 216 414 141–2 303 180 008)	1529 (1350–1746)	707 149 953 (689 188 844–726 762 998)	518 (460–590)
Eastern Mediterranean	365 784 (276 927–425 606)	696 946 (572 748–839 621)	39 022 (31 829–46 170)	734 112 300 (725 034 203–741 608 147)	3103 (2572–3709)	204 724 873 (199 428 990–208 872 949)	916 (764–1089)
European	27 371 (22 732–31 178)	50 934 (40 980–63 404)	3399 (2769–4168)	124 488 678 (122 306 773–125 698 808)	8029 (6397–9824)	33 626 612 (32 728 382–34 150 534)	2296 (1823–2787)
Americas	18 008 (15 794–20 187)	73 021 (64 269–82 984)	4116 (3582–4672)	171 920 446 (171 588 444–172 257 790)	6906 (6078–7780)	44 131 477 (43 959 008–44 296 609)	1805 (1593–2027)
South-East Asia	621 872 (520 519–726 634)	2 084 045 (1 604 222–2 601 984)	121 133 (95 325–149 399)	1 706 349 685 (1 669 442 563–1 747 866 731)	2716 (2179–3467)	471 589 687 (456 718 679–488 853 809)	792 (644–1003)
Western Pacific	227 666 (173 806–275 302)	738 874 (503 070–985 172)	42 999 (29 498–56 697)	988 284 849 (979 430 506–996 400 124)	4302 (3129–6088)	265 143 309 (260 892 599–269 430 981)	1206 (890–1691)
Global	3 205 049 (2 993 292–3 437 458)	8 753 585 (7 813 404–9 675 847)	532 516 (477 647–586 976)	NC	NC	NC	NC

Data are modelled estimate (95% UI). Results are incremental to a hepatitis B birth-dose vaccination. Costs and health effects (undiscounted), are shown from 2024 to 2100. ICERs were calculated from 2024 to 2100 using 3% discounting for costs and health effects. DALYs=disability-adjusted life-years. HBV=hepatitis B virus. ICER=incremental cost-effectiveness ratio. NC=not calculated. PAP=peripartum antiviral prophylaxis. PAP-VL=PAP for women with a high viral load. 95% UI=95% uncertainty interval.

Table 3: **Health impact, cost, and cost-effectiveness estimates for the PAP-VL strategy, by WHO region**

and PAP-HBeAg strategies, the cost of antenatal screening with HBsAg contributes to the largest proportion of incremental costs ($4554 million [76·2%] of $5979 million for PAP-VL and $4554 million [84·9%] of $5361 million for PAP-HBeAg, to 2100). The costs of antiviral drugs and of further diagnostic tests (HBV viral load or HBeAg) accounted for a smaller percentage of the total PAP strategy expenditure (to 2100, $264 million [4·4%] of $5979 million for drugs and $1162 million [19·4%] of $5979 million for tests for the PAP-VL strategy, and $221 million [4·1%] of $5361 million for drugs and $587 million [11·0%] of $5361 million for tests for the PAP-HBeAg strategy).

The PAP-HBeAg strategy was found to be slightly less effective and less costly than the PAP-VL strategy (tables 3, 4; appendix 2) to 2100. This result was expected, because HBeAg status is a good, but imperfect, proxy of viral load, which is the proximate determinant of transmission risk. The relative cost-effectiveness of each of these PAP approaches depends on the cost of the respective diagnostic test used (figure 4). When we used central cost estimates for diagnostics in our analysis, PAP-VL was more cost-effective than the PAP-HBeAg strategy, apart from in the WHO African region, but the difference in cost per DALY averted to 2100 was slight ($1529 [95% UI 1350–1746] for PAP-VL *vs* $1419 [1262–1621] for PAP-HBeAg). The isoclines for these two strategies varied by WHO region; in regions with a lower prevalence of infection, a higher cost of viral load diagnostics could still be more cost-effective than using HBeAg testing, as fewer such tests are needed.

PAP-universal (ie, without the use of a second diagnostic test to guide treatment eligibility) was found to have a greater impact than the strategies that limited giving PAP to women at high risk of transmission (approximately 4·9 million [95% UI 4·7 million–5·1 million] neonatal cases averted and 13·5 million [12·3 million–14·6 million] DALYs averted relative to the HepB-BD strategy in the 110 countries modelled to 2100; appendix 2). However, the overall use of antiviral treatment could be more than five times as great as the PAP-VL strategy: 75·7 million (95% UI 72·1 million–79·0 million) versus 13·2 million (12·4 million–14·1 million) pregnant women could require antiviral therapy with a PAP-universal strategy compared with a PAP-VL one. The ICER for PAP-universal compared with HepB-BD per DALY averted to 2100 for the six WHO regions ranged from $985 (95% UI 878–1128) for the African region to $6587 (5511–7730) for the European region (appendix 2). At central cost estimates and compared with HepB-BD, the PAP-universal strategy had a lower ICER than the PAP-VL strategy in most countries but would probably only be cost-effective (within the cost-effectiveness threshold for each country) in 42 (40%) of 106 countries to 2100.

The relative cost-effectiveness of PAP-universal and PAP-VL (each compared with HepB-BD) depended on the relative costs of the antiviral drug used and the cost of providing the second diagnostic test (figure 5). Thus, for each country in our analysis (ie, those in the African and Western Pacific regions), there was a range of costs for which the PAP-universal strategy would be more cost-effective than PAP-VL. Our analysis showed that for all countries this difference was finely balanced, such that a small variation in either cost category would affect the cost-effectiveness of the PAP-universal strategy.

Discussion

This study is the first, to our knowledge, to evaluate the impact and cost-effectiveness of PAP strategies

	Number of neonatal cases averted	Number of DALYs averted	Number of HBV deaths averted	Incremental cost at central cost assumptions (US$)	ICER per DALY averted at central cost assumptions (US$)	Incremental cost at optimistic cost assumptions (US$)	ICER per DALY averted at optimistic cost assumptions (US$)
African	1 452 211 (1 274 224–1 618 789)	4 116 134 (3 549 385–4 666 563)	254 040 (218 088–288 278)	1 854 559 337 (1 830 109 935–1 882 017 711)	1419 (1262–1621)	585 505 419 (571 068 646–600 833 241)	498 (442–563)
Eastern Mediterranean	327 866 (237 555–388 609)	589 578 (468 170–728 565)	33 290 (26 123–40 065)	695 074 589 (687 049 034–701 125 399)	3381 (2718–4164)	193 980 689 (188 044 150–197 866 654)	1004 (814–1236)
European	21 344 (17 487–25 051)	43 232 (34 337–54 212)	2850 (2300–3510)	117 964 687 (116 732 665–118 715 738)	8567 (6766–10 771)	31 678 991 (31 041 490–32 120 807)	2438 (1947–3020)
Americas	15 609 (13 343–17 833)	61 319 (52 051–70 756)	3493 (2959–4022)	169 519 676 (169 269 487–169 768 585)	8072 (6972–9415)	43 447 705 (43 276 613–43 606 047)	2104 (1824–2446)
South-East Asia	480 022 (395 568–580 697)	1 639 252 (1 218 356–2 108 594)	94 634 (71 377–120 237)	1 588 621 420 (1 568 034 852–1 612 063 028)	3086 (2400–4100)	436 411 881 (426 259 028–448 153 788)	897 (709–1175)
Western Pacific	170 674 (115 453–219 486)	577 547 (333 984–824 849)	33 334 (19 278–47 301)	937 794 108 (931 388 514–944 125 241)	5170 (3427–8335)	249 886 781 (245 329 630–254 175 318)	1437 (971–2280)
Global	2 467 725 (2 243 480–2 676 393)	7 027 061 (6 181 392–7 823 655)	421 639 (373 208–468 806)	NC	NC	NC	NC

Data are modelled estimate (95% UI). Results are incremental to a hepatitis B birth-dose vaccination strategy. Costs and health effects (undiscounted), are shown from 2024 to 2100. ICERs were calculated from 2024 to 2100 using 3% discounting for costs and health effects. DALYs=disability-adjusted life-years. HBV=hepatitis B virus. ICER=incremental cost-effectiveness ratio. NC=not calculated. PAP=peripartum antiviral prophylaxis. 95% UI=95% uncertainty interval.

Table 4: **Health impact, cost, and cost-effectiveness estimates for the PAP-HBeAg strategy, by WHO region**

Figure 4: **Comparison of the cost-effectiveness of PAP-HBeAg versus PAP-VL strategies, by region**

The cost of the diagnostics tests (ie, HBV viral load and HBeAg) determine which PAP strategy is most likely to be cost-effective to 2100 at 3% discounting. Isoclines are presented as banded shaded areas that represent results from stochastic estimates for each WHO region (ie, 95% of 200 particle estimates are contained within the shaded area). Cost combinations shown above and to the left of the isocline indicate that the PAP-VL strategy is more cost-effective, whereas cost combinations shown below and to the right of the isocline indicate that the PAP-HBeAg strategy is more cost-effective. The figure only represents which strategy dominates and does not show a comparison to a threshold. The red triangle represents central costs modelled. Black triangles represent optimistic and high diagnostic cost assumptions. PAP=peripartum antiviral prophylaxis. PAP-VL=PAP for pregnant women with high viral load.

recommended by WHO in all regions globally. Our study shows that the addition of PAP to HepB-BD could lead to important health gains in terms of reducing new neonatal infections and averting DALYs. However, in many settings, a PAP strategy might not be cost-effective at central cost estimates when benchmarked against country-level health opportunity costs, although access to lower diagnostic costs (ie, around a 60–75% reduction in costs) would improve cost-effectiveness. This result has important public health implications and careful consideration needs to be given at a country level when implementing such a strategy, including the need to secure reduced cost diagnostics whenever possible.

Consistent with previous studies on HepB-BD, we have shown that scaling up HepB-BD will probably deliver the largest impact for the lowest cost, and would therefore be considered the most cost-effective strategy for the prevention of mother-to-child HBV transmission.[20,22–24] This approach supports WHO's longstanding recommendation for a HepB-BD vaccination policy as the foundation of mother-to-child HBV transmission prevention efforts.

We found that the cost of HBsAg tests contributed more to the total cost of a PAP intervention than the cost of the antiviral drug did, despite the potentially low unit

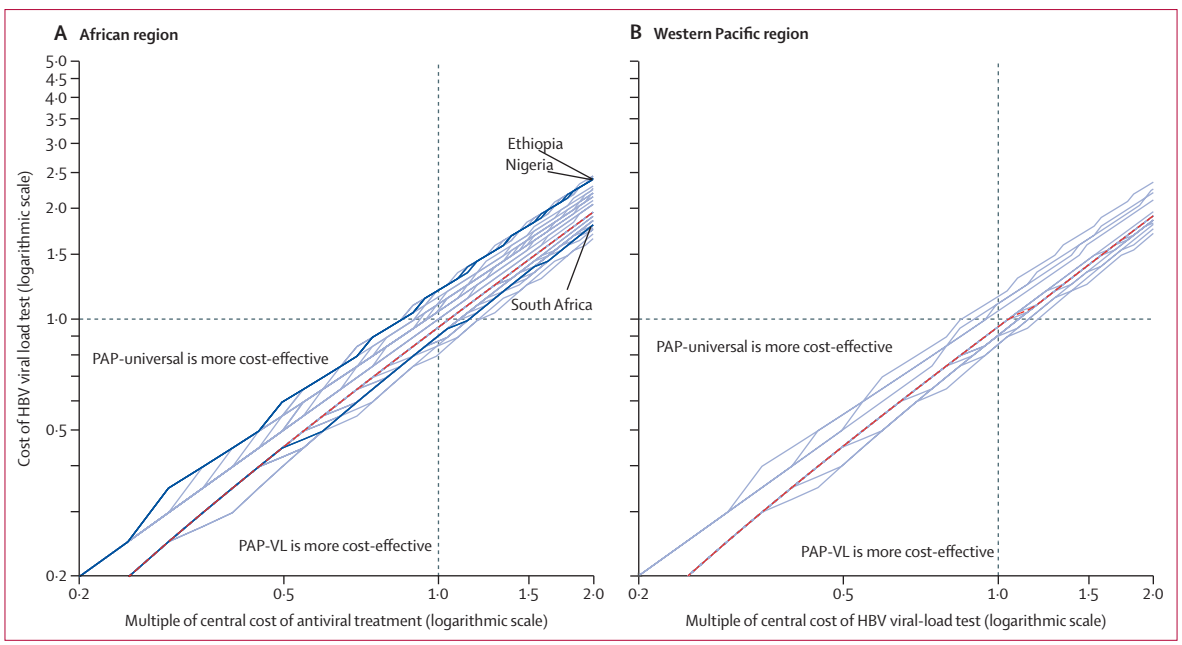


Figure 5: **Cost assumptions for antiviral treatment and HBV viral-load test, under which PAP-universal and PAP-VL would be cost-effective in two WHO regions**

The changes from our central cost of antiviral treatment and viral load tests that would lead to PAP-universal or PAP-VL being cost effective in the African and Western Pacific WHO regions. Unit costs of antiviral treatment and viral load tests are scaled such that 1·0 is the central estimate (table 2). ICERs allow for discounting cost at 3% per year and costs and impact up to year 2100. Each blue line shows the threshold for a particular country that separates the assumptions under which PAP-universal or PAP-VL is cost-effective. Ethiopia, South Africa, and Nigeria are denoted by bold blue lines. The dashed red line shows the average for the region. For descriptions of PAP-universal and PAP-VL, see table 1. HBV=hepatitis B virus. PAP=peripartum antiviral prophylaxis. PAP-VL=PAP for pregnant women with a high viral load.

cost (around $1·60 per test) of rapid diagnostic tests, as every pregnant woman requires testing. By contrast, tests for HBV DNA and HBeAg contributed less to overall costs, despite their higher unit costs, as they were only used for a minority of pregnant women who were found to be HBsAg-positive.

Unfortunately, many countries do not have access to diagnostic tests at the central cost estimates that we modelled. Our study provides additional information on how the relative costs of drugs and diagnostics affect cost-effectiveness, which is useful for countries to consider when planning their programmes to prevent mother-to-child HBV transmission, and could help to inform price negotiations for diagnostics. Theoretically, GeneXpert HBV vial load test kits are available for $15,[19] but consideration would need to be given to the capacity of these existing platforms (which are usually used for tuberculosis and HIV) to integrate HBV testing. Furthermore, we modelled the use of laboratory-based HBeAg tests with high diagnostic accuracy, as the performance of currently available rapid diagnostic tests for HBeAg has been disappointing so far, with low sensitivities of 28–72%.[8,9] If countries remain reliant on the use of a centralised laboratory-based HBeAg testing mechanism, this stance might limit the potential advantage of using a HBeAg strategy over one guided by viral load.

During childbearing years, a woman's chance of a change in HBV infection status is small, with respect to acquiring a new infection or having a spontaneous loss of HBsAg. Therefore, we assumed that a pragmatic approach would be taken, such that each pregnant woman would only require one HBsAg screening test per childbearing lifetime. However, in practice, there might be a tendency towards re-testing at each pregnancy (particularly in circumstances in which there is imperfect record keeping or high mobility of people between clinics, or because of health-care worker preferences), which we found would make a PAP strategy less cost-effective. Also, it might be preferable for pregnant women who are HBsAg-positive and require PAP to continue antiviral medications throughout their childbearing years to reduce the stopping and starting of medications, particularly in settings in which the fertility rate is high. As these factors might have a large influence on the overall cost and cost-effectiveness of PAP approaches, they should be taken into account during the early stages of strategic planning, as should considerations about how health informatics systems can be strengthened to accomplish linkage and streamlined management between pregnancies.

Increasingly, a universal PAP strategy is being discussed, owing to it being a simplified model of care with no requirement for the second diagnostic test, which still remains a limiting financial and logistical factor in many low-income and middle-income countries and rural settings and can delay or hinder the initiation of antiviral prophylaxis in pregnancy.[8,11] We found that

such a strategy has the potential to be more efficient than the PAP policy guided by HBV viral load, as recommended by WHO, mainly because antiviral drug cost would be cheaper than extra HBV viral load tests. However, such an approach would still probably not be cost-effective in most countries. A previous modelling study of South Africa also suggested that treating all women who are HBsAg-positive might be more cost-effective than treating only women who are HBeAg-positive.[25] However, the effectiveness of tenofovir disoproxil fumarate might have been overestimated, as the risk reduction assumed for this drug without HepB-BD was based on literature about the combined efficacy of HepB-BD, HBIg, and tenofovir disoproxil fumarate.[4] However, questions remain about the feasibility and acceptability of, and adherence to, medications given within a universal PAP strategy, which thus need evaluation before wide-scale implementation. We found that a universal PAP strategy could lead to the treatment of more than five times as many pregnant women, who would otherwise not be eligible for antiviral medications under current guidance. Although tenofovir disoproxil fumarate is widely used in pregnancy, particularly in HIV regimens, and has a good safety profile, the implications of scaling up its use are still an important consideration when balancing perspectives between individual patients and public-health interventions. Furthermore, this simplified approach, without HBV viral load testing or assessment for the presence of clinically significant liver disease, raises questions about how the need for long-term antiviral therapy for the sake of the mother's own health is evaluated. There is also a risk of post-partum hepatic flares, particularly on discontinuation of antiviral therapy.[5,26]

These results provide a useful guide for policy making at the country and regional level, but, with the data that are available currently, can only give a broad indication as to the likelihood of these strategies being cost-effective. Given the macroscopic perspective of the analysis, we did not detail all cost components, but rather focused on those factors that would guide choice of strategy and need further research. Data are also sparse on the costs of management of HBV-related decompensated cirrhosis and liver cancer, and only 10% of people globally are estimated to have been diagnosed and to be aware of their HBV infection status.[27] Therefore, in low-income and middle-income countries, many people who are HBV-positive present late in the course of their illness. We therefore took the conservative perspective of excluding any such costs. Recognising that these interventions would benefit from the use of existing infrastructure, we also excluded programme, management, overhead, and human resources costs. Hence, decisions about the allocation of resources at the local level would benefit from detailed, careful analysis using comprehensive local data in each country and a full appraisal of feasible alternatives.

Among the limitations of any modelling in this area is the uncertainty about the risks of transmission and the efficacy of interventions, particularly in the WHO African region. Most studies evaluating the efficacy of PAP have used PAP in combination with HepB-BD and HBIg, and HBIg is not feasible in many settings.[4,7] A study in Cambodia found that treating pregnant women who were HBeAg-positive with a HBIg-free PAP intervention was effective, which is encouraging, especially for countries in which HBIg is not an option.[15] Furthermore, there are few data outside of the Western Pacific region on the proportion of women with a high HBV viral load who are HBeAg-positive. Another limitation is that we did not model every single country in the world or in each region; however, the model includes countries that collectively account for 92% of the global total number of people living with HBV and more than 99% of such people in the WHO African and South-East Asia regions, which have the greatest burdens (appendix 1 p 12). It would be beneficial to revisit this analysis as additional data on the effectiveness of these strategies are gathered and as progress can be evaluated following actual implementations.

In summary, this study has shown that HepB-BD remains the most cost-effective intervention for the prevention of mother-to-child HBV transmission. A PAP strategy could have substantial extra health benefits but might not be cost-effective in all countries without further reductions in the cost of diagnostics. Although cost-effectiveness considerations form only one part of overall decision making, careful country-level planning is needed about how such a strategy is implemented (including who is rescreened, which diagnostic is used, and the cost of the diagnostic). Promising theoretical strategies of offering prophylaxis to all pregnant women who are HBsAg-positive without accompanying risk stratification could also improve feasibility and cost-effectiveness, depending on the prevailing costs of diagnostics and of providing antiviral therapy, and the extent to which this strategy might be achieved requires further research on implementation.

Contributors

SN and TBH conceived and designed the study. MJdV, SN, and TBH developed the model, MJdV did the analysis using the model, and SN, MJdV, and TBH interpreted the results. MJdV and SN and interpreted the results. MJdV and SN accessed and verified the underlying data. SN prepared the first manuscript draft and TBH edited it. SN, YS, ML, and MRT provided clinical input into model parameterisation. SN, TBH, and NW interpreted the findings and assessed the implications for decision making. All authors were involved in critical review and edited and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SN reports grants to their institution not connected to this work from Gavi, the Vaccine Alliance. YS reports grants to their institution not connected to this work from Gilead Sciences, and equipment to their other projects from Abbott Laboratories and Fujirebio. ML reports grants to their institution not connected to this work from the UK Medical Research Council (MRC), the French National Agency for

Research on AIDS, Cepheid UK, and Gilead Sciences USA; consultancy fees from Gilead Sciences USA; and equipment to their other projects from Abbott USA. TBH reports grants to their institution not connected to this work from Gavi. All other authors declare no competing interests.

Data sharing

The data used were all accessed from publicly available sources. The code of the model used for the analysis and electronic versions of the results tables are publicly available at https://github.com/mrc-ide/icl-hbv.

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